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(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.

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

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

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

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

[0006] 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 nucleosides of said second strand comprise a 2' sugar and bond modification pattern as follows (5'-3'):

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

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

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

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

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

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

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[0007] 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 nucleosides of said second strand comprise a 2' sugar and abasic modification pattern as follows (5'-3'):

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

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

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

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

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

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

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

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

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

[0008] 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 nucleosides of said second strand comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

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

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

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

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

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

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

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

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

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

[0009] A nucleic acid as described herein typically includes a first strand that comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2'- F sugar modifications at least at positions 2, 14 and 16, and / or

2'-Me sugar modifications at positions 17 to 23, or said first strand comprises at least eight 2' – F sugar modifications, such as 2'- F sugar modifications at least at positions 2, 4, 6, 12, 14, 16, 18 and 20, and / or

2'-Me sugar modifications at positions 1, 3 to 5, 10 to 13, or said first strand comprises at least eight 2' – F sugar modifications, such as 2'- F sugar modifications at least at positions 2, 4, 6, 12, 14, 16, 18 and 20, and / or

a 2'-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2'-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically can be the same 2' sugar modification,

whereby typically the first strand can comprise the following modification pattern (5'- 3'):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'- 3'):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'- 3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'- 3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

[0010] Typically $(M)_4$ as set out above represents any one of the following 2' sugar modification patterns (5' – 3'):

F – Me – Me – F

Me – F – Me – F

F – Me – F – Me

F – F – F – F

Me – F – F – Me

Me – Me – F – F

F – F – Me – Me

Me – Me – Me – Me

[0011] Typically, two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in both 5' and 3' terminal regions of the first strand s as described herein, 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 where appropriate there may further be present two phosphorothioate internucleoside linkages between three consecutive positions in the 3' terminal region of the second strand, whereby the 3' terminal nucleoside is attached to an adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and said penultimate nucleoside is attached to an adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage, and / or where appropriate there may further be present two phosphorothioate internucleoside linkages between three consecutive positions in the 5' terminal region of the second strand, whereby the 5' terminal nucleoside is attached to an adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and said penultimate nucleoside is attached to an adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage.

[0012] 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 nucleosides of said second strand comprise a 2' sugar and abasic modification pattern as follows:

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

or position 7 on the second strand includes a sugar modification that is a 2'-Me modification, wherein position 1 is the 5' terminal nucleoside of the second strand and the direction of counting is 5' – 3', and there are typically present two inverted abasic nucleosides at 5' terminal region of the second strand,

where such second strands are typically used together with a first strand as defined herein.

[0013] 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 nucleosides of said second and first strands comprise a 2' sugar modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

[0014] 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 nucleosides of said second and first strands comprise a 2' sugar modification pattern as follows (5'-3'):

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

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

or

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

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

[0015] 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows:

(5'-3'):Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[0016] 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows (5'-3'):

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

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

or

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[0017] 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows:

(5'-3'):Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[0018] 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 nucleosides of said second and first strands comprise a 2' sugar and abasic modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

wherein ia represents an inverted abasic nucleoside.

[0019] 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 nucleosides of said second and first strands comprise a 2' sugar and abasic modification pattern as follows (5'-3'):

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

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

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

wherein ia represents an inverted abasic nucleoside.

[0020] 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 nucleosides of said second and first strands comprise a 2' sugar and abasic modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

First strand (5’-3’): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 3:

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

First strand (5’-3’): Me - F - Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 4:

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

First strand (5’-3’): Me - F - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me

Or Modification pattern 5:

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

First strand (5’-3’): Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me

Or Modification pattern 6:

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

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

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

[0021] 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 nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

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

[0022] 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 nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

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

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

or

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

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

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

[0023] A nucleic acid for inhibiting expression of ZPI or HCII, comprising a duplex region that comprises: a first strand that is at least partially complementary to a portion of RNA transcribed from ZPI or HCII, and a second strand that is at least partially complementary to the first strand, wherein nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

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

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

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

[0024] A nucleic acid for inhibiting expression of B4GALT1, comprising a duplex region that comprises: a first strand that is at least partially complementary to a portion of RNA transcribed from B4GALT1, and a second strand that is at least partially complementary to the first strand, wherein nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-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 - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

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

[0025] 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 nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

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

[0026] A particularly suitable nucleic acid for inhibiting expression of a target gene according to the present invention, 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, counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification, or

the second strand comprises the following modification pattern:

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

[0027] Particularly suitable nucleic acids according to the present invention are as follows:

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 – Me

together with a first strand that comprises a modification pattern selected from the following (5'- 3'), wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

(5'- 3') Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'- 3'):

(5'- 3') Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'- 3'):

(5'- 3') Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'- 3'):

(5'- 3') Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

[0028] 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' or 3' terminal region of the second strand, and counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification.

[0029] Particularly suitable according to the present invention is 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 said second and first strands comprise the following modification patterns:

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 – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

[0030] 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: counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, two phosphorothioate internucleoside linkages that are respectively present between positions 1 and 2, and 2 and 3 of the second strand, or counting from the 3' terminus position 1 of the second strand, which is the 3' most nucleoside not including abasic nucleosides, two phosphorothioate internucleoside linkages that are respectively present between positions 1 and 2, and 2 and 3 of the second strand, and counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification.

[0031] 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: counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification, and at the 3' terminus of the second strand the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, wherein the ligand moiety preferably 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.

[0032] Each of the above second strand sequences and constructs can be used with any of the first strands as described herein.

[0033] 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 said second strand has the following modification pattern:

Modification pattern 1:

Second strand (5'-3'): ia – ia –F – Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F – Me – F, optionally in combination with

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

Or Modification pattern 2:

Second strand (5'-3'): F – Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F – Me – F - ia – ia, optionally in combination with

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

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

[0034] 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 said second strand has the following modification pattern:

Modification pattern 1:

Second strand (5'-3'): ia – ia –F(s)Me(s) F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F – Me – F, optionally in combination with

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

Or Modification pattern 2:

Second strand (5'-3'): F – Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me – F(s)Me(s)F - ia – ia, optionally in combination with

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

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

[0035] Further nucleic acids according to the present invention include 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows (5'-3'):

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

wherein the 2'-Me or 2'-F modified nucleosides of said first strand include any one of the following modification patterns (5'-3'):

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

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

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

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

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

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

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

First strand (5’-3’): Me(s) F(s) Me – Me – Me – Me – F – Me – F– Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – F – F – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – Me – F – F – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – Me – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – F – F – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

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

wherein: (s) is a phosphorothioate internucleoside linkage.

[0036] Further nucleic acids according to the present invention include 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 nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

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

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

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

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

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

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

wherein the 2'-Me or 2'-F modified nucleosides of said first strand include any one of the following modification patterns (5'-3'):

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

wherein:

(s) is a phosphorothioate internucleoside linkage,

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

[0037] 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.

[0038] 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.

[0039] Typically a first strand as described above comprises nucleosides 2-18 of any one of the sequences defined in Tables 2 or 3.

[0040] 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 second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0041] 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.

[0042] 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 second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

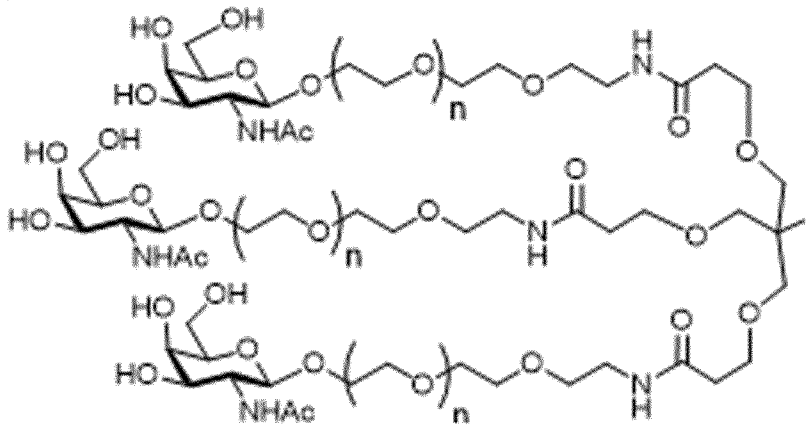
[0047] A nucleic acid according to the present invention, wherein the second strand comprises any one of the second strand sequences as listed in Table 4.

[0048] 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.

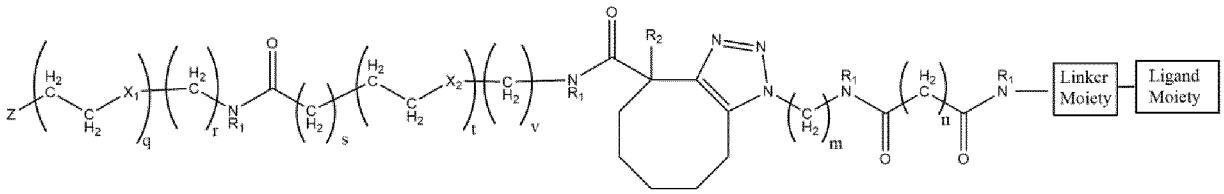
[0049] A nucleic acid according to the present invention, wherein the nucleic acid is an siRNA oligonucleoside.

[0050] 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.

[0051] A nucleic acid according to the present invention, comprising a ligand moiety comprising the following structure:



[0052] A nucleic acid according to the present invention, comprising a ligand moiety comprising the following 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;

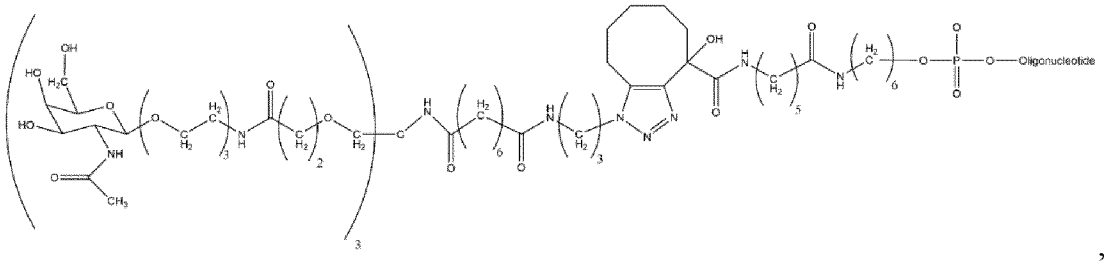
m is an integer of from 1 to 6;

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: 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.

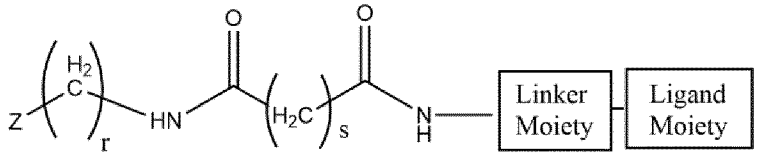
[0053] A nucleic acid according to the present invention, comprising the structure



,

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

[0054] Alternatively, a nucleic acid according to the present invention, comprising a ligand moiety comprising the following structure:

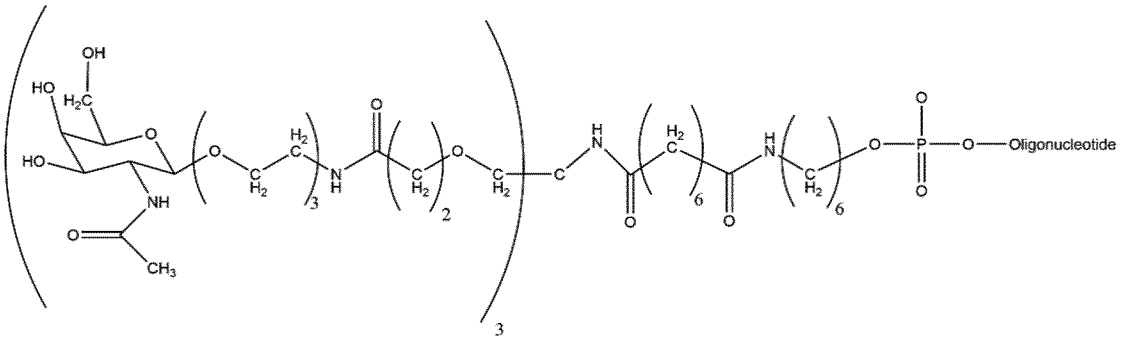


wherein:

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

Z is an oligonucleoside.

[0055] A nucleic acid according to the present invention, comprising the structure



,

[0056] wherein [oligonucleotide] represents the contiguous nucleosides of the second strand.

[0057] The present invention further provides a pharmaceutical composition comprising a nucleic acid as described herein, in combination with a pharmaceutically acceptable excipient or carrier.

[0058] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in therapy.

[0059] 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.

[0060] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in prevention or treatment of cardiovascular disease.

[0061] The present invention further provides a nucleic acid or pharmaceutical composition as described herein, for use in prevention or treatment of diabetes.

FIGURES

[0062] 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).

[0063] 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).

[0064] 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.

[0065] 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.

[0066] Figure 5: Formulae described in Sentences 1-101 disclosed herein.

[0067] Figure 6: Formulae described in Clauses 1-56 disclosed herein.

[0068] Figures 7a and 7b: Inverted abasic constructs that can be used with nucleic acid sequences according to the present invention as described herein. For Figure 7a, a galnac linker is attached to the 5' end region of the sense strand in use (not depicted in Figure 7a). For Figure 7b, a galnac linker is attached to the 3' end region of the sense strand in use (not depicted in Figure 7b).

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

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

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

[0069] Figures 8 (8a and 8b): Duplex constructs according to Table 5.

[0070] Figure 9 (9a and 9b): Results of dose-response experiments for inhibition of HCII or ZPI mRNA expression in human Huh7 cells. Points represent mean relative expression of HCII or ZPI mRNA compared to untreated wells after treatment with siRNA construct at the indicated concentrations on the x-axis. Error bars represent standard deviation of the mean. Dotted curves represent 95% confidence intervals. Dotted lines and shaded areas represent the mean relative expression +/- standard deviation from untreated wells on the same plate.

[0071] Figure 10: Inhibition of ZPI expression by ETXM1184 (ETXS1036 & ETXS1035) and ETXM1199 (ETXS2398 & ETXS2397).

[0072] Figure 11: Inhibition of B4GALT1 expression by ETXM1200 (ETXS2400 & ETXS2399) and ETXM1201 (ETXS2402 & ETXS2401).

[0073] Figure 12: Inhibition of B4GALT1 expression by ETXM1203 (ETXS2406 & ETXS2405) and ETXM1204 (ETXS2408 & ETXS2407).

[0074] Figure 13: Joint Protection: Several Endpoints Document Dose-Responsive Effect. Prophylactic administration of ETXM1184 shows dose-dependent protection in key tissue readouts at 10 days post-injury. ETXM1184 shows efficacy in the same range as clinical comparators: FVIII replacement therapy as gold-standard for emergency treatments (Advate) and siRNA-based rebalancing agent for prophylaxis that demonstrated good bleed protection in late-stage clinical development (fitusiran). * Scale: 0 = Normal; 1 = Minimal; 2 = Moderate; 3 = Marked; 4 = Severe. [1] Glasson et al., Osteoarthritis Cartilage. 2010 Oct;18 Suppl 3:S17-23. doi: 10.1016/j.joca.2010.05.025. PMID: 20864019.

[0075] Figure 14: Composite haemarthrosis histopathology score quantifies: Tendonitis, Tendon degeneration, Tenosynovitis, Periostitis, Osteolysis, Osteoclastic bone resorption, Haemorrhage, Haematoma, Haemosiderin deposition, Chondrocyte necrosis, Cartilage OARSI Grade, Subchondral bone sclerosis and Bone marrow hyperplasia. ETX-148 shows significant dose-responsive effect (Bayesian linear model fitted to composite score). Median reduction of composite score compared to control: -1.25 for the ETXM1184 10 mg/kg group (significance level equivalent to $p<0.01$); -0.91 for the ETXM1184 3 mg/kg group (significance level equivalent to $p<0.05$). Comparator fitusiran shows median reduction of -1.04 for the 3 mg/kg group (significance level equivalent to $p<0.05$).

[0076] Figure 15: Prophylactic administration of ETXM1184 improves haemarthrosis joint pathology in haemophilia A mice. Administration of 3 mg/kg ETXM1184 resulted in improved hemarthrosis knee joint pathology, reduced inflammation, and resulted in smaller areas of haemorrhage.

[0077] Figure 16: Prophylactic administration of ETXM1184 reduces post-injury bleeding in hemophilia A mice (in-life visual bleeding score (VBS)). A bleeding event was introduced into the knee joint of Hemophilia A mice 8 days after siRNA administration. Bleeding was monitored for 10 days post-injury and terminal histological analysis was conducted. Prophylactic administration of a single 10 mg/kg dose of ETXM1184 effectively reduced visual bleeding score (VBS) comparably to Factor VIII replacement (Advate) by 10 days post-injury.

[0078] Figure 17: Prophylactic administration of ETXM1184 reduces post-injury bleeding into the knee joint of hemophilia A mice (in-life measurement of injured knee diameter compared to non-injured knee diameter). A bleeding event was introduced into the knee joint of Hemophilia A mice 8 days after siRNA administration. Bleeding was monitored for 10 days post-injury and terminal histological analysis conducted. Prophylactic ETXM1184 administered as a single 10 mg/kg dose effectively reduced blood accumulation in knee joint comparably to Factor VIII replacement (Advate) by 10 days post-injury.

[0079] Figure 18: Prophylactic administration of ETXM1184 reduces hemarthrosis in a Hemophilia A mouse model (terminal measurements taken 18 days post-siRNA dosing and 10 days post-injury). Prophylactic ETXM1184 administered as a single 10 mg/kg dose effectively reduced joint bleeding and characteristics of hemophilic arthropathy comparably to Factor VIII replacement (Advate) by 10 days post-injury.

DEFINITIONS

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] In another embodiment, the nucleoside mismatch is, for example, in the 3'- terminal nucleoside of the nucleic acid e.g. siRNA.

[0087] 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.

[0088] 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.

[0089] The term "ribonucleoside" or "nucleoside" can also refer to a modified nucleoside, as further detailed below.

[0090] A nucleic acid can be a DNA or an RNA, and can comprise modified nucleosides. RNA is a preferred nucleic acid.

[0091] 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).

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] "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.

[0099] 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).

[00100] 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".

[00101] "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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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:3-42 and 443-448. 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.

[00108] Accordingly, in some preferred embodiments, the antisense oligonucleosides as disclosed herein are fully complementary to the target gene sequence.

[00109] 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.

[00110] In certain embodiments, the first (antisense) strand of a nucleic acid according to the invention is partially or fully complementary to a contiguous portion of RNA transcribed from the HCII gene. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of at least 17 nucleosides of the HCII mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of the HCII mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of any one of the sequences as listed in Table 1, i.e., any one of SEQ ID NOs: 3-22 and 445-446.

[00111] In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the HCII mRNA if it comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of the HCII mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 3-22 and 445-446. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 19 nucleosides, wherein at least 14, 15, 16, 17, 18 or all 19 nucleosides of said

contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 3-22 and 445-446. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 23 nucleosides, wherein at least 18, 19, 20, 21, 22 or all 23 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 3-22 and 445-446.

[00112] In certain embodiments, the first (antisense) strand of a nucleic acid according to the invention is partially or fully complementary to a contiguous portion of RNA transcribed from the ZPI gene. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of at least 17 nucleosides of the ZPI mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of the ZPI mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of any one of the sequences as listed in Table 1, i.e., any one of SEQ ID NOs: 23-42 and 443-444.

[00113] In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the ZPI mRNA if it comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of the ZPI mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 23-42 and 443-444. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 19 nucleosides, wherein at least 14, 15, 16, 17, 18 or all 19 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 23-42 and 443-444. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 23 nucleosides, wherein at least 18, 19, 20, 21, 22 or all 23 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous

portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 23-42 and 443-444.

[00114] In certain embodiments, the first (antisense) strand of a nucleic acid according to the invention is partially or fully complementary to a contiguous portion of RNA transcribed from the B4GALT1 gene. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of at least 17 nucleosides of the B4GALT1 mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of the B4GALT1 mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention is partially or fully complementary to a contiguous portion of 17, 18, 19, 20, 21, 22 or 23 nucleosides of any one of the sequences as listed in Table 1, i.e., any one of SEQ ID NOs: 447-448.

[00115] In certain embodiments, the first (antisense) strand of the nucleic acid according to the invention is partially complementary to a contiguous portion of the B4GALT1 mRNA if it comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of the B4GALT1 mRNA. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of at least 17 nucleosides, wherein at least 14, 15, 16 or 17 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 447-448. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 19 nucleosides, wherein at least 14, 15, 16, 17, 18 or all 19 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 447-448. In certain embodiments, the first strand of the nucleic acid according to the invention comprises a contiguous nucleoside sequence of 23 nucleosides, wherein at least 18, 19, 20, 21, 22 or all 23 nucleosides of said contiguous nucleoside sequence are complementary to a contiguous portion of any one of the sequences listed in Table 1, i.e., any one of SEQ ID NOs: 447-448.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] "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).

[00121] 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.

[00122] 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.

[00123] 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.

[00124] 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.

[00125] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

[00126] 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."

[00127] 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.

[00128] The term "at least" prior to a number or series of numbers is understood to include the number adjacent to the term "at least", and all subsequent numbers or integers that could logically be included, as clear from context. For example, the number of nucleosides in a nucleic acid molecule must be an integer. For example, "at least 18 nucleosides of a 21 nucleoside nucleic acid molecule" means that 18, 19, 20, or 21 nucleosides have the indicated property. When at least is present before a series of numbers or a range, it is understood that "at least" can modify each of the numbers in the series or range.

[00129] 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.

[00130] The terminal region of a strand is the last 5 nucleosides from the 5' or the 3' end.

[00131] Various embodiments of the invention can be combined as determined appropriate by one of skill in the art.

Abasic Nucleosides

[00132] 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.

[00133] 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.

[00134] 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.

[00135] Preferably there is an abasic nucleoside at the terminus of the second strand.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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).

[00143] 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.

[00144] 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

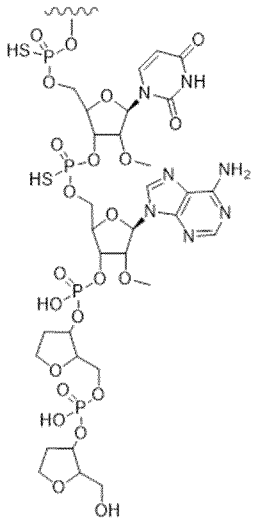
of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 5' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present 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.

[00145] Alternatively the second strand comprises 2 consecutive abasic nucleosides preferably in an overhang in the 3' terminal region of the second strand, wherein one such abasic nucleoside is a terminal nucleoside at the 3' terminal region of the second strand and the other abasic nucleoside is a penultimate nucleoside at the 3' terminal region of the second strand, wherein: (a) said penultimate abasic nucleoside is connected to an adjacent first basic nucleoside in an adjacent 3' near terminal region through a reversed internucleoside linkage; and (b) the reversed linkage is a 3-3' reversed linkage; and (c) the linkage between the terminal and penultimate abasic nucleosides is 5'-3' when reading towards the terminus comprising the terminal and penultimate abasic nucleosides. More typically, (i) the first strand and the second strand each has a length of 23 nucleosides; (ii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in said 3' near terminal region of the second strand, wherein a first phosphorothioate internucleoside linkage is present between said adjacent first basic nucleoside of (a) and an adjacent second basic nucleoside in said 3' near terminal region of the second strand, and a second phosphorothioate internucleoside linkage is present between said adjacent second basic nucleoside and an adjacent third basic nucleoside in said 3' near terminal region of the second strand; (iii) two phosphorothioate internucleoside linkages are respectively between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective 5' and 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each first 5' and 3' penultimate nucleoside is

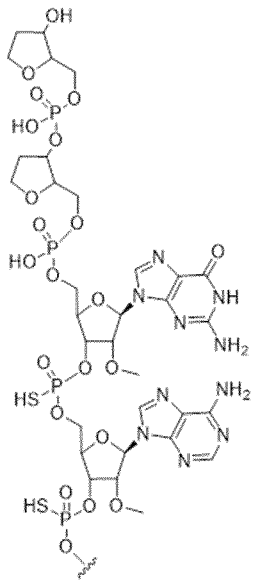
attached to a respective 5' and 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage; and (iv) the second strand of the nucleic acid is conjugated directly or indirectly to one or more ligand moieties at the 5' terminal region of the second strand.

[00146] 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)



[00147] 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.

[00148] 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.

[00149] 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.

[00150] 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.

[00151] 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.

[00152] 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.

[00153] For example, in the structure shown below there are abasic residues in the first 2 positions located at the 5' end. Where the terminal nucleoside has an inverted orientation then the 5' end indicated in the diagram below, which is the conventional 5' end, can in fact comprise a 3' OH in view of the inverted nucleoside at the terminal position. Nevertheless the majority of the molecule will comprise conventional internucleoside linkages that run from the 3' OH of the sugar to the 5' phosphate of the next sugar, when reading in the standard 5' [PO4] to 3' [OH] direction of a nucleic acid molecule (with reference to the numbering of ring atoms on the nucleoside sugars), which can be used to determine the conventional 5' and 3' ends that would be found absent the inverted end configuration.

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

[00154] 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.

[00155] GalNAc-siRNA constructs with a 5'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00156] GalNAc-siRNA constructs with a 3'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00157] 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.

[00158] 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;

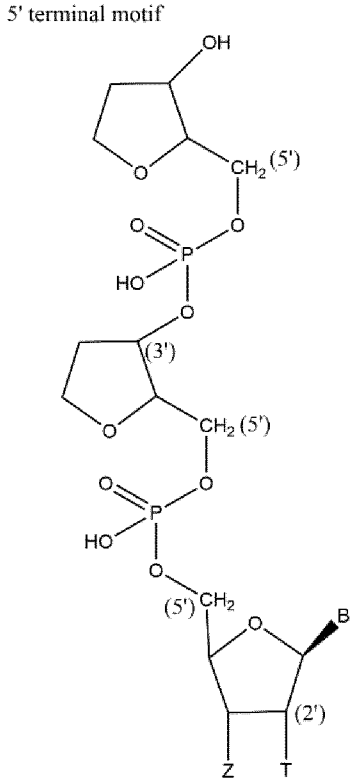
(iv) two phosphorothioate internucleoside linkages are respectively present between three consecutive positions in both 5' and 3' terminal regions of the first strand, whereby a terminal nucleoside respectively at each of the 5' and 3' terminal regions of said first strand is each attached to a respective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

[00159] 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,

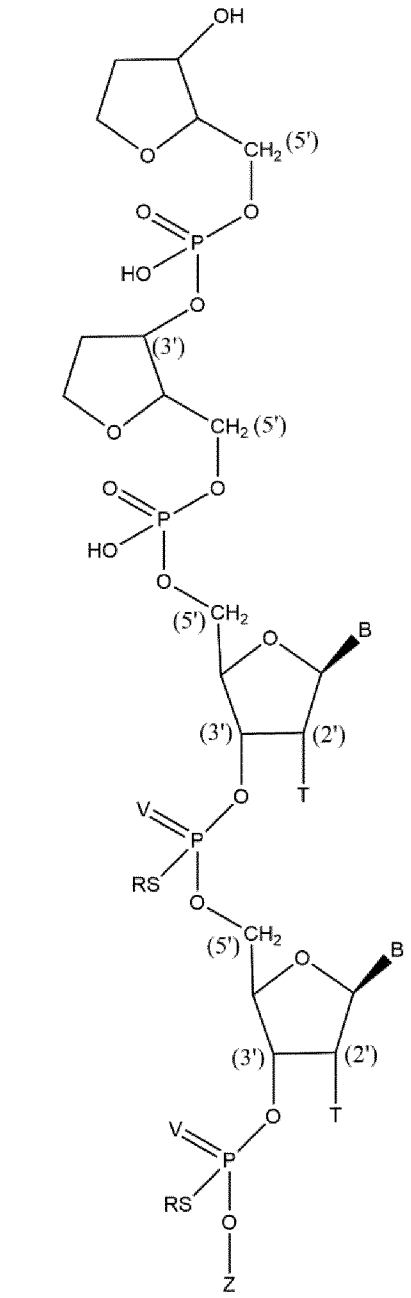
Z represents the remaining nucleosides of said second strand.

[00160] 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,

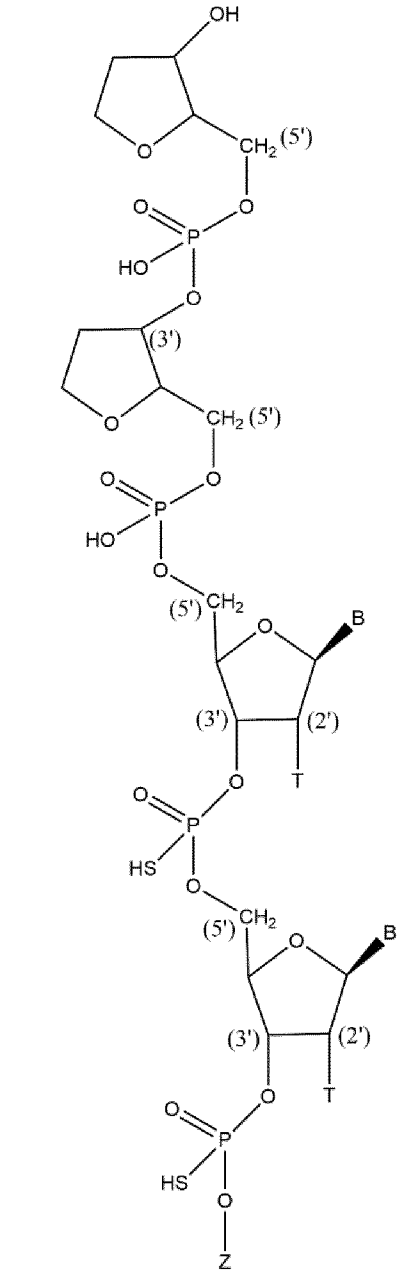
V represent O or S (preferably O),

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,

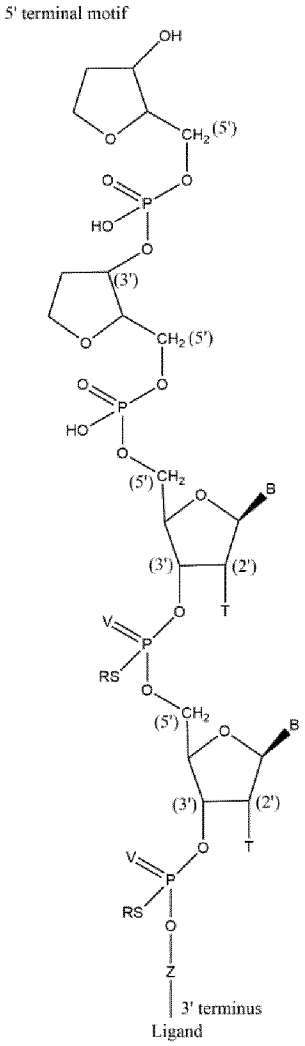
T represent H, OH or a 2' ribose modification,

Z represents the remaining nucleosides of said second strand.

[00161] 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,

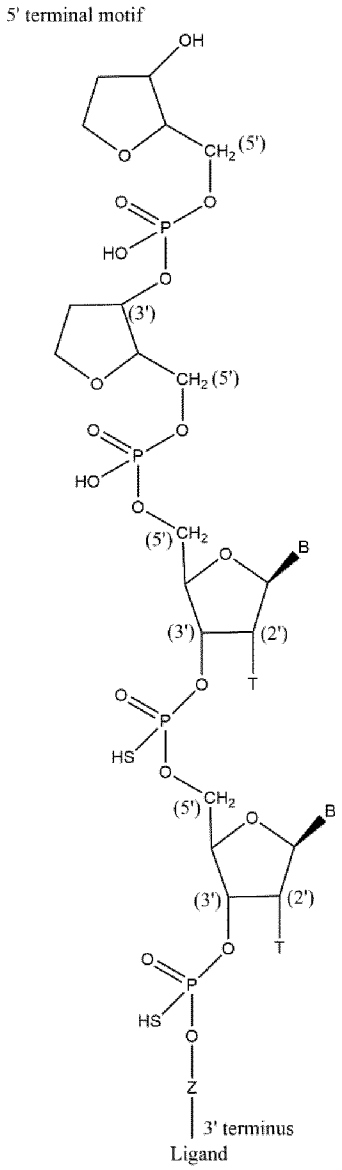
T represent H, OH or a 2' ribose modification,

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,

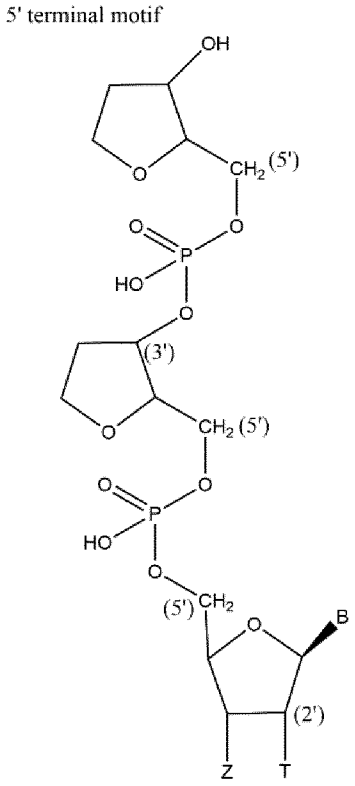
T represent H, OH or a 2' ribose modification,

[00162] Z comprises 11 to 26 contiguous nucleosides, preferably 15 to 21 contiguous nucleosides, and more preferably 19 contiguous nucleosides.

[00163] 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 - F - Me - F - F - F - F - 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.

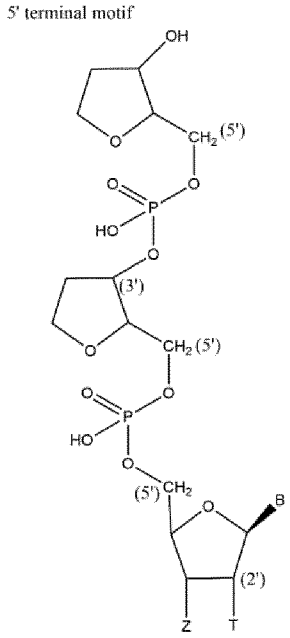
In such embodiments, the modification pattern of the first strand of the nucleic acid preferably comprises or consists of

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

[00164] 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 – 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.

In such embodiments, the modification pattern of the first strand of the nucleic acid preferably comprises or consists of

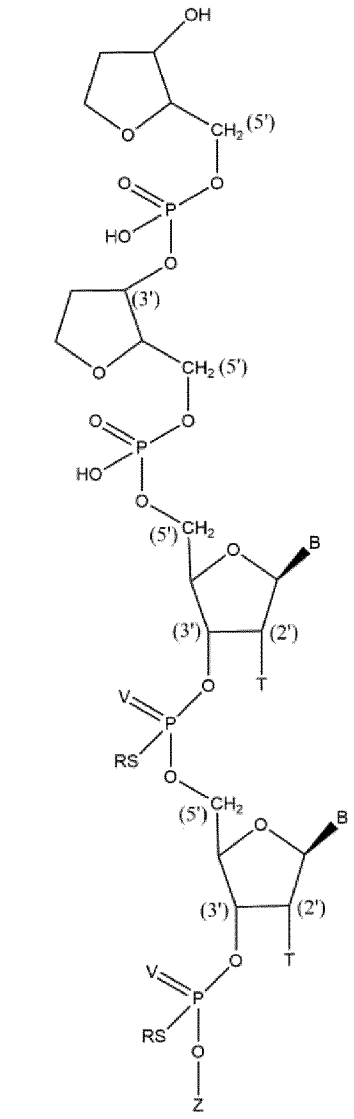
Me - F - Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me - Me – Me.

[00165] 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 - F - Me - F - 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,

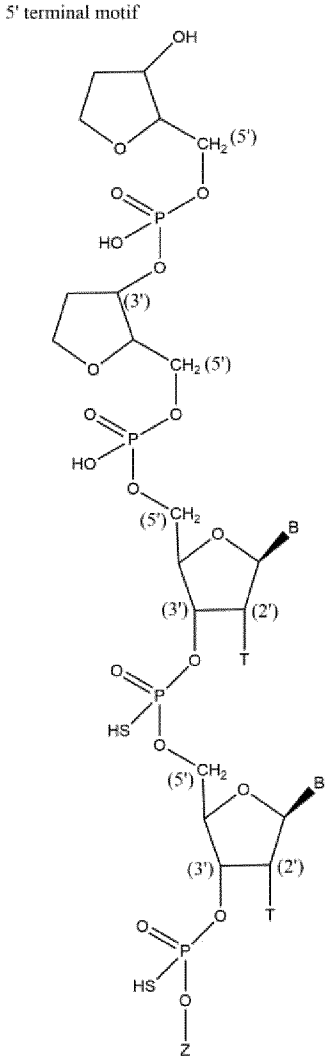
T represents a 2'Me ribose modification,

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.

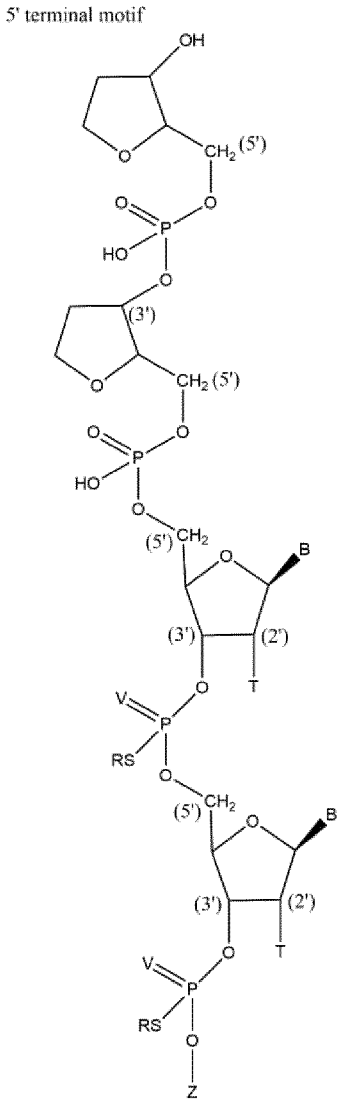
In such embodiments, the modification pattern of the first strand of the nucleic acid preferably comprises or consists of

Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me, wherein (s) is a phosphorothioate internucleoside linkage.

[00166] 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



wherein:

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

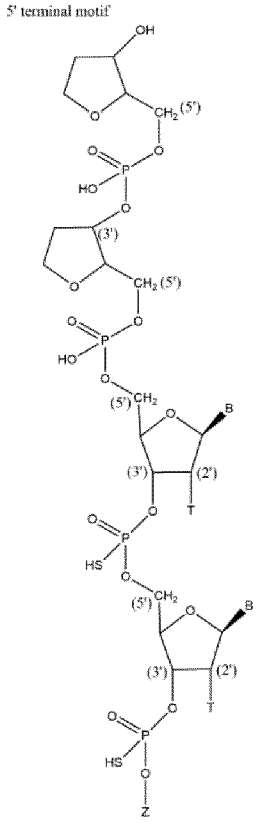
T represents a 2'Me ribose modification,

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.

In such embodiments, the modification pattern of the first strand of the nucleic acid preferably comprises or consists of

Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me, wherein (s) is a phosphorothioate internucleoside linkage.

[00167] 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.

[00168] GalNAc-siRNA constructs with a 5'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

[00169] GalNAc-siRNA constructs with a 3'-GalNAc on the sense strand can have a reversed linkage on the opposite end of the sense strand.

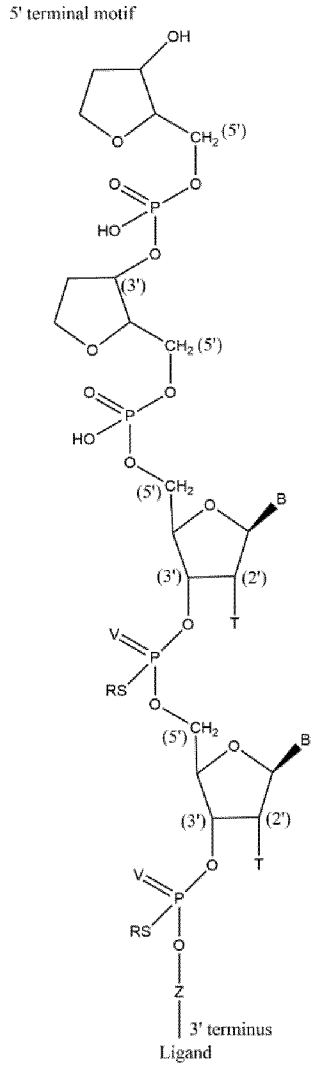
[00170] In a preferred embodiment, the modification pattern of the second (sense) strand of the nucleic acid according to the invention comprises or consists of

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

or

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

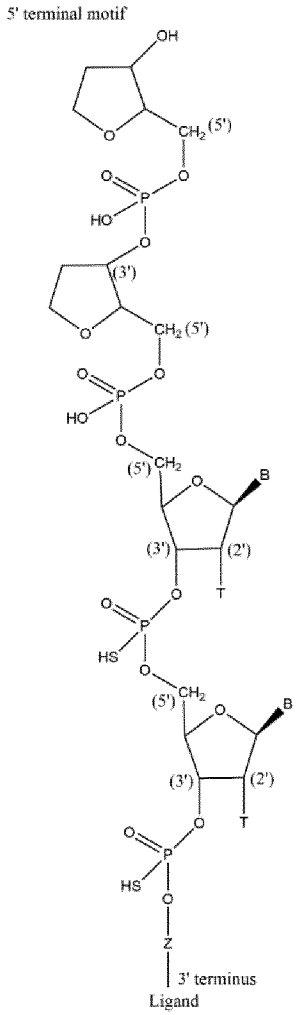
T represents a 2'Me ribose modification,

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.

In such embodiments, the modification pattern of the first strand of the nucleic acid preferably comprises or consists of

Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me, wherein (s) is a phosphorothioate internucleoside linkage,

or

Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me, wherein (s) is a phosphorothioate internucleoside linkage.

Nucleic Acid Lengths

[00171] 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.

[00172] 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

[00173] 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.

[00174] 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.

[00175] In certain embodiments of the invention, substantially all of the nucleosides are modified.

[00176] 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.

[00177] 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.

[00178] 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.

[00179] 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.

[00180] Modified nucleic acids e.g. RNAs can also contain one or more substituted sugar moieties. The nucleic acids e.g. siRNAs, e.g., dsiRNAs, featured herein can include one of the following at the 2'-position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted. 2'O- methyl and 2' -F are preferred modifications.

[00181] In certain preferred embodiments, the nucleic acid comprises at least one modified nucleoside.

[00182] The nucleic acid of the invention may comprise one or more modified nucleosides on the first strand and/or the second strand.

[00183] In some embodiments, substantially all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

[00184] In some embodiments, all of the nucleosides of the sense strand and substantially all of the nucleosides of the antisense strand comprise a modification.

[00185] In some embodiments, all of the nucleosides of the sense strand and all of the nucleosides of the antisense strand comprise a modification.

[00186] 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).

[00187] 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.

[00188] One preferred modification is a modification at the 2'-OH group of the ribose sugar, optionally selected from 2'-Me or 2'-F modifications.

[00189] 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:

[00190] 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.

[00191] A nucleic acid wherein the first strand comprises a 2'-F modification at any of position 2, position 6, position 14, or any combination thereof, counting from position 1 of said first strand.

[00192] A nucleic acid wherein the second strand comprises a 2'-F modification at any of position 7, position 9, position 11, or any combination thereof, counting from position 1 of said second strand.

[00193] A nucleic acid wherein the first and second strand each comprise 2'-Me and 2'-F modifications.

[00194] 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.

[00195] A nucleic acid which comprises at least one thermally destabilizing modification at position 7 of the first strand, counting from position 1 of the first strand.

[00196] A nucleic acid which is an siRNA oligonucleoside, wherein the siRNA oligonucleoside comprises 3 or more 2'-F modifications at positions 6 to 12 of the second strand, such as 4, 5, 6 or 7 2'-F modifications at positions 6 to 12 of the second strand, counting from position 1 of said second strand.

[00197] A nucleic acid which is an siRNA oligonucleoside, wherein said second strand comprises at least 3, such as 4, 5 or 6, 2'-Me modifications at positions 1 to 6 of the second strand, counting from position 1 of said second strand.

[00198] A nucleic acid which is an siRNA oligonucleoside, wherein said first strand comprises at least 5 2'-Me consecutive modifications at the 3' terminal region, preferably including the

terminal nucleoside at the 3' terminal region, or at least within 1 or 2 nucleosides from the terminal nucleoside at the 3' terminal region.

[00199] A nucleic acid which is an siRNA oligonucleoside, wherein said first strand comprises 7 2'-Me consecutive modifications at the 3' terminal region, preferably including the terminal nucleoside at the 3' terminal region.

[00200] A nucleic acid which is an siRNA oligonucleoside, wherein each of the first and second strands comprises an alternating modification pattern, preferably a fully alternating modification pattern along the entire length of each of the first and second strands, wherein the nucleosides of the first strand are modified by (i) 2'Me modifications on the odd numbered nucleosides counting from position 1 of the first strand, and (ii) 2'F modifications on the even numbered nucleosides counting from position 1 of the first strand, and nucleosides of the second strand are modified by (i) 2'F modifications on the odd numbered nucleosides counting from position 1 of the second strand, and (ii) 2'Me modifications on the even numbered nucleosides counting from position 1 of the second strand. Typically such fully alternating modification patterns are present in a blunt ended oligonucleoside, wherein each of the first and second strands are 19 nucleosides in length.

[00201] 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.

[00202] 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.

[00203] 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.

[00204] 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.

[00205] 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.

[00206] 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.

[00207] 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.

[00208] At least one of the oligoribonucleoside strands preferably comprises at least two consecutive phosphorothioate modifications in the last 3 nucleosides of the oligonucleoside.

[00209] 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.

[00210] 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.

[00211] The nucleic acid strand may be an RNA comprising a phosphorothioate internucleoside linkage between the three nucleosides contiguous with 2 terminally located abasic nucleosides.

[00212] A preferred nucleic acid is a double stranded RNA comprising 2 adjacent abasic nucleosides at the 5' terminus of the second strand and a ligand moiety comprising one or more GalNAc ligand moieties at the opposite 3' end of the second strand. Further preferred, the same nucleic acid may also comprise a phosphorothioate bond between nucelotides at positions 3-4 and 4-5 of the second strand, reading from the position 1 of the second strand. Further preferred, the same nucleic acid may also comprise a 2' F modification at positions 7, 9 and 11 of the second strand.

[00213] Preferred modifications are as follows.

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

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

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

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

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

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

[00214] A nucleic acid wherein modified nucleosides of said second strand have a modification pattern according to any one of the following (5'-3'):

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

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

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

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

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

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

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

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

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[00215] A nucleic acid wherein modified nucleosides of said second strand have a modification pattern according to any one of the following (5'-3'):

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

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

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

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

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

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

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

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

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

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

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

[00216] A nucleic acid wherein modified nucleosides of said second strand have a modification pattern according to any one of the following (5'-3'):

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

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

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

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

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

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

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

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

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

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

wherein:

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

[00217] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

[00218] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

or

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

[00219] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[00220] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

or

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

wherein (s) is a phosphorothioate internucleoside linkage.

[00221] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

[00222] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

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

wherein ia represents an inverted abasic nucleoside.

[00223] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

or

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

wherein ia represents an inverted abasic nucleoside.

[00224] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

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

[00225] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

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

wherein:

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

[00226] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

or

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

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

[00227] A nucleic acid wherein modified nucleosides have the following modification patterns:

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

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

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

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

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

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

wherein: (s) is a phosphorothioate internucleoside linkage, ia represents an inverted abasic nucleoside, and when the inverted abasic nucleosides as represented by ia - ia are present at

the 3' terminus of the second strand, said inverted abasic nucleosides are present in a 2 nucleoside overhang.

[00228] Particularly preferred is a nucleic acid wherein modified nucleosides have the following modification patterns:

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

or

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

wherein:

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

Conjugation

[00229] 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.

[00230] 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.

[00231] The ligand can be attached to the 3' or 5' end of the sense strand.

[00232] The ligand is preferably conjugated to 3' end of the sense strand of the nucleic acid e.g. an siRNA agent.

[00233] 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.

[00234] 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.

[00235] In certain embodiments, the ligand moiety comprises a GalNAc or GalNAc derivative attached to the nucleic acid eg dsiRNA through a linker.

[00236] 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.

[00237] 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.

[00238] GalNAc ligands are well known in the art and described in, inter alia, EP3775207A1.

[00239] 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.

[00240] 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.

[00241] 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

[00242] 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 - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me

or

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

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.

[00243] 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 - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me – Me

or

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

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.

[00244] 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 - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me

or

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

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.

[00245] 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'):

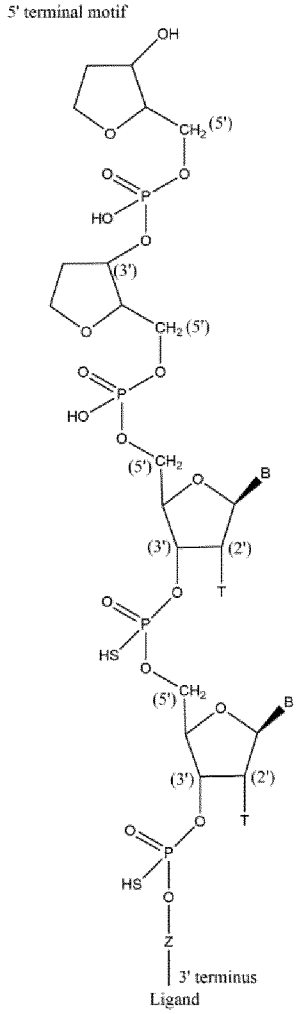
ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me

or

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

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.

[00246] 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'):

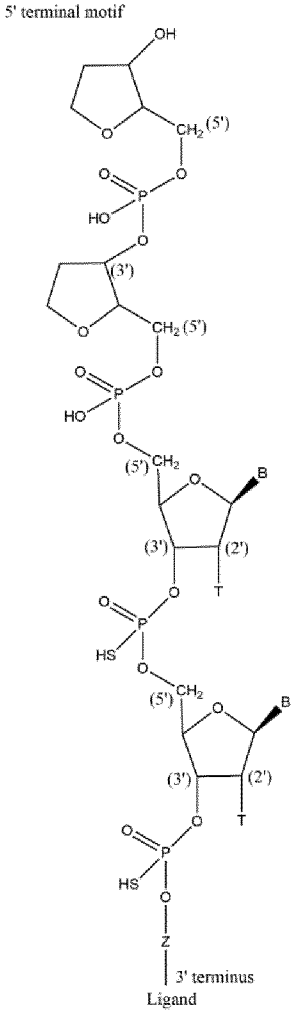
ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me

or

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

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.

[00247] 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'):

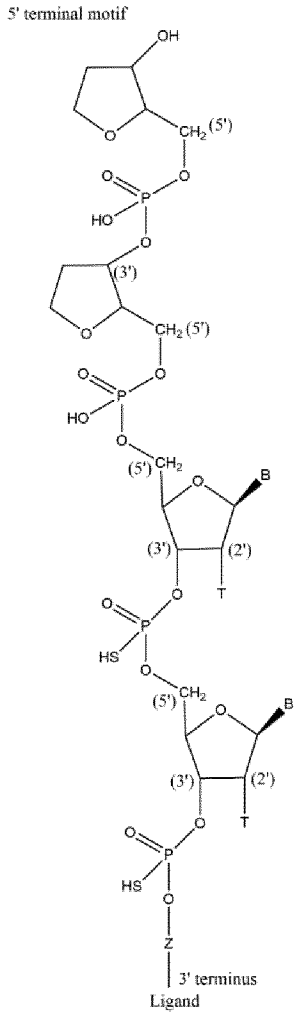
ia – ia - Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me

or

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

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

[00248] In one aspect, the invention provides a cell containing a nucleic acid, such as inhibitory RNA [RNAi] as described herein.

[00249] In one aspect, the invention provides a cell comprising a vector as described herein.

Pharmaceutically Acceptable Compositions

[00250] 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.

[00251] The pharmaceutically acceptable composition may comprise an excipient and or carrier.

[00252] 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.

[00253] 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).

[00254] 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.

[00255] 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.

[00256] 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

[00257] 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.

[00258] 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).

[00259] 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).

[00260] 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.

[00261] 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.

[00262] 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.

[00263] 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.

[00264] 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.

[00265] In one embodiment, the nucleic acid e.g. agent is administered to the subject subcutaneously.

[00266] 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

[00267] 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.

[00268] 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.

[00269] The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating", "suppressing", and other similar terms, and includes any level of inhibition.

[00270] 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

[00271] In some embodiments, when transfected into the cells, the nucleic acid of the invention inhibits expression of a target gene with an IC50 value lower than 2000 pM, 1900 pM, 1800 pM, 1700 pM, 1600 pM, 1500 pM, 1400 pM, 1300 pM, 1200 pM, 1100 pM, 1000 pM, 900 pM, 800 pM, 700 pM, 600 pM, 500 pM, 400 pM, 300 pM, 200 pM or 100 pM, preferably when determined by qPCR, more preferably by reverse transcriptase (RT)-qPCR, as described herein.

[00272] In a preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of a target gene with an IC50 value lower than 2000 pM. In a more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of a target gene with an IC50 value lower than 1000 pM. In an even more preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of a target gene with an IC50 value lower than 500 pM. In a most preferred embodiment, when transfected into the cells, the nucleic acid of the invention inhibits expression of a target gene with an IC50 value lower than 100 pM.

[00273] Inhibition of a 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 transcribed from a target gene or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:487), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:486)) 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 a target gene and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00274] qPCR may be performed in duplicate on cDNA derived from each well and the mean cycle threshold (Ct) calculated. Relative target gene expression may be calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of target gene expression and IC50 values may be calculated using a four parameter (variable slope) model using GraphPad Prism 9.

[00275] 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.

[00276] 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.

[00277] 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.

[00278] 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:487), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3'(SEQ ID NO:486)) 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.

[00279] 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.

[00280] 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

[00281] 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.

[00282] 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.

[00283] 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. 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.

[00284] 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.

[00285] 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.

[00286] 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, in particular when the target gene is HCII or ZPI as disclosed herein.

[00287] 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.

[00288] 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.

[00289] 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.

[00290] 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.

[00291] The disease to be treated can be diabetes, in particular when the target gene is B4GALT1 as disclosed herein.

[00292] 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.

[00293] 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).

[00294] The disease to be treated can be a cardiovascular disease, in particular when the target gene is B4GALT1 as disclosed herein.

[00295] 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.

[00296] 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.

[00297] 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.

[00298] Alternatively, a nucleic acid e.g. siRNA of the invention may be administered as a pharmaceutical composition, such as a dsiRNA liposomal formulation.

[00299] 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.

[00300] Subjects can be administered a therapeutic amount of nucleic acid e.g. siRNA, such as about 0.01 mg/kg to about 200 mg/kg, so as to treat disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia or to treat diabetes or to treat cardiovascular disease.

[00301] 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.

[00302] 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).

[00303] In one aspect, the nucleic acid disclosed herein may be a nucleic acid as defined hereinafter in Sentences 1 to 45:

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

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

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

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

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

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

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

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

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

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

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

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

wherein:

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

5. A nucleic acid according to any preceding sentence, wherein the first strand comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2'- F sugar modifications at least at positions 2, 14 and 16, and / or

2'-Me sugar modifications at positions 17 to 23, or said first strand comprises at least eight 2' – F sugar modifications, such as 2'- F sugar modifications at least at positions 2, 4, 6, 12, 14, 16, 18 and 20, and / or

2'-Me sugar modifications at positions 1, 3 to 5, 10 to 13, or said first strand comprises at least eight 2' – F sugar modifications, such as 2'- F sugar modifications at least at positions 2, 4, 6, 12, 14, 16, 18 and 20, and / or

a 2'-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2'-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically can be the same 2' sugar modification,

whereby typically the first strand can comprise the following modification pattern (5'-3'):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at

position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

6. 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 nucleosides of said second strand comprise a 2' sugar and abasic modification pattern as follows:

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

or

position 7 on the second strand includes a sugar modification that is a 2'-Me modification, wherein position 1 is the 5' terminal nucleoside of the second strand and the direction of counting is 5' – 3', and there are typically present two inverted abasic nucleosides at 5' terminal region of the second strand, and

the first strand modification pattern comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2'- F sugar modifications at least at positions 2, 14 and 16, and / or

2'-Me sugar modifications at positions 17 to 23, and / or

2'-Me sugar modifications at positions 1, 3 to 5, 10 to 13, and / or

a 2'-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2'-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically can be the same 2' sugar modification,

whereby typically the first strand can comprise the following modification pattern (5'-3'):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

7. A nucleic acid according to sentence 5 or 6, wherein $(M)_4$ represents any one of the following 2' sugar modification patterns (5' – 3'):

F – Me – Me – F
Me – F – Me – F
F – Me – F – Me
F – F – F – F
Me – F – F – Me
Me – Me – F – F
F – F – Me – Me
Me – Me – Me – Me

8. A nucleic acid according to any of sentences 5 to 7, 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, and

where appropriate there may further be present two phosphorothioate internucleoside linkages between three consecutive positions in the 3' terminal region of the second strand, whereby the 3' terminal nucleoside is attached to an adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and said penultimate nucleoside is attached to an adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage, and / or

where appropriate there may further be present two phosphorothioate internucleoside linkages between three consecutive positions in the 5' terminal region of the second strand, whereby the 5' terminal nucleoside is attached to an adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and said penultimate nucleoside is attached to an adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage.

9. 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 nucleosides of said second and first strands comprise a 2' sugar modification pattern as follows (5'-3'):

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

10. 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

11. 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows (5'-3'):

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

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

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

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

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

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

wherein (s) is a phosphorothioate internucleoside linkage.

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

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

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

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

Or Modification pattern 3:

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

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

Or Modification pattern 4:

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

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

Or Modification pattern 5:

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

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

Or Modification pattern 6:

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

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

wherein ia represents an inverted abasic nucleoside.

13. 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 nucleosides of said second and first strands comprise a 2' sugar and abasic modification pattern as follows:

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

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

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

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

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

Or Modification pattern 6:

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

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

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

14. 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 nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

Modification pattern 1:

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

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

Or Modification pattern 2:

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

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

Or Modification pattern 3:

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

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

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

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

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

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

15. 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 nucleosides of said second and first strands comprise a 2’ sugar, abasic and bond modification pattern as follows (5’-3’):

Modification pattern 1:

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

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 2:

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

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 3:

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

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - F - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 4:

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

First strand (5’-3’): Me(s)F(s)Me - F - Me - F - Me - Me - Me - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 5:

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

First strand (5’-3’): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

Or Modification pattern 6:

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

First strand (5’-3’): Me(s)F(s)Me - Me - Me - F - Me - Me - F - Me - Me - Me - Me - F - Me - F - Me - Me - Me - Me - Me(s)Me(s)Me

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

16. 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:

counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification, or

said second strand comprises the following modification pattern:

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

and wherein the first strand comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2'- F sugar modifications at least at positions 2, 14 and 16, and / or

2'-Me sugar modifications at positions 17 to 23, and / or

2'-Me sugar modifications at positions 1, 3 to 5, 10 to 13, and / or

a 2'-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2'-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically can be the same 2' sugar modification,

whereby typically the first strand can comprise the following modification pattern (5'-3'):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

17. 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' or 3' terminal region of the second strand, and

counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification,

and optionally wherein the first strand comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2’- F sugar modifications at least at positions 2, 14 and 16, and / or

2’-Me sugar modifications at positions 17 to 23, and / or

2’-Me sugar modifications at positions 1, 3 to 5, 10 to 13, and / or

a 2’-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2’-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2’-Me sugar modification and a 2’-F sugar modification, and typically can be the same 2’ sugar modification,

whereby typically the first strand can comprise the following modification pattern (5’-3’):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2’-Me sugar modification, a 2’-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2’-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5’-3’):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

18. 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:

wherein two phosphorothioate internucleoside linkages are present between three consecutive positions in either the 5' or 3' terminal region of the second strand, whereby

a terminal nucleoside respectively at either the 5' or 3' terminal region of said second strand is each attached to a respective 5' or 3' adjacent penultimate nucleoside by a phosphorothioate internucleoside linkage, and each 5' or 3' penultimate nucleoside is attached to a respective 5' or 3' adjacent antepenultimate nucleoside by a phosphorothioate internucleoside linkage,

and

counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification,

and optionally wherein the first strand comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2'- F sugar modifications at least at positions 2, 14 and 16, and / or

2'-Me sugar modifications at positions 17 to 23, and / or

2'-Me sugar modifications at positions 1, 3 to 5, 10 to 13, and / or

a 2'-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2'-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically can be the same 2' sugar modification,

whereby typically the first strand can comprise the following modification pattern (5'-3'):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

19. 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:

counting from the 5' terminus position 1 of the second strand, which is the 5' most nucleoside not including abasic nucleosides, position 7 on the second strand includes a sugar modification that is a 2'-Me modification, and

at the 3' terminus of the second strand the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, wherein the ligand moiety typically comprises:

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

and optionally wherein the first strand comprises a modification pattern selected from the following, or any combination thereof, wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

2'- F sugar modifications at least at positions 2, 14 and 16, and / or

2'-Me sugar modifications at positions 17 to 23, and / or

2'-Me sugar modifications at positions 1, 3 to 5, 10 to 13, and / or

a 2'-Me sugar modification at position 7 or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 7, and / or

a 2'-F sugar modification or a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, at position 6, and / or

positions 8 and 9 can be a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically can be the same 2' sugar modification,

whereby typically the first strand can comprise the following modification pattern (5'-3'):

Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

20. 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 said second strand comprises the following 2' sugar and abasic modification pattern:

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

and the first strand comprises a modification pattern selected from the following (5'- 3'), wherein position 1 is the 5' terminal nucleoside of the first strand and the direction of counting is 5' – 3':

(5'- 3') Me – F – Me – Me – Me – $(M)_4$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, that may typically be present at position 6, and it may typically be that a 2'-Me sugar modification is present at position 7,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

(5'- 3') Me – F – Me – Me – Me – (M1) - $(M2)_3$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

(5'- 3') Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a modification selected from a 2'-Me sugar modification, a 2'-F sugar modification and a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification,

or whereby typically the first strand comprises the following modification pattern (5'-3'):

(5'- 3') Me – F – Me – Me – Me – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

21. 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 said second and first strands comprise the following modification patterns:

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 – (M1) – Me - $(M2)_2$ – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – Me – Me

where M1 represents a thermally destabilising modification, such as typically a modified unlocked nucleic acid or a glycol nucleic acid, and M2 represents a modification selected from a 2'-Me sugar modification and a 2'-F sugar modification, and typically M2 can be the same 2' sugar modification.

22. 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 said second strand comprises the following 2' sugar and abasic modification pattern:

Modification pattern 1:
Second strand (5'-3'): ia – ia –F – Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F - Me - F – Me – F, optionally in combination with

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

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

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

23. 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 said second strand comprises the following 2' sugar, abasic and bond modification pattern:

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

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

wherein:

(s) is a phosphorothioate internucleoside linkage,

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

24. 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 nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows (5'-3'):

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

wherein the 2'-Me or 2'-F modified nucleosides of said first strand include any one of the following modification patterns (5'-3'):

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

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

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

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

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

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

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

First strand (5’-3’): Me(s) F(s) Me – Me – Me – Me – F – Me – F– Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – F – F – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – Me – F – F – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – Me – Me – F – F – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

First strand (5’-3’): Me(s) F(s) Me – Me – Me – F – F – Me – Me – Me – Me – Me – Me – F – Me – F – Me – Me – Me – Me – Me(s)Me(s) Me, or

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

wherein: (s) is a phosphorothioate internucleoside linkage.

25. 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 nucleosides of said second and first strands comprise a 2’ sugar, abasic and bond modification pattern as follows (5’-3’):

Second strand (5’-3’): Me(s)Me(s)Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me - Me – Me, or

Second strand (5’-3’): Me – Me - Me - Me - Me - Me - F - Me - F - F - F - Me - Me - Me - Me - Me - Me - Me - Me(s)Me(s)Me, or

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

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

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

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

wherein the 2'-Me or 2'-F modified nucleosides of said first strand include any one of the following modification patterns (5'-3'):

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

wherein:

(s) is a phosphorothioate internucleoside linkage,

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

26. A nucleic acid according to any preceding sentence, wherein said first strand comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

27. A nucleic acid according to any preceding sentence, wherein said first strand comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 3.

28. A nucleic acid according to sentence 26 or 27, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in sentence 26 or 27.

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

30. A nucleic acid according to any preceding sentence, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

31. A nucleic acid according to any preceding sentence, wherein the first strand comprises any one of the first strand sequences as listed in Table 2.

32. A nucleic acid according to any preceding sentence, wherein the first strand comprises any one of the first strand sequences as listed in Table 3.

33. A nucleic acid according to any preceding sentence, wherein the second strand comprises any one of the second strand sequences as listed in Table 2.

34. A nucleic acid according to any preceding sentence, wherein the second strand comprises any one of the second strand sequences as listed in Table 4.

35. A nucleic acid according to any preceding sentence, wherein the nucleic acid is an siRNA oligonucleoside.

36. A nucleic acid according to any preceding sentence, 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.

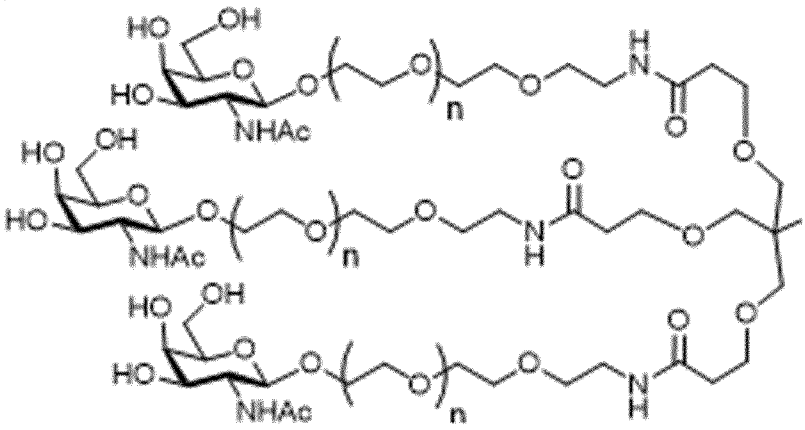
37. A nucleic acid according to sentence 36, wherein the ligand moiety comprises:

(i) one or more N-acetyl galactosamine (GalNAc) ligands, and / or
(ii) one or more N-acetyl galactosamine (GalNAc) ligand derivatives, and/or
(iii) one or more N-acetyl galactosamine (GalNAc) ligands and/or derivatives thereof,

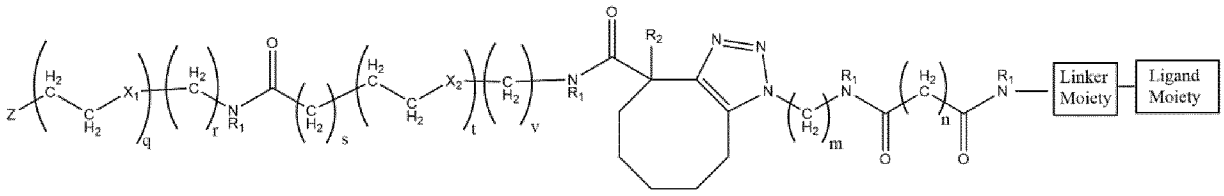
conjugated to the nucleic acid through a linker.

38. A nucleic acid according to sentence 37, wherein said one or more GalNAc ligands and / or GalNAc ligand derivatives are conjugated directly or indirectly to the 5' or 3' terminal region of the second strand of the nucleic acid, typically at the 3' terminal region thereof.

39. A nucleic acid according to any one of sentences36 to 38, wherein the ligand moiety comprises the following structure:



40. A nucleic acid according to any one of sentences 36 to 39, 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;

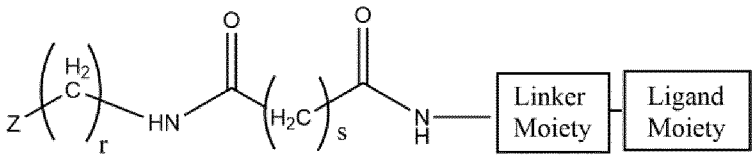
m is an integer of from 1 to 6;

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.

41. A nucleic acid according to any one of sentences 36 to 39, having the structure:



wherein:

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

Z is an oligonucleoside.

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

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

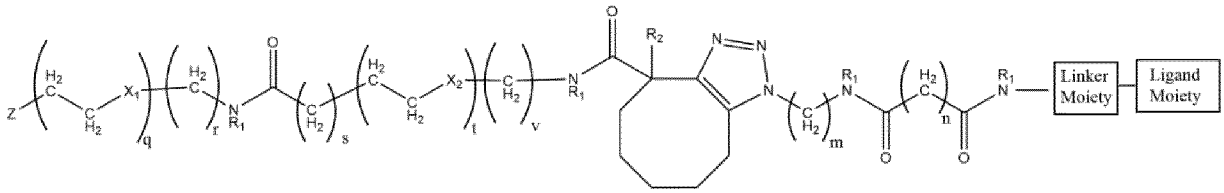
44. A nucleic acid or pharmaceutical composition according to any preceding sentence, for use in prevention or treatment of a disease related to a disorder of haemostasis, such as a disease related to a disorder of haemostasis, such as haemophilia.

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

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

[00304] 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 or HCII 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,

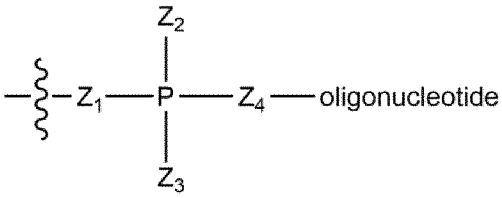
r = 3,

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.

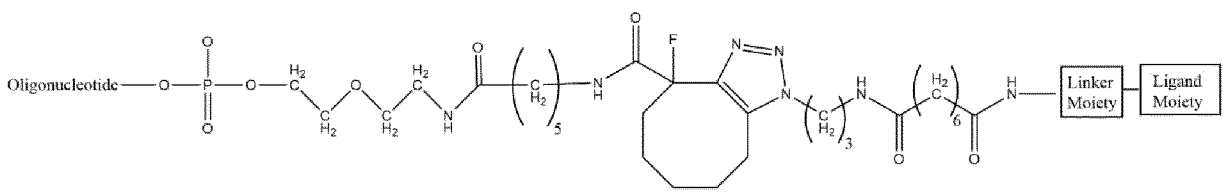
23. A compound according to Sentence 22, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

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.

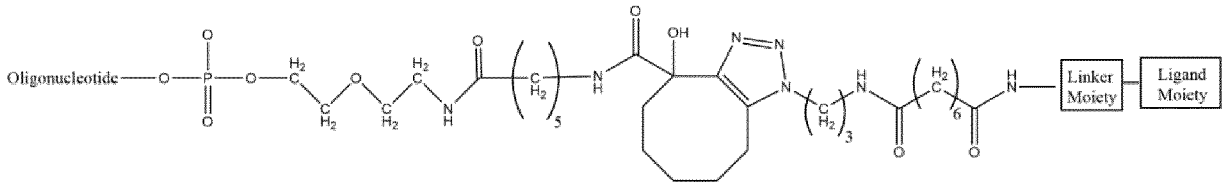
26. A compound according to Sentence 24, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

27. A compound of Formula (II):



Formula (II)

28. A compound of Formula (III):



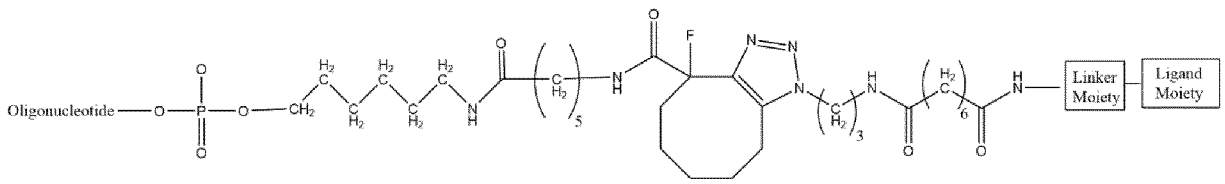
Formula (III)

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.

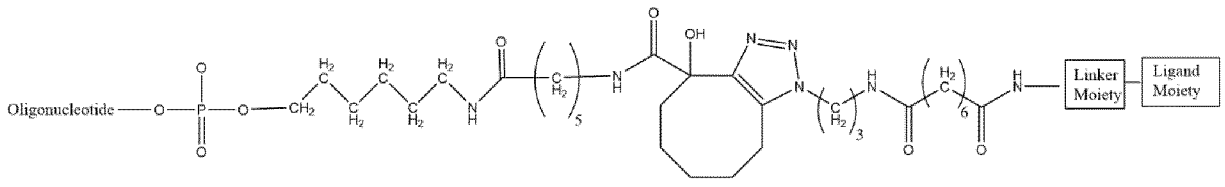
31. A composition according to Sentence 30, wherein said compound of Formula (III) as defined in Sentence 28 is present in an amount in the range of 10 to 15% by weight of said composition.

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.

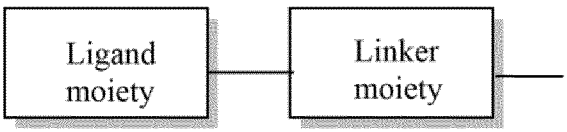
45. A compound according to Sentence 44, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

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

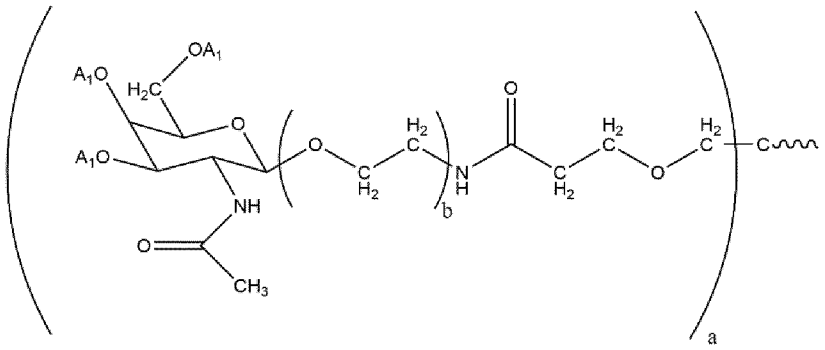
47. A compound according to any of Sentences 41 to 46, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

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):



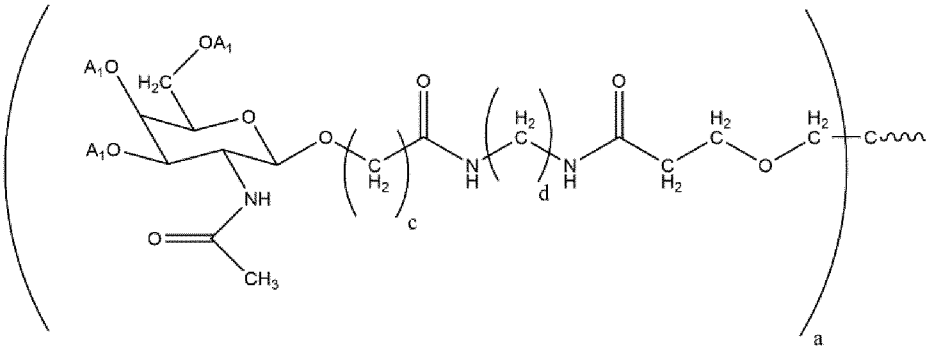
Formula (VIa)

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



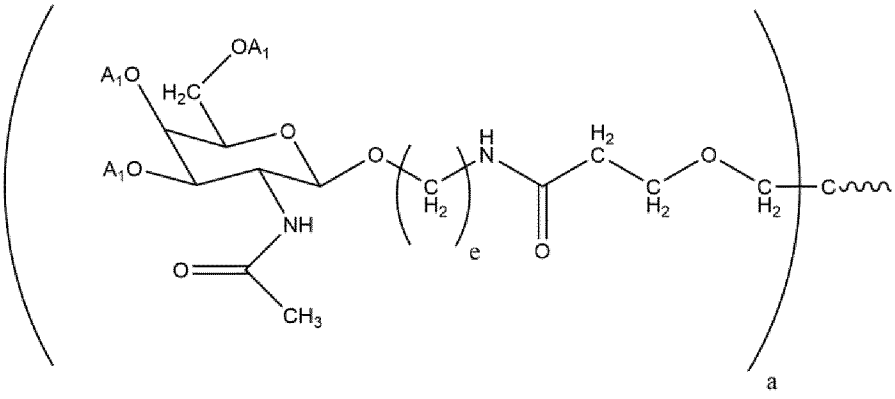
Formula (VIb)

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)

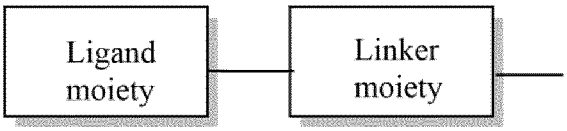
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

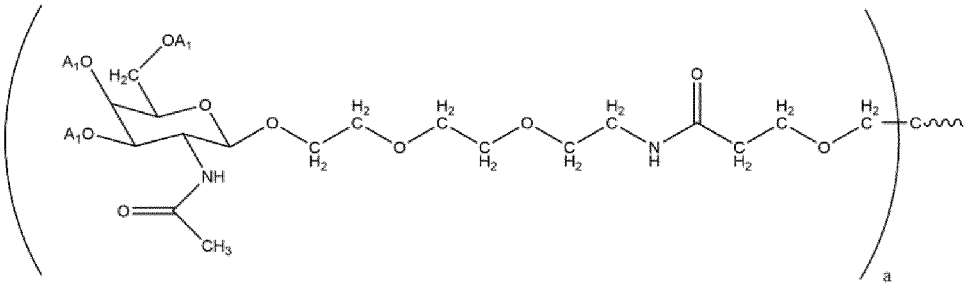
a is an integer of 2 or 3; and

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;

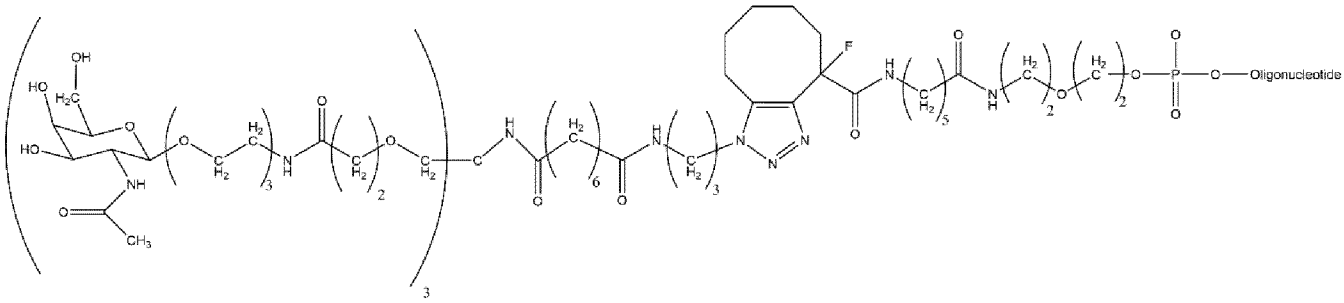
a is an integer of 2 or 3.

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

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

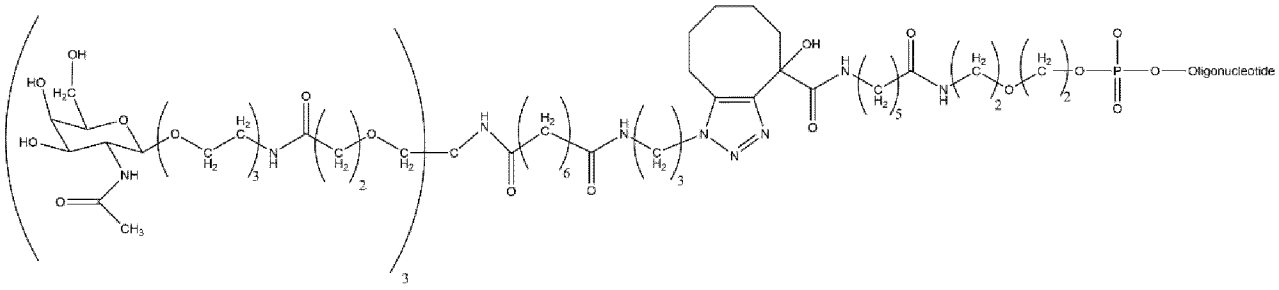
53. A compound according to Sentence 49, wherein b = 3.

54. A compound of Formula (VIII):



Formula (VIII)

55. A compound of Formula (IX):



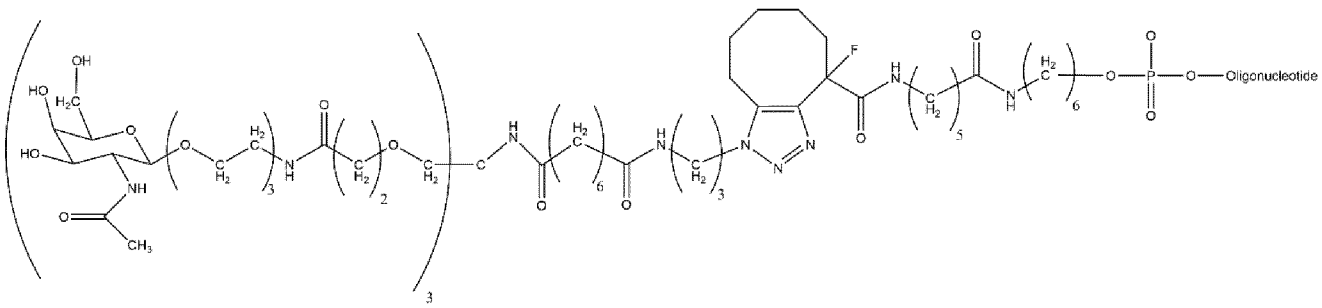
Formula (IX)

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.

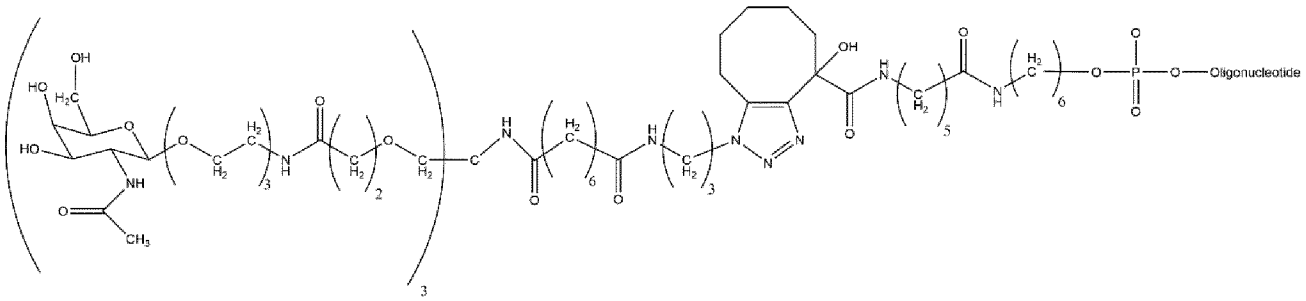
58. A composition according to Sentence 57, wherein said compound of Formula (IX) as defined in Sentence 55 is present in an amount in the range of 10 to 15% by weight of said composition.

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.

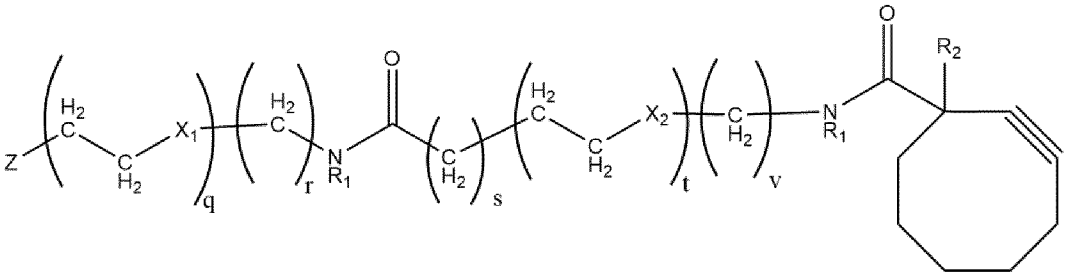
65. A compound according to Sentence 64, wherein the modifications are chosen from 2'-O-methyl, 2'-deoxy-fluoro, and 2'-deoxy.

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.

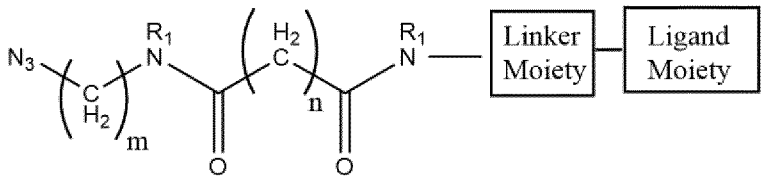
67. A compound according to Sentence 66, wherein said one or more degradation protective moieties are not present at the end of the oligonucleoside strand that carries the ligand moieties, and / or wherein said one or more degradation protective moieties is selected from phosphorothioate internucleoside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

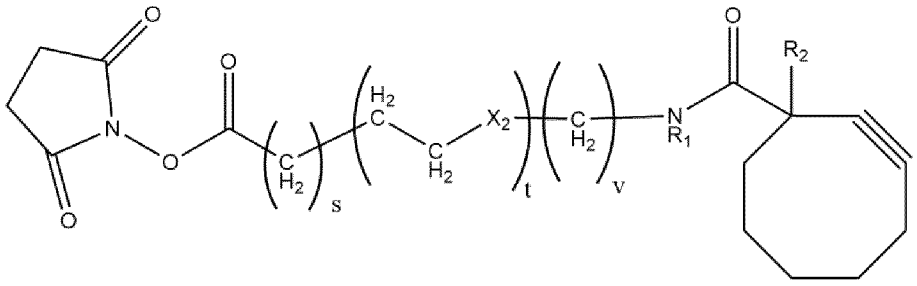
(i) q and r cannot both be 0 at the same time; and

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

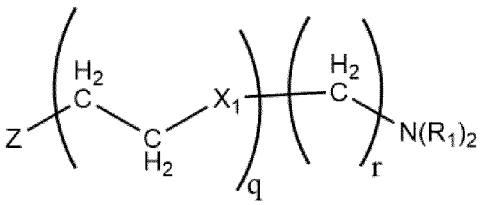
Z is an oligonucleoside moiety;

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:

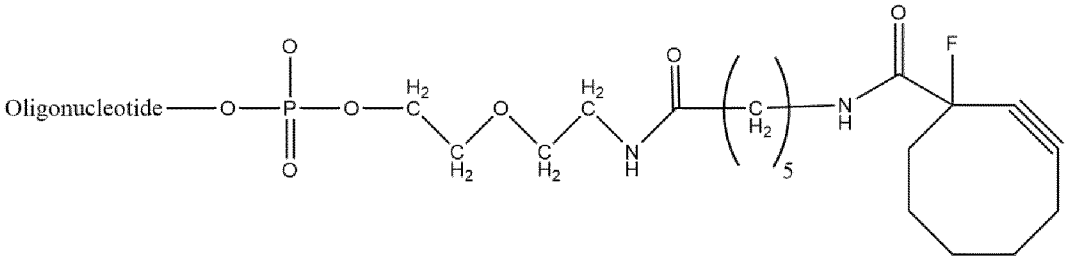
(i) q and r cannot both be 0 at the same time; and

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

Z is an oligonucleoside moiety.

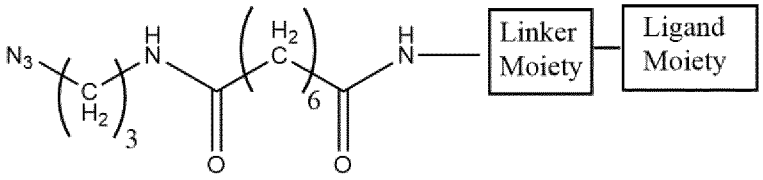
70. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 27, 29, 54, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

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



Formula (XIIa)

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

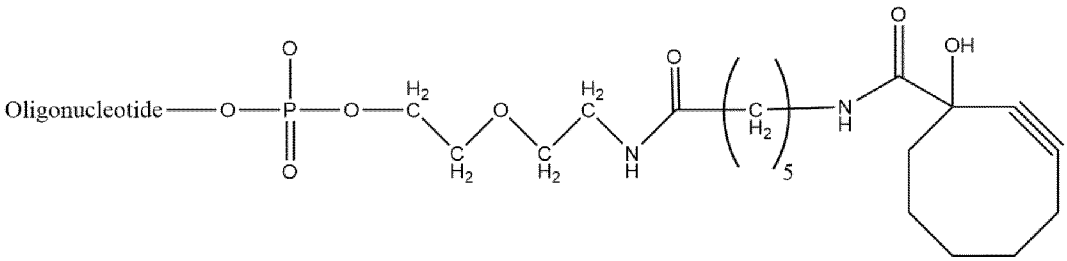


Formula (XIIIa)

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.

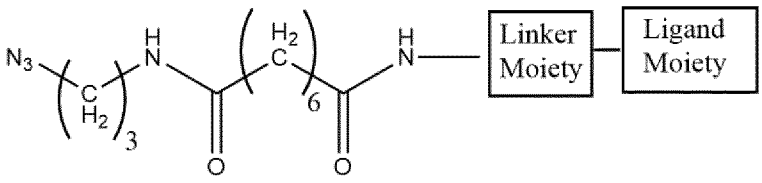
71. A process according to Sentence 68, to prepare a compound according to any of Sentences 20, 25, 28, 29, 55, 56, and / or a composition according to any of Sentences 30, 31, 57, 58, wherein:

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



Formula (XIIb)

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

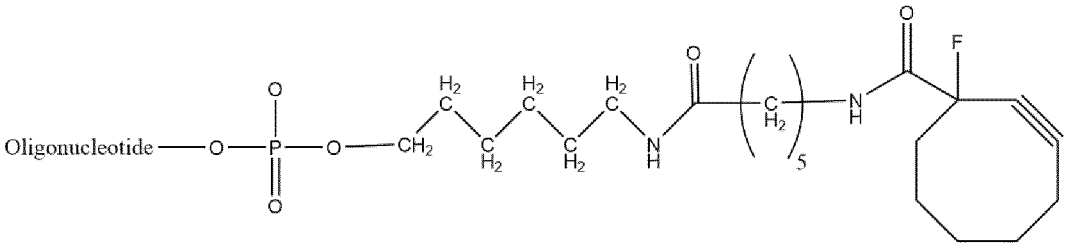


Formula (XIIIa)

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.

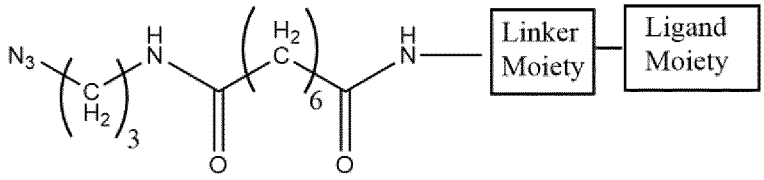
72. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 32, 34, 59, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

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



Formula (XIIc)

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

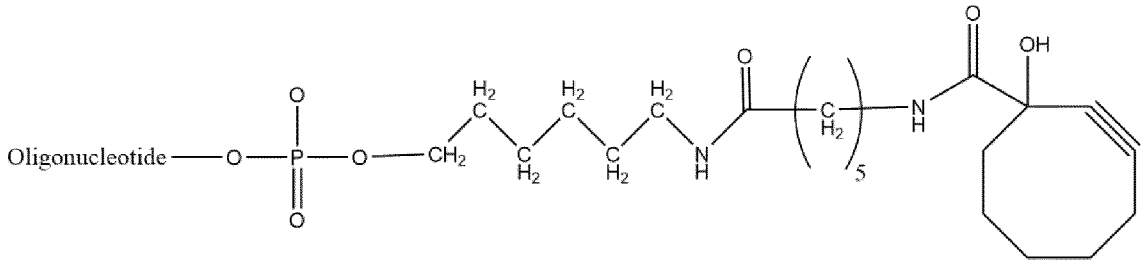


Formula (XIIIa)

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.

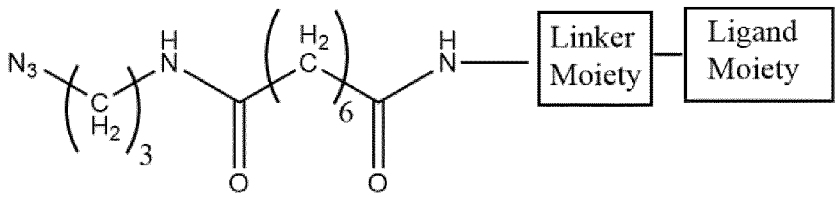
73. A process according to Sentence 68, to prepare a compound according to any of Sentences 21, 26, 33, 34, 60, 61, and / or a composition according to any of Sentences 35, 36, 62, 63, wherein:

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



Formula (XIId)

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



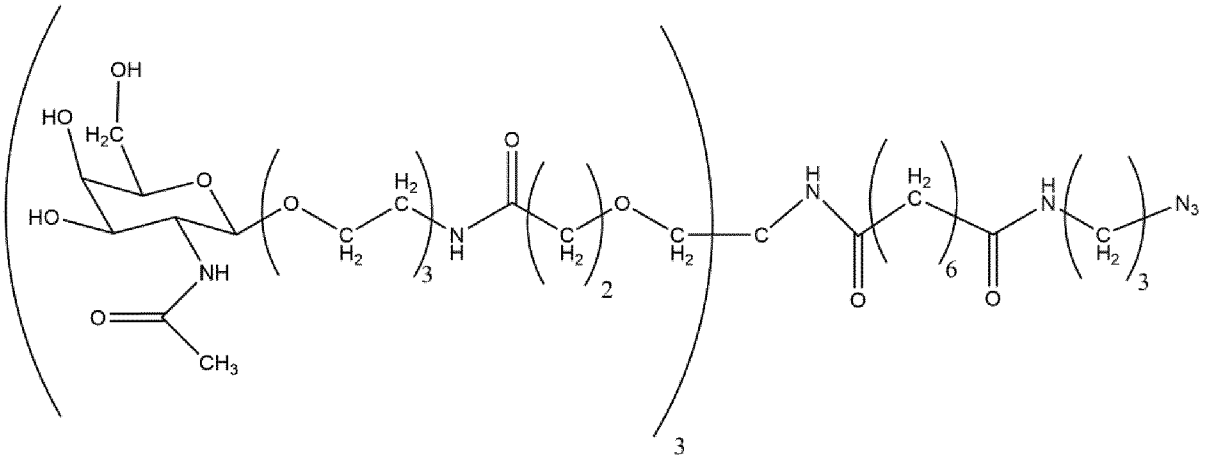
Formula (XIIIa)

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:

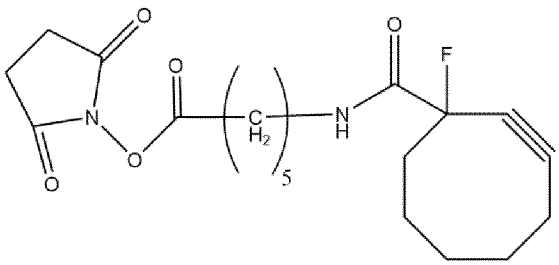
compound of Formula (XIIIa) is Formula (XIIIb):



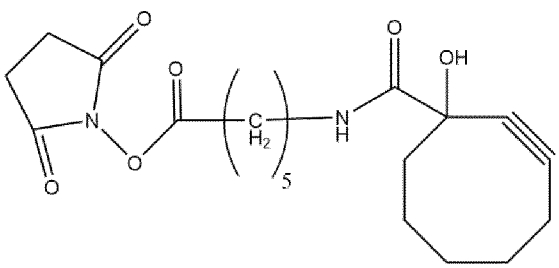
Formula (XIIIb)

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):

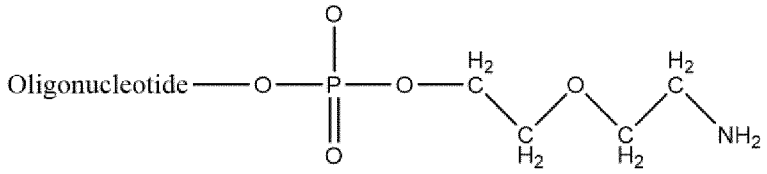


Formula (XIVa)

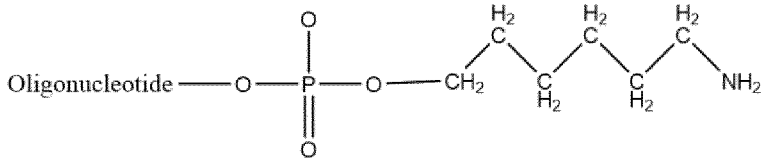


Formula (XIVb)

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



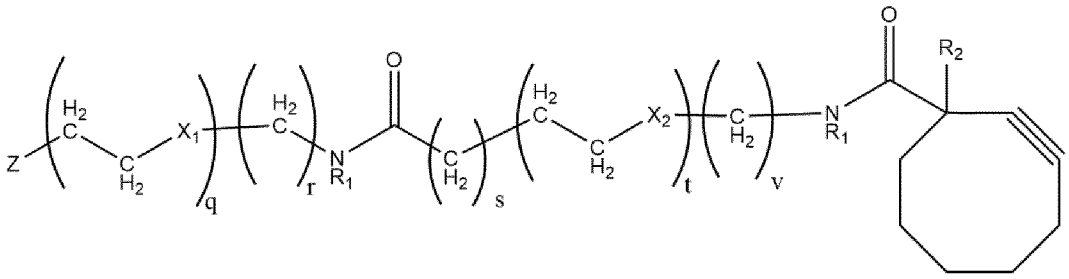
Formula (XVa)



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;

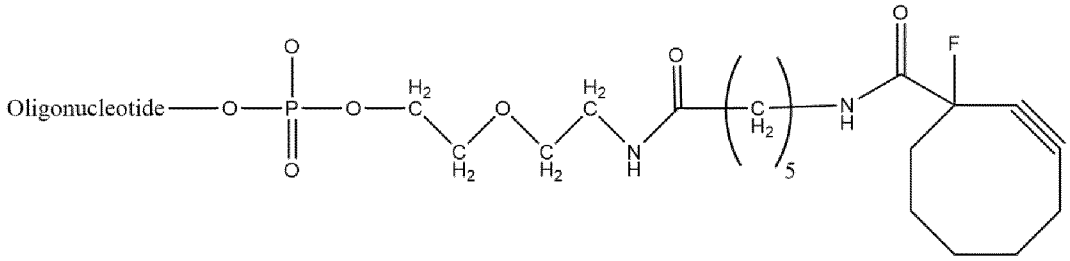
q, r, s, t, v are independently integers from 0 to 4, with the proviso that:

(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;

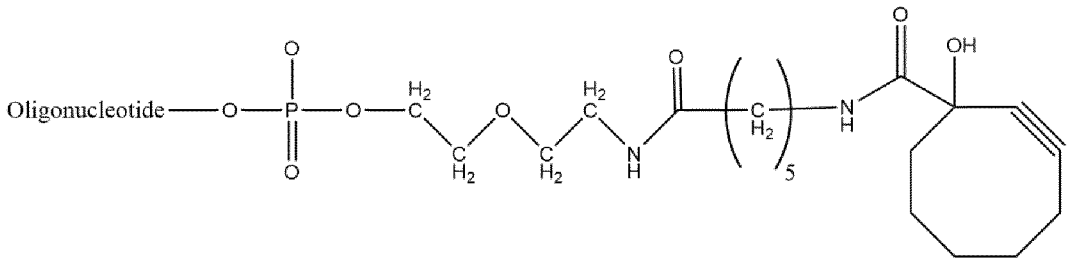
Z is an oligonucleoside moiety.

77. A compound of Formula (XIIa):



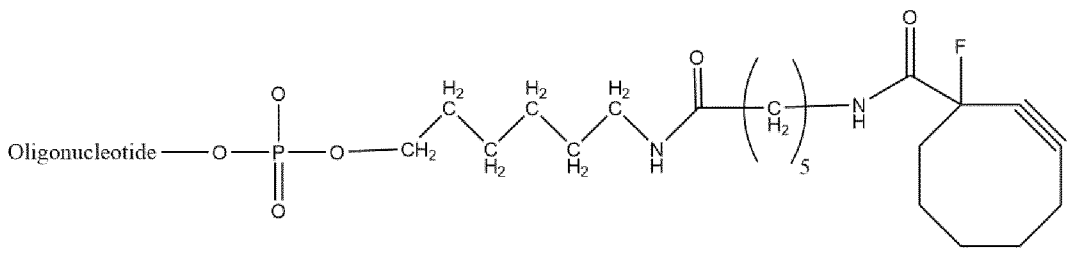
Formula (XIIa)

78. A compound of Formula (XIIb):



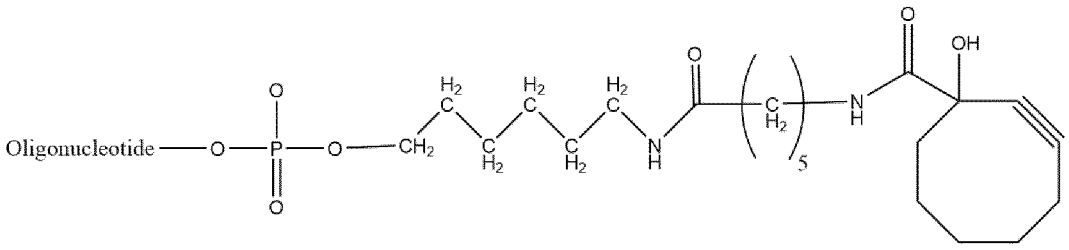
Formula (XIIb)

79. A compound of Formula (XIIc):



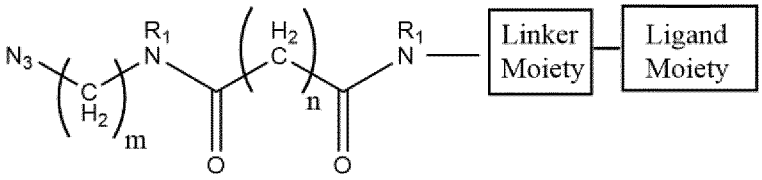
Formula (XIIc)

80. A compound of Formula (XIId):



Formula (XIId)

81. A compound of Formula (XIII):



Formula (XIII)

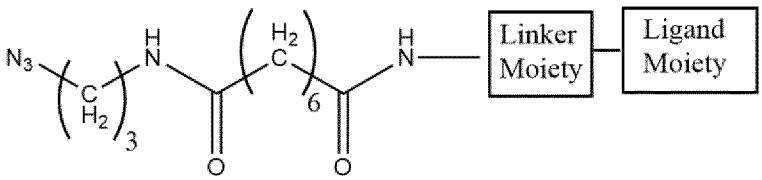
wherein:

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;

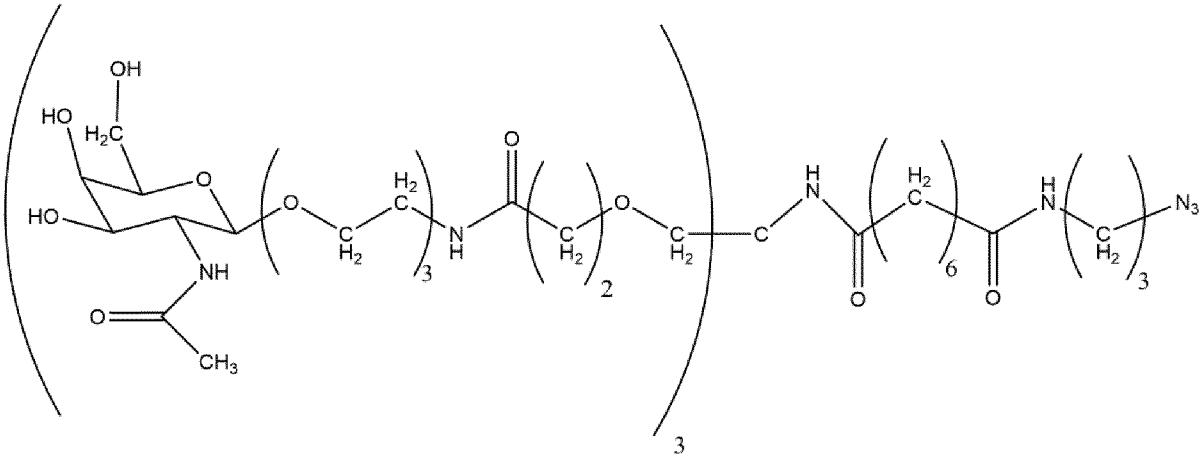
n is an integer of from 1 to 10.

82. A compound of Formula (XIIIa):



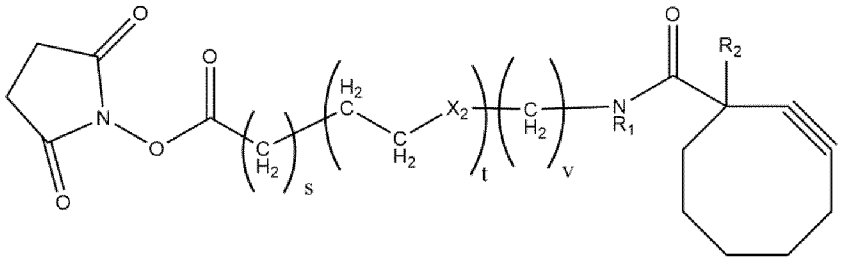
Formula (XIIIa)

83. A compound of Formula (XIIIb):



Formula (XIIIb)

84. A compound of Formula (XIV):



Formula (XIV)

wherein:

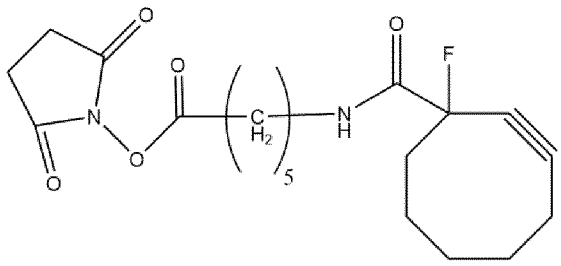
R_1 is selected from the group consisting of hydrogen, methyl and ethyl;

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;

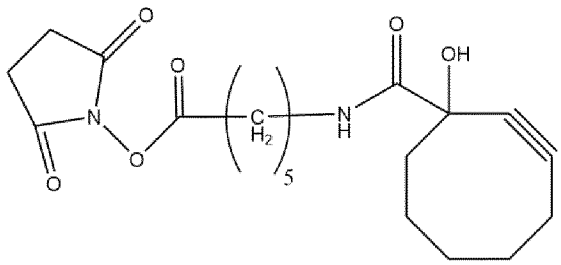
s, t, v are independently integers from 0 to 4, with the proviso that s, t and v cannot all be 0 at the same time.

85. A compound of Formula (XIVa):



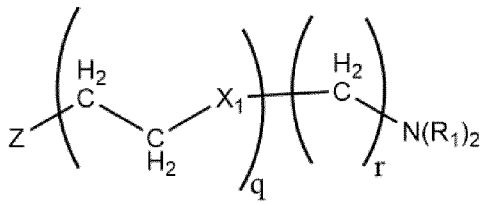
Formula (XIVa)

86. A compound of Formula (XIVb):



Formula (XIVb)

87. A compound of Formula (XV):



Formula (XV)

wherein:

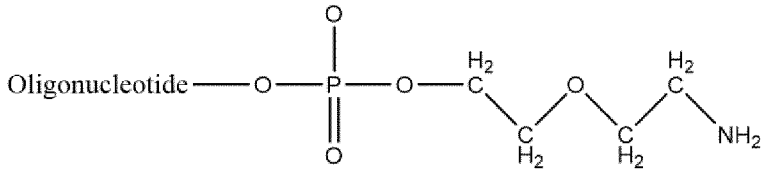
R_1 at each occurrence is independently selected from the group consisting of hydrogen, methyl and ethyl;

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;

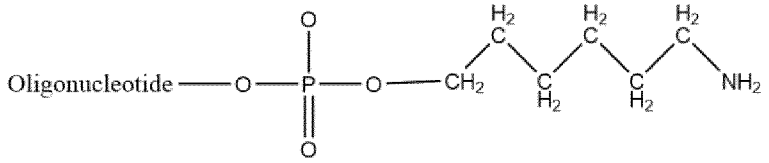
Z is an oligonucleoside moiety.

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.

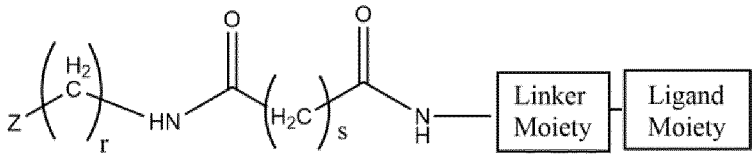
99. A compound or composition obtained, or obtainable by a process according to any of Sentences 68 to 75.

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.

[00305] 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 or HCII 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.

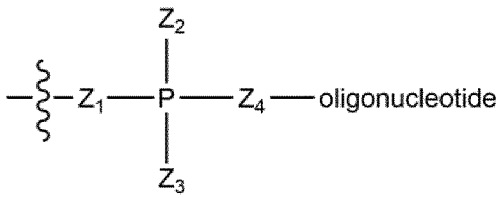
5. A compound according to Clause 4, wherein r is 6.

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.

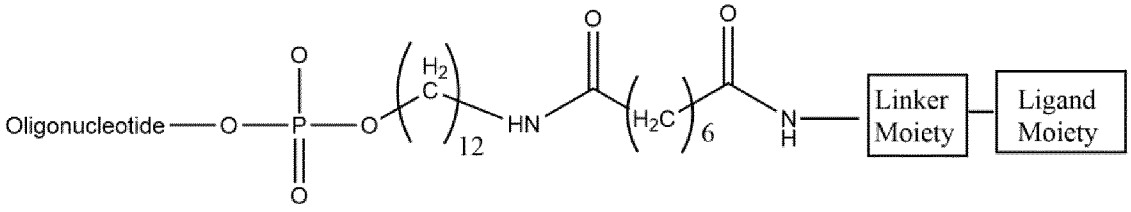
10. A compound according to any of Clauses 1 to 9, wherein said oligonucleoside is an RNA compound capable of modulating, preferably inhibiting, expression of a target gene.

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.

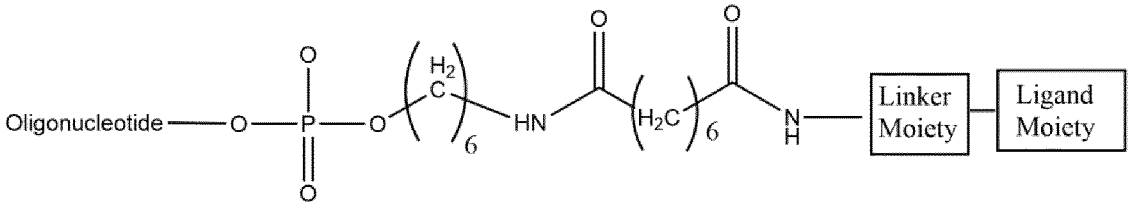
13. A compound according to Clause 11, preferably also dependent on Clauses 3 and 5, wherein the RNA compound is attached at the 3' end of its second strand to the adjacent phosphate.

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.

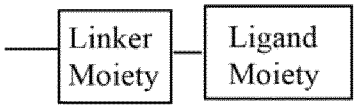
24. A compound according to Clause 23, wherein said one or more carbohydrates comprise one or more N-Acetyl-Galactosamine moieties.

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

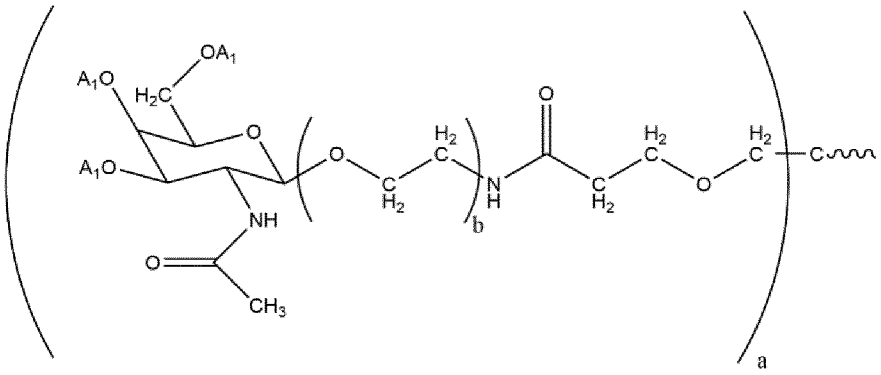
26. A compound according to any of the preceding Clauses, wherein said one or more ligands are attached in a linear configuration, or in a branched configuration.

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):



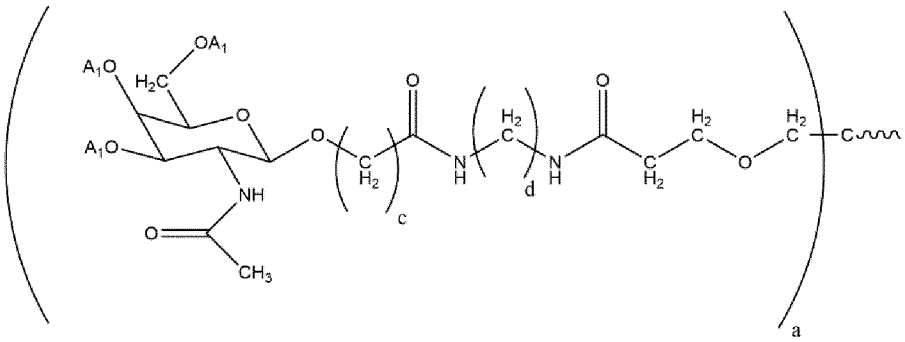
Formula (IV)

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



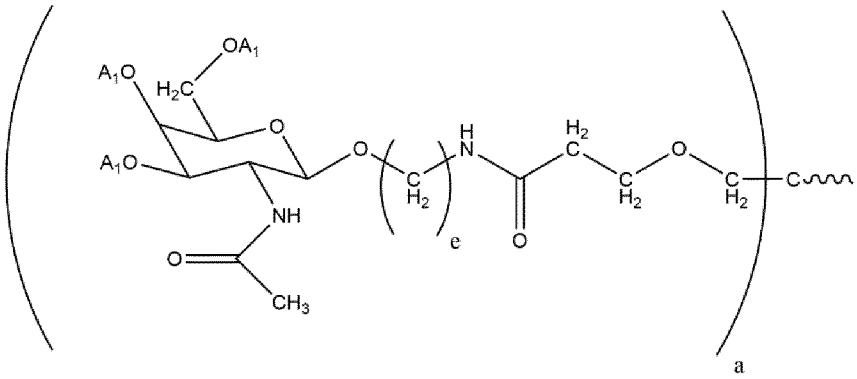
Formula (V)

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)

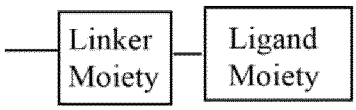
wherein:

A_I is hydrogen, or a suitable hydroxy protecting group;

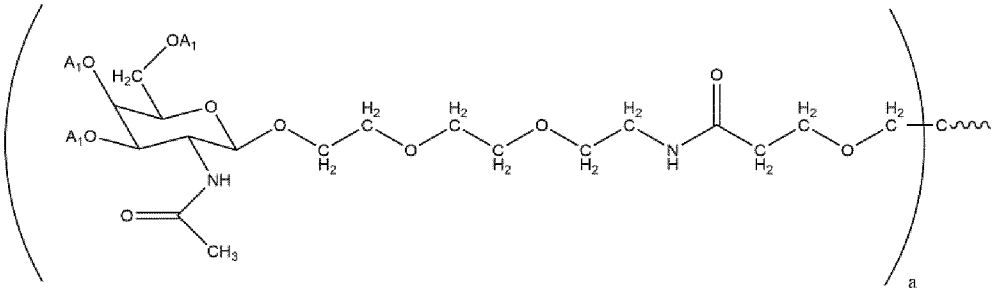
a is an integer of 2 or 3; and

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;

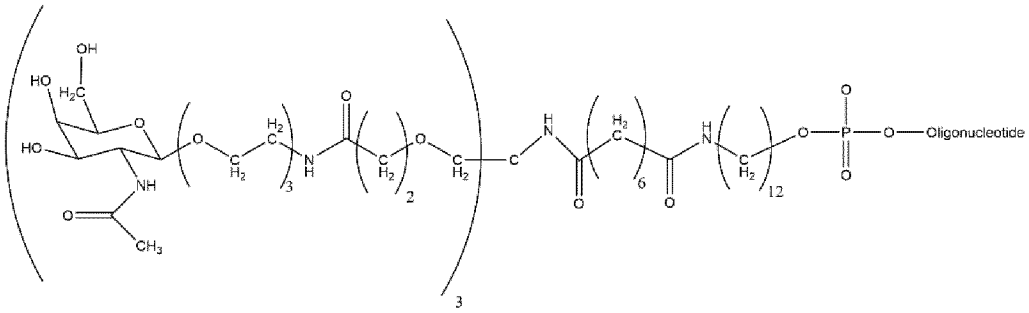
a is an integer of 2 or 3.

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

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

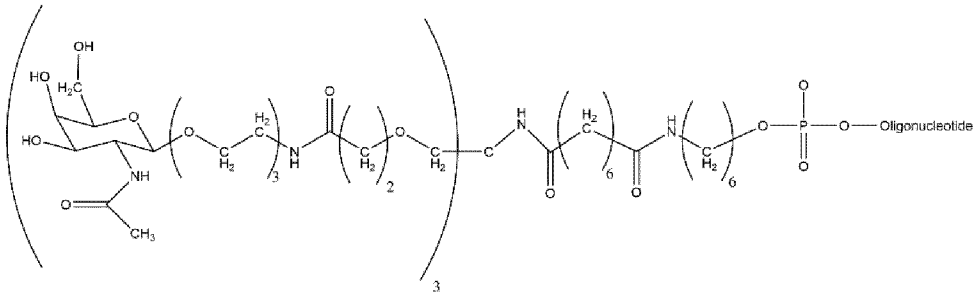
32. A compound according to Clause 28, wherein b = 3.

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.

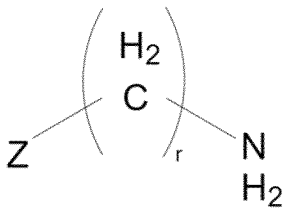
37. A compound according to any of Clauses 33 to 36, wherein the oligonucleoside further comprises one or more degradation protective moieties at one or more ends.

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.

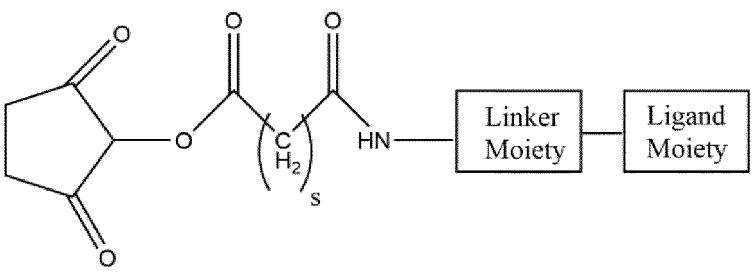
39. A compound according to Clause 33, wherein the oligonucleoside comprises an RNA duplex comprising first and second strands, wherein the first strand is at least partially complementary to an RNA sequence of a target gene, and the second strand is at least partially complementary to said first strand,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

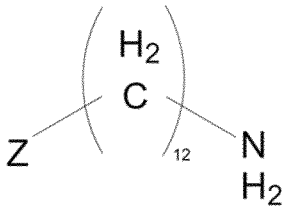
r and s are independently an integer selected from 1 to 16; and

Z is an oligonucleoside moiety;

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

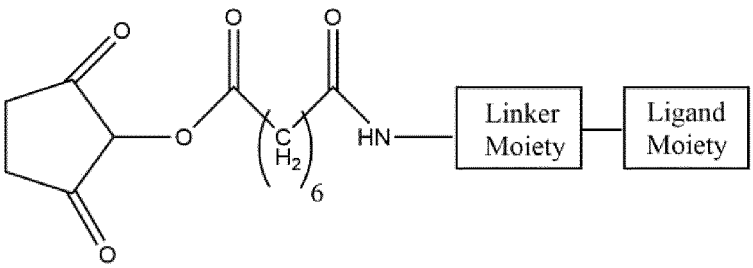
42. A process according to Clause 41, to prepare a compound according to any of Clauses 6, 8 to 14, 16 to 33, and 35 to 40, wherein:

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



Formula (Xa)

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

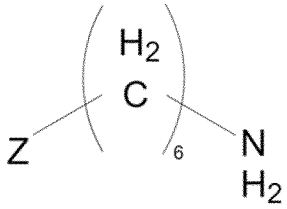


Formula (XIa)

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.

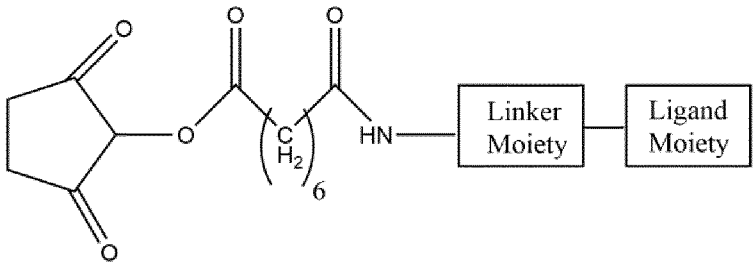
43. A process according to Clause 41, to prepare a compound according to any of Clauses 5, 7, 9 to 13, 15 to 32, and 34 to 40, wherein:

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



Formula (Xb)

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

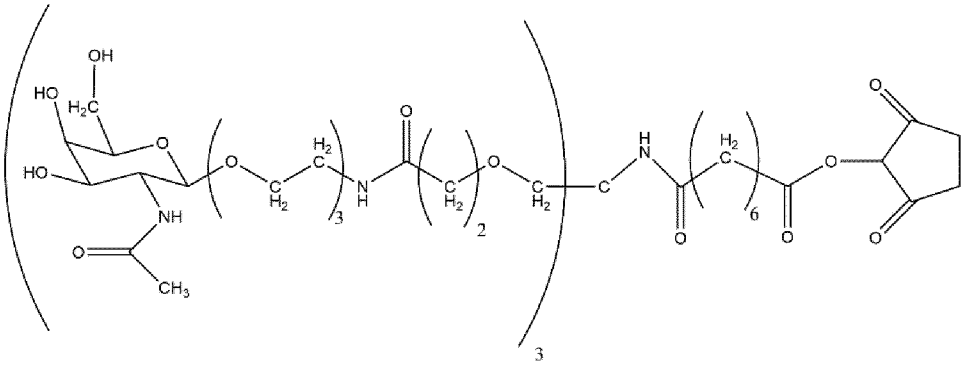


Formula (XIa)

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.

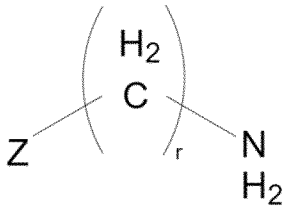
44. A process according to Clauses 42 or 43, wherein:

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



Formula (XIb)

45. A compound of Formula (X):



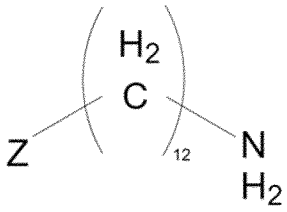
Formula (X)

wherein:

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

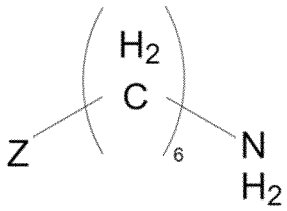
Z is an oligonucleoside moiety.

46. A compound of Formula (Xa):



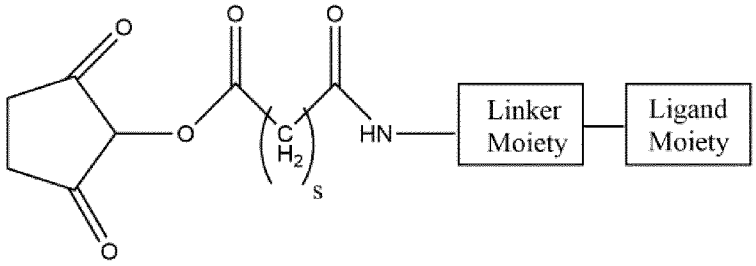
Formula (Xa)

47. A compound of Formula (Xb):



Formula (Xb)

48. A compound of Formula (XI):



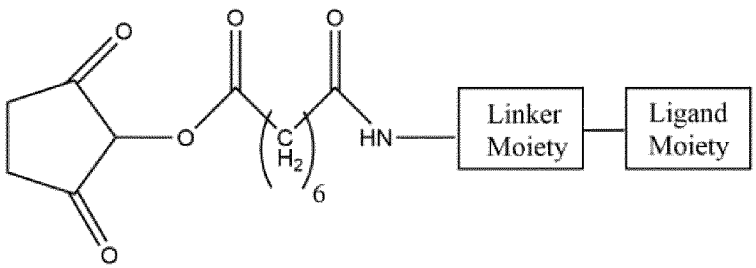
Formula (XI)

wherein:

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

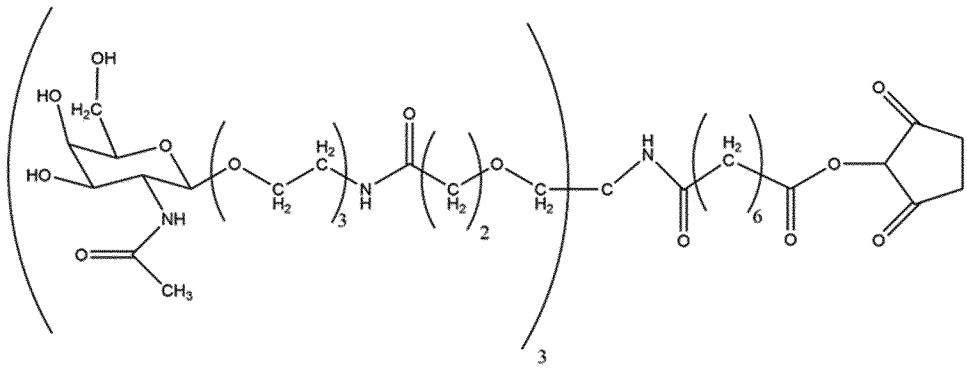
Z is an oligonucleoside moiety.

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

[00306] 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:

[00307] 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).

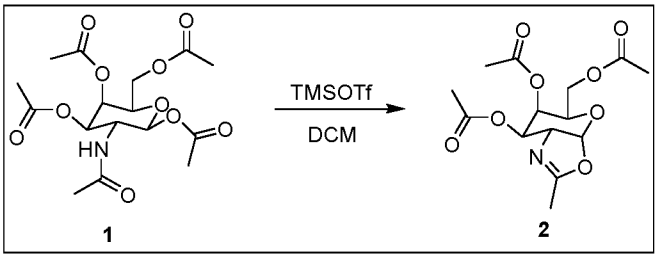
[00308] All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents

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

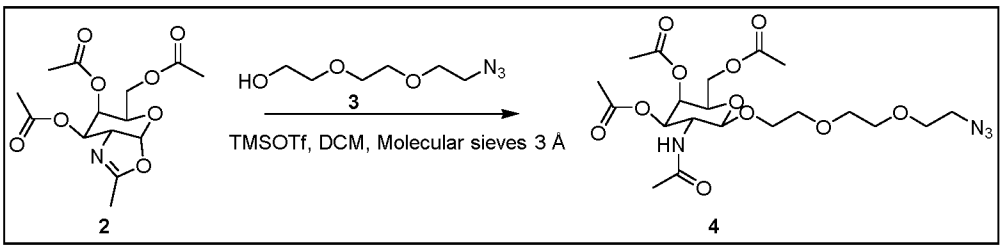
[00309] HPLC/ESI-MS was performed on a Dionex UltiMate 3000 RS UHPLC system and Thermo Scientific MSQ Plus Mass spectrometer using an Acquity UPLC Protein BEH C4 column from Waters (300Å, 1.7 µm, 2.1 x 100 mm) at 60 °C. The solvent system consisted of solvent A with H_2O containing 0.1% formic acid and 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.

[00310] ^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).

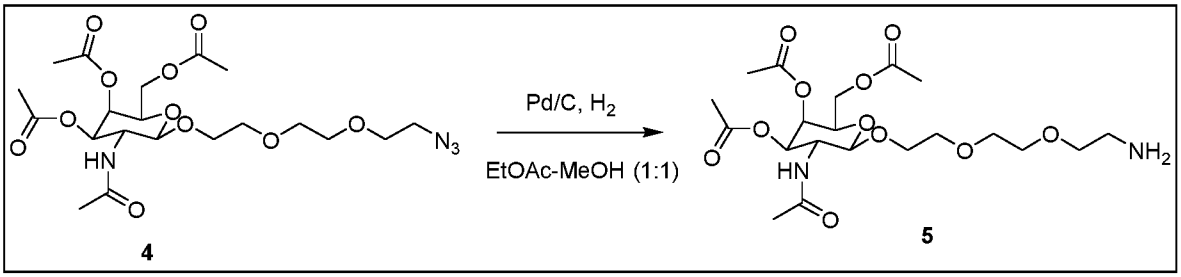
Synthesis route for the conjugate building block TriGalNAc _Tether1:



[00311] 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)).

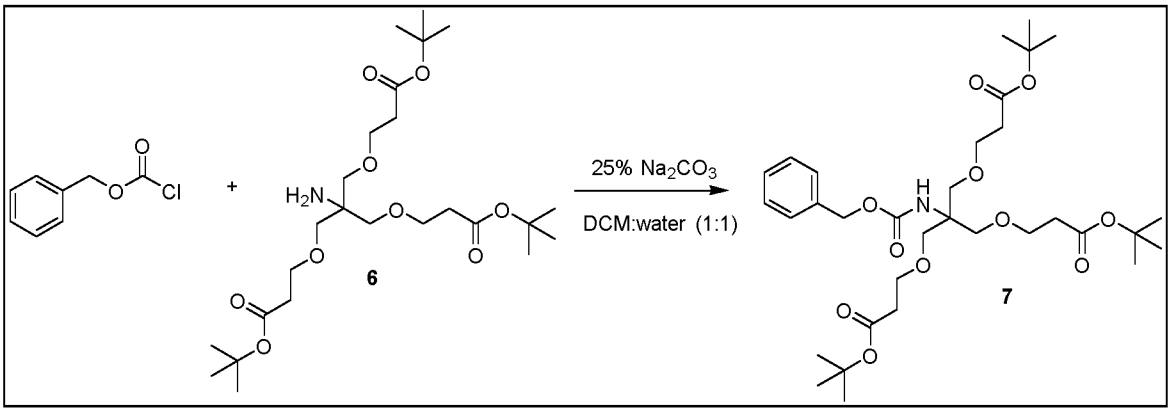


[00312] Preparation of compound **4**: Compound **2** (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at room temperature for 1 h. TMSOTf (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).

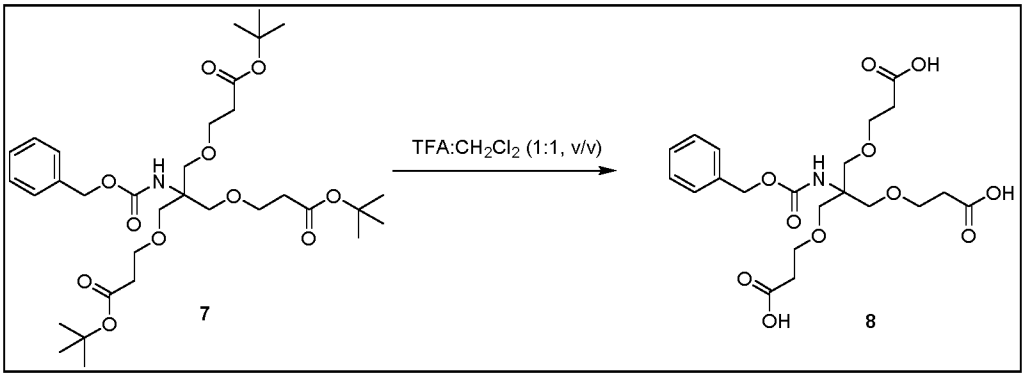


[00313] Preparation of compound **5**: Compound **4** (1.00 g, 1.98 mmol, 1.0 eq.) was dissolved in a mixture of ethyl acetate (EtOAc) and MeOH (30 mL 1:1 v/v) and Pd/C (100 mg) was added. The reaction mixture was degassed using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. 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.

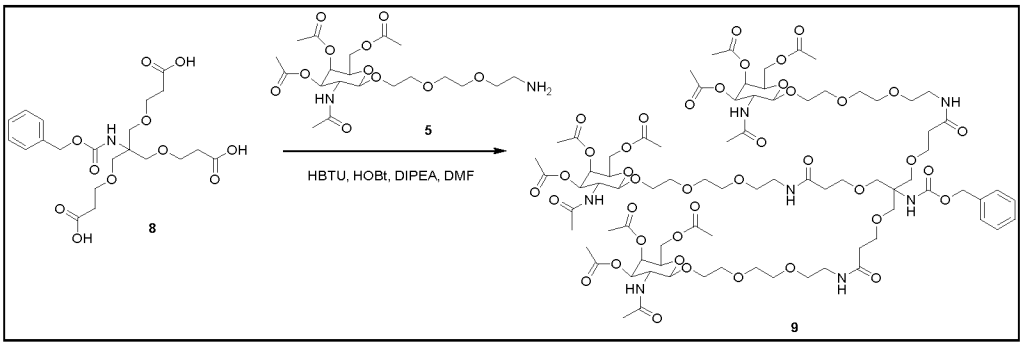


[00314] Preparation of compound **7**: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine **6** (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 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).

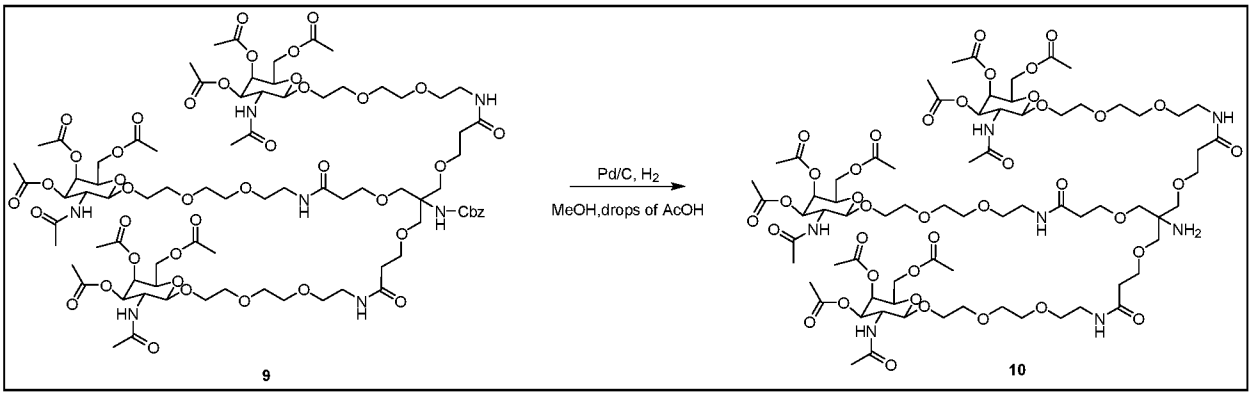


[00315] Preparation of compound **8**: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the

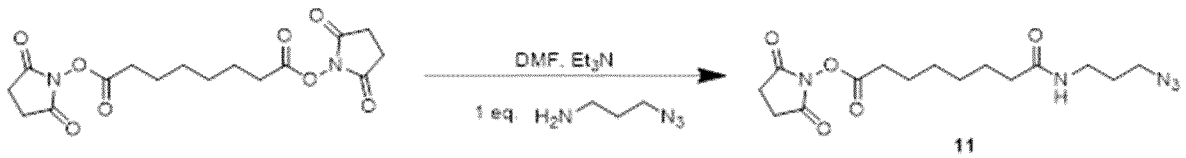
reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated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



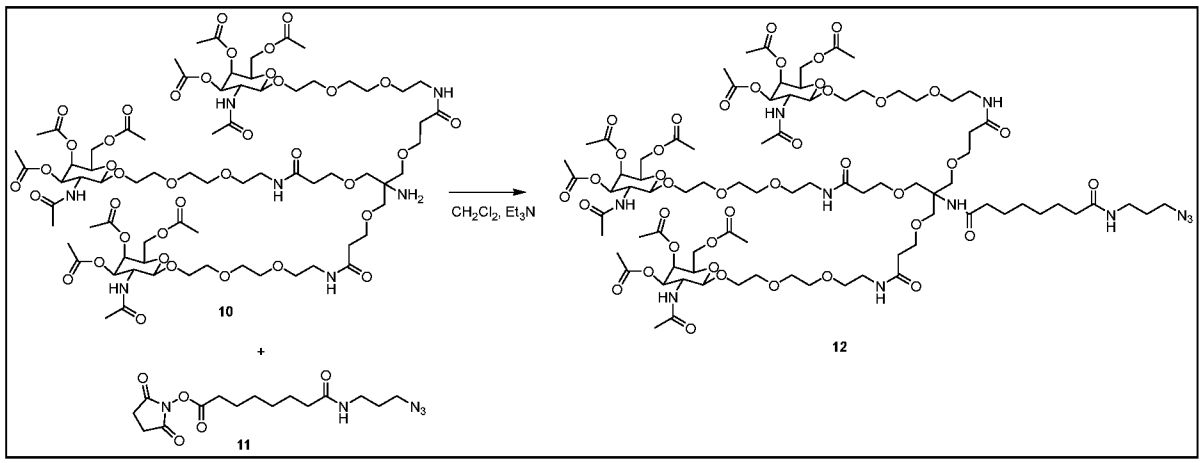
[00316] Preparation of compound **9**: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in *N,N*-dimethylformamide (DMF) (25 mL). Then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 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).



[00317] 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.



[00318] 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.



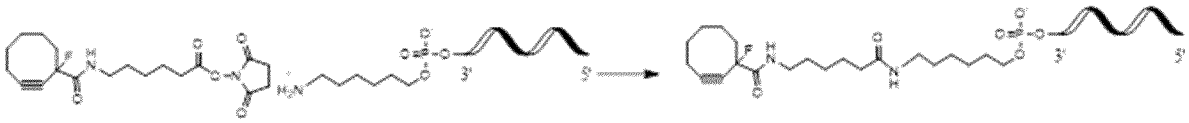
[00319] Preparation of TriGalNAc (**12**): Triantennary GalNAc compound **10** (0.35 g, 0.24 mmol, 1.0 eq.) and compound **11** (0.11 g, 0.31 mmol, 1.5 eq.) were dissolved in DCM (5 mL) under argon and triethylamine (0.1 mL, 0.61 mmol, 3.0 eq.) was added. The reaction was stirred at room temperature 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



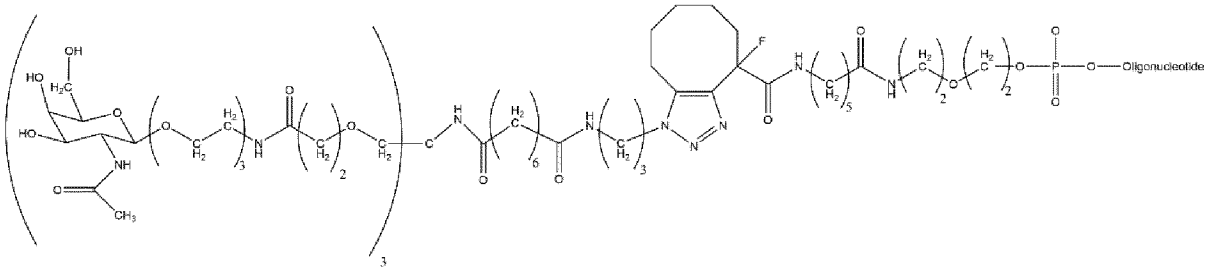
[00320] General conditions for MFCO conjugation: Amine-modified single strand was dissolved at 700 OD/mL in 50 mM carbonate/bicarbonate buffer pH 9.6/dimethyl sulfoxide

(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).

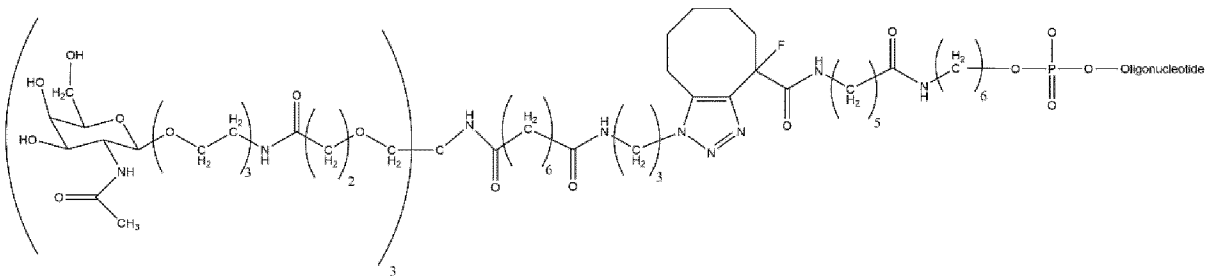
[00321] Purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM TEAAc pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

[00322] 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



[00323] 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).

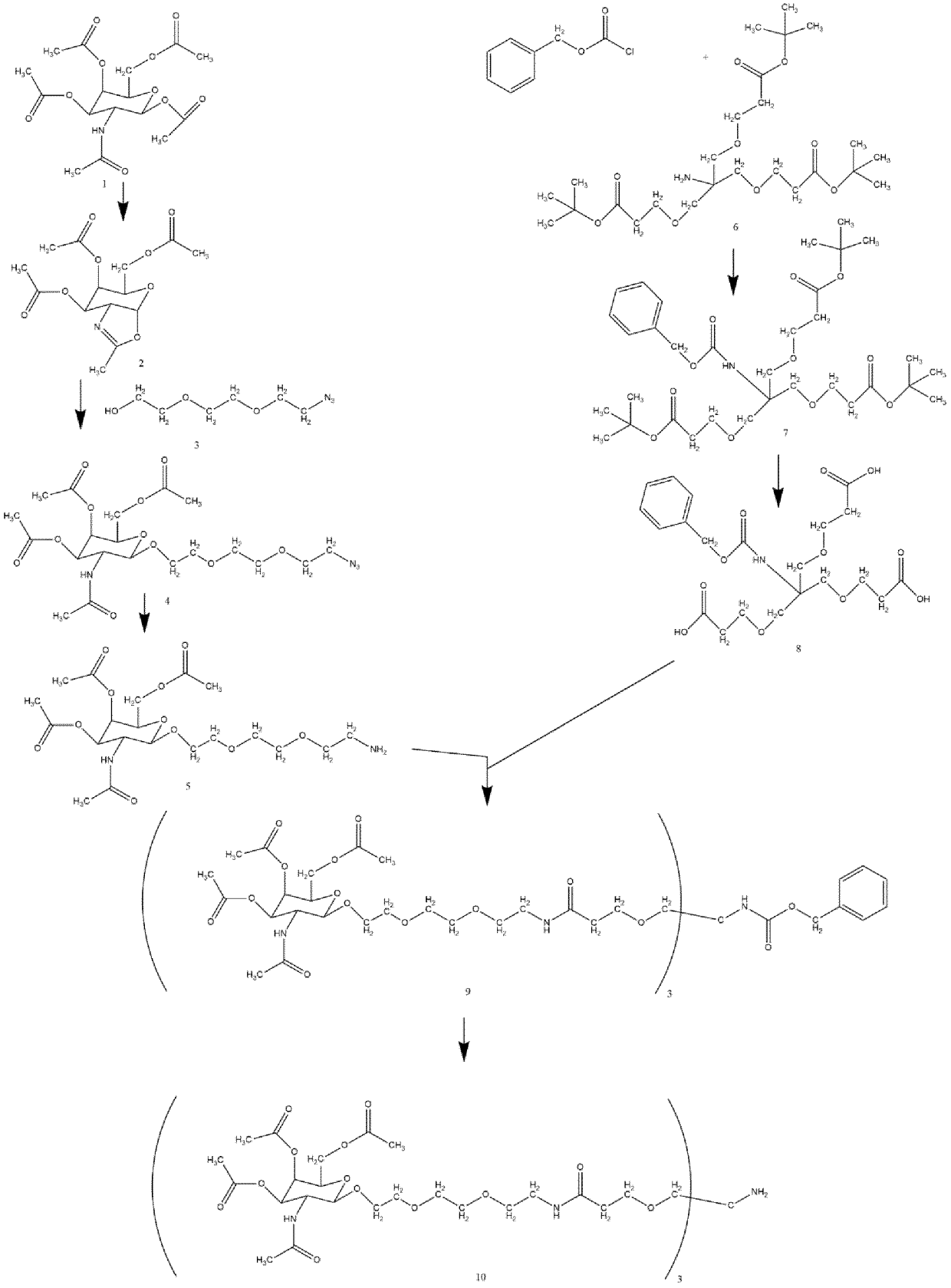
[00324] RP HPLC purification was performed using a XBridge C18 Prep 19 x 50 mm column from Waters. Buffer A was 100 mM triethylammonium acetate pH 7 and buffer B contained 95% acetonitrile in buffer A. A flow rate of 10 mL/min and a temperature of 60°C were employed. UV traces at 280 nm were recorded. A gradient of 0-100% B within 60 column volumes was employed.

[00325] Fractions containing full-length conjugated oligonucleotide were pooled, precipitated in the freezer with 3 M NaOAc, pH 5.2 and 85% ethanol and the collected pellet was dissolved in water 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.

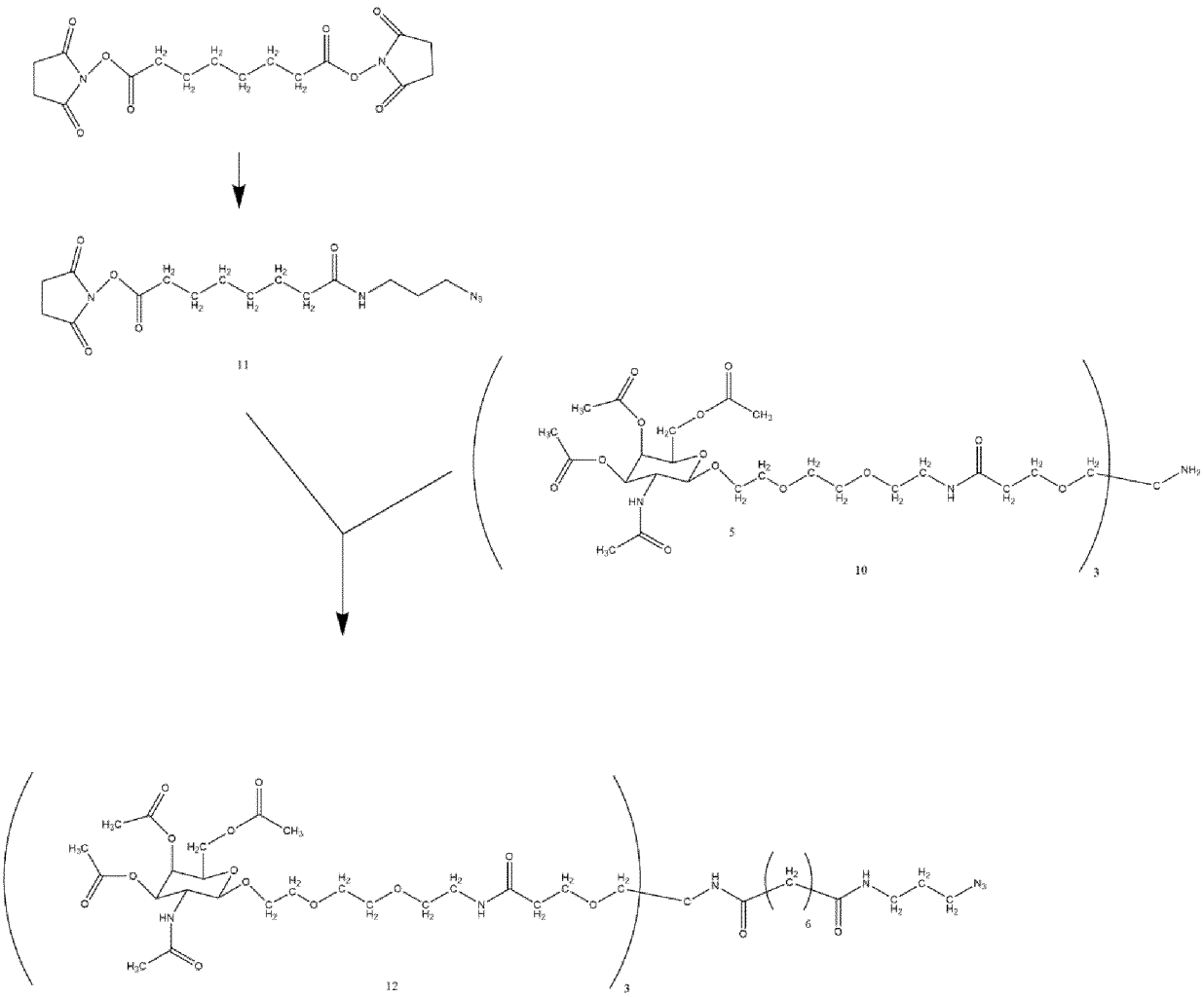
[00326] The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 50–70%.

[00327] The following schemes further set out the routes of synthesis:

Scheme 1:

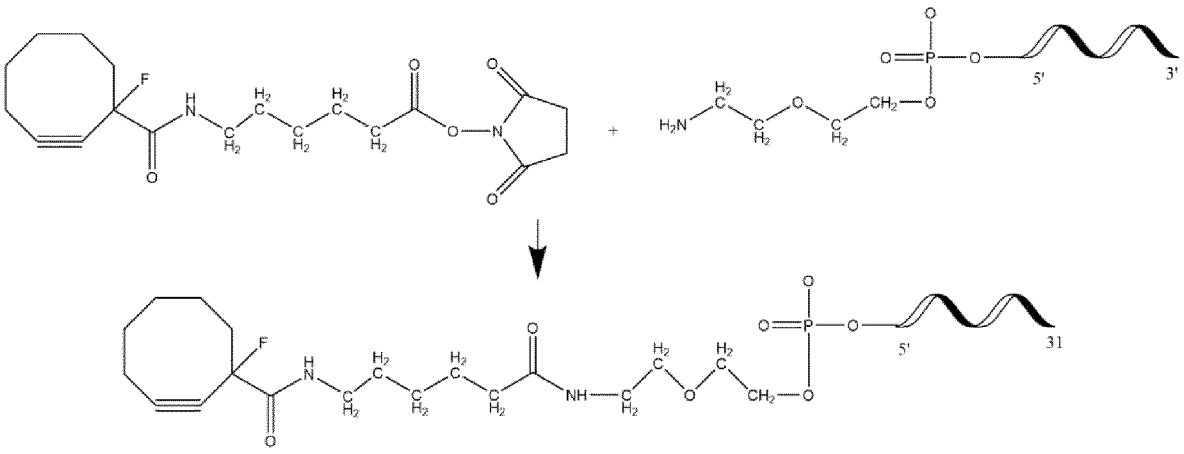


Scheme 2:

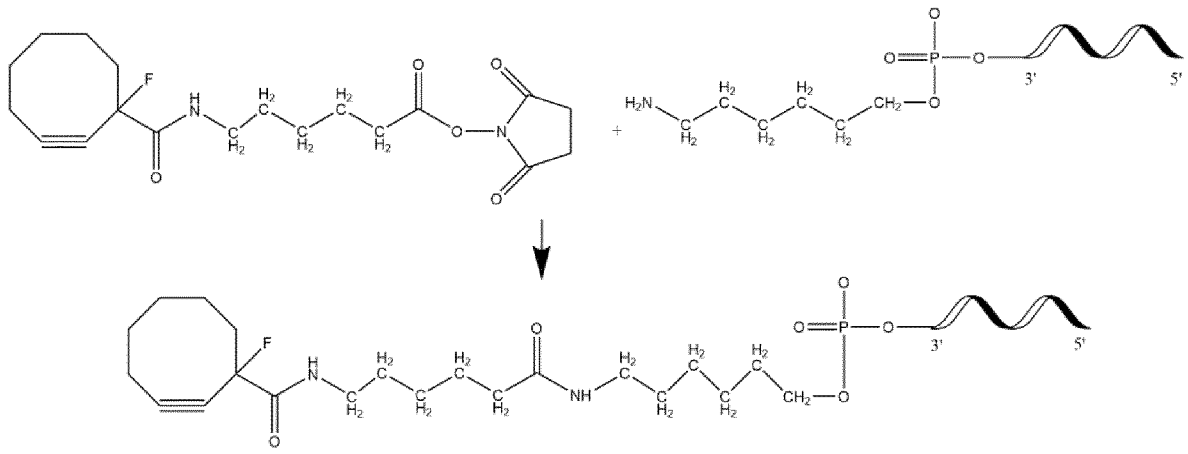


Scheme 3:

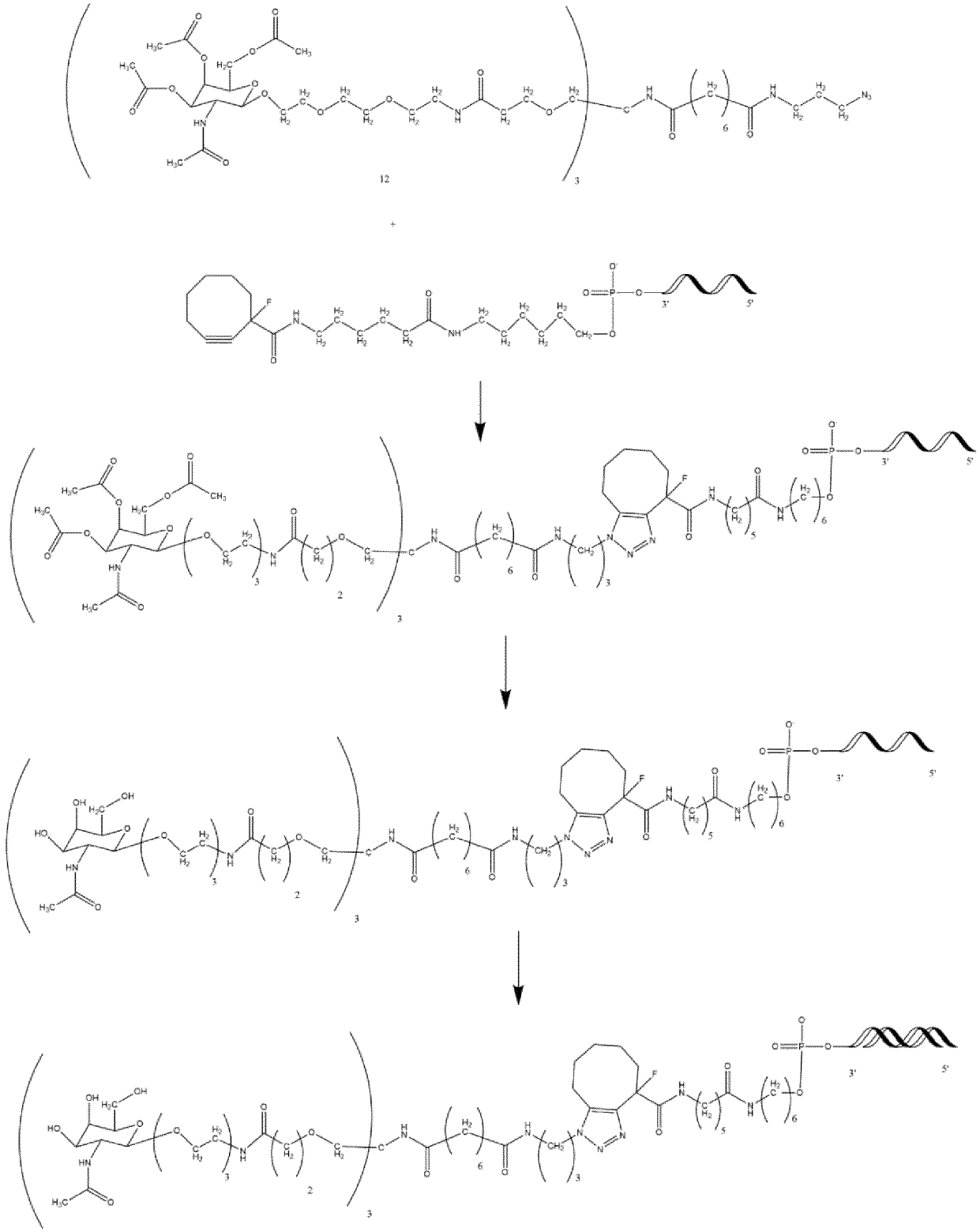
5' end MFCO conjugation



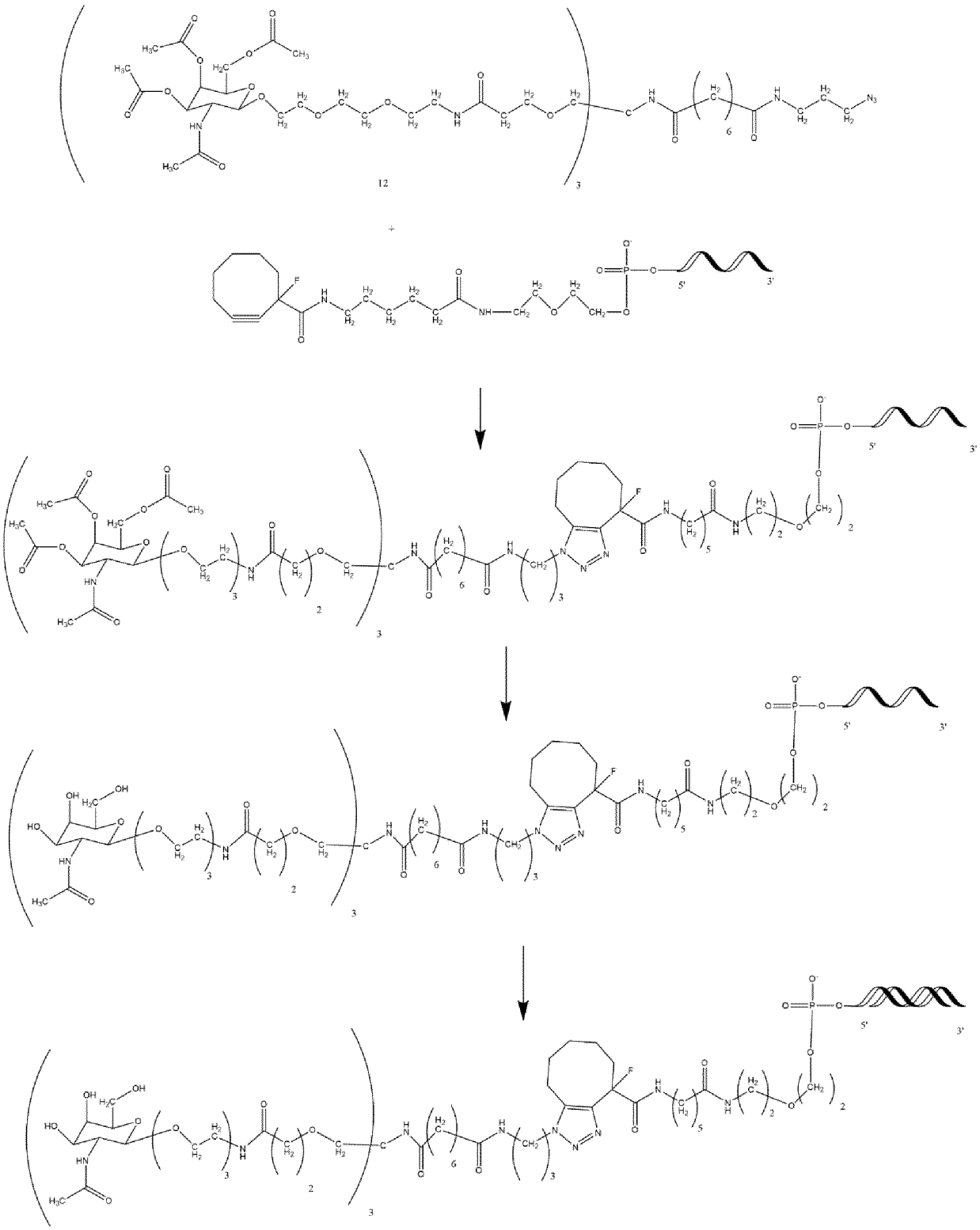
3' end MFCO conjugation



Scheme 4:



Scheme 5:



Example 2: Duplex Annealing

[00328] 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.

[00329] 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:

[00330] 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).

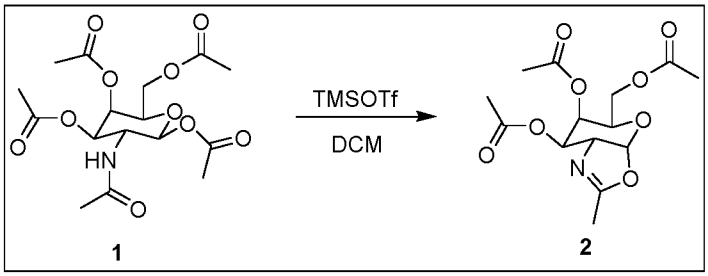
[00331] All moisture-sensitive reactions were carried out under anhydrous conditions using dry glassware, anhydrous solvents, and argon atmosphere. All commercially available reagents were purchased from Sigma-Aldrich and solvents from Carl Roth GmbH + Co. KG. D-Galactosamine pentaacetate was purchased from AK scientific.

[00332] 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

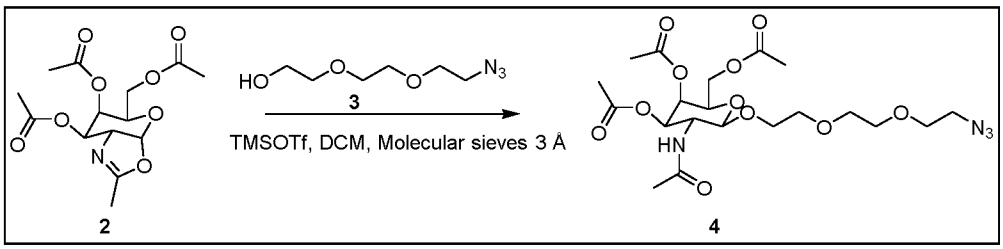
0.4 mL/min was employed. Detector and conditions: Corona ultra-charged aerosol detection (from esa). Nebulizer Temp.: 25 °C. N_2 pressure: 35.1 psi. Filter: Corona.

[00333] ^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:

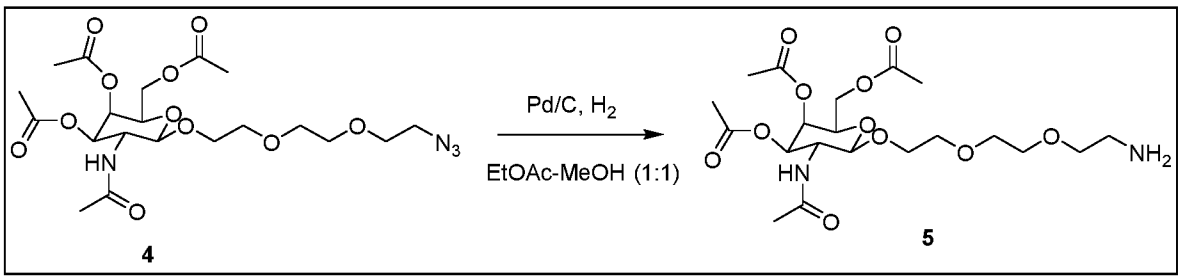


[00334] Preparation of compound 2: D-Galactosamine pentaacetate (3.00 g, 7.71 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (DCM) (30 mL) under argon and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.28 g, 19.27 mmol, 2.5 eq.) was added. The reaction was stirred at room temperature 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)).

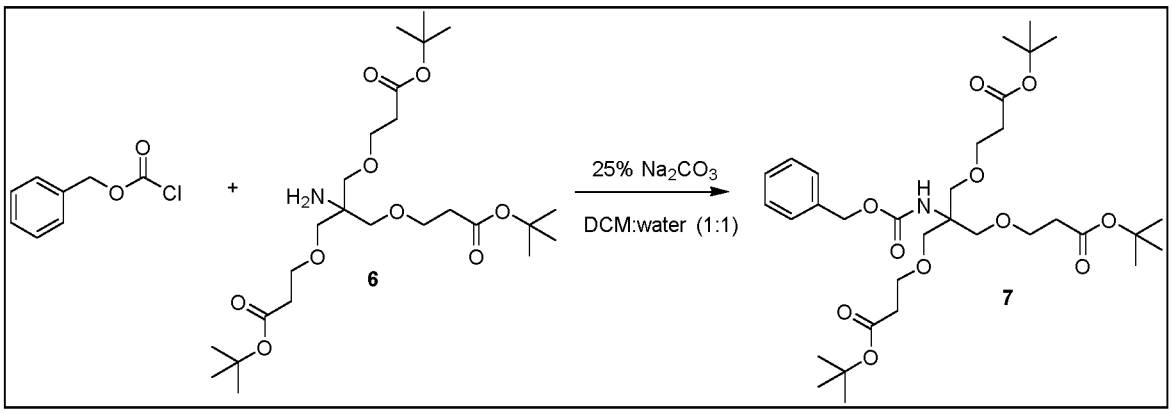


[00335] Preparation of compound **4**: Compound **2** (2.30 g, 6.98 mmol, 1.0 eq.) and azido-PEG3-OH (1.83 g, 10.5 mmol, 1.5 eq.) were dissolved in anhydrous DCM (40 mL) under argon and molecular sieves 3 Å (5 g) were added to the solution. The mixture was stirred at

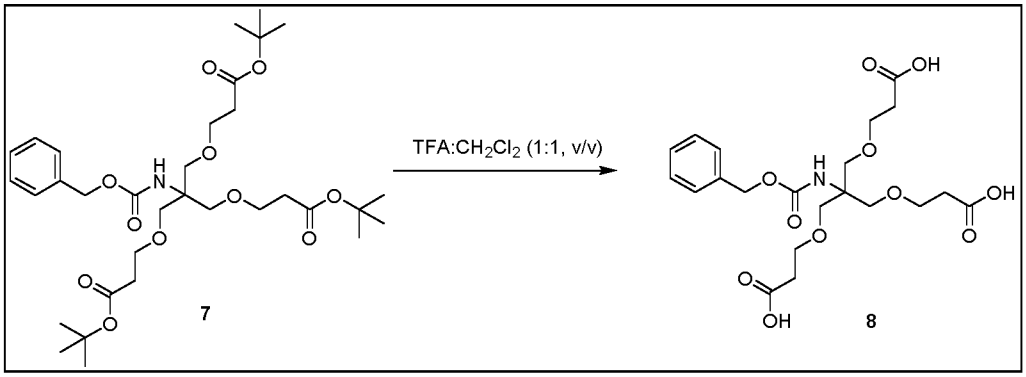
room temperature for 1 h. TMSOTf (0.77 g, 3.49 mmol, 0.5 eq.) was then added to the mixture and the reaction was stirred overnight. The molecular sieves were filtered, the filtrate was diluted with DCM (100 mL) and washed with cold saturated aq. $NaHCO_3$ (100 mL) and water (100 mL). The organic layer 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).



[00336] 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.

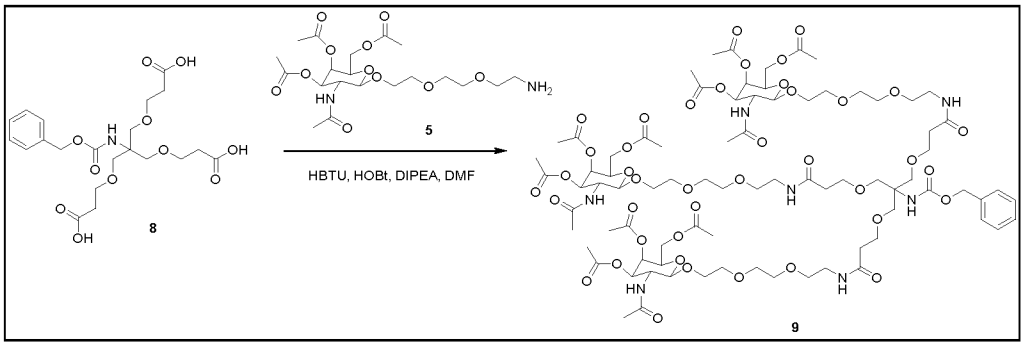


[00337] Preparation of compound **7**: Tris{[2-(tert-butoxycarbonyl)ethoxy]methyl}-methylamine **6** (3.37 g, 6.67 mmol, 1.0 eq.) was dissolved in a mixture of DCM/water (40 mL 1:1 v/v) and Na_2CO_3 (0.18 g, 1.7 mmol, 0.25 eq.) was added while stirring vigorously. Benzyl chloroformate (2.94 mL, 20.7 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).

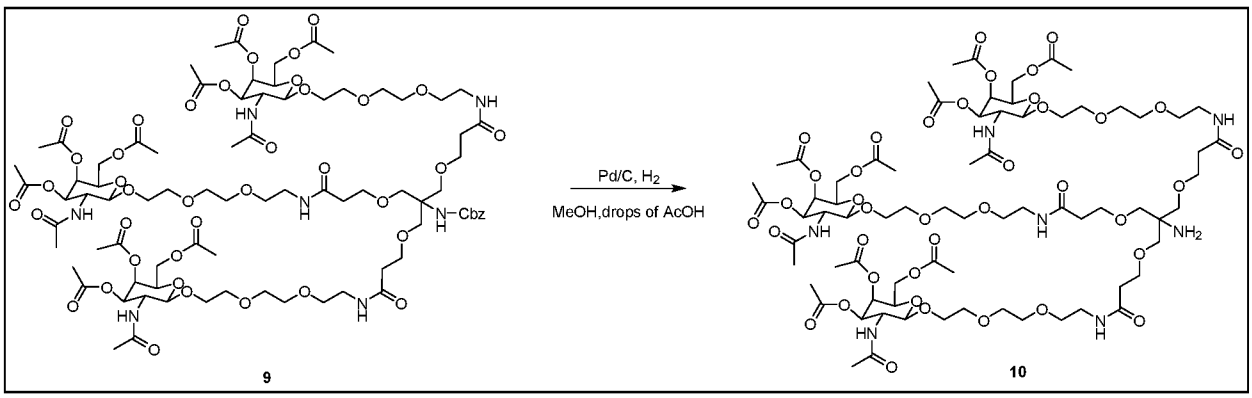


[00338] Preparation of compound **8**: Cbz-NH-tris-Boc-ester **7** (0.20 g, 0.39 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1 mL) under argon, trifluoroacetic acid (TFA, 1 mL) was added and the reaction was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was co-evaporated 3 times with toluene (5 mL) and dried under high

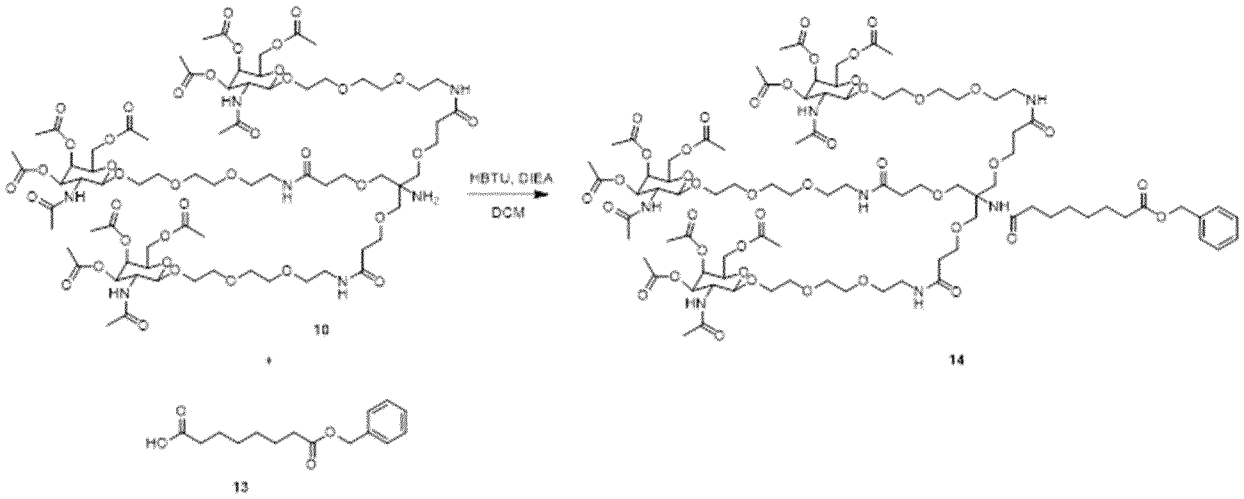
vacuum to get the compound as its TFA salt (0.183 g, 98%). The compound was used without further purification. MS: calculated for $C_{21}H_{29}NO_{11}$, 471.6. Found 472.4.



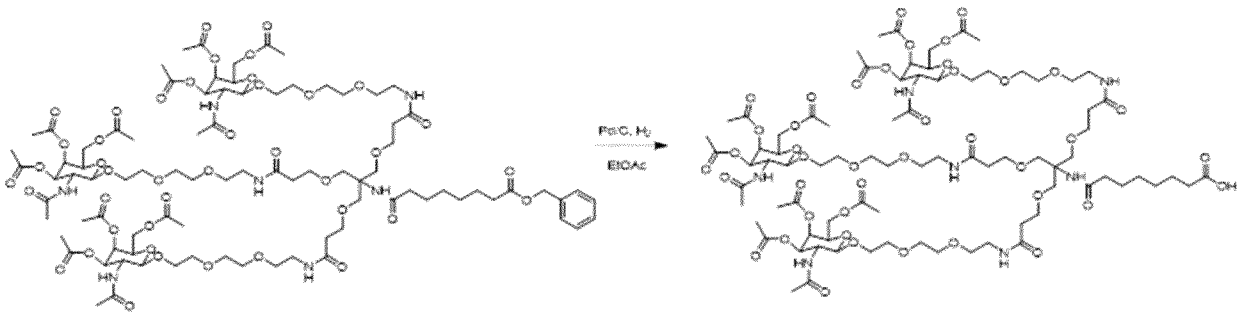
[00339] Preparation of compound **9**: CbzNH-tris-COOH **8** (0.72 g, 1.49 mmol, 1.0 eq.) and GalNAc-PEG3-NH_2 **5** (3.56 g, 7.44 mmol, 5.0 eq.) were dissolved in *N,N*-dimethylformamide (DMF) (25 mL). Then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (2.78 g, 7.44 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).



[00340] 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.



[00341] 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.

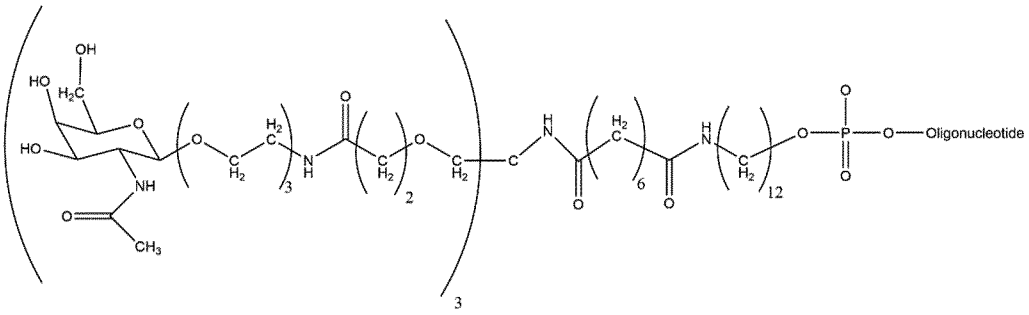


14 15

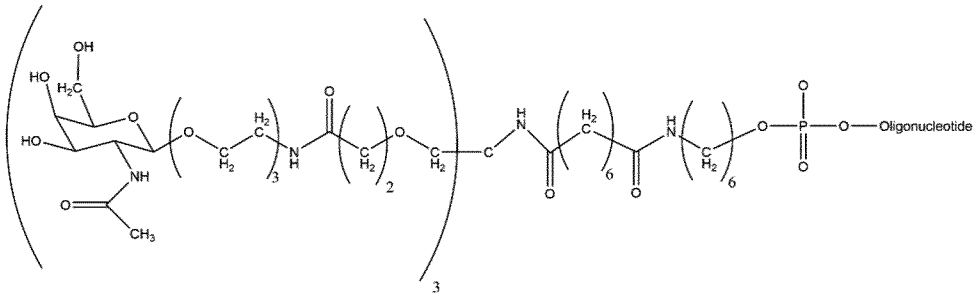
[00342] Preparation of TriGalNAc (15): Triantennary GalNAc compound 14 (0.31 g, 0.15 mmol, 1.0 eq.) was dissolved in EtOAc (15 mL) and Pd/C (40 mg) was added. The reaction mixture was degassed by using vacuum/argon cycles (3x) and hydrogenated under balloon pressure overnight. The completion of the reaction 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



[00343] 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.

[00344] 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.

[00345] 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.

[00346] 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).

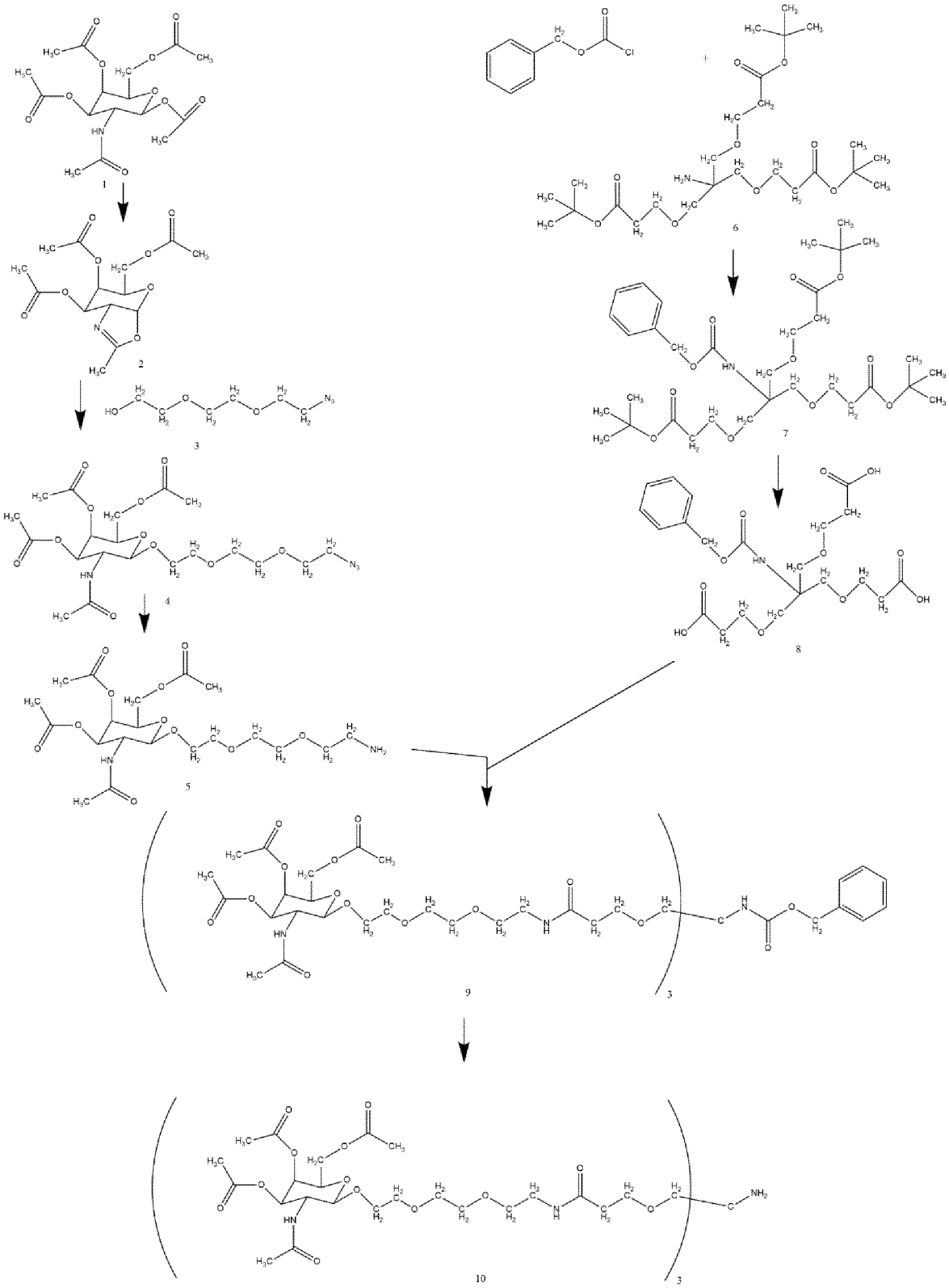
[00347] The conjugates were desalted by size exclusion chromatography using Sephadex G25 Fine resin (GE Healthcare) on an Äkta Pure (GE Healthcare) instrument to yield the conjugated oligonucleotides in an isolated yield of 60–80%.

[00348] 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.

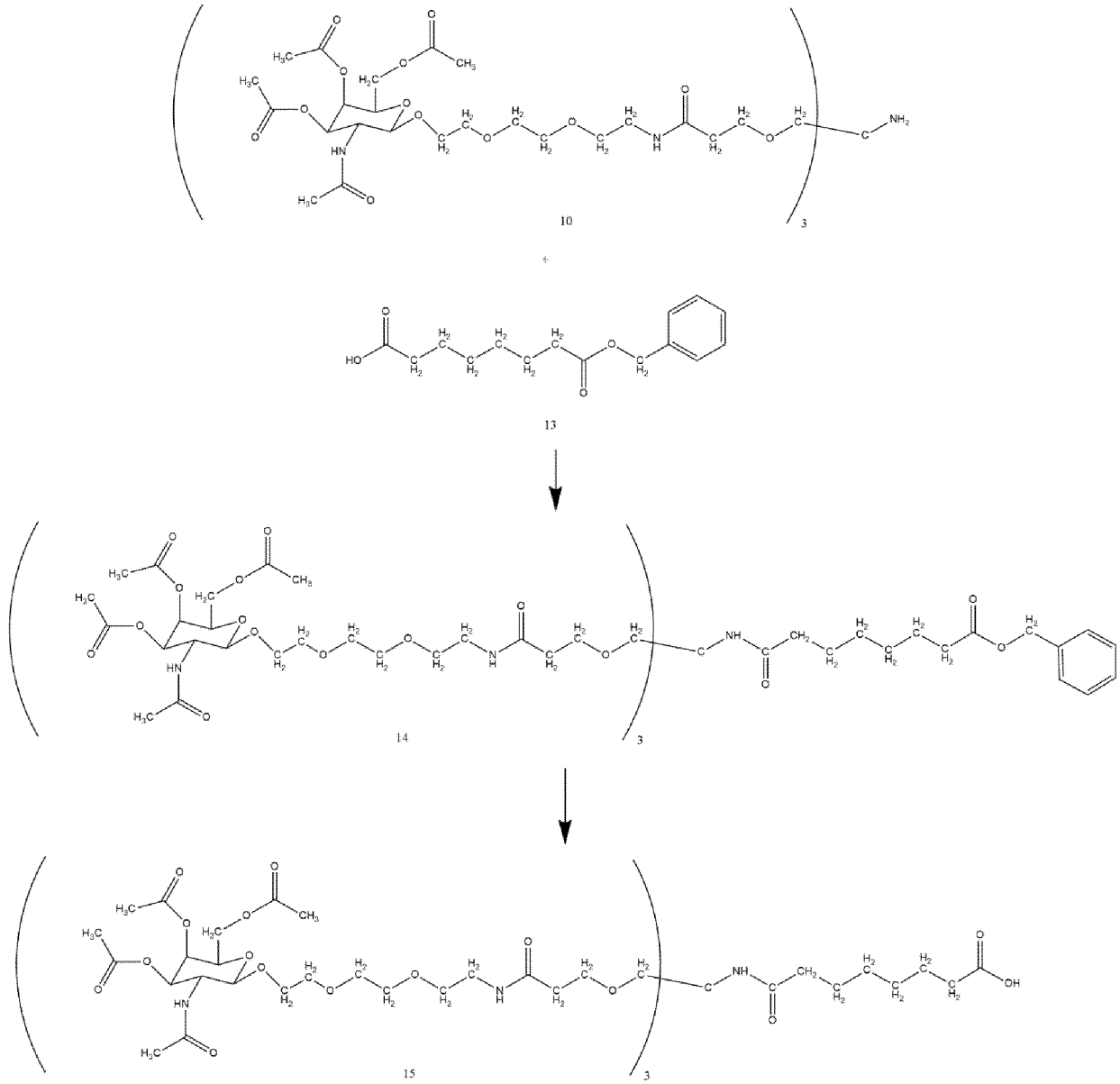
UV traces at 260 and 280 nm were recorded. A gradient of 1-100% B within 31 min was employed.

[00349] The following schemes further set out the routes of synthesis:

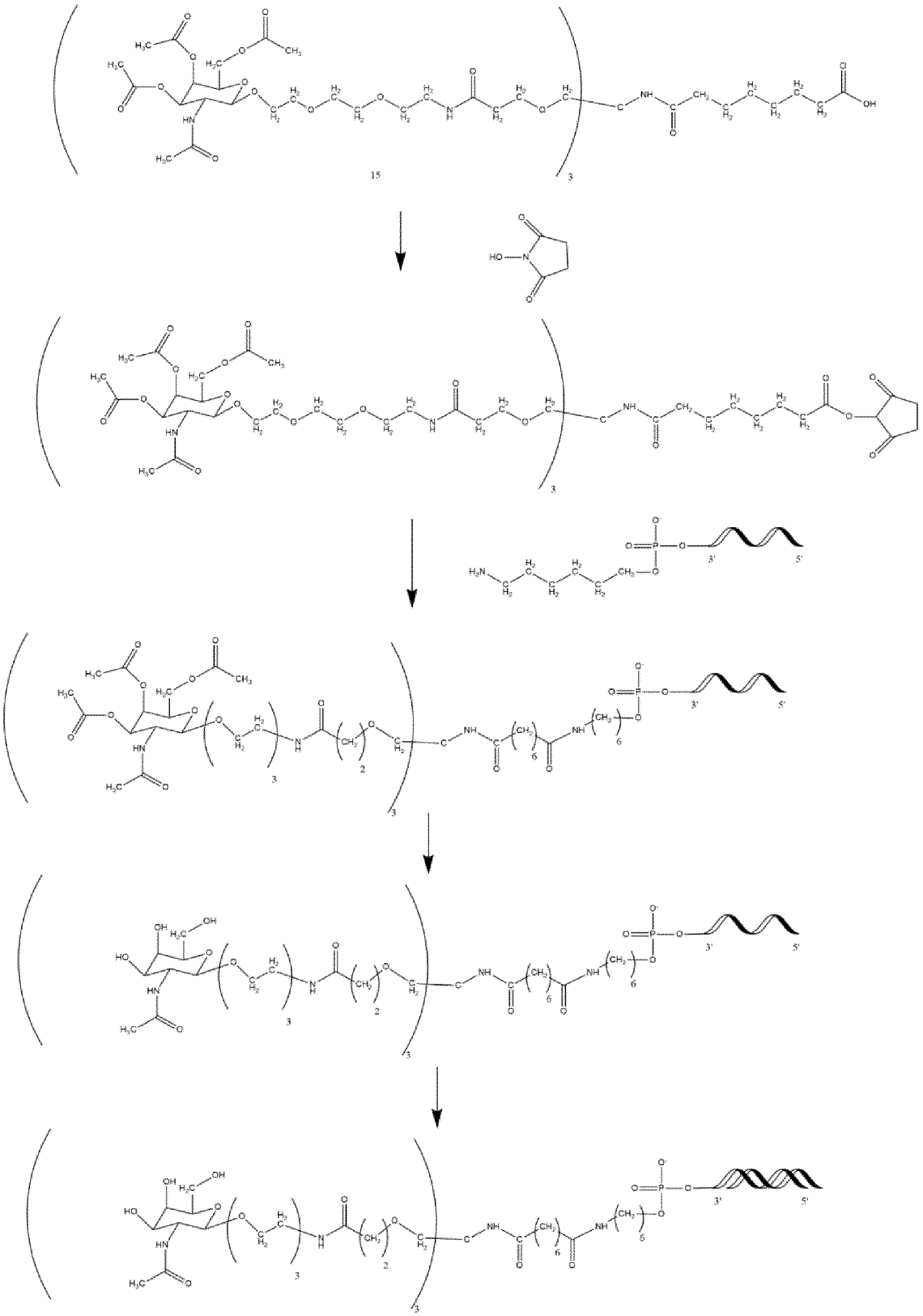
Scheme 6:



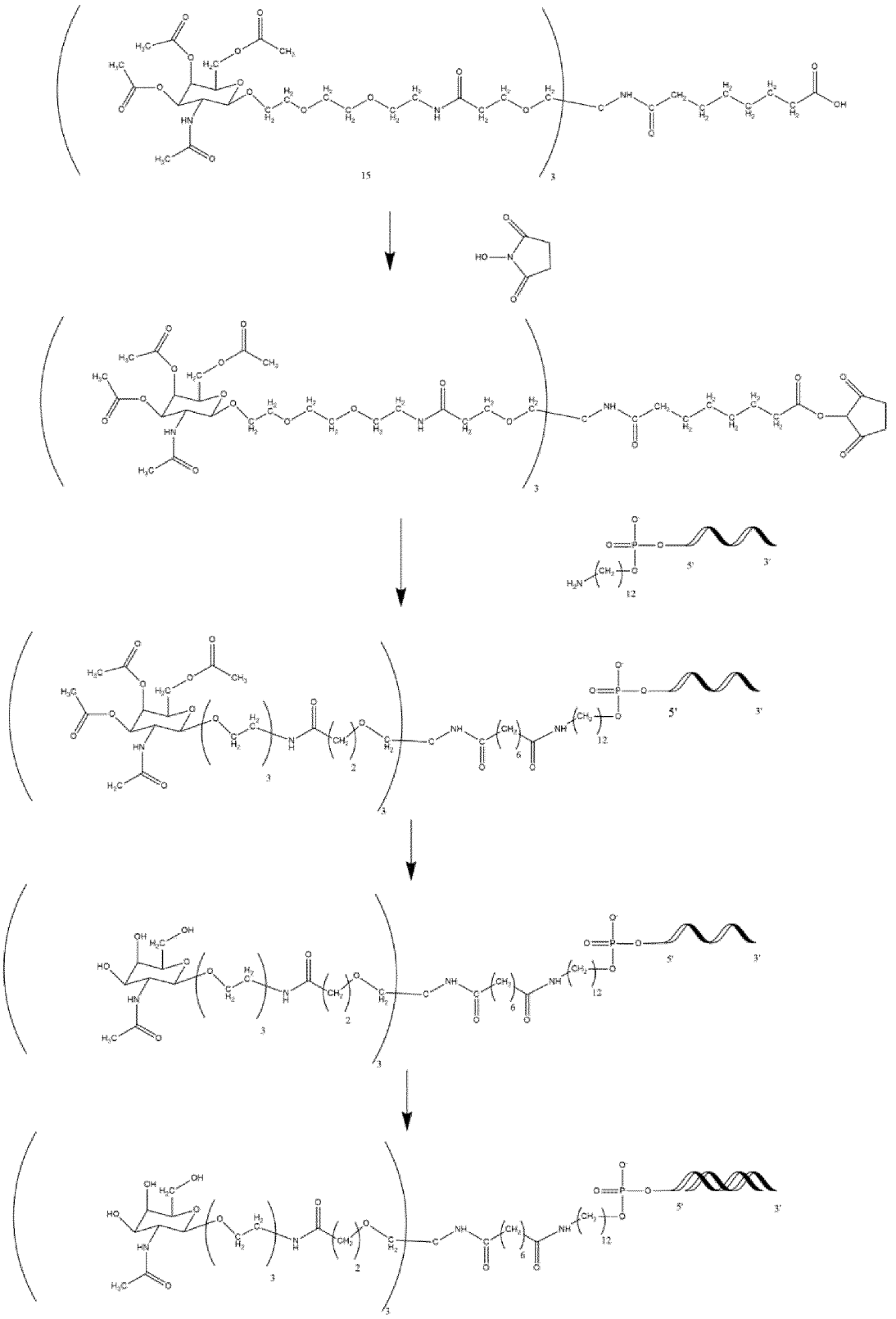
Scheme 7:



Scheme 8:



Scheme 9:

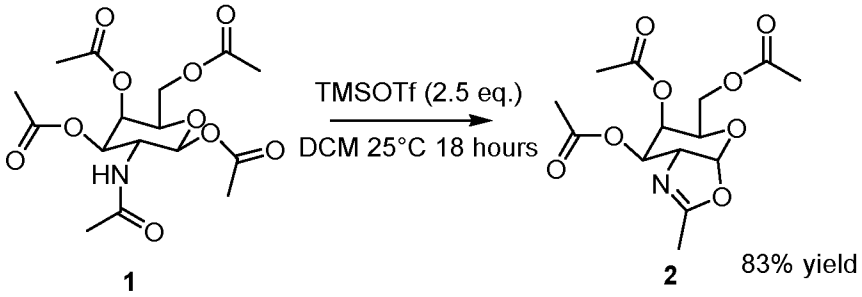


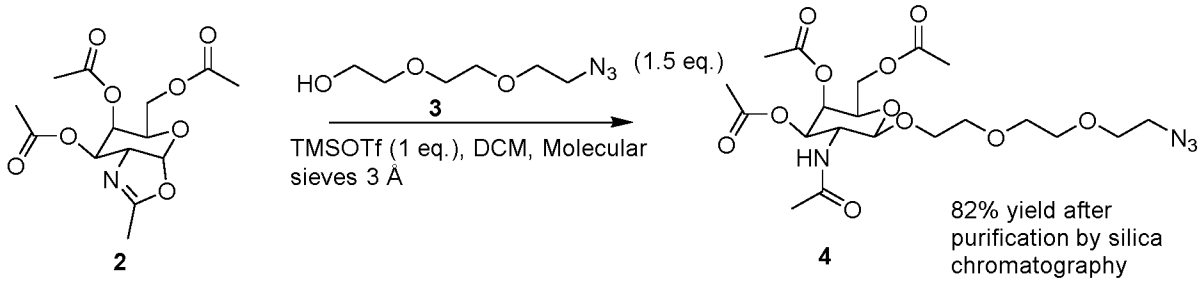
Example 4: Duplex Annealing

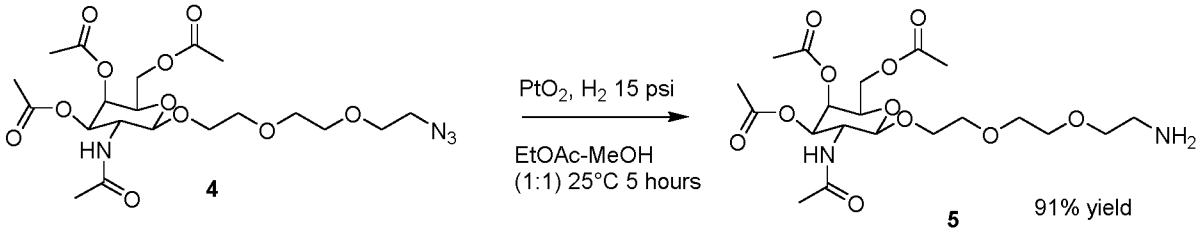
[00350] To generate the desired siRNA duplex, the two complementary strands were annealed by combining equimolar aqueous solutions of both strands. The mixtures were placed into a water bath at 70°C for 5 minutes and subsequently allowed to cool to ambient temperature within 2 h. The duplexes were lyophilized for 2 days and stored at -20°C.

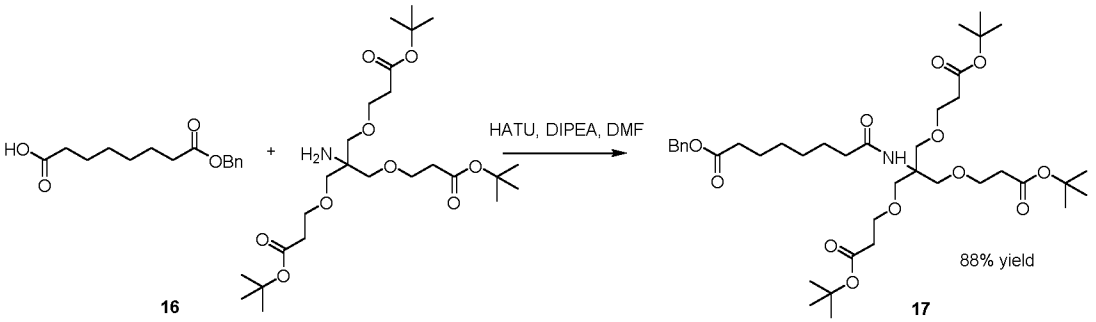
[00351] The duplexes were analyzed by analytical SEC HPLC on Superdex™ 75 Increase 5/150 GL column 5 x 153-158 mm (Cytiva) on a Dionex Ultimate 3000 (Thermo Fisher Scientific) HPLC system. Mobile phase consisted of 1x PBS containing 10% acetonitrile. An isocratic gradient was run in 10 min at a flow 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).

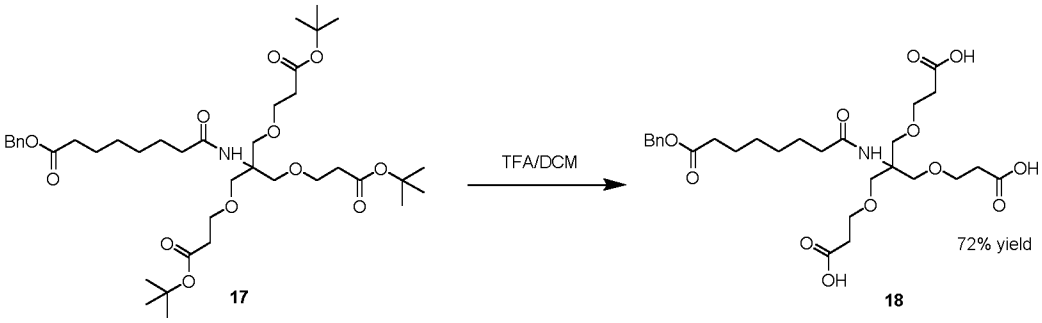
Example 5: Alternative synthesis route for the conjugate building block TriGalNAc _Tether2:

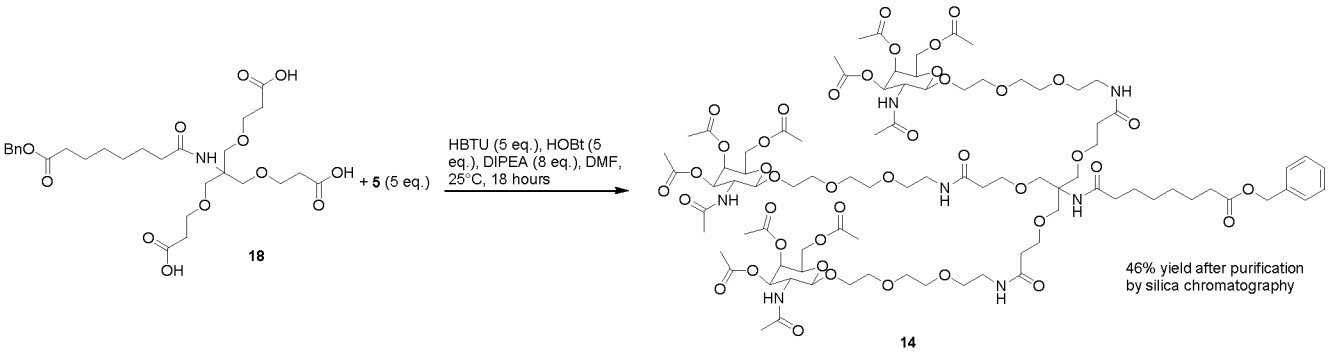


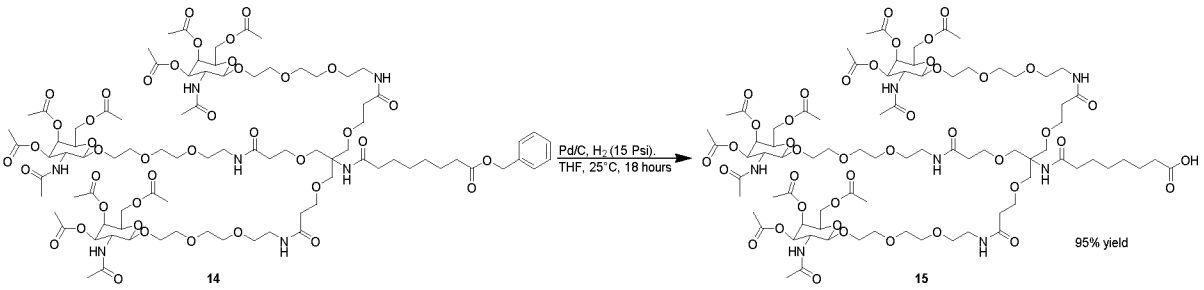



PtO2, H2 15 psi
EtOAc-MeOH
(1:1) 25°C 5 hours
4
5
91% yield


HATU, DIPEA, DMF
16
17
88% yield

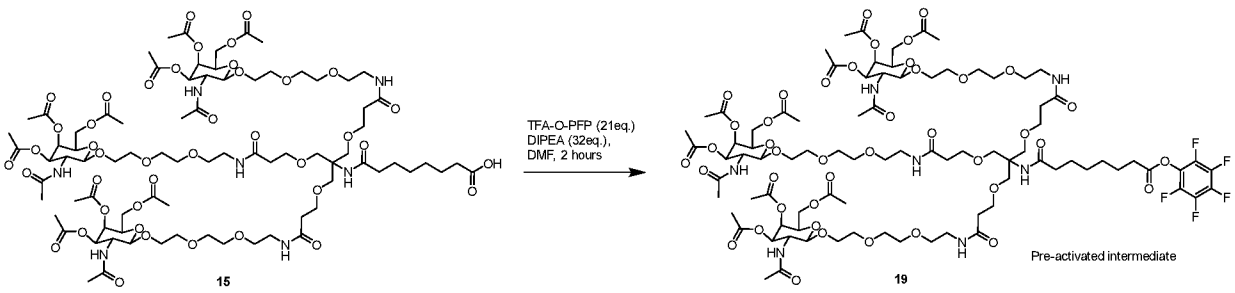

TFA/DCM
17
18
72% yield


+ 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

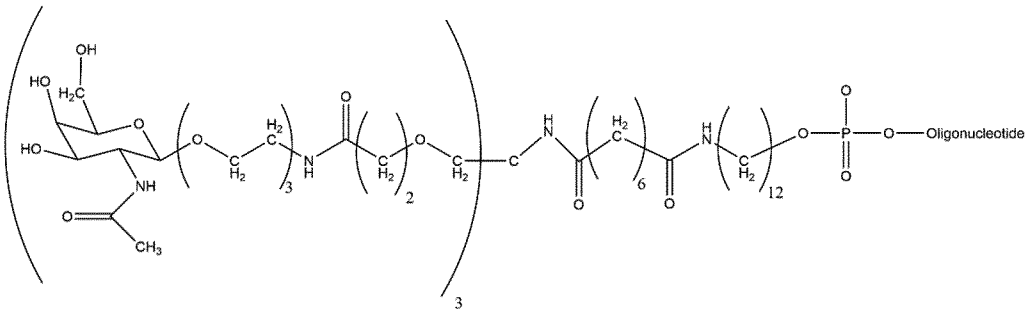
Conjugation conditions



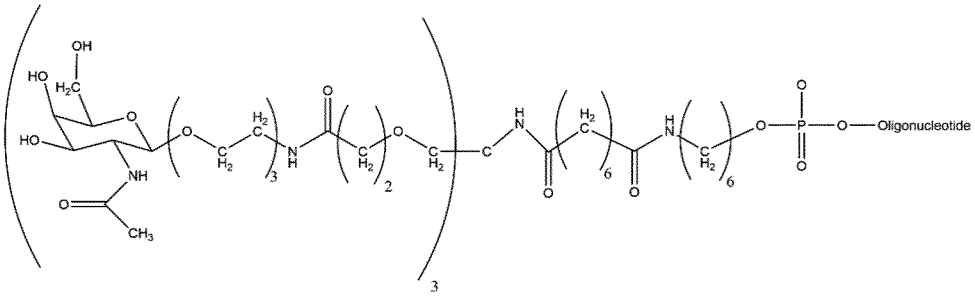
[00352] Pre-activation: To a solution of compound **15** (16 umol, 4 eq.) in DMF (160 µL) was added TFA-O-PFP (15 µl, 21 eq.) followed by DIPEA (23 µl, 32 eq.) at 25°C. The tube was shaken for 2 h at 25°C. The reaction was quenched with H_2O (10 µL).

[00353] 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

[00354] 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).

[00355] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[00356] 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.

[00357] 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.

[00358] 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.

[00359] 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).

[00360] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[00361] The coupling time was 180 seconds. The oxidizer contact time was set to 80 seconds and thiolation time was 2*100 seconds.

[00362] 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.

[00363] 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.

[00364] 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

[00365] 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).

[00366] RNA phosphoramidites were purchased from ChemGenes or Hongene.

[00367] 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.

[00368] 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.

[00369] 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).

[00370] 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.

[00371] At each cycle, the DMT was removed by deblock solution, 3% TCA in DCM (DNAchem).

[00372] 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.

[00373] 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

[00374] 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.

[00375] Oligonucleotide were treated to form the sodium salt by EtOH precipitation from 1M sodium acetate.

[00376] 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.

[00377] 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).

[00378] Sense strand were conjugated as per protocols provided in any of examples 1, 3 or 5.

[00379] 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:

[00380] siRNA oligonucleosides suitable for use according to the present invention can target HCII and ZPI. The full DNA sequences of the HCII and ZPI targets are respectively as follows (SEQ ID NOs: 1 and 2):

[00381] SEQ ID NO: 1 (HCII)

TTGCGCTTCTAGAATGCTTCCCTCTCAATGAGAACAGTAGCTCCACGTGGCTGGGAAGTTCAAAGTGG
TTTTGACACAGAAAAGAGGAAGTAAGTGGACTCTATCTTTGATTTGGGATCCTACTCCTGACCCTGTG
AACTTCTTGGCTCCCTCTTGAGGACGTTGGCTTGAAAGTGGCTCTGTGGGTTCTCCCTGCTCTCTGACTT
CTCCGAGCCTGCTGGCCACTGTCTTGGCTGAGACTGCTCTAGTCTCCAGAAAGGAGATCTGCTCACTCC
TAAGAAGTATCAAGGTCAGGCCAGGTGTGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCAA
GACAGGCAGATCAGGAGGTCAGGAGATCGAGATCAGCCTGGCTAACACGGTAAAACCCCATCTCTAC
TAAAAATACAAAAAATTAGCCAGGCGTGGTGGCACACACCTGTAGTCCCAGGTACTCGGGAGGCTGA
AGCAGGAGAATCGCTTGAAACCAGGAGGCCGAGGTTGCAGTGAGCCAAGATTGCGCCACTGCACTGC
AGCCTGGGCGACAGAGCGAGACGCCATTTCAAAAAAAAAAAAAAAATCAAGGTCAGGGGGGAAGTGG
GAAGACTGAAATAGATAAAGGATTCTAAAGAGATATAACAGTCAAATGCGACACATGAAACCCTGAC
CAGATAAAAATTAAAAACCCATAAAATACATGTTTGAAGTCATAGAGTAATCTGACTTGGACTAGACA
TGTGATATATGTGAGGCTTGTGATCTTCCCAGGAGTGATGGTAGCACAGCACAGGGCAGAGACCCGTC
CATGGAAGAAACACTGGTGCTAGTGCCCAGGGCAGAAGTGAGTGATGTCTTTAAGTGGATATGGAAA
AATATTAACTATTCTACCTAGGTTGTGGGTGTATGGATATTTAGTATTCAATTATTCCAATTTCTCTGTG
TATGTATACATATTTTTTTTAGAGACAGGGTCTCACTCTGTCGACCACACTGGAGTAGGGGGTACAATC
ATAGCTCACTGTACATACTCAAGTGATCCTTCTGCCTCAGCCTCCTGAGCAGATGGGACTACAGGTGT
GCAGCATCATGGCCCAGTTTTTTTTTTTTTGGTAGAGATGGGTTTTGCTAGCCGGGAGCAGTGGCTCAT
GCCTGTAATCCTAGCACTTTGGGAGGCTGAGGCGGGCAGATCATCTGAGGTCAGGAGTTCAAGACCAG
CCTGGGCAACATGGTAAAACCCTGTCTCTACTAAAAACACAAAAATTAGCCAGGCATGATGGCAGGC
GCCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCAGGAGGCAGAGGTTG
CAGCAAGCTAAGATTGAGCCACTGCACTCCAGCCTGGGCAACAGAGCAAAAACTCCGTCTCAAAAAA

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AGTGATCCTCCTGCCTCAGCCTCCCAAAGTGCTGGGATGATAGGCATGAGCCACCGTGCCTGACCCCT
CTGTATATTTTTAGAATTTCATGTTAAAAGATGGAAAAGTCTGGATGAGGTAGTTCACGCCTGTCTTCC
CAGCTCTTTGGGAGGCCAAGGTGGGAAGACTGCTTGAAGCCAGACGTTCAAGACCAACTTGGCCAAC
ATAGTGAGACCCCGCTTTTTTCTAACTAAAAAAATTTTTTTCCAAGTTGGAAAAAATATCTAGCCATAA
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GGATCATGAGGTTAGGAGTTCAAGACCAGCCTGGCCAGCATGGTGAAACCCGTCTCTACTAAAAATAC
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CATTTAATTTTCTCATTTAATTAATGAGATAAATTAATGTATCTCATTTAATTTTCACAACAACCTCATG
CAGTAGGTGTAACTGTCACCCTCATTTCAGAGAGCAGAATACTGAGAGCTGGAGGCCAAGGGGCAAT
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CTGGTCTGCAGGGATGGTGTCCTGGGCAGAAAGAATAGCAAGTGCCAGGGCTGTGCTGGGGCCGGGC
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TGGGGATGTCAGAACTTAACTAACCACTGCTCCTTCTGTGTGTATGTTTTTCCTCCAGCCTACCTTATGT
TCAGTATTTTGGAGGTGTCTCTGCTCTAAGTAAACAACAGTTTCTAACCATCAATGGATTTCCTAATAA
TTATTGGGGCTGGGGAGGAGAAGATGATGACATTTTTAACAGGTAATGGTCATAACTTAGATATCTTT
CTCCTCTGTCAACCTTCACTTCCAGTTTTTTAACCAATGCTTGGTTGTTCCCCAAGGACTGACCCTCAGA
TGGGATGCACCCCTAGTCAGCCCACATTCTTAGGTGTGGCTTCCTACAGGTCCTGCAGGTGCTAAAAG
GGATCTGTAGGAAAATGAGTTTCTGAGATTTTTGTATTGGCCTGGAAAAATGTCAAATGGGAACCAAG
TGACGGGGCAAGTTTACTTTGACTTGCTGCATGCCGTTTTGTACTCAAGGAGTAAACCAATGTCCTTTG
TAAAAATCCCTCCTTTCATTATGGTCCCCTTTCACTGTGAAACAAGTTTCCTTGAGCAGAATCCTAACT
GTCTTCACAGAAGCTTTGTGTTATATTTTTATTTTGGAGTATTTTCACATATACAAAAGAGATACTGTA
GTATAATAAACCTTTGAGGACCTATCCAGCCCCAGCAACCATTATGGCCTGGTCAGTTCTGTCCCATCC
ACATCCTGGGGCTCTTTTTAAGCTGGTAAATCATTATGATGTGGGTTGTCATTTACAGTGGTAAAAAAC
ATCTATCAGTAGCATTTGAAAGAACATTCTGCTCAGTCCTCTGGCTGTAGAGGCTTCAACCCCACCAGC
CACCGATGAGCACCTTCTCCCTCCAGGAGCCAGTCTGAGCTCATTACTGAGTTTAATATCAGAATACA
CCCTGGTGCAGCCTTTCTAAATTGCAGTACCAGTTAACAGAAGGTGTCTGTCAGAGCAACACCCAAGT
CATTCAAGTTACCATTGTGTGCAAACTTAACAGAGACCCACGTCTTCAATATAAGCCTTGAAGGAAAC
TCCAGTTTTAGTATGTAGATGGGGTATCAAGTGTGTGCACATTGAACATCTGCTGCATACAGAGCACT
GTGCCAGGCAGGCCCAGGACACTGAAAACCTGGACATAGGGTCCAGACAGAAGCAAGCCTGCTTCCA
CAGAGGCACTCCTGGGCAGACACTCTGGACTGATATGACAGTGTGCAGGGCCGACAGGATACCACAG
GTCTGAATGGTCAGAACAGCTGGGGAGGGAGGGAGCATCCGCAGGCATCTAGTCCCATGCTAACGCA
GTGGCACTAGAAGGATGGGTGGTGTGTGGAGCAACTTTCTTGAAAGATAAAGGACCTAACACTTTCTA
TGCACCACTTACTGTGTGCCAGGCAAGGCCAGGAATGTTTAAGTGGTCTGGGATCAGCCAGTTCTGCC
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ACAGAATCCTCCACCCTGTTCTGGCTGCCTCTAGTCTTGTTCTCAGCCCTCCATTTGTTTTTTTCTGCCTT
TTCCCACATGTTCTGAAGCCCTCCATTCGTATACTACTTTCCAGAGACTTCCCCATGGCTAAAAGCATT
TTGGAAATACTGTATATTAGGCCCCTTTCAGATACTGGCAACCGTTTGTGGGATGCTCTGAGAAGGCCT
CTGTGACTTAGCCTGGCCCTTTTCAGCCCATCACCTGCCACGTCCTACCCCAGACCCTTGTCACCAGTC
CCCAGGAGCTTACGTTGCTCCCTGAGGGCACTAGGCTTGCTCTCACTTCCATGCCTTTGCCTGTGCCAT
CCTGGCTGCCCAAAATGCTATGGCAGATACCTGTTCATCCTCAACTGGGCTCTGCCTAGGCTTGCTCCA
GCAGAGGTTACAAACTCTATGCTTCTTCCTCTGTGTCTCCAACCTCATCTTCCTCTTCTCACCTCCATCC
TGGCCCTAAAGGCCCTATGTTTGAAGCATTCACACTGTATATTCTGTGGGGCACACGGCCCCAGTGTCT
GGCACATGGTAGTCAACACCACAAACCGCAGAACCAGTTGTAAAAGGACATGGAGTCGGAATGTGAG
TTTTAACCAGGGTCATGCTGGGCTGGGTTCTGGCATGATGCTGGGTTGTGGGCTGAGTGAGAACAGCA
AGGGTGATGGTGGATGGAGCAACAGTCTTGCAGCCGGGGCTCTCAGGCCAAGTGTATGGCAGCTCTGT
GATAATGACTTTCCCTTTACTCTTTGCAGATTAGTTTTTAGAGGCATGTCTATATCTCGCCCAAATGCTG
TGGTCGGGAGGTGTCGCATGATCCGCCACTCAAGAGACAAGAAAAATGAACCCAATCCTCAGAGGTG
CATTCTTTGTTTATTCATACTCCTTCCCCCTTTAGGATGAGGTAGGCTGCAGGTCCGAGGCTCTGGGCC
TAGAGGGAAATTGAGGTGGTCAGGTTACAGTGGAGAGGGAGGAGGAAGTACGTGTGATGATTTCTTC
TTAAGATTTTTGTTTTAAGACAATCTCCTTGTGCTCTTTTCCTTGTAGGTTTGACCGAATTGCACACACA
AAGGAGACAATGCTCTCTGATGGTTTGAACTCACTCACCTACCAGGTGCTGGATGTACAGAGATACCC
ATTGTATACCCAAATCACAGTGGACATCGGGACACCGAGCTAGCGTTTTGGTACACGGATAAGAGACC
TGAAATTAGCCAGGGACCTCTGCTGTGTGTCTCTGCCAATCTGCTGGGCTGGTCCCTCTCATTTTTACC
AGTCTGAGTGACAGGTCCCCTTCGCTCATCATTCAGATGGCTTTCCAGATGACCAGGACGAGTGGGAT
ATTTTGCCCCCAACTTGGCTCGGCATGTGAATTCTTAGCTCTGCAAGGTGTTTATGCCTTTGCGGGTTTC
TTGATGTGTTCGCAGTGTCACCCCAGAGTCAGAACTGTACACATCCCAAAATTTGGTGGCCGTGGAAC
ACATTCCCGGTGATAGAATTGCTAAATTGTCGTGAAATAGGTTAGAATTTTTCTTTAAATTATGGTTTT
CTTATTCGTGAAAATTCGGAGAGTGCTGCTAAAATTGGATTGGTGTGATCTTTTTGGTAGTTGTAATTT
AACAGAAAAACACAAAATTTCAACCATTCTTAATGTTACGTCCTCCCCCCACCCCCTTCTTTCAGTGGT
ATGCAACCACTGCAATCACTGTGCATATGTCTTTTCTTAGCAAAAGGATTTTAAAACTTGAGCCCTGGA
CCTTTTGTCCTATGTGTGTGGATTCCAGGGCAACTCTAGCATCAGAGCAAAAGCCTTGGGTTTCTCGCA
TTCAGTGGCCTATCTCCAGATTGTCTGATTTCTGAATGTAAAGTTGTTGTGTTTTTTTTTAAATAGTAGT
TTGTAGTATTTTAAAGAAAGAACAGATCGAGTTCTAATTATGATCTAGCTTGATTTTGTGTTGATCCAA
ATTTGCATAGCTGTTTAATGTTAAGTCATGACAATTTATTTTTCTTGGCATGCTATGTAAACTTGAATTT
CCTATGTATTTTTATTGTGGTGTTTTAAATATGGGGAGGGGTATTGAGCATTTTTTAGGGAGAAAAATA
AATATATGCTGTAGTGGCCACAAATAGGCCTATGATTTAGCTGGCAGGCCAGGTTTTCTCAAGAGCAA
AATCACCCTCTGGCCCCTTGGCAGGTAAGGCCTCCCGGTCAGCATTATCCTGCCAGACCTCGGGGAGG
ATACCTGGGAGACAGAAGCCTCTGCACCTACTGTGCAGAACTCTCCACTTCCCCAACCCTCCCCAGGT
GGGCAGGGCGGAGGGAGCCTCAGCCTCCTTAGACTGACCCCTCAGGCCCCTAGGCTGGGGGGTTGTA
AATAACAGCAGTCAGGTTGTTTACCAGCCCTTTGCACCTCCCCAGGCAGAGGGAGCCTCTGTTCTGGT
GGGGGCCACCTCCCTCAGAGGCTCTGCTAGCCACACTCCGTGGCCCACCCTTTGTTACCAGTTCTTCCT
CCTTCCTCTTTTCCCCTGCCTTTCTCATTCCTTCCTTCGTCTCCCTTTTTGTTCCTTTGCCTCTTGCCTGTC
CCCTAAAACTTGACTGTGGCACTCAGGGTCAAACAGACTATCCATTCCCCAGCATGAATGTGCCTTTTA
ATTAGTGATCTAGAAAGAAGTTCAGCCGAACCCACACCCCAACTCCCTCCCAAGAACTTCGGTGCCTA
AAGCCTCCTGTTCCACCTCAGGTTTTCACAGGTGCTCCCACCCCAGTTGAGGCTCCCACCCACAGGGCT
GTCTGTCACAAACCCACCTCTGTTGGGAGCTATTGAGCCACCTGGGATGAGATGACACAAGGCACTCC
TACCACTGAGCGCCTTTGCCAGGTCCAGCCTGGGCTCAGGTTCCAAGACTCAGCTGCCTAATCCCAGG
GTTGAGCCTTGTGCTCGTGGCGGACCCCAAACCACTGCCCTCCTGGGTACCAGCCCTCAGTGTGGAGG
CTGAGCTGGTGCCTGGCCCCAGTCTTATCTGTGCCTTTACTGCTTTGCGCATCTCAGATGCTAACTTGG
TTCTTTTTCCAGAAGCCTTTGTATTGGTTAAAAATTATTTTCCATTGCAGAAGCAGCTGGACTATGCAA
AAAGTATTTCTCTGTCAGTTCCCCACTCTATACCAAGGATATTATTAAAACTAGAAATGACTGCATTGA
GAGGGAGTTGTGGGAAATAAGAAGAATGAAAGCCTCTCTTTCTGTCCGCAGATCCTGACTTTTCCAAA
GTGCCTTAAAAGAAATCAGACAAATGCCCTGAGTGGTAACTTCTGTGTTATTTTACTCTTAAAACCAA
ACTCTACCTTTTCTTGTTGTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGTTACCTTCTCATTCATGTCAAGTA
TGTGGTTCATTCTTAGAACCAAGGGAAATACTGCTCCCCCCATTTGCTGACGTAGTGCTCTCATGGGCT
CACCTGGGCCCAAGGCACAGCCAGGGCACAGTTAGGCCTGGATGTTTGCCTGGTCCGTGAGATGCCGC
GGGTCCTGTTTCCTTACTGGGGATTTCAGGGCTGGGGGTTCAGGGAGCATTTCCTTTTCCTGGGAGTTA
TGACCGCGAAGTTGTCATGTGCCGTGCCCTTTTCTGTTTCTGTGTATCCTATTGCTGGTGACTCTGTGTG
AACTGGCCTTTGGGAAAGATCAGAGAGGGCAGAGGTGGCACAGGACAGTAAAGGAGATGCTGTGCTG
GCCTTCAGCCTGGACAGGGTCTCTGCTGACTGCCAGGGGCGGGGGCTCTGCATAGCCAGGATGACGGC
TTTCATGTCCCAGAGACCTGTTGTGCTGTGTATTTTGATTTCCTGTGTATGCAAATGTGTGTATTTACCA
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ATATAACGTGAATAAATGACCCTATCTTTGTAACTGCAGGTGGTTTCTGTTTGCCAGGTGTAAGGGTTG
TCATGGCTGTGGGATGGGGTGGGGACAGGGTCATTCCCTGGTCTGTGACCCATACAAATACACATGCC
TCCCTGGAATCAGACATTTCCCCATCTGAACTTCATTCTCTTATCTGTAAAATGGGAATAATAACACAT
AGGGACTTTTTTGAGGCTTAAAAGTGACGATATATGTAAAACAATGACTAATGCCTCACAAGTACTCA

CTACATAGTAGCTAGTGCCATTTCAAAGTAGAATTTTTTTCCCCTAGCAGTTCTTGGGCCACATTCTGC
TATTTTCAACAGATACCAGGATCATTCAGATGTAGATCTCAGGGCCATTTGCACCAGGTGCTCACAGT
GTAACTTGAAGGGAATTATCCAAAATGAGGTTTCTTGTCAGTCTCAGGAAATGTAACCATAAGCTCTA
AAAGGTCTTAGTTTTTACCCAGGTGCCTCCTCCTTGGTGGCCCTGGGTCAGGCTGGTTGGATTGAATTG
GCACTCCTGAAGAAGGGCTGCAGGAAACCAGTGAGCAGGAGAGCCACCCTTGGCAGGGAGCTGCAGG
CCCTGCCTGCATGTCACTGCTGGAGGGATCCCTGGTGACCTCAGGCCTGTGCAAAGGTGGCCTGGGGT
TCAGATCTGGCCTTCAAACAGGACAACTCTGGTCCTTTGGACAAAATGCTGCCTTAGAGGGTCTGACA
AAATTAAAAACAAACAAAAAAAAAACCTGTTTCTTTCCTTCTCACACACCACCACTCACAACACTTCAG
TTCTGCCCCTAGATATGTAGGGATTTCTCCCCACCAACAAGCAGTTTTCTAGTGGACACTAGCTGGGTG
TCCTACAGTTTAACTCAATTCTGACACTGTCTGCCTGGAGATAGCAACGGATCCCACAGGTTGAGGGC
TCAGTCTCACAAGACTGCCTCCACTGCAGATGCCAGTCACAAGTAGTTGGTTGTGACCTATGCTTTACA
AAAATGTTTTTTGGATACAGGGCCTTGCTGTGTCACCCAGGCTGGCCTGAAACTCCTGGGCTCACACA
ATCCTCCCGCCACAACTTAGAAGTAGCTGAGCTGCAGGTTTATACCACTCACCCAGCTATAGTTGTGA
CCTATACTTCTGACCAACCAGCTATAAATTGGGGTTTCTATGAGCCTCTTCTTGGGTTTAATTTGCTAG
GTCAGCTTACAGAACTCAGTGTAACACTTAACATTTACTGGTCTTATTATAAGTGATATTAGAAAGGAT
ACTGATGAAGAACCGGATGGAGAGATGCATAGGGCAAGGCATGGGGGAGGGGGAGAGAAGCTTCCA
TGCCCTCTCCAGGGGCTCCACCCTCCAGACACCTCCACGTGTTCAGCTATCTGGAAGCTCATCTGACCC
TGTCCTTCTGGTTTTTATGGAAGCTTCATCACATAGGCCTGATAGACTACATCATCGGCCATTGCCAGT
CAGCTCAACCTTCAGCCCTTTTCCCCTTCCTGAAGGATGGGAGTGGGACTGAAAGTGCCAACCTTCTCA
TCATGGCTTGGTCTTTCTGGTGACCAGTCCCCATCCAGGAGTTCACTGAGAATCATTTCATTAAAACAA
AAGACGTTCCTATCACCCGGGAAATTCCAAGGGATTAGAAGCTCTGTCAGGAACCAGGGTCAAGCAC
CAAATATTAGAACAAAAGATTCTCCTAGCATAAATATTAGAACAAAAGATTCTCCTAGCATAAATATT
AGAACAAAAAATTCTCCTATTGCTCAGGAAATTATAAGAGTTTTAGGGGCTCTGTACCAGGAACCCAG
CGCAGAGGCCAAATATATATATTTTATTATCTCACAGTGCCACACAGGACTTTGCAAGCTGTCAGGTCT
GAGTGAGATGGAGCACACCAGTGAAAGGTTAAGTTCACCCTTTCACTGATGTGCTCCACTTCACTGAG
ACACATATCCACACAGACACACAGAGACACACACATCCACCCAGACGCACGCA

[00384] Following Table 1 provides oligonucleoside mRNA target sequences of HCII, ZPI and B4GALT1, together with the corresponding positions in transcripts NM_000185.4, NM_016186.3 and NM_001497.4, respectively.

Table 1

SEQ ID NO	Oligonucleoside mRNA target sequence 5' → 3'	Starting position on reference sequence	Reference sequence ID
SEQ ID NO: 3	GGUGAAUAAAUUCCCAGUGGAAA	946	NM_000185.4
SEQ ID NO: 4	AACUGCAUCUACUUCAAAGGAUC	920	NM_000185.4
SEQ ID NO: 5	CAACUGCAUCUACUUCAAAGGAU	919	NM_000185.4
SEQ ID NO: 6	AAGGGAGAGACCCAUGAACAAGU	557	NM_000185.4
SEQ ID NO: 7	UGGGUGAAUAAAUUCCCAGUGGA	944	NM_000185.4
SEQ ID NO: 8	CUUCAGGAGGAAUUUUGGGUACA	676	NM_000185.4
SEQ ID NO: 9	CAGCUGCCUGCUCUUCAUGGGAA	1501	NM_000185.4
SEQ ID NO: 10	CUCACCAAGGGCCUCAUAAAAGA	854	NM_000185.4
SEQ ID NO: 11	GACCUUUAUAUCCAGAAGCAGUU	716	NM_000185.4
SEQ ID NO: 12	CUCAACUGCAUCUACUUCAAAGG	917	NM_000185.4
SEQ ID NO: 13	AAGAGCCGGAUCCAGCGUCUUAA	407	NM_000185.4
SEQ ID NO: 14	GGAUCCAGCGUCUUAACAUCCUC	414	NM_000185.4
SEQ ID NO: 15	GGCAAAAAAGCAUGACAAACAGA	1191	NM_000185.4
SEQ ID NO: 16	UUCAGGAGGAAUUUUGGGUACAC	677	NM_000185.4

SEQ ID NO: 17	CACAACCACAACUUCCGGCUGAA	974	NM_000185.4
SEQ ID NO: 18	AUGGCAAAAAAGCAUGACAAACA	1189	NM_000185.4
SEQ ID NO: 19	GUGAAUAAAUUCCCAGUGGAAAU	947	NM_000185.4
SEQ ID NO: 20	GGGGGCAUCAGCAUGCUAAUUGU	1100	NM_000185.4
SEQ ID NO: 21	CAAAAAAGCAUGACAAACAGAAC	1193	NM_000185.4
SEQ ID NO: 22	GAGAGUAUUACUUUGCUGAGGCC	771	NM_000185.4
SEQ ID NO: 23	UUUGCCUUCAUCCACAAGGAUUU	991	NM_016186.3
SEQ ID NO: 24	GCUGCGAAAGAUCUCCAUGAGGC	756	NM_016186.3
SEQ ID NO: 25	AUGCUGGUGGUCCUCAUGGAGAA	1390	NM_016186.3
SEQ ID NO: 26	CUGCGAAAGAUCUCCAUGAGGCA	757	NM_016186.3
SEQ ID NO: 27	AAGUAUGAGAUGCAUGAGCUGCU	1531	NM_016186.3
SEQ ID NO: 28	CUGUUUGAUGAGAUUAAUCCUGA	1156	NM_016186.3
SEQ ID NO: 29	GAUGAGAUUAAUCCUGAAACCAA	1162	NM_016186.3
SEQ ID NO: 30	UUUGAUGAGAUUAAUCCUGAAAC	1159	NM_016186.3
SEQ ID NO: 31	UGAUGAGAUUAAUCCUGAAACCA	1161	NM_016186.3
SEQ ID NO: 32	UUGAUGAGAUUAAUCCUGAAACC	1160	NM_016186.3
SEQ ID NO: 33	AACUGUUUGAUGAGAUUAAUCCU	1154	NM_016186.3
SEQ ID NO: 34	AGUUUUGCCUUCAUCCACAAGGA	988	NM_016186.3
SEQ ID NO: 35	UGCGAAAGAUCUCCAUGAGGCAC	758	NM_016186.3
SEQ ID NO: 36	CAUGCUGGUGGUCCUCAUGGAGA	1389	NM_016186.3
SEQ ID NO: 37	UGCCUUCAUCCACAAGGAUUUUG	993	NM_016186.3
SEQ ID NO: 38	GCGAAAGAUCUCCAUGAGGCACG	759	NM_016186.3
SEQ ID NO: 39	CCUUCAUCCACAAGGAUUUUGAU	995	NM_016186.3
SEQ ID NO: 40	UGUUUGAUGAGAUUAAUCCUGAA	1157	NM_016186.3
SEQ ID NO: 41	UUUUGCCUUCAUCCACAAGGAUU	990	NM_016186.3
SEQ ID NO: 42	AAGAUCUCCAUGAGGCACGAUGG	763	NM_016186.3
SEQ ID NO: 443	CCUACCAAGGAAAUGCCACCAUG	1370	NM_016186.3
SEQ ID NO: 444	CGAAAGAUCUCCAUGAGGCACGA	760	NM_016186.3
SEQ ID NO: 445	CAAAAAAGCAUGACAAACAGAAC	1193	NM_000185.4
SEQ ID NO: 446	AAAAGCAUGACAAACAGAACUCG	1196	NM_000185.4
SEQ ID NO: 447	GUAAACUUGAAUUUCCUAUGUAU	2209	NM_001497.4
SEQ ID NO: 448	AACUUGAAUUUCCUAUGUAUUUU	2212	NM_001497.4

[00385] 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 and 485 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: 43	UUUCCACUGGGAAUUUAUUCACC	SEQ ID NO: 83	UGAAUAAAUUCCCAGUGGAAA	946-967	NM_000185.4
SEQ ID NO: 44	GAUCCUUUGAAGUAGAUGCAGUU	SEQ ID NO: 84	CUGCAUCUACUUCAAAGGAUC	920-941	NM_000185.4
SEQ ID NO: 45	AUCCUUUGAAGUAGAUGCAGUUG	SEQ ID NO: 85	ACUGCAUCUACUUCAAAGGAU	919-940	NM_000185.4
SEQ ID NO: 46	ACUUGUUCAUGGGUCUCUCCCUU	SEQ ID NO: 86	GGGAGAGACCCAUGAACAAGU	557-578	NM_000185.4
SEQ ID NO: 47	UCCACUGGGAAUUUAUUCACCCA	SEQ ID NO: 87	GGUGAAUAAAUUCCCAGUGGA	944-965	NM_000185.4
SEQ ID NO: 48	UGUACCCAAAAUUCCUCCUGAAG	SEQ ID NO: 88	UCAGGAGGAAUUUUGGGUACA	676-697	NM_000185.4
SEQ ID NO: 49	UUCCCAUGAAGAGCAGGCAGCUG	SEQ ID NO: 89	GCUGCCUGCUCUUCAUGGGAA	1501-1522	NM_000185.4
SEQ ID NO: 50	UCUUUUAUGAGGCCCUUGGUGAG	SEQ ID NO: 90	CACCAAGGGCCUCAUAAAAGA	854-875	NM_000185.4
SEQ ID NO: 51	AACUGCUUCUGGAUAUAAAGGUC	SEQ ID NO: 91	CCUUUAUAUCCAGAAGCAGUU	716-737	NM_000185.4
SEQ ID NO: 52	CCUUUGAAGUAGAUGCAGUUGAG	SEQ ID NO: 92	CAACUGCAUCUACUUCAAAGG	917-938	NM_000185.4
SEQ ID NO: 53	UUAAGACGCUGGAUCCGGCUCUU	SEQ ID NO: 93	GAGCCGGAUCCAGCGUCUUAA	407-428	NM_000185.4
SEQ ID NO: 54	GAGGAUGUUAAGACGCUGGAUCC	SEQ ID NO: 94	AUCCAGCGUCUUAACAUCCUC	414-435	NM_000185.4
SEQ ID NO: 55	UCUGUUUGUCAUGCUUUUUUGCC	SEQ ID NO: 95	CAAAAAAGCAUGACAAACAGA	1191-1212	NM_000185.4
SEQ ID NO: 56	GUGUACCCAAAAUUCCUCCUGAA	SEQ ID NO: 96	CAGGAGGAAUUUUGGGUACAC	677-698	NM_000185.4
SEQ ID NO: 57	UUCAGCCGGAAGUUGUGGUUGUG	SEQ ID NO: 97	CAACCACAACUUCCGGCUGAA	974-995	NM_000185.4
SEQ ID NO: 58	UGUUUGUCAUGCUUUUUUGCCAU	SEQ ID NO: 98	GGCAAAAAAGCAUGACAAACA	1189-1210	NM_000185.4
SEQ ID NO: 59	AUUUCCACUGGGAAUUUAUUCAC	SEQ ID NO: 99	GAAUAAAUUCCCAGUGGAAAU	947-968	NM_000185.4

SEQ ID NO: 60	ACAAUUAGCAUGCUG AUGCCCCC	SEQ ID NO: 100	GGGCAUCAGCAUG CUAAUUGU	1100-1121	NM_000185.4
SEQ ID NO: 61	GUUCUGUUUGUCAUG CUUUUUUG	SEQ ID NO: 101	AAAAAGCAUGACA AACAGAAC	1193-1214	NM_000185.4
SEQ ID NO: 62	GGCCUCAGCAAAGUA AUACUCUC	SEQ ID NO: 102	GAGUAUUACUUUG CUGAGGCC	771-792	NM_000185.4
SEQ ID NO: 63	AAAUCCUUGUGGAUG AAGGCAAA	SEQ ID NO: 103	UGCCUUCAUCCAC AAGGAUUU	991-1012	NM_016186.3
SEQ ID NO: 64	GCCUCAUGGAGAUCU UUCGCAGC	SEQ ID NO: 104	UGCGAAAGAUCUC CAUGAGGC	756-777	NM_016186.3
SEQ ID NO: 65	UUCUCCAUGAGGACC ACCAGCAU	SEQ ID NO: 105	GCUGGUGGUCCUC AUGGAGAA	1390-1411	NM_016186.3
SEQ ID NO: 66	UGCCUCAUGGAGAUC UUUCGCAG	SEQ ID NO: 106	GCGAAAGAUCUCC AUGAGGCA	757-778	NM_016186.3
SEQ ID NO: 67	AGCAGCUCAUGCAUC UCAUACUU	SEQ ID NO: 107	GUAUGAGAUGCAU GAGCUGCU	1531-1552	NM_016186.3
SEQ ID NO: 68	UCAGGAUUAAUCUCA UCAAACAG	SEQ ID NO: 108	GUUUGAUGAGAUU AAUCCUGA	1156-1177	NM_016186.3
SEQ ID NO: 69	UUGGUUUCAGGAUUA AUCUCAUC	SEQ ID NO: 109	UGAGAUUAAUCCU GAAACCAA	1162-1183	NM_016186.3
SEQ ID NO: 70	GUUUCAGGAUUAAUC UCAUCAAA	SEQ ID NO: 110	UGAUGAGAUUAAU CCUGAAAC	1159-1180	NM_016186.3
SEQ ID NO: 71	UGGUUUCAGGAUUAA UCUCAUCA	SEQ ID NO: 111	AUGAGAUUAAUCC UGAAACCA	1161-1182	NM_016186.3
SEQ ID NO: 72	GGUUUCAGGAUUAAU CUCAUCAA	SEQ ID NO: 112	GAUGAGAUUAAUC CUGAAACC	1160-1181	NM_016186.3
SEQ ID NO: 73	AGGAUUAAUCUCAUC AAACAGUU	SEQ ID NO: 113	CUGUUUGAUGAGA UUAAUCCU	1154-1175	NM_016186.3
SEQ ID NO: 74	UCCUUGUGGAUGAAG GCAAAACU	SEQ ID NO: 114	UUUUGCCUUCAUC CACAAGGA	988-1009	NM_016186.3
SEQ ID NO: 75	GUGCCUCAUGGAGAU CUUUCGCA	SEQ ID NO: 115	CGAAAGAUCUCCA UGAGGCAC	758-779	NM_016186.3
SEQ ID NO: 76	UCUCCAUGAGGACCA CCAGCAUG	SEQ ID NO: 116	UGCUGGUGGUCCU CAUGGAGA	1389-1410	NM_016186.3
SEQ ID NO: 77	CAAAAUCCUUGUGGA UGAAGGCA	SEQ ID NO: 117	CCUUCAUCCACAA GGAUUUUG	993-1014	NM_016186.3
SEQ ID NO: 78	CGUGCCUCAUGGAGA UCUUUCGC	SEQ ID NO: 118	GAAAGAUCUCCAU GAGGCACG	759-780	NM_016186.3
SEQ ID NO: 79	AUCAAAAUCCUUGUG GAUGAAGG	SEQ ID NO: 119	UUCAUCCACAAGG AUUUUGAU	995-1016	NM_016186.3

SEQ ID NO: 80	UUCAGGAUUAAUCUCAUCAAACA	SEQ ID NO: 120	UUUGAUGAGAUUAAUCCUGAA	1157-1178	NM_016186.3
SEQ ID NO: 81	AAUCCUUGUGGAUGAAGGCAAAA	SEQ ID NO: 121	UUGCCUUCAUCCACAAGGAUU	990-1011	NM_016186.3
SEQ ID NO: 82	CCAUCGUGCCUCAUGGAGAUCUU	SEQ ID NO: 122	GAUCUCCAUGAGGCACGAUGG	763-784	NM_016186.3
SEQ ID NO: 449	CAUGGUGGCAUUUCCUUGGUAGG	SEQ ID NO: 455	UACCAAGGAAAUGCCACCAUG	1370-1391	NM_016186.3
SEQ ID NO: 450	UCGUGCCUCAUGGAGAUCUUUCG	SEQ ID NO: 456	AAAGAUCUCCAUGAGGCACGA	760-781	NM_016186.3
SEQ ID NO: 451	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 457	AAAAAGCAUGACAAACAGAAC	1193-1214	NM_000185.4
SEQ ID NO: 452	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 458	AAGCAUGACAAACAGAACUCG	1196-1217	NM_000185.4
SEQ ID NO: 453	AUACAUAGGAAAUUCAAGUUUAC	SEQ ID NO: 459	AAACUUGAAUUUCCUAUGUAU	2209-2230	NM_001497.4
SEQ ID NO: 454	AAAAUACAUAGGAAAUUCAAGUU	SEQ ID NO: 460	CUUGAAUUUCCUAUGUAUUUU	2212-2233	NM_001497.4

[00386] 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)
ETXS472	UmsUfsUmCfCmAfCmUfGfGmGmAmAmUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 123	UUUCCACUGGGAAUUUAUUCACC	SEQ ID NO: 43
ETXS474	GmsAfsUmCfCmUfUmUfGfAmAmGmUmAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 124	GAUCCUUUGAAGUAGAUGCAGUU	SEQ ID NO: 44
ETXS476	AmsUfsCmCfUmUfUmGfAfAmGmUmAmGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 125	AUCCUUUGAAGUAGAUGCAGUUG	SEQ ID NO: 45
ETXS478	AmsCfsUmUfGmUfUmCfAfUmGmGmGmUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 126	ACUUGUUCAUGGGUCUCUCCCUU	SEQ ID NO: 46

ETXS480	UmsCfsCmAfCmUfGmGfGfAmAmUmU mUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 127	UCCACUGGGAAUUUAU UCACCCA	SEQ ID NO: 47
ETXS482	UmsGfsUmAfCmCfCmAfAfAmAmUmU mCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 128	UGUACCCAAAAUUCCU CCUGAAG	SEQ ID NO: 48
ETXS484	UmsUfsCmCfCmAfUmGfAfAmGmAmG mCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 129	UUCCCAUGAAGAGCAG GCAGCUG	SEQ ID NO: 49
ETXS486	UmsCfsUmUfUmUfAmUfGfAmGmGmC mCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 130	UCUUUUAUGAGGCCCU UGGUGAG	SEQ ID NO: 50
ETXS488	AmsAfsCmUfGmCfUmUfCfUmGmGmA mUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 131	AACUGCUUCUGGAUAU AAAGGUC	SEQ ID NO: 51
ETXS490	CmsCfsUmUfUmGfAmAfGfUmAmGmA mUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 132	CCUUUGAAGUAGAUGC AGUUGAG	SEQ ID NO: 52
ETXS492	UmsUfsAmAfGmAfCmGfCfUmGmGmA mUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 133	UUAAGACGCUGGAUCC GGCUCUU	SEQ ID NO: 53
ETXS494	GmsAfsGmGfAmUfGmUfUfAmAmGmA mCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 134	GAGGAUGUUAAGACGC UGGAUCC	SEQ ID NO: 54
ETXS496	UmsCfsUmGfUmUfUmGfUfCmAmUmG mCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 135	UCUGUUUGUCAUGCUU UUUUGCC	SEQ ID NO: 55
ETXS498	GmsUfsGmUfAmCfCmCfAfAmAmAmU mUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 136	GUGUACCCAAAAUUCC UCCUGAA	SEQ ID NO: 56
ETXS500	UmsUfsCmAfGmCfCmGfGfAmAmGmU mUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 137	UUCAGCCGGAAGUUGU GGUUGUG	SEQ ID NO: 57
ETXS502	UmsGfsUmUfUmGfUmCfAfUmGmCmU mUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 138	UGUUUGUCAUGCUUUU UUGCCAU	SEQ ID NO: 58
ETXS504	AmsUfsUmUfCmCfAmCfUfGmGmGmA mAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 139	AUUUCCACUGGGAAUU UAUUCAC	SEQ ID NO: 59
ETXS506	AmsCfsAmAfUmUfAmGfCfAmUmGmC mUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 140	ACAAUUAGCAUGCUGA UGCCCCC	SEQ ID NO: 60
ETXS508	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 141	GUUCUGUUUGUCAUGC UUUUUUG	SEQ ID NO: 61
ETXS510	GmsGfsCmCfUmCfAmGfCfAmAmAmG mUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 142	GGCCUCAGCAAAGUAA UACUCUC	SEQ ID NO: 62
ETXS512	UmsUfsUmCfCmAfCmUfGfGmGmAmA mUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 143	UUUCCACUGGGAAUUU AUUCACC	SEQ ID NO: 43
ETXS514	GmsAfsUmCfCmUfUmUfGfAmAmGmU mAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 144	GAUCCUUUGAAGUAGA UGCAGUU	SEQ ID NO: 44
ETXS516	AmsUfsCmCfUmUfUmGfAfAmGmUmA mGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 145	AUCCUUUGAAGUAGAU GCAGUUG	SEQ ID NO: 45
ETXS518	AmsCfsUmUfGmUfUmCfAfUmGmGmG mUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 146	ACUUGUUCAUGGGUCU CUCCCUU	SEQ ID NO: 46

ETXS520	UmsCfsCmAfCmUfGmGfGfAmAmUmU mUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 147	UCCACUGGGAAUUUAU UCACCCA	SEQ ID NO: 47
ETXS522	UmsGfsUmAfCmCfCmAfAfAmAmUmU mCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 148	UGUACCCAAAAUUCCU CCUGAAG	SEQ ID NO: 48
ETXS524	UmsUfsCmCfCmAfUmGfAfAmGmAmG mCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 149	UUCCCAUGAAGAGCAG GCAGCUG	SEQ ID NO: 49
ETXS526	UmsCfsUmUfUmUfAmUfGfAmGmGmC mCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 150	UCUUUUAUGAGGCCCU UGGUGAG	SEQ ID NO: 50
ETXS528	AmsAfsCmUfGmCfUmUfCfUmGmGmA mUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 151	AACUGCUUCUGGAUAU AAAGGUC	SEQ ID NO: 51
ETXS530	CmsCfsUmUfUmGfAmAfGfUmAmGmA mUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 152	CCUUUGAAGUAGAUGC AGUUGAG	SEQ ID NO: 52
ETXS532	UmsUfsAmAfGmAfCmGfCfUmGmGmA mUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 153	UUAAGACGCUGGAUCC GGCUCUU	SEQ ID NO: 53
ETXS534	GmsAfsGmGfAmUfGmUfUfAmAmGmA mCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 154	GAGGAUGUUAAGACGC UGGAUCC	SEQ ID NO: 54
ETXS536	UmsCfsUmGfUmUfUmGfUfCmAmUmG mCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 155	UCUGUUUGUCAUGCUU UUUUGCC	SEQ ID NO: 55
ETXS538	GmsUfsGmUfAmCfCmCfAfAmAmAmU mUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 156	GUGUACCCAAAAUUCC UCCUGAA	SEQ ID NO: 56
ETXS540	UmsUfsCmAfGmCfCmGfGfAmAmGmU mUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 157	UUCAGCCGGAAGUUGU GGUUGUG	SEQ ID NO: 57
ETXS542	UmsGfsUmUfUmGfUmCfAfUmGmCmU mUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 158	UGUUUGUCAUGCUUUU UUGCCAU	SEQ ID NO: 58
ETXS544	AmsUfsUmUfCmCfAmCfUfGmGmGmA mAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 159	AUUUCCACUGGGAAUU UAUUCAC	SEQ ID NO: 59
ETXS546	AmsCfsAmAfUmUfAmGfCfAmUmGmC mUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 160	ACAAUUAGCAUGCUGA UGCCCCC	SEQ ID NO: 60
ETXS548	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 161	GUUCUGUUUGUCAUGC UUUUUUG	SEQ ID NO: 61
ETXS550	GmsGfsCmCfUmCfAmGfCfAmAmAmG mUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 162	GGCCUCAGCAAAGUAA UACUCUC	SEQ ID NO: 62
ETXS552	UmsUfsUmCfCmAfCmUfGfGmGmAmA mUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 163	UUUCCACUGGGAAUUU AUUCACC	SEQ ID NO: 43
ETXS554	GmsAfsUmCfCmUfUmUfGfAmAmGmU mAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 164	GAUCCUUUGAAGUAGA UGCAGUU	SEQ ID NO: 44
ETXS556	AmsUfsCmCfUmUfUmGfAfAmGmUmA mGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 165	AUCCUUUGAAGUAGAU GCAGUUG	SEQ ID NO: 45
ETXS558	AmsCfsUmUfGmUfUmCfAfUmGmGmG mUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 166	ACUUGUUCAUGGGUCU CUCCCUU	SEQ ID NO: 46

ETXS560	UmsCfsCmAfCmUfGmGfGfAmAmUmU mUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 167	UCCACUGGGAAUUUAU UCACCCA	SEQ ID NO: 47
ETXS562	UmsGfsUmAfCmCfCmAfAfAmAmUmU mCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 168	UGUACCCAAAAUUCCU CCUGAAG	SEQ ID NO: 48
ETXS564	UmsUfsCmCfCmAfUmGfAfAmGmAmG mCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 169	UUCCCAUGAAGAGCAG GCAGCUG	SEQ ID NO: 49
ETXS566	UmsCfsUmUfUmUfAmUfGfAmGmGmC mCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 170	UCUUUUAUGAGGCCCU UGGUGAG	SEQ ID NO: 50
ETXS568	AmsAfsCmUfGmCfUmUfCfUmGmGmA mUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 171	AACUGCUUCUGGAUAU AAAGGUC	SEQ ID NO: 51
ETXS570	CmsCfsUmUfUmGfAmAfGfUmAmGmA mUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 172	CCUUUGAAGUAGAUGC AGUUGAG	SEQ ID NO: 52
ETXS572	UmsUfsAmAfGmAfCmGfCfUmGmGmA mUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 173	UUAAGACGCUGGAUCC GGCUCUU	SEQ ID NO: 53
ETXS574	GmsAfsGmGfAmUfGmUfUfAmAmGmA mCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 174	GAGGAUGUUAAGACGC UGGAUCC	SEQ ID NO: 54
ETXS576	UmsCfsUmGfUmUfUmGfUfCmAmUmG mCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 175	UCUGUUUGUCAUGCUU UUUUGCC	SEQ ID NO: 55
ETXS578	GmsUfsGmUfAmCfCmCfAfAmAmAmU mUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 176	GUGUACCCAAAAUUCC UCCUGAA	SEQ ID NO: 56
ETXS580	UmsUfsCmAfGmCfCmGfGfAmAmGmU mUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 177	UUCAGCCGGAAGUUGU GGUUGUG	SEQ ID NO: 57
ETXS582	UmsGfsUmUfUmGfUmCfAfUmGmCmU mUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 178	UGUUUGUCAUGCUUUU UUGCCAU	SEQ ID NO: 58
ETXS584	AmsUfsUmUfCmCfAmCfUfGmGmGmA mAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 179	AUUUCCACUGGGAAUU UAUUCAC	SEQ ID NO: 59
ETXS586	AmsCfsAmAfUmUfAmGfCfAmUmGmC mUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 180	ACAAUUAGCAUGCUGA UGCCCCC	SEQ ID NO: 60
ETXS588	GmsUfsUmCfUmGfUmUfUfGmUmCmA mUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 181	GUUCUGUUUGUCAUGC UUUUUUG	SEQ ID NO: 61
ETXS590	GmsGfsCmCfUmCfAmGfCfAmAmAmG mUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 182	GGCCUCAGCAAAGUAA UACUCUC	SEQ ID NO: 62
ETXS592	UmsUfsUmCfCmAfCmUmGmGmGmAm AmUfUmUfAmUmUmCmAmsCmsCm	SEQ ID NO: 183	UUUCCACUGGGAAUUU AUUCACC	SEQ ID NO: 43
ETXS594	GmsAfsUmCfCmUfUmUmGmAmAmGm UmAfGmAfUmGmCmAmGmsUmsUm	SEQ ID NO: 184	GAUCCUUUGAAGUAGA UGCAGUU	SEQ ID NO: 44
ETXS596	AmsUfsCmCfUmUfUmGmAmAmGmUm AmGfAmUfGmCmAmGmUmsUmsGm	SEQ ID NO: 185	AUCCUUUGAAGUAGAU GCAGUUG	SEQ ID NO: 45
ETXS598	AmsCfsUmUfGmUfUmCmAmUmGmGm GmUfCmUfCmUmCmCmCmsUmsUm	SEQ ID NO: 186	ACUUGUUCAUGGGUCU CUCCCUU	SEQ ID NO: 46

ETXS600	UmsCfsCmAfCmUfGmGmGmAmAmUm UmUfAmUfUmCmAmCmCmsCmsAm	SEQ ID NO: 187	UCCACUGGGAAUUUAU UCACCCA	SEQ ID NO: 47
ETXS602	UmsGfsUmAfCmCfCmAmAmAmAmUm UmCfCmUfCmCmUmGmAmsAmsGm	SEQ ID NO: 188	UGUACCCAAAAUUCCU CCUGAAG	SEQ ID NO: 48
ETXS604	UmsUfsCmCfCmAfUmGmAmAmGmAm GmCfAmGfGmCmAmGmCmsUmsGm	SEQ ID NO: 189	UUCCCAUGAAGAGCAG GCAGCUG	SEQ ID NO: 49
ETXS606	UmsCfsUmUfUmUfAmUmGmAmGmG mCmCfCmUfUmGmGmUmGmsAmsGm	SEQ ID NO: 190	UCUUUUAUGAGGCCCU UGGUGAG	SEQ ID NO: 50
ETXS608	AmsAfsCmUfGmCfUmUmCmUmGmGm AmUfAmUfAmAmAmGmGmsUmsCm	SEQ ID NO: 191	AACUGCUUCUGGAUAU AAAGGUC	SEQ ID NO: 51
ETXS610	CmsCfsUmUfUmGfAmAmGmUmAmGm AmUfGmCfAmGmUmUmGmsAmsGm	SEQ ID NO: 192	CCUUUGAAGUAGAUGC AGUUGAG	SEQ ID NO: 52
ETXS612	UmsUfsAmAfGmAfCmGmCmUmGmGm AmUfCmCfGmGmCmUmCmsUmsUm	SEQ ID NO: 193	UUAAGACGCUGGAUCC GGCUCUU	SEQ ID NO: 53
ETXS614	GmsAfsGmGfAmUfGmUmUmAmAmG mAmCfGmCfUmGmGmAmUmsCmsCm	SEQ ID NO: 194	GAGGAUGUUAAGACGC UGGAUCC	SEQ ID NO: 54
ETXS616	UmsCfsUmGfUmUfUmGmUmCmAmUm GmCfUmUfUmUmUmUmGmsCmsCm	SEQ ID NO: 195	UCUGUUUGUCAUGCUU UUUUGCC	SEQ ID NO: 55
ETXS618	GmsUfsGmUfAmCfCmCmAmAmAmAm UmUfCmCfUmCmCmUmGmsAmsAm	SEQ ID NO: 196	GUGUACCCAAAAUUCC UCCUGAA	SEQ ID NO: 56
ETXS620	UmsUfsCmAfGmCfCmGmGmAmAmGm UmUfGmUfGmGmUmUmGmsUmsGm	SEQ ID NO: 197	UUCAGCCGGAAGUUGU GGUUGUG	SEQ ID NO: 57
ETXS622	UmsGfsUmUfUmGfUmCmAmUmGmCm UmUfUmUfUmUmGmCmCmsAmsUm	SEQ ID NO: 198	UGUUUGUCAUGCUUUU UUGCCAU	SEQ ID NO: 58
ETXS624	AmsUfsUmUfCmCfAmCmUmGmGmGm AmAfUmUfUmAmUmUmCmsAmsCm	SEQ ID NO: 199	AUUUCCACUGGGAAUU UAUUCAC	SEQ ID NO: 59
ETXS626	AmsCfsAmAfUmUfAmGmCmAmUmGm CmUfGmAfUmGmCmCmCmsCmsCm	SEQ ID NO: 200	ACAAUUAGCAUGCUGA UGCCCCC	SEQ ID NO: 60
ETXS628	GmsUfsUmCfUmGfUmUmUmGmUmCm AmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 201	GUUCUGUUUGUCAUGC UUUUUUG	SEQ ID NO: 61
ETXS630	GmsGfsCmCfUmCfAmGmCmAmAmAm GmUfAmAfUmAmCmUmCmsUmsCm	SEQ ID NO: 202	GGCCUCAGCAAAGUAA UACUCUC	SEQ ID NO: 62
ETXS872	AmsAfsAmUfCmCfUmUfGfUmGmGmA mUfGmAfAmGmGmCmAmsAmsAm	SEQ ID NO: 203	AAAUCCUUGUGGAUGA AGGCAAA	SEQ ID NO: 63
ETXS874	GmsCfsCmUfCmAfUmGfGfAmGmAmU mCfUmUfUmCmGmCmAmsGmsCm	SEQ ID NO: 204	GCCUCAUGGAGAUCUU UCGCAGC	SEQ ID NO: 64
ETXS876	UmsUfsCmUfCmCfAmUfGfAmGmGmA mCfCmAfCmCmAmGmCmsAmsUm	SEQ ID NO: 205	UUCUCCAUGAGGACCA CCAGCAU	SEQ ID NO: 65
ETXS878	UmsGfsCmCfUmCfAmUfGfGmAmGmA mUfCmUfUmUmCmGmCmsAmsGm	SEQ ID NO: 206	UGCCUCAUGGAGAUCU UUCGCAG	SEQ ID NO: 66

ETXS880	AmsGfsCmAfGmCfUmCfAfUmGmCmA mUfCmUfCmAmUmAmCmsUmsUm	SEQ ID NO: 207	AGCAGCUCAUGCAUCU CAUACUU	SEQ ID NO: 67
ETXS882	UmsCfsAmGfGmAfUmUfAfAmUmCmU mCfAmUfCmAmAmAmCmsAmsGm	SEQ ID NO: 208	UCAGGAUUAAUCUCAU CAAACAG	SEQ ID NO: 68
ETXS884	UmsUfsGmGfUmUfUmCfAfGmGmAmU mUfAmAfUmCmUmCmAmsUmsCm	SEQ ID NO: 209	UUGGUUUCAGGAUUAA UCUCAUC	SEQ ID NO: 69
ETXS886	GmsUfsUmUfCmAfGmGfAfUmUmAmA mUfCmUfCmAmUmCmAmsAmsAm	SEQ ID NO: 210	GUUUCAGGAUUAAUCU CAUCAAA	SEQ ID NO: 70
ETXS888	UmsGfsGmUfUmUfCmAfGfGmAmUmU mAfAmUfCmUmCmAmUmsCmsAm	SEQ ID NO: 211	UGGUUUCAGGAUUAAU CUCAUCA	SEQ ID NO: 71
ETXS890	GmsGfsUmUfUmCfAmGfGfAmUmUmA mAfUmCfUmCmAmUmCmsAmsAm	SEQ ID NO: 212	GGUUUCAGGAUUAAUC UCAUCAA	SEQ ID NO: 72
ETXS892	AmsGfsGmAfUmUfAmAfUfCmUmCmA mUfCmAfAmAmCmAmGmsUmsUm	SEQ ID NO: 213	AGGAUUAAUCUCAUCA AACAGUU	SEQ ID NO: 73
ETXS894	UmsCfsCmUfUmGfUmGfGfAmUmGmA mAfGmGfCmAmAmAmAmsCmsUm	SEQ ID NO: 214	UCCUUGUGGAUGAAGG CAAAACU	SEQ ID NO: 74
ETXS896	GmsUfsGmCfCmUfCmAfUfGmGmAmG mAfUmCfUmUmUmCmGmsCmsAm	SEQ ID NO: 215	GUGCCUCAUGGAGAUC UUUCGCA	SEQ ID NO: 75
ETXS898	UmsCfsUmCfCmAfUmGfAfGmGmAmC mCfAmCfCmAmGmCmAmsUmsGm	SEQ ID NO: 216	UCUCCAUGAGGACCAC CAGCAUG	SEQ ID NO: 76
ETXS900	CmsAfsAmAfAmUfCmCfUfUmGmUmG mGfAmUfGmAmAmGmGmsCmsAm	SEQ ID NO: 217	CAAAAUCCUUGUGGAU GAAGGCA	SEQ ID NO: 77
ETXS902	CmsGfsUmGfCmCfUmCfAfUmGmGmA mGfAmUfCmUmUmUmCmsGmsCm	SEQ ID NO: 218	CGUGCCUCAUGGAGAU CUUUCGC	SEQ ID NO: 78
ETXS904	AmsUfsCmAfAmAfAmUfCfCmUmUmG mUfGmGfAmUmGmAmAmsGmsGm	SEQ ID NO: 219	AUCAAAAUCCUUGUGG AUGAAGG	SEQ ID NO: 79
ETXS906	UmsUfsCmAfGmGfAmUfUfAmAmUmC mUfCmAfUmCmAmAmAmsCmsAm	SEQ ID NO: 220	UUCAGGAUUAAUCUCA UCAAACA	SEQ ID NO: 80
ETXS908	AmsAfsUmCfCmUfUmGfUfGmGmAmU mGfAmAfGmGmCmAmAmsAmsAm	SEQ ID NO: 221	AAUCCUUGUGGAUGAA GGCAAAA	SEQ ID NO: 81
ETXS910	CmsCfsAmUfCmGfUmGfCfCmUmCmA mUfGmGfAmGmAmUmCmsUmsUm	SEQ ID NO: 222	CCAUCGUGCCUCAUGG AGAUCUU	SEQ ID NO: 82
ETXS912	AmsAfsAmUfCmCfUmUfGfUmGmGmA mUfGmAfAmGmGmCmAmsAmsAm	SEQ ID NO: 223	AAAUCCUUGUGGAUGA AGGCAAA	SEQ ID NO: 63
ETXS914	GmsCfsCmUfCmAfUmGfGfAmGmAmU mCfUmUfUmCmGmCmAmsGmsCm	SEQ ID NO: 224	GCCUCAUGGAGAUCUU UCGCAGC	SEQ ID NO: 64
ETXS916	UmsUfsCmUfCmCfAmUfGfAmGmGmA mCfCmAfCmCmAmGmCmsAmsUm	SEQ ID NO: 225	UUCUCCAUGAGGACCA CCAGCAU	SEQ ID NO: 65
ETXS918	UmsGfsCmCfUmCfAmUfGfGmAmGmA mUfCmUfUmUmCmGmCmsAmsGm	SEQ ID NO: 226	UGCCUCAUGGAGAUCU UUCGCAG	SEQ ID NO: 66

ETXS920	AmsGfsCmAfGmCfUmCfAfUmGmCmAmUfCmUfCmAmUmAmCmsUmsUm	SEQ ID NO: 227	AGCAGCUCAUGCAUCUCAUACUU	SEQ ID NO: 67
ETXS922	UmsCfsAmGfGmAfUmUfAfAmUmCmUmCfAmUfCmAmAmAmCmsAmsGm	SEQ ID NO: 228	UCAGGAUUAAUCUCAUCAAACAG	SEQ ID NO: 68
ETXS924	UmsUfsGmGfUmUfUmCfAfGmGmAmUmUfAmAfUmCmUmCmAmsUmsCm	SEQ ID NO: 229	UUGGUUUCAGGAUUAAUCUCAUC	SEQ ID NO: 69
ETXS926	GmsUfsUmUfCmAfGmGfAfUmUmAmAmUfCmUfCmAmUmCmAmsAmsAm	SEQ ID NO: 230	GUUUCAGGAUUAAUCUCAUCAAA	SEQ ID NO: 70
ETXS928	UmsGfsGmUfUmUfCmAfGfGmAmUmUmAfAmAfUmCmUmCmAmUmsCmsAm	SEQ ID NO: 231	UGGUUUCAGGAUUAAUCUCAUCA	SEQ ID NO: 71
ETXS930	GmsGfsUmUfUmCfAmGfGfAmUmUmAmAfUmCfUmCmAmUmCmsAmsAm	SEQ ID NO: 232	GGUUUCAGGAUUAAUCUCAUCAA	SEQ ID NO: 72
ETXS932	AmsGfsGmAfUmUfAmAfUfCmUmCmAmUfCmAfAmAmCmAmGmsUmsUm	SEQ ID NO: 233	AGGAUUAAUCUCAUCAAACAGUU	SEQ ID NO: 73
ETXS934	UmsCfsCmUfUmGfUmGfGfAmUmGmAmAfGmGfCmAmAmAmAmsCmsUm	SEQ ID NO: 234	UCCUUGUGGAUGAAGGCAAAACU	SEQ ID NO: 74
ETXS936	GmsUfsGmCfCmUfCmAfUfGmGmAmGmAfUmCfUmUmUmCmGmsCmsAm	SEQ ID NO: 235	GUGCCUCAUGGAGAUCUUUCGCA	SEQ ID NO: 75
ETXS938	UmsCfsUmCfCmAfUmGfAfGmGmAmCmCfAmCfCmAmGmCmAmsUmsGm	SEQ ID NO: 236	UCUCCAUGAGGACCACCAGCAUG	SEQ ID NO: 76
ETXS940	CmsAfsAmAfAmUfCmCfUfUmGmUmGmGfAmUfGmAmAmGmGmsCmsAm	SEQ ID NO: 237	CAAAAUCCUUGUGGAUGAAGGCA	SEQ ID NO: 77
ETXS942	CmsGfsUmGfCmCfUmCfAfUmGmGmAmGfAmUfCmUmUmUmCmsGmsCm	SEQ ID NO: 238	CGUGCCUCAUGGAGAUCUUUCGC	SEQ ID NO: 78
ETXS944	AmsUfsCmAfAmAfAmUfCfCmUmUmGmUfGmGfAmUmGmAmAmsGmsGm	SEQ ID NO: 239	AUCAAAAUCCUUGUGGAUGAAGG	SEQ ID NO: 79
ETXS946	UmsUfsCmAfGmGfAmUfUfAmAmUmCmUfCmAfUmCmAmAmAmsCmsAm	SEQ ID NO: 240	UUCAGGAUUAAUCUCAUCAAACA	SEQ ID NO: 80
ETXS948	AmsAfsUmCfCmUfUmGfUfGmGmAmUmGfAmAfGmGmCmAmAmsAmsAm	SEQ ID NO: 241	AAUCCUUGUGGAUGAAGGCAAAA	SEQ ID NO: 81
ETXS950	CmsCfsAmUfCmGfUmGfCfCmUmCmAmUfGmGfAmGmAmUmCmsUmsUm	SEQ ID NO: 242	CCAUCGUGCCUCAUGGAGAUCUU	SEQ ID NO: 82
ETXS952	AmsAfsAmUfCmCfUmUfGfUmGmGmAmUfGmAfAmGmGmCmAmsAmsAm	SEQ ID NO: 243	AAAUCCUUGUGGAUGAAGGCAAA	SEQ ID NO: 63
ETXS954	GmsCfsCmUfCmAfUmGfGfAmGmAmUmCfUmUfUmCmGmCmAmsGmsCm	SEQ ID NO: 244	GCCUCAUGGAGAUCUUUCGCAGC	SEQ ID NO: 64
ETXS956	UmsUfsCmUfCmCfAmUfGfAmGmGmAmCfCmAfCmCmAmGmCmsAmsUm	SEQ ID NO: 245	UUCUCCAUGAGGACCACCAGCAU	SEQ ID NO: 65
ETXS958	UmsGfsCmCfUmCfAmUfGfGmAmGmAmUfCmUfUmUmCmGmCmsAmsGm	SEQ ID NO: 246	UGCCUCAUGGAGAUCUUUCGCAG	SEQ ID NO: 66

ETXS960	AmsGfsCmAfGmCfUmCfAfUmGmCmA mUfCmUfCmAmUmAmCmsUmsUm	SEQ ID NO: 247	AGCAGCUCAUGCAUCU CAUACUU	SEQ ID NO: 67
ETXS962	UmsCfsAmGfGmAfUmUfAfAmUmCmU mCfAmUfCmAmAmAmCmsAmsGm	SEQ ID NO: 248	UCAGGAUUAAUCUCAU CAAACAG	SEQ ID NO: 68
ETXS964	UmsUfsGmGfUmUfUmCfAfGmGmAmU mUfAmAfUmCmUmCmAmsUmsCm	SEQ ID NO: 249	UUGGUUUCAGGAUUAA UCUCAUC	SEQ ID NO: 69
ETXS966	GmsUfsUmUfCmAfGmGfAfUmUmAmA mUfCmUfCmAmUmCmAmsAmsAm	SEQ ID NO: 250	GUUUCAGGAUUAAUCU CAUCAAA	SEQ ID NO: 70
ETXS968	UmsGfsGmUfUmUfCmAfGfGmAmUmU mAfAmUfCmUmCmAmUmsCmsAm	SEQ ID NO: 251	UGGUUUCAGGAUUAAU CUCAUCA	SEQ ID NO: 71
ETXS970	GmsGfsUmUfUmCfAmGfGfAmUmUmA mAfUmCfUmCmAmUmCmsAmsAm	SEQ ID NO: 252	GGUUUCAGGAUUAAUC UCAUCAA	SEQ ID NO: 72
ETXS972	AmsGfsGmAfUmUfAmAfUfCmUmCmA mUfCmAfAmAmCmAmGmsUmsUm	SEQ ID NO: 253	AGGAUUAAUCUCAUCA AACAGUU	SEQ ID NO: 73
ETXS974	UmsCfsCmUfUmGfUmGfGfAmUmGmA mAfGmGfCmAmAmAmAmsCmsUm	SEQ ID NO: 254	UCCUUGUGGAUGAAGG CAAAACU	SEQ ID NO: 74
ETXS976	GmsUfsGmCfCmUfCmAfUfGmGmAmG mAfUmCfUmUmUmCmGmsCmsAm	SEQ ID NO: 255	GUGCCUCAUGGAGAUC UUUCGCA	SEQ ID NO: 75
ETXS978	UmsCfsUmCfCmAfUmGfAfGmGmAmC mCfAmCfCmAmGmCmAmsUmsGm	SEQ ID NO: 256	UCUCCAUGAGGACCAC CAGCAUG	SEQ ID NO: 76
ETXS980	CmsAfsAmAfAmUfCmCfUfUmGmUmG mGfAmUfGmAmAmGmGmsCmsAm	SEQ ID NO: 257	CAAAAUCCUUGUGGAU GAAGGCA	SEQ ID NO: 77
ETXS982	CmsGfsUmGfCmCfUmCfAfUmGmGmA mGfAmUfCmUmUmUmCmsGmsCm	SEQ ID NO: 258	CGUGCCUCAUGGAGAU CUUUCGC	SEQ ID NO: 78
ETXS984	AmsUfsCmAfAmAfAmUfCfCmUmUmG mUfGmGfAmUmGmAmAmsGmsGm	SEQ ID NO: 259	AUCAAAAUCCUUGUGG AUGAAGG	SEQ ID NO: 79
ETXS986	UmsUfsCmAfGmGfAmUfUfAmAmUmC mUfCmAfUmCmAmAmAmsCmsAm	SEQ ID NO: 260	UUCAGGAUUAAUCUCA UCAAACA	SEQ ID NO: 80
ETXS988	AmsAfsUmCfCmUfUmGfUfGmGmAmU mGfAmAfGmGmCmAmAmsAmsAm	SEQ ID NO: 261	AAUCCUUGUGGAUGAA GGCAAAA	SEQ ID NO: 81
ETXS990	CmsCfsAmUfCmGfUmGfCfCmUmCmA mUfGmGfAmGmAmUmCmsUmsUm	SEQ ID NO: 262	CCAUCGUGCCUCAUGG AGAUCUU	SEQ ID NO: 82
ETXS992	AmsAfsAmUfCmCfUmUmGmUmGmGm AmUfGmAfAmGmGmCmAmsAmsAm	SEQ ID NO: 263	AAAUCCUUGUGGAUGA AGGCAAA	SEQ ID NO: 63
ETXS994	GmsCfsCmUfCmAfUmGmGmAmGmAm UmCfUmUfUmCmGmCmAmsGmsCm	SEQ ID NO: 264	GCCUCAUGGAGAUCUU UCGCAGC	SEQ ID NO: 64
ETXS996	UmsUfsCmUfCmCfAmUmGmAmGmGm AmCfCmAfCmCmAmGmCmsAmsUm	SEQ ID NO: 265	UUCUCCAUGAGGACCA CCAGCAU	SEQ ID NO: 65
ETXS998	UmsGfsCmCfUmCfAmUmGmGmAmGm AmUfCmUfUmUmCmGmCmsAmsGm	SEQ ID NO: 266	UGCCUCAUGGAGAUCU UUCGCAG	SEQ ID NO: 66

ETXS1000	AmsGfsCmAfGmCfUmCmAmUmGmCmAmUfCmUfCmAmUmAmCmsUmsUm	SEQ ID NO: 267	AGCAGCUCAUGCAUCUCAUACUU	SEQ ID NO: 67
ETXS1002	UmsCfsAmGfGmAfUmUmAmAmUmCmUmCfAmUfCmAmAmAmCmsAmsGm	SEQ ID NO: 268	UCAGGAUUAAUCUCAUCAAACAG	SEQ ID NO: 68
ETXS1004	UmsUfsGmGfUmUfUmCmAmGmGmAmUmUfAmAfUmCmUmCmAmsUmsCm	SEQ ID NO: 269	UUGGUUUCAGGAUUAAUCUCAUC	SEQ ID NO: 69
ETXS1006	GmsUfsUmUfCmAfGmGmAmUmUmAmAmUfCmUfCmAmUmCmAmsAmsAm	SEQ ID NO: 270	GUUUCAGGAUUAAUCUCAUCAAA	SEQ ID NO: 70
ETXS1008	UmsGfsGmUfUmUfCmAmGmGmAmUmUmAfAmUfCmUmCmAmUmsCmsAm	SEQ ID NO: 271	UGGUUUCAGGAUUAAUCUCAUCA	SEQ ID NO: 71
ETXS1010	GmsGfsUmUfUmCfAmGmGmAmUmUmAmAfUmCfUmCmAmUmCmsAmsAm	SEQ ID NO: 272	GGUUUCAGGAUUAAUCUCAUCAA	SEQ ID NO: 72
ETXS1012	AmsGfsGmAfUmUfAmAmUmCmUmCmAmUfCmAfAmAmCmAmGmsUmsUm	SEQ ID NO: 273	AGGAUUAAUCUCAUCAAACAGUU	SEQ ID NO: 73
ETXS1014	UmsCfsCmUfUmGfUmGmGmAmUmGmAmAfGmGfCmAmAmAmAmsCmsUm	SEQ ID NO: 274	UCCUUGUGGAUGAAGGCAAAACU	SEQ ID NO: 74
ETXS1016	GmsUfsGmCfCmUfCmAmUmGmGmAmGmAfUmCfUmUmUmCmGmsCmsAm	SEQ ID NO: 275	GUGCCUCAUGGAGAUCUUUCGCA	SEQ ID NO: 75
ETXS1018	UmsCfsUmCfCmAfUmGmAmGmGmAmCmCfAmCfCmAmGmCmAmsUmsGm	SEQ ID NO: 276	UCUCCAUGAGGACCACCAGCAUG	SEQ ID NO: 76
ETXS1020	CmsAfsAmAfAmUfCmCmUmUmGmUmGmGfAmUfGmAmAmGmGmsCmsAm	SEQ ID NO: 277	CAAAAUCCUUGUGGAUGAAGGCA	SEQ ID NO: 77
ETXS1022	CmsGfsUmGfCmCfUmCmAmUmGmGmAmGfAmUfCmUmUmUmCmsGmsCm	SEQ ID NO: 278	CGUGCCUCAUGGAGAUCUUUCGC	SEQ ID NO: 78
ETXS1024	AmsUfsCmAfAmAfAmUmCmCmUmUmGmUfGmGfAmUmGmAmAmsGmsGm	SEQ ID NO: 279	AUCAAAAUCCUUGUGGAUGAAGG	SEQ ID NO: 79
ETXS1026	UmsUfsCmAfGmGfAmUmUmAmAmUmCmUfCmAfUmCmAmAmAmsCmsAm	SEQ ID NO: 280	UUCAGGAUUAAUCUCAUCAAACA	SEQ ID NO: 80
ETXS1028	AmsAfsUmCfCmUfUmGmUmGmGmAmUmGfAmAfGmGmCmAmAmsAmsAm	SEQ ID NO: 281	AAUCCUUGUGGAUGAAGGCAAAA	SEQ ID NO: 81
ETXS1030	CmsCfsAmUfCmGfUmGmCmCmUmCmAmUfGmGfAmGmAmUmCmsUmsUm	SEQ ID NO: 282	CCAUCGUGCCUCAUGGAGAUCUU	SEQ ID NO: 82
ETXS1036	CmsAfsUmGfGmUfGmGmCmAmUmUmUmCfCmUfUmGmGmUmAmsGmsGm	SEQ ID NO: 461	CAUGGUGGCAUUUCCUUGGUAGG	SEQ ID NO: 449
ETXS2398	CmsAfsUmGmGmUfGmGmCfAmUmUmUmCfCmUfUmGmGmUmAmsGmsGm	SEQ ID NO: 462	CAUGGUGGCAUUUCCUUGGUAGG	SEQ ID NO: 449
ETXS1040	UmsCfsGmUfGmCfCmUmCmAmUmGmGmAfGmAfUmCmUmUmUmsCmsGm	SEQ ID NO: 463	UCGUGCCUCAUGGAGAUCUUUCG	SEQ ID NO: 450
ETXS2416	UmsCfsGmUmGmCfCmUmCfAmUmGmGmAfGmAfUmCmUmUmUmsCmsGm	SEQ ID NO: 464	UCGUGCCUCAUGGAGAUCUUUCG	SEQ ID NO: 450

ETXS636	GmsUfsUmCfUmGfUmUmUmGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 465	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 451
ETXS2434	GmsUfsUmCmUmGfUmUmUfGmUmCmAmUfGmCfUmUmUmUmUmsUmsGm	SEQ ID NO: 466	GUUCUGUUUGUCAUGCUUUUUUG	SEQ ID NO: 451
ETXS644	CmsGfsAmGfUmUfCmUmGmUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 467	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 452
ETXS2452	CmsGfsAmGmUmUfCmUmGfUmUmUmGmUfCmAfUmGmCmUmUmsUmsUm	SEQ ID NO: 468	CGAGUUCUGUUUGUCAUGCUUUU	SEQ ID NO: 452
ETXS2400	AmsUfsAmCfAmUfAmGmGmAmAmAmUmUfCmAfAmGmUmUmUmsAmsCm	SEQ ID NO: 469	AUACAUAGGAAAUUCAAGUUUAC	SEQ ID NO: 453
ETXS2402	AmsUfsAmCmAmUfAmGmGfAmAmAmUmUfCmAfAmGmUmUmUmsAmsCm	SEQ ID NO: 470	AUACAUAGGAAAUUCAAGUUUAC	SEQ ID NO: 453
ETXS2406	AmsAfsAmAfUmAfCmAmUmAmGmGmAmAfAmUfAmGmUmCmAmAmGmsUmsUm	SEQ ID NO: 471	AAAAUACAUAGGAAAUUCAAGUU	SEQ ID NO: 454
ETXS2408	AmsAfsAmAmUmAfCmAmUfAmGmGmAmAfAmUfAmGmUmCmAmAmGmsUmsUm	SEQ ID NO: 472	AAAAUACAUAGGAAAUUCAAGUU	SEQ ID NO: 454

[00387] 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)
ETXS471	UmsGmsAmAmUmAmAfAfUfUfCfCmCmAmGmUmGmGmAfAmAm	SEQ ID NO: 283	UGAAUAAAUUCCCAGUGGAAA	SEQ ID NO: 83
ETXS473	CmsUmsGmCmAmUmCfUfAfCfUfUmCmAmAmAmGmGmAfUmCm	SEQ ID NO: 284	CUGCAUCUACUUCAAAGGAUC	SEQ ID NO: 84
ETXS475	AmsCmsUmGmCmAmUfCfUfAfCfUmUmCmAmAmAmGmGfAmUm	SEQ ID NO: 285	ACUGCAUCUACUUCAAAGGAU	SEQ ID NO: 85
ETXS477	GmsGmsGmAmGmAmGfAfCfCfCfAmUmGmAmAmCmAmAfGmUm	SEQ ID NO: 286	GGGAGAGACCCAUGAACAAGU	SEQ ID NO: 86
ETXS479	GmsGmsUmGmAmAmUfAfAfAfUfUmCmCmCmAmGmUmGfGmAm	SEQ ID NO: 287	GGUGAAUAAAUUCCCAGUGGA	SEQ ID NO: 87

ETXS481	UmsCmsAmGmGmAmGfGfAfAfUfUmU mUmGmGmGmUmAfCmAm	SEQ ID NO: 288	UCAGGAGGAAUUUUGG GUACA	SEQ ID NO: 88
ETXS483	GmsCmsUmGmCmCmUfGfCfUfCfUmU mCmAmUmGmGmGfAmAm	SEQ ID NO: 289	GCUGCCUGCUCUUCAU GGGAA	SEQ ID NO: 89
ETXS485	CmsAmsCmCmAmAmGfGfGfCfCfUmC mAmUmAmAmAmAfGmAm	SEQ ID NO: 290	CACCAAGGGCCUCAUA AAAGA	SEQ ID NO: 90
ETXS487	CmsCmsUmUmUmAmUfAfUfCfCfAmG mAmAmGmCmAmGfUmUm	SEQ ID NO: 291	CCUUUAUAUCCAGAAG CAGUU	SEQ ID NO: 91
ETXS489	CmsAmsAmCmUmGmCfAfUfCfUfAmC mUmUmCmAmAmAfGmGm	SEQ ID NO: 292	CAACUGCAUCUACUUC AAAGG	SEQ ID NO: 92
ETXS491	GmsAmsGmCmCmGmGfAfUfCfCfAmG mCmGmUmCmUmUfAmAm	SEQ ID NO: 293	GAGCCGGAUCCAGCGU CUUAA	SEQ ID NO: 93
ETXS493	AmsUmsCmCmAmGmCfGfUfCfUfUmA mAmCmAmUmCmCfUmCm	SEQ ID NO: 294	AUCCAGCGUCUUAACA UCCUC	SEQ ID NO: 94
ETXS495	CmsAmsAmAmAmAmAfGfCfAfUfGmA mCmAmAmAmCmAfGmAm	SEQ ID NO: 295	CAAAAAAGCAUGACAA ACAGA	SEQ ID NO: 95
ETXS497	CmsAmsGmGmAmGmGfAfAfUfUfUmU mGmGmGmUmAmCfAmCm	SEQ ID NO: 296	CAGGAGGAAUUUUGGG UACAC	SEQ ID NO: 96
ETXS499	CmsAmsAmCmCmAmCfAfAfCfUfUmC mCmGmGmCmUmGfAmAm	SEQ ID NO: 297	CAACCACAACUUCCGG CUGAA	SEQ ID NO: 97
ETXS501	GmsGmsCmAmAmAmAfAfAfGfCfAmU mGmAmCmAmAmAfCmAm	SEQ ID NO: 298	GGCAAAAAAGCAUGAC AAACA	SEQ ID NO: 98
ETXS503	GmsAmsAmUmAmAmAfUfUfCfCfCmA mGmUmGmGmAmAfAmUm	SEQ ID NO: 299	GAAUAAAUUCCCAGUG GAAAU	SEQ ID NO: 99
ETXS505	GmsGmsGmCmAmUmCfAfGfCfAfUmG mCmUmAmAmUmUfGmUm	SEQ ID NO: 300	GGGCAUCAGCAUGCUA AUUGU	SEQ ID NO: 100
ETXS507	AmsAmsAmAmAmGmCfAfUfGfAfCmA mAmAmCmAmGmAfAmCm	SEQ ID NO: 301	AAAAAGCAUGACAAAC AGAAC	SEQ ID NO: 101
ETXS509	GmsAmsGmUmAmUmUfAfCfUfUfUmG mCmUmGmAmGmGfCmCm	SEQ ID NO: 302	GAGUAUUACUUUGCUG AGGCC	SEQ ID NO: 102
ETXS511	UmsGmsAmAmUmAfAfAmUfUfCfCfC mAmGmUmGmGmAmAmAm	SEQ ID NO: 303	UGAAUAAAUUCCCAGU GGAAA	SEQ ID NO: 83
ETXS513	CmsUmsGmCmAmUfCfUmAfCfUfUfUfCm AmAmAmGmGmAmUmCm	SEQ ID NO: 304	CUGCAUCUACUUCAAA GGAUC	SEQ ID NO: 84
ETXS515	AmsCmsUmGmCmAfUfCmUfAfCfUfU mCmAmAmAmGmGmAmUm	SEQ ID NO: 305	ACUGCAUCUACUUCAA AGGAU	SEQ ID NO: 85
ETXS517	GmsGmsGmAmGmAfGfAmCfCfCfAfU mGmAmAmCmAmAmGmUm	SEQ ID NO: 306	GGGAGAGACCCAUGAA CAAGU	SEQ ID NO: 86
ETXS519	GmsGmsUmGmAmAfUfAmAfAfUfUfC mCmCmAmGmUmGmGmAm	SEQ ID NO: 307	GGUGAAUAAAUUCCCA GUGGA	SEQ ID NO: 87

ETXS521	UmsCmsAmGmGmAfGfGmAfAfUfUfU mUmGmGmGmUmAmCmAm	SEQ ID NO: 308	UCAGGAGGAAUUUUGG GUACA	SEQ ID NO: 88
ETXS523	GmsCmsUmGmCmCfUfGmCfUfCfUfUm CmAmUmGmGmGmAmAm	SEQ ID NO: 309	GCUGCCUGCUCUUCAU GGGAA	SEQ ID NO: 89
ETXS525	CmsAmsCmCmAmAfGfGmGfCfCfUfCm AmUmAmAmAmAmGmAm	SEQ ID NO: 310	CACCAAGGGCCUCAUA AAAGA	SEQ ID NO: 90
ETXS527	CmsCmsUmUmUmAfUfAmUfCfCfAfG mAmAmGmCmAmGmUmUm	SEQ ID NO: 311	CCUUUAUAUCCAGAAG CAGUU	SEQ ID NO: 91
ETXS529	CmsAmsAmCmUmGfCfAmUfCfUfAfCm UmUmCmAmAmAmGmGm	SEQ ID NO: 312	CAACUGCAUCUACUUC AAAGG	SEQ ID NO: 92
ETXS531	GmsAmsGmCmCmGfGfAmUfCfCfAfG mCmGmUmCmUmUmAmAm	SEQ ID NO: 313	GAGCCGGAUCCAGCGU CUUAA	SEQ ID NO: 93
ETXS533	AmsUmsCmCmAmGfCfGmUfCfUfUfA mAmCmAmUmCmCmUmCm	SEQ ID NO: 314	AUCCAGCGUCUUAACA UCCUC	SEQ ID NO: 94
ETXS535	CmsAmsAmAmAmAfAfGmCfAfUfGfA mCmAmAmAmCmAmGmAm	SEQ ID NO: 315	CAAAAAAGCAUGACAA ACAGA	SEQ ID NO: 95
ETXS537	CmsAmsGmGmAmGfGfAmAfUfUfUfU mGmGmGmUmAmCmAmCm	SEQ ID NO: 316	CAGGAGGAAUUUUGGG UACAC	SEQ ID NO: 96
ETXS539	CmsAmsAmCmCmAfCfAmAfCfUfUfCm CmGmGmCmUmGmAmAm	SEQ ID NO: 317	CAACCACAACUUCCGG CUGAA	SEQ ID NO: 97
ETXS541	GmsGmsCmAmAmAfAfAmAfGfCfAfU mGmAmCmAmAmAmCmAm	SEQ ID NO: 318	GGCAAAAAAGCAUGAC AAACA	SEQ ID NO: 98
ETXS543	GmsAmsAmUmAmAfAfUmUfCfCfCfA mGmUmGmGmAmAmAmUm	SEQ ID NO: 319	GAAUAAAUUCCCAGUG GAAAU	SEQ ID NO: 99
ETXS545	GmsGmsGmCmAmUfCfAmGfCfAfUfG mCmUmAmAmUmUmGmUm	SEQ ID NO: 320	GGGCAUCAGCAUGCUA AUUGU	SEQ ID NO: 100
ETXS547	AmsAmsAmAmAmGfCfAmUfGfAfCfA mAmAmCmAmGmAmAmCm	SEQ ID NO: 321	AAAAAGCAUGACAAAC AGAAC	SEQ ID NO: 101
ETXS549	GmsAmsGmUmAmUfUfAmCfUfUfUfG mCmUmGmAmGmGmCmCm	SEQ ID NO: 322	GAGUAUUACUUUGCUG AGGCC	SEQ ID NO: 102
ETXS551	UmsGmsAmAmUmAmAfAmUfUfCfCfC mAmGmUmGmGmAmAmAm	SEQ ID NO: 323	UGAAUAAAUUCCCAGU GGAAA	SEQ ID NO: 83
ETXS553	CmsUmsGmCmAmUmCfUmAfCfUfUfC mAmAmAmGmGmAmUmCm	SEQ ID NO: 324	CUGCAUCUACUUCAAA GGAUC	SEQ ID NO: 84
ETXS555	AmsCmsUmGmCmAmUfCmUfAfCfUfU mCmAmAmAmGmGmAmUm	SEQ ID NO: 325	ACUGCAUCUACUUCAA AGGAU	SEQ ID NO: 85
ETXS557	GmsGmsGmAmGmAmGfAmCfCfCfAfU mGmAmAmCmAmAmGmUm	SEQ ID NO: 326	GGGAGAGACCCAUGAA CAAGU	SEQ ID NO: 86
ETXS559	GmsGmsUmGmAmAmUfAmAfAfUfUfC mCmCmAmGmUmGmGmAm	SEQ ID NO: 327	GGUGAAUAAAUUCCCA GUGGA	SEQ ID NO: 87

ETXS561	UmsCmsAmGmGmAmGfGmAfAfUfUfU mUmGmGmGmUmAmCmAm	SEQ ID NO: 328	UCAGGAGGAAUUUUGG GUACA	SEQ ID NO: 88
ETXS563	GmsCmsUmGmCmCmUfGmCfUfCfUfU mCmAmUmGmGmGmAmAm	SEQ ID NO: 329	GCUGCCUGCUCUUCAU GGGAA	SEQ ID NO: 89
ETXS565	CmsAmsCmCmAmAmGfGmGfCfCfUfC mAmUmAmAmAmAmGmAm	SEQ ID NO: 330	CACCAAGGGCCUCAUA AAAGA	SEQ ID NO: 90
ETXS567	CmsCmsUmUmUmAmUfAmUfCfCfAfG mAmAmGmCmAmGmUmUm	SEQ ID NO: 331	CCUUUAUAUCCAGAAG CAGUU	SEQ ID NO: 91
ETXS569	CmsAmsAmCmUmGmCfAmUfCfUfAfC mUmUmCmAmAmAmGmGm	SEQ ID NO: 332	CAACUGCAUCUACUUC AAAGG	SEQ ID NO: 92
ETXS571	GmsAmsGmCmCmGmGfAmUfCfCfAfG mCmGmUmCmUmUmAmAm	SEQ ID NO: 333	GAGCCGGAUCCAGCGU CUUAA	SEQ ID NO: 93
ETXS573	AmsUmsCmCmAmGmCfGmUfCfUfUfA mAmCmAmUmCmCmUmCm	SEQ ID NO: 334	AUCCAGCGUCUUAACA UCCUC	SEQ ID NO: 94
ETXS575	CmsAmsAmAmAmAmAfGmCfAfUfGfA mCmAmAmAmCmAmGmAm	SEQ ID NO: 335	CAAAAAAGCAUGACAA ACAGA	SEQ ID NO: 95
ETXS577	CmsAmsGmGmAmGmGfAmAfUfUfUfU mGmGmGmUmAmCmAmCm	SEQ ID NO: 336	CAGGAGGAAUUUUGGG UACAC	SEQ ID NO: 96
ETXS579	CmsAmsAmCmCmAmCfAmAfCfUfUfC mCmGmGmCmUmGmAmAm	SEQ ID NO: 337	CAACCACAACUUCCGG CUGAA	SEQ ID NO: 97
ETXS581	GmsGmsCmAmAmAmAfAmAfGfCfAfU mGmAmCmAmAmAmCmAm	SEQ ID NO: 338	GGCAAAAAAGCAUGAC AAACA	SEQ ID NO: 98
ETXS583	GmsAmsAmUmAmAmAfUmUfCfCfCfA mGmUmGmGmAmAmAmUm	SEQ ID NO: 339	GAAUAAAUUCCCAGUG GAAAU	SEQ ID NO: 99
ETXS585	GmsGmsGmCmAmUmCfAmGfCfAfUfG mCmUmAmAmUmUmGmUm	SEQ ID NO: 340	GGGCAUCAGCAUGCUA AUUGU	SEQ ID NO: 100
ETXS587	AmsAmsAmAmAmGmCfAmUfGfAfCfA mAmAmCmAmGmAmAmCm	SEQ ID NO: 341	AAAAAGCAUGACAAAC AGAAC	SEQ ID NO: 101
ETXS589	GmsAmsGmUmAmUmUfAmCfUfUfUfG mCmUmGmAmGmGmCmCm	SEQ ID NO: 342	GAGUAUUACUUUGCUG AGGCC	SEQ ID NO: 102
ETXS591	UmsGmsAmAmUmAmAfAmUfUfCfCfC mAmGmUmGmGmAmAmAm	SEQ ID NO: 343	UGAAUAAAUUCCCAGU GGAAA	SEQ ID NO: 83
ETXS593	CmsUmsGmCmAmUmCfUmAfCfUfUfC mAmAmAmGmGmAmUmCm	SEQ ID NO: 344	CUGCAUCUACUUCAAA GGAUC	SEQ ID NO: 84
ETXS595	AmsCmsUmGmCmAmUfCmUfAfCfUfU mCmAmAmAmGmGmAmUm	SEQ ID NO: 345	ACUGCAUCUACUUCAA AGGAU	SEQ ID NO: 85
ETXS597	GmsGmsGmAmGmAmGfAmCfCfCfAfU mGmAmAmCmAmAmGmUm	SEQ ID NO: 346	GGGAGAGACCCAUGAA CAAGU	SEQ ID NO: 86
ETXS599	GmsGmsUmGmAmAmUfAmAfAfUfUfC mCmCmAmGmUmGmGmAm	SEQ ID NO: 347	GGUGAAUAAAUUCCCA GUGGA	SEQ ID NO: 87

ETXS601	UmsCmsAmGmGmAmGfGmAfAfUfUfU mUmGmGmGmUmAmCmAm	SEQ ID NO: 348	UCAGGAGGAAUUUUGG GUACA	SEQ ID NO: 88
ETXS603	GmsCmsUmGmCmCmUfGmCfUfCfUfU mCmAmUmGmGmGmAmAm	SEQ ID NO: 349	GCUGCCUGCUCUUCAU GGGAA	SEQ ID NO: 89
ETXS605	CmsAmsCmCmAmAmGfGmGfCfCfUfC mAmUmAmAmAmAmGmAm	SEQ ID NO: 350	CACCAAGGGCCUCAUA AAAGA	SEQ ID NO: 90
ETXS607	CmsCmsUmUmUmAmUfAmUfCfCfAfG mAmAmGmCmAmGmUmUm	SEQ ID NO: 351	CCUUUAUAUCCAGAAG CAGUU	SEQ ID NO: 91
ETXS609	CmsAmsAmCmUmGmCfAmUfCfUfAfC mUmUmCmAmAmAmGmGm	SEQ ID NO: 352	CAACUGCAUCUACUUC AAAGG	SEQ ID NO: 92
ETXS611	GmsAmsGmCmCmGmGfAmUfCfCfAfG mCmGmUmCmUmUmAmAm	SEQ ID NO: 353	GAGCCGGAUCCAGCGU CUUAA	SEQ ID NO: 93
ETXS613	AmsUmsCmCmAmGmCfGmUfCfUfUfA mAmCmAmUmCmCmUmCm	SEQ ID NO: 354	AUCCAGCGUCUUAACA UCCUC	SEQ ID NO: 94
ETXS615	CmsAmsAmAmAmAmAfGmCfAfUfGfA mCmAmAmAmCmAmGmAm	SEQ ID NO: 355	CAAAAAAGCAUGACAA ACAGA	SEQ ID NO: 95
ETXS617	CmsAmsGmGmAmGmGfAmAfUfUfUfU mGmGmGmUmAmCmAmCm	SEQ ID NO: 356	CAGGAGGAAUUUUGGG UACAC	SEQ ID NO: 96
ETXS619	CmsAmsAmCmCmAmCfAmAfCfUfUfC mCmGmGmCmUmGmAmAm	SEQ ID NO: 357	CAACCACAACUUCCGG CUGAA	SEQ ID NO: 97
ETXS621	GmsGmsCmAmAmAmAfAmAfGfCfAfU mGmAmCmAmAmAmCmAm	SEQ ID NO: 358	GGCAAAAAAGCAUGAC AAACA	SEQ ID NO: 98
ETXS623	GmsAmsAmUmAmAmAfUmUfCfCfCfA mGmUmGmGmAmAmAmUm	SEQ ID NO: 359	GAAUAAAUUCCCAGUG GAAAU	SEQ ID NO: 99
ETXS625	GmsGmsGmCmAmUmCfAmGfCfAfUfG mCmUmAmAmUmUmGmUm	SEQ ID NO: 360	GGGCAUCAGCAUGCUA AUUGU	SEQ ID NO: 100
ETXS627	AmsAmsAmAmAmGmCfAmUfGfAfCfA mAmAmCmAmGmAmAmCm	SEQ ID NO: 361	AAAAAGCAUGACAAAC AGAAC	SEQ ID NO: 101
ETXS629	GmsAmsGmUmAmUmUfAmCfUfUfUfG mCmUmGmAmGmGmCmCm	SEQ ID NO: 362	GAGUAUUACUUUGCUG AGGCC	SEQ ID NO: 102
ETXS871	UmsGmsCmCmUmUmCfAfUfCfCfAmC mAmAmGmGmAmUfUmUm	SEQ ID NO: 363	UGCCUUCAUCCACAAG GAUUU	SEQ ID NO: 103
ETXS873	UmsGmsCmGmAmAmAfGfAfUfCfUmC mCmAmUmGmAmGfGmCm	SEQ ID NO: 364	UGCGAAAGAUCUCCAU GAGGC	SEQ ID NO: 104
ETXS875	GmsCmsUmGmGmUmGfGfUfCfCfUmC mAmUmGmGmAmGfAmAm	SEQ ID NO: 365	GCUGGUGGUCCUCAUG GAGAA	SEQ ID NO: 105
ETXS877	GmsCmsGmAmAmAmGfAfUfCfUfCmC mAmUmGmAmGmGfCmAm	SEQ ID NO: 366	GCGAAAGAUCUCCAUG AGGCA	SEQ ID NO: 106
ETXS879	GmsUmsAmUmGmAmGfAfUfGfCfAmU mGmAmGmCmUmGfCmUm	SEQ ID NO: 367	GUAUGAGAUGCAUGAG CUGCU	SEQ ID NO: 107

ETXS881	GmsUmsUmUmGmAmUfGfAfGfAfUmU mAmAmUmCmCmUfGmAm	SEQ ID NO: 368	GUUUGAUGAGAUUAAU CCUGA	SEQ ID NO: 108
ETXS883	UmsGmsAmGmAmUmUfAfAfUfCfCmU mGmAmAmAmCmCfAmAm	SEQ ID NO: 369	UGAGAUUAAUCCUGAA ACCAA	SEQ ID NO: 109
ETXS885	UmsGmsAmUmGmAmGfAfUfUfAfAmU mCmCmUmGmAmAfAmCm	SEQ ID NO: 370	UGAUGAGAUUAAUCCU GAAAC	SEQ ID NO: 110
ETXS887	AmsUmsGmAmGmAmUfUfAfAfUfCmC mUmGmAmAmAmCfCmAm	SEQ ID NO: 371	AUGAGAUUAAUCCUGA AACCA	SEQ ID NO: 111
ETXS889	GmsAmsUmGmAmGmAfUfUfAfAfUmC mCmUmGmAmAmAfCmCm	SEQ ID NO: 372	GAUGAGAUUAAUCCUG AAACC	SEQ ID NO: 112
ETXS891	CmsUmsGmUmUmUmGfAfUfGfAfGmA mUmUmAmAmUmCfCmUm	SEQ ID NO: 373	CUGUUUGAUGAGAUUA AUCCU	SEQ ID NO: 113
ETXS893	UmsUmsUmUmGmCmCfUfUfCfAfUmC mCmAmCmAmAmGfGmAm	SEQ ID NO: 374	UUUUGCCUUCAUCCAC AAGGA	SEQ ID NO: 114
ETXS895	CmsGmsAmAmAmGmAfUfCfUfCfCmA mUmGmAmGmGmCfAmCm	SEQ ID NO: 375	CGAAAGAUCUCCAUGA GGCAC	SEQ ID NO: 115
ETXS897	UmsGmsCmUmGmGmUfGfGfUfCfCmU mCmAmUmGmGmAfGmAm	SEQ ID NO: 376	UGCUGGUGGUCCUCAU GGAGA	SEQ ID NO: 116
ETXS899	CmsCmsUmUmCmAmUfCfCfAfCfAmA mGmGmAmUmUmUfUmGm	SEQ ID NO: 377	CCUUCAUCCACAAGGA UUUUG	SEQ ID NO: 117
ETXS901	GmsAmsAmAmGmAmUfCfUfCfCfAmU mGmAmGmGmCmAfCmGm	SEQ ID NO: 378	GAAAGAUCUCCAUGAG GCACG	SEQ ID NO: 118
ETXS903	UmsUmsCmAmUmCmCfAfCfAfAfGmG mAmUmUmUmUmGfAmUm	SEQ ID NO: 379	UUCAUCCACAAGGAUU UUGAU	SEQ ID NO: 119
ETXS905	UmsUmsUmGmAmUmGfAfGfAfUfUmA mAmUmCmCmUmGfAmAm	SEQ ID NO: 380	UUUGAUGAGAUUAAUC CUGAA	SEQ ID NO: 120
ETXS907	UmsUmsGmCmCmUmUfCfAfUfCfCmA mCmAmAmGmGmAfUmUm	SEQ ID NO: 381	UUGCCUUCAUCCACAA GGAUU	SEQ ID NO: 121
ETXS909	GmsAmsUmCmUmCmCfAfUfGfAfGmG mCmAmCmGmAmUfGmGm	SEQ ID NO: 382	GAUCUCCAUGAGGCAC GAUGG	SEQ ID NO: 122
ETXS911	UmsGmsCmCmUmUfCfAmUfCfCfAfCm AmAmGmGmAmUmUmUm	SEQ ID NO: 383	UGCCUUCAUCCACAAG GAUUU	SEQ ID NO: 103
ETXS913	UmsGmsCmGmAmAfAfGmAfUfCfUfC mCmAmUmGmAmGmGmCm	SEQ ID NO: 384	UGCGAAAGAUCUCCAU GAGGC	SEQ ID NO: 104
ETXS915	GmsCmsUmGmGmUfGfGmUfCfCfUfC mAmUmGmGmAmGmAmAm	SEQ ID NO: 385	GCUGGUGGUCCUCAUG GAGAA	SEQ ID NO: 105
ETXS917	GmsCmsGmAmAmAfGfAmUfCfUfCfC mAmUmGmAmGmGmCmAm	SEQ ID NO: 386	GCGAAAGAUCUCCAUG AGGCA	SEQ ID NO: 106
ETXS919	GmsUmsAmUmGmAfGfAmUfGfCfAfU mGmAmGmCmUmGmCmUm	SEQ ID NO: 387	GUAUGAGAUGCAUGAG CUGCU	SEQ ID NO: 107

ETXS921	GmsUmsUmUmGmAfUfGmAfGfAfUfU mAmAmUmCmCmUmGmAm	SEQ ID NO: 388	GUUUGAUGAGAUUAAU CCUGA	SEQ ID NO: 108
ETXS923	UmsGmsAmGmAmUfUfAmAfUfCfCfU mGmAmAmAmCmCmAmAm	SEQ ID NO: 389	UGAGAUUAAUCCUGAA ACCAA	SEQ ID NO: 109
ETXS925	UmsGmsAmUmGmAfGfAmUfUfAfAfU mCmCmUmGmAmAmAmCm	SEQ ID NO: 390	UGAUGAGAUUAAUCCU GAAAC	SEQ ID NO: 110
ETXS927	AmsUmsGmAmGmAfUfUmAfAfUfCfC mUmGmAmAmAmCmCmAm	SEQ ID NO: 391	AUGAGAUUAAUCCUGA AACCA	SEQ ID NO: 111
ETXS929	GmsAmsUmGmAmGfAfUmUfAfAfUfC mCmUmGmAmAmAmCmCm	SEQ ID NO: 392	GAUGAGAUUAAUCCUG AAACC	SEQ ID NO: 112
ETXS931	CmsUmsGmUmUmUfGfAmUfGfAfGfA mUmUmAmAmUmCmCmUm	SEQ ID NO: 393	CUGUUUGAUGAGAUUA AUCCU	SEQ ID NO: 113
ETXS933	UmsUmsUmUmGmCfCfUmUfCfAfUfC mCmAmCmAmAmGmGmAm	SEQ ID NO: 394	UUUUGCCUUCAUCCAC AAGGA	SEQ ID NO: 114
ETXS935	CmsGmsAmAmAmGfAfUmCfUfCfCfA mUmGmAmGmGmCmAmCm	SEQ ID NO: 395	CGAAAGAUCUCCAUGA GGCAC	SEQ ID NO: 115
ETXS937	UmsGmsCmUmGmGfUfGmGfUfCfCfU mCmAmUmGmGmAmGmAm	SEQ ID NO: 396	UGCUGGUGGUCCUCAU GGAGA	SEQ ID NO: 116
ETXS939	CmsCmsUmUmCmAfUfCmCfAfCfAfAm GmGmAmUmUmUmUmGm	SEQ ID NO: 397	CCUUCAUCCACAAGGA UUUUG	SEQ ID NO: 117
ETXS941	GmsAmsAmAmGmAfUfCmUfCfCfAfU mGmAmGmGmCmAmCmGm	SEQ ID NO: 398	GAAAGAUCUCCAUGAG GCACG	SEQ ID NO: 118
ETXS943	UmsUmsCmAmUmCfCfAmCfAfAfGfG mAmUmUmUmUmGmAmUm	SEQ ID NO: 399	UUCAUCCACAAGGAUU UUGAU	SEQ ID NO: 119
ETXS945	UmsUmsUmGmAmUfGfAmGfAfUfUfA mAmUmCmCmUmGmAmAm	SEQ ID NO: 400	UUUGAUGAGAUUAAUC CUGAA	SEQ ID NO: 120
ETXS947	UmsUmsGmCmCmUfUfCmAfUfCfCfAm CmAmAmGmGmAmUmUm	SEQ ID NO: 401	UUGCCUUCAUCCACAA GGAUU	SEQ ID NO: 121
ETXS949	GmsAmsUmCmUmCfCfAmUfGfAfGfG mCmAmCmGmAmUmGmGm	SEQ ID NO: 402	GAUCUCCAUGAGGCAC GAUGG	SEQ ID NO: 122
ETXS951	UmsGmsCmCmUmUmCfAmUfCfCfAfC mAmAmGmGmAmUmUmUm	SEQ ID NO: 403	UGCCUUCAUCCACAAG GAUUU	SEQ ID NO: 103
ETXS953	UmsGmsCmGmAmAmAfGmAfUfCfUfC mCmAmUmGmAmGmGmCm	SEQ ID NO: 404	UGCGAAAGAUCUCCAU GAGGC	SEQ ID NO: 104
ETXS955	GmsCmsUmGmGmUmGfGmUfCfCfUfC mAmUmGmGmAmGmAmAm	SEQ ID NO: 405	GCUGGUGGUCCUCAUG GAGAA	SEQ ID NO: 105
ETXS957	GmsCmsGmAmAmAmGfAmUfCfUfCfC mAmUmGmAmGmGmCmAm	SEQ ID NO: 406	GCGAAAGAUCUCCAUG AGGCA	SEQ ID NO: 106
ETXS959	GmsUmsAmUmGmAmGfAmUfGfCfAfU mGmAmGmCmUmGmCmUm	SEQ ID NO: 407	GUAUGAGAUGCAUGAG CUGCU	SEQ ID NO: 107

ETXS961	GmsUmsUmUmGmAmUfGmAfGfAfUfU mAmAmUmCmCmUmGmAm	SEQ ID NO: 408	GUUUGAUGAGAUUAAU CCUGA	SEQ ID NO: 108
ETXS963	UmsGmsAmGmAmUmUfAmAfUfCfCfU mGmAmAmAmCmCmAmAm	SEQ ID NO: 409	UGAGAUUAAUCCUGAA ACCAA	SEQ ID NO: 109
ETXS965	UmsGmsAmUmGmAmGfAmUfUfAfAfU mCmCmUmGmAmAmAmCm	SEQ ID NO: 410	UGAUGAGAUUAAUCCU GAAAC	SEQ ID NO: 110
ETXS967	AmsUmsGmAmGmAmUfUmAfAfUfCfC mUmGmAmAmAmCmCmAm	SEQ ID NO: 411	AUGAGAUUAAUCCUGA AACCA	SEQ ID NO: 111
ETXS969	GmsAmsUmGmAmGmAfUmUfAfAfUfC mCmUmGmAmAmAmCmCm	SEQ ID NO: 412	GAUGAGAUUAAUCCUG AAACC	SEQ ID NO: 112
ETXS971	CmsUmsGmUmUmUmGfAmUfGfAfGfA mUmUmAmAmUmCmCmUm	SEQ ID NO: 413	CUGUUUGAUGAGAUUA AUCCU	SEQ ID NO: 113
ETXS973	UmsUmsUmUmGmCmCfUmUfCfAfUfC mCmAmCmAmAmGmGmAm	SEQ ID NO: 414	UUUUGCCUUCAUCCAC AAGGA	SEQ ID NO: 114
ETXS975	CmsGmsAmAmAmGmAfUmCfUfCfCfA mUmGmAmGmGmCmAmCm	SEQ ID NO: 415	CGAAAGAUCUCCAUGA GGCAC	SEQ ID NO: 115
ETXS977	UmsGmsCmUmGmGmUfGmGfUfCfCfU mCmAmUmGmGmAmGmAm	SEQ ID NO: 416	UGCUGGUGGUCCUCAU GGAGA	SEQ ID NO: 116
ETXS979	CmsCmsUmUmCmAmUfCmCfAfCfAfA mGmGmAmUmUmUmUmGm	SEQ ID NO: 417	CCUUCAUCCACAAGGA UUUUG	SEQ ID NO: 117
ETXS981	GmsAmsAmAmGmAmUfCmUfCfCfAfU mGmAmGmGmCmAmCmGm	SEQ ID NO: 418	GAAAGAUCUCCAUGAG GCACG	SEQ ID NO: 118
ETXS983	UmsUmsCmAmUmCmCfAmCfAfAfGfG mAmUmUmUmUmGmAmUm	SEQ ID NO: 419	UUCAUCCACAAGGAUU UUGAU	SEQ ID NO: 119
ETXS985	UmsUmsUmGmAmUmGfAmGfAfUfUfA mAmUmCmCmUmGmAmAm	SEQ ID NO: 420	UUUGAUGAGAUUAAUC CUGAA	SEQ ID NO: 120
ETXS987	UmsUmsGmCmCmUmUfCmAfUfCfCfA mCmAmAmGmGmAmUmUm	SEQ ID NO: 421	UUGCCUUCAUCCACAA GGAUU	SEQ ID NO: 121
ETXS989	GmsAmsUmCmUmCmCfAmUfGfAfGfG mCmAmCmGmAmUmGmGm	SEQ ID NO: 422	GAUCUCCAUGAGGCAC GAUGG	SEQ ID NO: 122
ETXS991	UmsGmsCmCmUmUmCfAmUfCfCfAfC mAmAmGmGmAmUmUmUm	SEQ ID NO: 423	UGCCUUCAUCCACAAG GAUUU	SEQ ID NO: 103
ETXS993	UmsGmsCmGmAmAmAfGmAfUfCfUfC mCmAmUmGmAmGmGmCm	SEQ ID NO: 424	UGCGAAAGAUCUCCAU GAGGC	SEQ ID NO: 104
ETXS995	GmsCmsUmGmGmUmGfGmUfCfCfUfC mAmUmGmGmAmGmAmAm	SEQ ID NO: 425	GCUGGUGGUCCUCAUG GAGAA	SEQ ID NO: 105
ETXS997	GmsCmsGmAmAmAmGfAmUfCfUfCfC mAmUmGmAmGmGmCmAm	SEQ ID NO: 426	GCGAAAGAUCUCCAUG AGGCA	SEQ ID NO: 106
ETXS999	GmsUmsAmUmGmAmGfAmUfGfCfAfU mGmAmGmCmUmGmCmUm	SEQ ID NO: 427	GUAUGAGAUGCAUGAG CUGCU	SEQ ID NO: 107

ETXS1001	GmsUmsUmUmGmAmUfGmAfGfAfUfU mAmAmUmCmCmUmGmAm	SEQ ID NO: 428	GUUUGAUGAGAUUAAU CCUGA	SEQ ID NO: 108
ETXS1003	UmsGmsAmGmAmUmUfAmAfUfCfCfU mGmAmAmAmCmCmAmAm	SEQ ID NO: 429	UGAGAUUAAUCCUGAA ACCAA	SEQ ID NO: 109
ETXS1005	UmsGmsAmUmGmAmGfAmUfUfAfAfU mCmCmUmGmAmAmAmCm	SEQ ID NO: 430	UGAUGAGAUUAAUCCU GAAAC	SEQ ID NO: 110
ETXS1007	AmsUmsGmAmGmAmUfUmAfAfUfCfC mUmGmAmAmAmCmCmAm	SEQ ID NO: 431	AUGAGAUUAAUCCUGA AACCA	SEQ ID NO: 111
ETXS1009	GmsAmsUmGmAmGmAfUmUfAfAfUfC mCmUmGmAmAmAmCmCm	SEQ ID NO: 432	GAUGAGAUUAAUCCUG AAACC	SEQ ID NO: 112
ETXS1011	CmsUmsGmUmUmUmGfAmUfGfAfGfA mUmUmAmAmUmCmCmUm	SEQ ID NO: 433	CUGUUUGAUGAGAUUA AUCCU	SEQ ID NO: 113
ETXS1013	UmsUmsUmUmGmCmCfUmUfCfAfUfC mCmAmCmAmAmGmGmAm	SEQ ID NO: 434	UUUUGCCUUCAUCCAC AAGGA	SEQ ID NO: 114
ETXS1015	CmsGmsAmAmAmGmAfUmCfUfCfCfA mUmGmAmGmGmCmAmCm	SEQ ID NO: 435	CGAAAGAUCUCCAUGA GGCAC	SEQ ID NO: 115
ETXS1017	UmsGmsCmUmGmGmUfGmGfUfCfCfU mCmAmUmGmGmAmGmAm	SEQ ID NO: 436	UGCUGGUGGUCCUCAU GGAGA	SEQ ID NO: 116
ETXS1019	CmsCmsUmUmCmAmUfCmCfAfCfAfA mGmGmAmUmUmUmUmGm	SEQ ID NO: 437	CCUUCAUCCACAAGGA UUUUG	SEQ ID NO: 117
ETXS1021	GmsAmsAmAmGmAmUfCmUfCfCfAfU mGmAmGmGmCmAmCmGm	SEQ ID NO: 438	GAAAGAUCUCCAUGAG GCACG	SEQ ID NO: 118
ETXS1023	UmsUmsCmAmUmCmCfAmCfAfAfGfG mAmUmUmUmUmGmAmUm	SEQ ID NO: 439	UUCAUCCACAAGGAUU UUGAU	SEQ ID NO: 119
ETXS1025	UmsUmsUmGmAmUmGfAmGfAfUfUfA mAmUmCmCmUmGmAmAm	SEQ ID NO: 440	UUUGAUGAGAUUAAUC CUGAA	SEQ ID NO: 120
ETXS1027	UmsUmsGmCmCmUmUfCmAfUfCfCfA mCmAmAmGmGmAmUmUm	SEQ ID NO: 441	UUGCCUUCAUCCACAA GGAUU	SEQ ID NO: 121
ETXS1029	GmsAmsUmCmUmCmCfAmUfGfAfGfG mCmAmCmGmAmUmGmGm	SEQ ID NO: 442	GAUCUCCAUGAGGCAC GAUGG	SEQ ID NO: 122
ETXS1035	iaiaUmsAmsCmCmAmAmGfGmAfAfAf UfGmCmCmAmCmCmAmUmGm	SEQ ID NO: 473	UACCAAGGAAAUGCCA CCAUG	SEQ ID NO: 455
ETXS2397	iaiaUmsAmsCmCmAmAmGmGmAfAfAf UmGmCmCmAmCmCmAmUmGm	SEQ ID NO: 474	UACCAAGGAAAUGCCA CCAUG	SEQ ID NO: 455
ETXS1039	iaiaAmsAmsAmGmAmUmCfUmCfCfAf UfGmAmGmGmCmAmCmGmAm	SEQ ID NO: 475	AAAGAUCUCCAUGAGG CACGA	SEQ ID NO: 456
ETXS2399	iaiaAmsAmsAmGmAmUmCmUmCfCfAf UmGmAmGmGmCmAmCmGmAm	SEQ ID NO: 476	AAAGAUCUCCAUGAGG CACGA	SEQ ID NO: 456
ETXS635	iaiaAmsAmsAmAmAmGmCfAmUfGfAf CfAmAmAmCmAmGmAmAmCm	SEQ ID NO: 477	AAAAAGCAUGACAAAC AGAAC	SEQ ID NO: 457

ETXS2433	iaiaAmsAmsAmAmAmGmCmAmUfGfAfCmAmAmAmCmAmGmAmAmCm	SEQ ID NO: 478	AAAAAGCAUGACAAACAGAAC	SEQ ID NO: 457
ETXS643	iaiaAmsAmsGmCmAmUmGfAmCfAfAfAfCmAmGmAmAmCmUmCmGm	SEQ ID NO: 479	AAGCAUGACAAACAGAACUCG	SEQ ID NO: 458
ETXS2435	iaiaAmsAmsGmCmAmUmGmAmCfAfAfAmCmAmGmAmAmCmUmCmGm	SEQ ID NO: 480	AAGCAUGACAAACAGAACUCG	SEQ ID NO: 458
ETXS2399	iaiaAmsAmsAmCmUmUmGfAmAfUfUfUfCmCmUmAmUmGmUmAmUm	SEQ ID NO: 481	AAACUUGAAUUUCCUAUGUAU	SEQ ID NO: 459
ETXS2401	iaiaAmsAmsAmCmUmUmGmAmAfUfUfUmCmCmUmAmUmGmUmAmUm	SEQ ID NO: 482	AAACUUGAAUUUCCUAUGUAU	SEQ ID NO: 459
ETXS2405	iaiaCmsUmsUmGmAmAmUfUmUfCfCfUfAmUmGmUmAmUmUmUmUm	SEQ ID NO: 483	CUUGAAUUUCCUAUGUAUUUU	SEQ ID NO: 460
ETXS2407	iaiaCmsUmsUmGmAmAmUmUmUfCfCfUmAmUmGmUmAmUmUmUmUm	SEQ ID NO: 484	CUUGAAUUUCCUAUGUAUUUU	SEQ ID NO: 460

[00388] Some of the modified second strand sequences as illustrated above in Table 4 include the preferred 5' iaia motif. However, it should also be understood that the scope of these modified second strand sequences additionally includes the Me / F modified second strand in the absence of the 5'iaia motif.

[00389] Table 5 identifies duplexes with Duplex IDs referencing the modified antisense and sense IDs from previous Tables 3 and 4.

Table 5

Duplex ID	Antisense strand ID	Sense strand ID
ETXM236	ETXS472	ETXS471
ETXM237	ETXS474	ETXS473
ETXM238	ETXS476	ETXS475
ETXM239	ETXS478	ETXS477
ETXM240	ETXS480	ETXS479
ETXM241	ETXS482	ETXS481
ETXM242	ETXS484	ETXS483
ETXM243	ETXS486	ETXS485
ETXM244	ETXS488	ETXS487
ETXM245	ETXS490	ETXS489
ETXM246	ETXS492	ETXS491
ETXM247	ETXS494	ETXS493
ETXM248	ETXS496	ETXS495

ETXM249	ETXS498	ETXS497
ETXM250	ETXS500	ETXS499
ETXM251	ETXS502	ETXS501
ETXM252	ETXS504	ETXS503
ETXM253	ETXS506	ETXS505
ETXM254	ETXS508	ETXS507
ETXM255	ETXS510	ETXS509
ETXM256	ETXS512	ETXS511
ETXM257	ETXS514	ETXS513
ETXM258	ETXS516	ETXS515
ETXM259	ETXS518	ETXS517
ETXM260	ETXS520	ETXS519
ETXM261	ETXS522	ETXS521
ETXM262	ETXS524	ETXS523
ETXM263	ETXS526	ETXS525
ETXM264	ETXS528	ETXS527
ETXM265	ETXS530	ETXS529
ETXM266	ETXS532	ETXS531
ETXM267	ETXS534	ETXS533
ETXM268	ETXS536	ETXS535
ETXM269	ETXS538	ETXS537
ETXM270	ETXS540	ETXS539
ETXM271	ETXS542	ETXS541
ETXM272	ETXS544	ETXS543
ETXM273	ETXS546	ETXS545
ETXM274	ETXS548	ETXS547
ETXM275	ETXS550	ETXS549
ETXM276	ETXS552	ETXS551
ETXM277	ETXS554	ETXS553
ETXM278	ETXS556	ETXS555
ETXM279	ETXS558	ETXS557
ETXM280	ETXS560	ETXS559
ETXM281	ETXS562	ETXS561
ETXM282	ETXS564	ETXS563
ETXM283	ETXS566	ETXS565
ETXM284	ETXS568	ETXS567
ETXM285	ETXS570	ETXS569
ETXM286	ETXS572	ETXS571
ETXM287	ETXS574	ETXS573
ETXM288	ETXS576	ETXS575

ETXM289	ETXS578	ETXS577
ETXM290	ETXS580	ETXS579
ETXM291	ETXS582	ETXS581
ETXM292	ETXS584	ETXS583
ETXM293	ETXS586	ETXS585
ETXM294	ETXS588	ETXS587
ETXM295	ETXS590	ETXS589
ETXM296	ETXS592	ETXS591
ETXM297	ETXS594	ETXS593
ETXM298	ETXS596	ETXS595
ETXM299	ETXS598	ETXS597
ETXM300	ETXS600	ETXS599
ETXM301	ETXS602	ETXS601
ETXM302	ETXS604	ETXS603
ETXM303	ETXS606	ETXS605
ETXM304	ETXS608	ETXS607
ETXM305	ETXS610	ETXS609
ETXM306	ETXS612	ETXS611
ETXM307	ETXS614	ETXS613
ETXM308	ETXS616	ETXS615
ETXM309	ETXS618	ETXS617
ETXM310	ETXS620	ETXS619
ETXM311	ETXS622	ETXS621
ETXM312	ETXS624	ETXS623
ETXM313	ETXS626	ETXS625
ETXM314	ETXS628	ETXS627
ETXM315	ETXS630	ETXS629
ETXM436	ETXS872	ETXS871
ETXM437	ETXS874	ETXS873
ETXM438	ETXS876	ETXS875
ETXM439	ETXS878	ETXS877
ETXM440	ETXS880	ETXS879
ETXM441	ETXS882	ETXS881
ETXM442	ETXS884	ETXS883
ETXM443	ETXS886	ETXS885
ETXM444	ETXS888	ETXS887
ETXM445	ETXS890	ETXS889
ETXM446	ETXS892	ETXS891
ETXM447	ETXS894	ETXS893
ETXM448	ETXS896	ETXS895

ETXM449	ETXS898	ETXS897
ETXM450	ETXS900	ETXS899
ETXM451	ETXS902	ETXS901
ETXM452	ETXS904	ETXS903
ETXM453	ETXS906	ETXS905
ETXM454	ETXS908	ETXS907
ETXM455	ETXS910	ETXS909
ETXM456	ETXS912	ETXS911
ETXM457	ETXS914	ETXS913
ETXM458	ETXS916	ETXS915
ETXM459	ETXS918	ETXS917
ETXM460	ETXS920	ETXS919
ETXM461	ETXS922	ETXS921
ETXM462	ETXS924	ETXS923
ETXM463	ETXS926	ETXS925
ETXM464	ETXS928	ETXS927
ETXM465	ETXS930	ETXS929
ETXM466	ETXS932	ETXS931
ETXM467	ETXS934	ETXS933
ETXM468	ETXS936	ETXS935
ETXM469	ETXS938	ETXS937
ETXM470	ETXS940	ETXS939
ETXM471	ETXS942	ETXS941
ETXM472	ETXS944	ETXS943
ETXM473	ETXS946	ETXS945
ETXM474	ETXS948	ETXS947
ETXM475	ETXS950	ETXS949
ETXM476	ETXS952	ETXS951
ETXM477	ETXS954	ETXS953
ETXM478	ETXS956	ETXS955
ETXM479	ETXS958	ETXS957
ETXM480	ETXS960	ETXS959
ETXM481	ETXS962	ETXS961
ETXM482	ETXS964	ETXS963
ETXM483	ETXS966	ETXS965
ETXM484	ETXS968	ETXS967
ETXM485	ETXS970	ETXS969
ETXM486	ETXS972	ETXS971
ETXM487	ETXS974	ETXS973
ETXM488	ETXS976	ETXS975

ETXM489	ETXS978	ETXS977
ETXM490	ETXS980	ETXS979
ETXM491	ETXS982	ETXS981
ETXM492	ETXS984	ETXS983
ETXM493	ETXS986	ETXS985
ETXM494	ETXS988	ETXS987
ETXM495	ETXS990	ETXS989
ETXM496	ETXS992	ETXS991
ETXM497	ETXS994	ETXS993
ETXM498	ETXS996	ETXS995
ETXM499	ETXS998	ETXS997
ETXM500	ETXS1000	ETXS999
ETXM501	ETXS1002	ETXS1001
ETXM502	ETXS1004	ETXS1003
ETXM503	ETXS1006	ETXS1005
ETXM504	ETXS1008	ETXS1007
ETXM505	ETXS1010	ETXS1009
ETXM506	ETXS1012	ETXS1011
ETXM507	ETXS1014	ETXS1013
ETXM508	ETXS1016	ETXS1015
ETXM509	ETXS1018	ETXS1017
ETXM510	ETXS1020	ETXS1019
ETXM511	ETXS1022	ETXS1021
ETXM512	ETXS1024	ETXS1023
ETXM513	ETXS1026	ETXS1025
ETXM514	ETXS1028	ETXS1027
ETXM515	ETXS1030	ETXS1029
ETXM1184	ETXS1036	ETXS1035
ETXM1199	ETXS2398	ETXS2397
ETXM1157	ETXS1040	ETXS1039
ETXM1208	ETXS2416	ETXS2399
ETXM1176	ETXS636	ETXS635
ETXM1217	ETXS2434	ETXS2433
ETXM1136	ETXS644	ETXS643
ETXM1226	ETXS2452	ETXS2435
ETXM1200	ETXS2400	ETXS2399
ETXM1201	ETXS2402	ETXS2401
ETXM1203	ETXS2406	ETXS2405
ETXM1204	ETXS2408	ETXS2407

[00390] For duplexes of Table 5, these can have a duplex structure according to Figure 8a with a 2 nucleoside overhang at the 3' end of the antisense; or a duplex structure according to Figure 8b, namely a 19mer blunt ended construct.

[00391] 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 HCII and ZPI Expression in Human Huh7 Cells

[00392] **HCII:** 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% CO2. Cells were transfected with siRNA duplexes targeting HCII mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:487), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:486)) at a final duplex concentration of 5 nM and 0.1 nM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells in two independent experiments.

[00393] cDNA synthesis was performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI

QuantStudio 7 with primers specific for human HCII (Hs00164821_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00394] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Based on the results of primary screen, siRNA duplexes displaying good activity were selected for dose-response follow-up. Results are shown in Figure 9. Sequences of RNAi molecules are depicted herein.

[00395] **ZPI:** 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% CO2. Cells were transfected with siRNA duplexes targeting ZPI mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:487), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:486)) at a final duplex concentration of 10 nM and 0.1 nM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells in two independent experiments.

[00396] cDNA synthesis was performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human ZPI (Hs01547819_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00397] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative ZPI expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Based on the results of primary screen, siRNA duplexes displaying good activity were selected for dose-response follow-up. Results are shown in Figure 9. Sequences of RNAi molecules are depicted herein.

Example 10: Dose-response for Inhibition of HCII Expression in Human Huh7 Cells

[00398] 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% CO2. Cells were transfected with siRNA duplexes targeting HCII mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:487), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:486)) using 10x3-fold serial dilutions over a final duplex concentration range of 20 nM to 1 pM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX (ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells in a single experiment.

[00399] cDNA synthesis was performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human HCII (Hs00164821_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00400] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative HCII expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of HCII expression and IC50 values were calculated using a four parameter (variable slope) model using GraphPad Prism 9. Results are shown in Figure 9. Sequences of RNAi molecules are depicted in the relevant Tables herein.

Example 11: Dose-response for Inhibition of ZPI Expression in Human Huh7 Cells

[00401] 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% CO2. Cells were transfected with siRNA duplexes targeting ZPI mRNA or a negative control siRNA (siRNA-control; sense strand 5'-UUCUCCGAACGUGUCACGUTT-3' (SEQ ID NO:487), antisense strand 5'-ACGUGACACGUUCGGAGAATT-3' (SEQ ID NO:486)) using 10x3-fold serial dilutions over a final duplex concentration range of 20 nM to 1 pM. Transfection was carried out by adding 9.7 µL Opti-MEM (ThermoFisher) plus 0.3 µL Lipofectamine RNAiMAX

(ThermoFisher) to 10 µL of each siRNA duplex. The mixture was incubated at room temperature for 15 minutes before being added to 100 µL of complete growth medium containing 20,000 Huh7 cells. Cells were incubated for 24 hours at 37°C/5% CO2 prior to total RNA purification using a RNeasy 96 Kit (Qiagen). Each duplex was tested by transfection in duplicate wells in a single experiment.

[00402] cDNA synthesis was performed using FastQuant RT (with gDNase) Kit (Tiangen). Real-time quantitative PCR (qPCR) was performed on an ABI Prism 7900HT or ABI QuantStudio 7 with primers specific for human ZPI (Hs01547819_m1) and human GAPDH (Hs02786624_g1) using FastStart Universal Probe Master Kit (Roche).

[00403] qPCR was performed in duplicate on cDNA derived from each well and the mean Ct calculated. Relative ZPI expression was calculated from mean Ct values using the comparative Ct (ΔΔCt) method, normalised to GAPDH and relative to untreated cells. Maximum percent inhibition of ZPI expression and IC50 values were calculated using a four parameter (variable slope) model using GraphPad Prism 9. Results are shown in Figure 9. Sequences of RNAi molecules are depicted in the relevant Tables herein.

Table 6 - Relative mRNA Expression

HCII:

Duplex ID	Antisense strand ID	SEQ ID NO (AS - mod)	Sense strand ID	SEQ ID NO (SS - mod)	Mean Relative Expression /0.1 nM	Mean Relative Expression/1 nM
ETXM236	ETXS472	SEQ ID NO: 123	ETXS471	SEQ ID NO: 283	0.81	0.3
ETXM237	ETXS474	SEQ ID NO: 124	ETXS473	SEQ ID NO: 284	0.92	0.37
ETXM238	ETXS476	SEQ ID NO: 125	ETXS475	SEQ ID NO: 285	0.67	0.24
ETXM239	ETXS478	SEQ ID NO: 126	ETXS477	SEQ ID NO: 286	1.09	0.77
ETXM240	ETXS480	SEQ ID NO: 127	ETXS479	SEQ ID NO: 287	0.93	0.58
ETXM241	ETXS482	SEQ ID NO: 128	ETXS481	SEQ ID NO: 288	1.12	0.91
ETXM242	ETXS484	SEQ ID NO: 129	ETXS483	SEQ ID NO: 289	1.1	1.03
ETXM243	ETXS486	SEQ ID NO: 130	ETXS485	SEQ ID NO: 290	1.09	0.89
ETXM244	ETXS488	SEQ ID NO: 131	ETXS487	SEQ ID NO: 291	0.91	0.48
ETXM245	ETXS490	SEQ ID NO: 132	ETXS489	SEQ ID NO: 292	0.93	0.56
ETXM246	ETXS492	SEQ ID NO: 133	ETXS491	SEQ ID NO: 293	0.69	0.34
ETXM247	ETXS494	SEQ ID NO: 134	ETXS493	SEQ ID NO: 294	0.93	0.7
ETXM248	ETXS496	SEQ ID NO: 135	ETXS495	SEQ ID NO: 295	0.8	0.44

ETXM249	ETXS498	SEQ ID NO: 136	ETXS497	SEQ ID NO: 296	0.84	0.44
ETXM250	ETXS500	SEQ ID NO: 137	ETXS499	SEQ ID NO: 297	0.81	0.39
ETXM251	ETXS502	SEQ ID NO: 138	ETXS501	SEQ ID NO: 298	0.67	0.41
ETXM252	ETXS504	SEQ ID NO: 139	ETXS503	SEQ ID NO: 299	0.51	0.34
ETXM253	ETXS506	SEQ ID NO: 140	ETXS505	SEQ ID NO: 300	0.57	0.37
ETXM254	ETXS508	SEQ ID NO: 141	ETXS507	SEQ ID NO: 301	0.65	0.43
ETXM255	ETXS510	SEQ ID NO: 142	ETXS509	SEQ ID NO: 302	0.73	0.65
ETXM256	ETXS512	SEQ ID NO: 143	ETXS511	SEQ ID NO: 303	0.77	0.36
ETXM257	ETXS514	SEQ ID NO: 144	ETXS513	SEQ ID NO: 304	0.92	0.43
ETXM258	ETXS516	SEQ ID NO: 145	ETXS515	SEQ ID NO: 305	0.62	0.24
ETXM259	ETXS518	SEQ ID NO: 146	ETXS517	SEQ ID NO: 306	0.96	0.58
ETXM260	ETXS520	SEQ ID NO: 147	ETXS519	SEQ ID NO: 307	0.86	0.54
ETXM261	ETXS522	SEQ ID NO: 148	ETXS521	SEQ ID NO: 308	0.92	0.67
ETXM262	ETXS524	SEQ ID NO: 149	ETXS523	SEQ ID NO: 309	0.89	0.73
ETXM263	ETXS526	SEQ ID NO: 150	ETXS525	SEQ ID NO: 310	0.76	0.59
ETXM264	ETXS528	SEQ ID NO: 151	ETXS527	SEQ ID NO: 311	0.78	0.42
ETXM265	ETXS530	SEQ ID NO: 152	ETXS529	SEQ ID NO: 312	0.74	0.52
ETXM266	ETXS532	SEQ ID NO: 153	ETXS531	SEQ ID NO: 313	0.79	0.32
ETXM267	ETXS534	SEQ ID NO: 154	ETXS533	SEQ ID NO: 314	0.98	0.51
ETXM268	ETXS536	SEQ ID NO: 155	ETXS535	SEQ ID NO: 315	0.92	0.39
ETXM269	ETXS538	SEQ ID NO: 156	ETXS537	SEQ ID NO: 316	0.78	0.34
ETXM270	ETXS540	SEQ ID NO: 157	ETXS539	SEQ ID NO: 317	0.82	0.51
ETXM271	ETXS542	SEQ ID NO: 158	ETXS541	SEQ ID NO: 318	0.7	0.39
ETXM272	ETXS544	SEQ ID NO: 159	ETXS543	SEQ ID NO: 319	0.56	0.22
ETXM273	ETXS546	SEQ ID NO: 160	ETXS545	SEQ ID NO: 320	0.58	0.27
ETXM274	ETXS548	SEQ ID NO: 161	ETXS547	SEQ ID NO: 321	0.71	0.34
ETXM275	ETXS550	SEQ ID NO: 162	ETXS549	SEQ ID NO: 322	0.78	0.51
ETXM276	ETXS552	SEQ ID NO: 163	ETXS551	SEQ ID NO: 323	0.93	0.43
ETXM277	ETXS554	SEQ ID NO: 164	ETXS553	SEQ ID NO: 324	1.12	0.76
ETXM278	ETXS556	SEQ ID NO: 165	ETXS555	SEQ ID NO: 325	0.75	0.35
ETXM279	ETXS558	SEQ ID NO: 166	ETXS557	SEQ ID NO: 326	1.02	1.01
ETXM280	ETXS560	SEQ ID NO: 167	ETXS559	SEQ ID NO: 327	1.01	0.9
ETXM281	ETXS562	SEQ ID NO: 168	ETXS561	SEQ ID NO: 328	1.2	0.98
ETXM282	ETXS564	SEQ ID NO: 169	ETXS563	SEQ ID NO: 329	1.23	0.98
ETXM283	ETXS566	SEQ ID NO: 170	ETXS565	SEQ ID NO: 330	1.22	0.91
ETXM284	ETXS568	SEQ ID NO: 171	ETXS567	SEQ ID NO: 331	0.97	0.45
ETXM285	ETXS570	SEQ ID NO: 172	ETXS569	SEQ ID NO: 332	1.34	0.94
ETXM286	ETXS572	SEQ ID NO: 173	ETXS571	SEQ ID NO: 333	0.88	0.48
ETXM287	ETXS574	SEQ ID NO: 174	ETXS573	SEQ ID NO: 334	0.84	0.64
ETXM288	ETXS576	SEQ ID NO: 175	ETXS575	SEQ ID NO: 335	0.85	0.43

ETXM289	ETXS578	SEQ ID NO: 176	ETXS577	SEQ ID NO: 336	0.76	0.42
ETXM290	ETXS580	SEQ ID NO: 177	ETXS579	SEQ ID NO: 337	0.81	0.45
ETXM291	ETXS582	SEQ ID NO: 178	ETXS581	SEQ ID NO: 338	0.81	0.4
ETXM292	ETXS584	SEQ ID NO: 179	ETXS583	SEQ ID NO: 339	0.48	0.28
ETXM293	ETXS586	SEQ ID NO: 180	ETXS585	SEQ ID NO: 340	0.56	0.25
ETXM294	ETXS588	SEQ ID NO: 181	ETXS587	SEQ ID NO: 341	0.62	0.32
ETXM295	ETXS590	SEQ ID NO: 182	ETXS589	SEQ ID NO: 342	1	0.67
ETXM296	ETXS592	SEQ ID NO: 183	ETXS591	SEQ ID NO: 343	0.71	0.5
ETXM297	ETXS594	SEQ ID NO: 184	ETXS593	SEQ ID NO: 344	0.74	0.46
ETXM298	ETXS596	SEQ ID NO: 185	ETXS595	SEQ ID NO: 345	0.65	0.29
ETXM299	ETXS598	SEQ ID NO: 186	ETXS597	SEQ ID NO: 346	0.82	0.65
ETXM300	ETXS600	SEQ ID NO: 187	ETXS599	SEQ ID NO: 347	0.81	0.6
ETXM301	ETXS602	SEQ ID NO: 188	ETXS601	SEQ ID NO: 348	0.97	0.94
ETXM302	ETXS604	SEQ ID NO: 189	ETXS603	SEQ ID NO: 349	1.13	0.85
ETXM303	ETXS606	SEQ ID NO: 190	ETXS605	SEQ ID NO: 350	1.08	0.69
ETXM304	ETXS608	SEQ ID NO: 191	ETXS607	SEQ ID NO: 351	0.99	0.41
ETXM305	ETXS610	SEQ ID NO: 192	ETXS609	SEQ ID NO: 352	1.14	0.78
ETXM306	ETXS612	SEQ ID NO: 193	ETXS611	SEQ ID NO: 353	0.74	0.43
ETXM307	ETXS614	SEQ ID NO: 194	ETXS613	SEQ ID NO: 354	0.81	0.53
ETXM308	ETXS616	SEQ ID NO: 195	ETXS615	SEQ ID NO: 355	0.68	0.36
ETXM309	ETXS618	SEQ ID NO: 196	ETXS617	SEQ ID NO: 356	0.63	0.26
ETXM310	ETXS620	SEQ ID NO: 197	ETXS619	SEQ ID NO: 357	0.76	0.43
ETXM311	ETXS622	SEQ ID NO: 198	ETXS621	SEQ ID NO: 358	0.71	0.36
ETXM312	ETXS624	SEQ ID NO: 199	ETXS623	SEQ ID NO: 359	0.62	0.25
ETXM313	ETXS626	SEQ ID NO: 200	ETXS625	SEQ ID NO: 360	0.79	0.31
ETXM314	ETXS628	SEQ ID NO: 201	ETXS627	SEQ ID NO: 361	0.65	0.25
ETXM315	ETXS630	SEQ ID NO: 202	ETXS629	SEQ ID NO: 362	0.96	0.66

ZPI:

Duplex ID	Antisense strand ID	SEQ ID NO (AS - mod)	Sense strand ID	SEQ ID NO (SS - mod)	Mean Relative Expression /0.1 nM	Mean Relative Expression/1 nM
ETXM436	ETXS872	SEQ ID NO: 203	ETXS871	SEQ ID NO: 363	0.72	0.44
ETXM437	ETXS874	SEQ ID NO: 204	ETXS873	SEQ ID NO: 364	0.98	0.47
ETXM438	ETXS876	SEQ ID NO: 205	ETXS875	SEQ ID NO: 365	1.05	0.75
ETXM439	ETXS878	SEQ ID NO: 206	ETXS877	SEQ ID NO: 366	0.91	0.49
ETXM440	ETXS880	SEQ ID NO: 207	ETXS879	SEQ ID NO: 367	0.91	0.46

ETXM441	ETXS882	SEQ ID NO: 208	ETXS881	SEQ ID NO: 368	0.74	0.36
ETXM442	ETXS884	SEQ ID NO: 209	ETXS883	SEQ ID NO: 369	0.62	0.36
ETXM443	ETXS886	SEQ ID NO: 210	ETXS885	SEQ ID NO: 370	0.73	0.3
ETXM444	ETXS888	SEQ ID NO: 211	ETXS887	SEQ ID NO: 371	1	0.59
ETXM445	ETXS890	SEQ ID NO: 212	ETXS889	SEQ ID NO: 372	0.71	0.37
ETXM446	ETXS892	SEQ ID NO: 213	ETXS891	SEQ ID NO: 373	0.73	0.27
ETXM447	ETXS894	SEQ ID NO: 214	ETXS893	SEQ ID NO: 374	0.81	0.39
ETXM448	ETXS896	SEQ ID NO: 215	ETXS895	SEQ ID NO: 375	0.81	0.61
ETXM449	ETXS898	SEQ ID NO: 216	ETXS897	SEQ ID NO: 376	0.91	0.8
ETXM450	ETXS900	SEQ ID NO: 217	ETXS899	SEQ ID NO: 377	0.97	0.52
ETXM451	ETXS902	SEQ ID NO: 218	ETXS901	SEQ ID NO: 378	0.96	0.61
ETXM452	ETXS904	SEQ ID NO: 219	ETXS903	SEQ ID NO: 379	0.4	0.24
ETXM453	ETXS906	SEQ ID NO: 220	ETXS905	SEQ ID NO: 380	0.62	0.3
ETXM454	ETXS908	SEQ ID NO: 221	ETXS907	SEQ ID NO: 381	0.81	0.46
ETXM455	ETXS910	SEQ ID NO: 222	ETXS909	SEQ ID NO: 382	0.94	0.68
ETXM456	ETXS912	SEQ ID NO: 223	ETXS911	SEQ ID NO: 383	0.75	0.36
ETXM457	ETXS914	SEQ ID NO: 224	ETXS913	SEQ ID NO: 384	0.98	0.52
ETXM458	ETXS916	SEQ ID NO: 225	ETXS915	SEQ ID NO: 385	1	0.61
ETXM459	ETXS918	SEQ ID NO: 226	ETXS917	SEQ ID NO: 386	0.92	0.44
ETXM460	ETXS920	SEQ ID NO: 227	ETXS919	SEQ ID NO: 387	0.86	0.4
ETXM461	ETXS922	SEQ ID NO: 228	ETXS921	SEQ ID NO: 388	0.84	0.27
ETXM462	ETXS924	SEQ ID NO: 229	ETXS923	SEQ ID NO: 389	0.72	0.33
ETXM463	ETXS926	SEQ ID NO: 230	ETXS925	SEQ ID NO: 390	0.76	0.35
ETXM464	ETXS928	SEQ ID NO: 231	ETXS927	SEQ ID NO: 391	0.95	0.55
ETXM465	ETXS930	SEQ ID NO: 232	ETXS929	SEQ ID NO: 392	0.77	0.36
ETXM466	ETXS932	SEQ ID NO: 233	ETXS931	SEQ ID NO: 393	0.84	0.33
ETXM467	ETXS934	SEQ ID NO: 234	ETXS933	SEQ ID NO: 394	0.91	0.39
ETXM468	ETXS936	SEQ ID NO: 235	ETXS935	SEQ ID NO: 395	1.14	0.8
ETXM469	ETXS938	SEQ ID NO: 236	ETXS937	SEQ ID NO: 396	1.17	0.67
ETXM470	ETXS940	SEQ ID NO: 237	ETXS939	SEQ ID NO: 397	1.12	0.79
ETXM471	ETXS942	SEQ ID NO: 238	ETXS941	SEQ ID NO: 398	1.16	0.86
ETXM472	ETXS944	SEQ ID NO: 239	ETXS943	SEQ ID NO: 399	0.49	0.25
ETXM473	ETXS946	SEQ ID NO: 240	ETXS945	SEQ ID NO: 400	0.91	0.34
ETXM474	ETXS948	SEQ ID NO: 241	ETXS947	SEQ ID NO: 401	1.12	0.68
ETXM475	ETXS950	SEQ ID NO: 242	ETXS949	SEQ ID NO: 402	1.25	0.84
ETXM476	ETXS952	SEQ ID NO: 243	ETXS951	SEQ ID NO: 403	0.87	0.42
ETXM477	ETXS954	SEQ ID NO: 244	ETXS953	SEQ ID NO: 404	1.12	0.52
ETXM478	ETXS956	SEQ ID NO: 245	ETXS955	SEQ ID NO: 405	1.03	0.62
ETXM479	ETXS958	SEQ ID NO: 246	ETXS957	SEQ ID NO: 406	1.13	0.51
ETXM480	ETXS960	SEQ ID NO: 247	ETXS959	SEQ ID NO: 407	0.93	0.56

ETXM481	ETXS962	SEQ ID NO: 248	ETXS961	SEQ ID NO: 408	0.89	0.36
ETXM482	ETXS964	SEQ ID NO: 249	ETXS963	SEQ ID NO: 409	0.68	0.46
ETXM483	ETXS966	SEQ ID NO: 250	ETXS965	SEQ ID NO: 410	0.82	0.5
ETXM484	ETXS968	SEQ ID NO: 251	ETXS967	SEQ ID NO: 411	1.06	0.74
ETXM485	ETXS970	SEQ ID NO: 252	ETXS969	SEQ ID NO: 412	0.91	0.41
ETXM486	ETXS972	SEQ ID NO: 253	ETXS971	SEQ ID NO: 413	0.68	0.23
ETXM487	ETXS974	SEQ ID NO: 254	ETXS973	SEQ ID NO: 414	0.8	0.31
ETXM488	ETXS976	SEQ ID NO: 255	ETXS975	SEQ ID NO: 415	0.89	0.64
ETXM489	ETXS978	SEQ ID NO: 256	ETXS977	SEQ ID NO: 416	0.89	0.67
ETXM490	ETXS980	SEQ ID NO: 257	ETXS979	SEQ ID NO: 417	0.91	0.56
ETXM491	ETXS982	SEQ ID NO: 258	ETXS981	SEQ ID NO: 418	1.06	0.75
ETXM492	ETXS984	SEQ ID NO: 259	ETXS983	SEQ ID NO: 419	0.43	0.22
ETXM493	ETXS986	SEQ ID NO: 260	ETXS985	SEQ ID NO: 420	0.59	0.33
ETXM494	ETXS988	SEQ ID NO: 261	ETXS987	SEQ ID NO: 421	0.93	0.59
ETXM495	ETXS990	SEQ ID NO: 262	ETXS989	SEQ ID NO: 422	1.08	0.74
ETXM496	ETXS992	SEQ ID NO: 263	ETXS991	SEQ ID NO: 423	0.73	0.42
ETXM497	ETXS994	SEQ ID NO: 264	ETXS993	SEQ ID NO: 424	1.01	0.59
ETXM498	ETXS996	SEQ ID NO: 265	ETXS995	SEQ ID NO: 425	0.95	0.59
ETXM499	ETXS998	SEQ ID NO: 266	ETXS997	SEQ ID NO: 426	1.08	0.53
ETXM500	ETXS1000	SEQ ID NO: 267	ETXS999	SEQ ID NO: 427	0.87	0.46
ETXM501	ETXS1002	SEQ ID NO: 268	ETXS1001	SEQ ID NO: 428	0.6	0.27
ETXM502	ETXS1004	SEQ ID NO: 269	ETXS1003	SEQ ID NO: 429	0.6	0.28
ETXM503	ETXS1006	SEQ ID NO: 270	ETXS1005	SEQ ID NO: 430	0.73	0.36
ETXM504	ETXS1008	SEQ ID NO: 271	ETXS1007	SEQ ID NO: 431	0.9	0.68
ETXM505	ETXS1010	SEQ ID NO: 272	ETXS1009	SEQ ID NO: 432	0.72	0.36
ETXM506	ETXS1012	SEQ ID NO: 273	ETXS1011	SEQ ID NO: 433	0.62	0.25
ETXM507	ETXS1014	SEQ ID NO: 274	ETXS1013	SEQ ID NO: 434	1.21	0.33
ETXM508	ETXS1016	SEQ ID NO: 275	ETXS1015	SEQ ID NO: 435	1.08	0.83
ETXM509	ETXS1018	SEQ ID NO: 276	ETXS1017	SEQ ID NO: 436	1.09	0.85
ETXM510	ETXS1020	SEQ ID NO: 277	ETXS1019	SEQ ID NO: 437	0.98	0.62
ETXM511	ETXS1022	SEQ ID NO: 278	ETXS1021	SEQ ID NO: 438	0.81	0.87
ETXM512	ETXS1024	SEQ ID NO: 279	ETXS1023	SEQ ID NO: 439	0.34	0.17
ETXM513	ETXS1026	SEQ ID NO: 280	ETXS1025	SEQ ID NO: 440	0.49	0.22
ETXM514	ETXS1028	SEQ ID NO: 281	ETXS1027	SEQ ID NO: 441	0.84	0.56
ETXM515	ETXS1030	SEQ ID NO: 282	ETXS1029	SEQ ID NO: 442	0.93	0.74

Table 7 - Dose-Response Data Table

HCII:

Duplex ID	Antisense strand ID	SEQ ID NO (AS - mod)	Sense strand ID	SEQ ID NO (SS - mod)	IC_{50} [pM]	% Max Inhibition
ETXM253	ETXS506	SEQ ID NO: 140	ETXS505	SEQ ID NO: 300	294	82
ETXM258	ETXS516	SEQ ID NO: 145	ETXS515	SEQ ID NO: 305	212	89
ETXM272	ETXS544	SEQ ID NO: 159	ETXS543	SEQ ID NO: 319	348	84
ETXM273	ETXS546	SEQ ID NO: 160	ETXS545	SEQ ID NO: 320	320	86
ETXM293	ETXS586	SEQ ID NO: 180	ETXS585	SEQ ID NO: 340	213	73
ETXM309	ETXS618	SEQ ID NO: 196	ETXS617	SEQ ID NO: 356	253	72
ETXM313	ETXS626	SEQ ID NO: 200	ETXS625	SEQ ID NO: 360	327	84
ETXM314	ETXS628	SEQ ID NO: 201	ETXS627	SEQ ID NO: 361	214	81

ZPI:

Duplex ID	Antisense strand ID	SEQ ID NO (AS - mod)	Sense strand ID	SEQ ID NO (SS - mod)	IC_{50} [pM]	% Max Inhibition
ETXM452	ETXS904	SEQ ID NO: 219	ETXS903	SEQ ID NO: 379	82	78
ETXM472	ETXS944	SEQ ID NO: 239	ETXS943	SEQ ID NO: 399	130	77
ETXM492	ETXS984	SEQ ID NO: 259	ETXS983	SEQ ID NO: 419	47	84
ETXM500	ETXS1000	SEQ ID NO: 267	ETXS999	SEQ ID NO: 427	607	70
ETXM501	ETXS1002	SEQ ID NO: 268	ETXS1001	SEQ ID NO: 428	190	74
ETXM502	ETXS1004	SEQ ID NO: 269	ETXS1003	SEQ ID NO: 429	132	76
ETXM503	ETXS1006	SEQ ID NO: 270	ETXS1005	SEQ ID NO: 430	322	75
ETXM505	ETXS1010	SEQ ID NO: 272	ETXS1009	SEQ ID NO: 432	199	72
ETXM506	ETXS1012	SEQ ID NO: 273	ETXS1011	SEQ ID NO: 433	162	82
ETXM512	ETXS1024	SEQ ID NO: 279	ETXS1023	SEQ ID NO: 439	76	84
ETXM513	ETXS1026	SEQ ID NO: 280	ETXS1025	SEQ ID NO: 440	146	77

Example 11: Dose-response for Inhibition of ZPI and B4GALT1 Expression in Human Huh7 Cells

[00404] Huh7 cells (human hepatocyte-derived cell line, obtained from JCRB Cell Bank) were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS at 37˚C in at atmosphere of 5% CO_2. Cells were transfected with siRNA duplexes designed 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.

[00405] 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).

[00406] 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.

[00407] For the inhibition of ZPI, the siRNA duplexes ETXM1184 and ETXM1199 were tested (Fig.10). For inhibition of B4GALT1, the siRNA duplexes ETXM1200, ETXM1201, ETXM 1203 and ETXM1204 were tested (Figs.11 and 12).

[00408] Example 12: In vivo Efficacy data in a haemophilia mouse model

[00409] Haemarthrosis is defined as a bleeding into joint spaces that is a common feature of haemophilia. A long-term consequence of repeated haemarthrosis is the development of permanent joint disease known as haemophilic arthropathy. Around 50% of patients with haemophilia develop severe arthropathy resulting in chronic joint pain, reduced range of motion and function, and reduced quality of life. Haemophilic arthropathy is characterised by synovial hyperplasia, chronic inflammation, fibrosis, and haemosiderosis.

[00410] The model of haemarthrosis used was the induction of a knee bleed in haem A mice and the appropriate background wild-type (WT) strain, with progression of the bleed into the joint monitored up to 10 days post-injury. Identical studies were conducted twice to increase number of animals for analysis.

[00411] The objective of these repeat studies was to demonstrate that prophylactic administration of ETXM1184 could reduce haemarthrosis in Haemophilia A mice after a joint bleed injury. Fitusiran (siRNA targeting antithrombin (AT)) was used as a reference. Advate (recombinant FVIII) was used as positive control.

[00412] For that, a total of 20 Haem A mice (Bi, L., Lawler, A., Antonarakis, S. et al. Targeted disruption of the mouse factor VIII gene produces a model of haemophilia A. Nat Genet 10,

119–121 (1995). https://doi.org/10.1038/ng0595-119) and 10 WT mice were used in this study:

Group	Mouse strain	Treatment	Dosing time (pre-injury; days)	Termination time (post injury; days)	N
1	WT	Vehicle	-8	10	10
2	Haem A	Vehicle	-8	10	10
3	Haem A	Fitusiran - 3 mg/kg s.c	-8	10	10
4	Haem A	Fitusiran - 10 mg/kg s.c	-8	10	10
5	Haem A	ETXM1184 - 3 mg/kg s.c.	-8	10	10
6	Haem A	ETXM1184 - 10 mg/kg s.c.	-8	10	10
7	Haem A	FVIII (Advate) - 300 IU/kg i.v	15 mins	10	10

[00413] 8 days prior to induction of knee bleed, mice were injected subcutaneously (s.c.) with the GalNAc-siRNA construct ETXM1184, fitusiran or a vehicle (0.9% saline) at a dose volume of 5 ml/kg. Advate was injected intravenously 15 minutes prior to joint bleed induction.

[00414] To induce knee bleed, mice were weighed and anaesthetised using isoflurane inhaled anaesthetic. Both legs were shaved to expose the knee joint. Mice were injected s.c. with buprenorphine at 10 ml/kg for analgesia and the diameter of both knees was measured with electronic calipers. Subsequently, both knees were wiped with 70% ethanol.

[00415] A 30 G sterile hypodermic needle was inserted into the infrapatellar ligament of one knee. The injected knee was randomised between left and right, and the injected side was recorded. Mice were removed from anaesthetic and allowed to recover in a warmed cage before being returned to the home cage.

[00416] Mice were monitored regularly for the first 6 hours and were injected subcutaneously with buprenorphine at 10 ml/kg for analgesia at 6 hours post injury. The visual bleeding score (VBS) of the injured knee was assessed at 72 hours and 10 days post-injury.

[00417] All mice were carefully inspected daily for clinical signs of excessive blood loss. Mice showing clinical signs of excessive blood loss, piloerection, withdrawing from cage mates or grimacing were killed for welfare reasons.

[00418] Mice were taken off study at 10 days post-injury.

[00419] A citrated blood sample was taken by cardiac puncture, under isoflurane anaesthesia, plasma prepared and aliquots frozen on dry ice before storing at -80°C. For that, blood was collected into 3.8% Sodium Citrate at a ratio of 1 to 9 followed by centrifugation at 7000 x g for 10 minutes at 4°C. In detail, the following steps were performed:

1. Collect blood by cardiac puncture.

2. Flush the syringe and needle with sodium citrate solution (3.8%), leaving solution in the hub of the syringe (~30 µl).

3. Following blood collection, expel sample into a 1.5 ml microcentrifuge tube and ensure sufficient sodium citrate solution (3.8%) is added to achieve a 1:9 ratio of sodium citrate:blood. Add the sodium citrate solution to the side of the tube, not directly to the sample. Mix by inverting 4-6 times. If not centrifuging sample immediately, keep in a fridge if available or alternatively on a wrapped ice block and continue to invert the collection tube regularly.

4. Centrifuge the samples as soon as possible at a spin speed of 7000 x g for 10 minutes at 4°C.

5. Remove all plasma from the sample and place into a fresh microcentrifuge tube.

6. Aliquot the plasma into pre-labelled tubes (Thermo Scientific; 10775974) as follows:

    - 30 µl for potential TGA assay
    - 100 µl for potential APTT assay
    - All remaining for potential target protein abundance analysis.

7. Place all aliquots on wet/dry ice immediately.

8. Transport samples on wet/dry ice.

9. Transfer samples to -20°C/-80°C freezer to be stored until use.

[00420] The liver was removed and up to 3 portions of each lobe were placed in RNA later and kept at 4°C for 24 to 72 hours. Tissue was then blotted dry, weighed and stored at -80°C. In detail, the following steps were performed:

1. Immediately after the cardiac puncture, kill the mouse by cervical dislocation.

2. Make an incision into the abdominal wall and remove the liver as quickly as possible.

3. Place the liver on a petri dish on wet ice, to minimise sample degradation.

4. Cut 3 x ~50 mg pieces of liver from each of the following lobes: left lateral lobe, medial lobe, right lateral lobe and caudate lobe. Place these liver pieces immediately into pre-labelled tubes (1.5 ml microcentrifuge tubes) containing 500 µl RNAlater, and place the collection tube on wet ice.

   a. Transport on wet ice and transfer to storage at 4˚C.

   b. After a period of 24-72 hours, blot the liver samples and weigh. Record the weights on the terminal sheet.

   c. Transfer to -80˚C for long-term storage.

5. Collect any spare liver and place into separate pre-labelled collection tubes (2 ml microcentrifuge tubes).

   a. Freeze on dry ice for potential future analyses.

   b. Transport samples on dry ice.

   c. Transfer to -80˚C for long-term storage.

6. Clean all dissection tools between animals to prevent any cross contamination.

[00421] The skin was removed from the legs and the knee joint measured. Legs were subsequently placed in 10% formalin before decalcification and slide preparation. In detail, the following steps were performed:

1. Following the removal of the liver, measure and record the diameter of both the injured and uninjured knee.

2. Remove the skin from both knees. Carry out a visual bleeding score and measure knee joints.

3. Dissect the legs from the top of the femur to the ankle joint and remove some excess muscle, being careful not to cause any damage to the knee and associated structures.

Place the knees in pre-labelled tubes (7 ml bijou tubes) containing 10% neutral buffered formalin to be processed for histological analysis.

[00422] Both at day 3 and day 10 after induction of knee bleed, Haem A mice that received the GalNAc-siRNA construct ETXM1184 showed a reduced visual bleeding score in comparison to Haem A mice that received the vehicle (0.9% saline) (see Fig.16A&B). Furthermore, the knee diameter of mice that received the GalNAc-siRNA construct ETXM1184 recovered faster following the induction of knee bleed compared to mice that received the vehicle (Fig 18 (top right)). This observation was confirmed by comparing the differences between the diameter of the injured and non-injured skinned knee diameter (Fig.18 (bottom left)).

[00423] Comparative data between ETXM1184 and fitusiran is provided in Figs. 13-18.

[00424] 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.

[00425] 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 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 nucleosides of said second and first strands comprise a 2' sugar modification pattern as follows (5'-3'):

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

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

2. A nucleic acid according to claim 1, wherein nucleosides of said second and first strands comprise a 2' sugar and bond modification pattern as follows (5'-3'):

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

or:

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

wherein (s) is a phosphorothioate internucleoside linkage.

3. A nucleic acid according to claim 1, wherein nucleosides of said second and first strands comprise a 2' sugar and abasic modification pattern as follows (5'-3'):

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

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

wherein ia represents an inverted abasic nucleoside.

4. A nucleic acid according to claim 1, wherein nucleosides of said second and first strands comprise a 2' sugar, abasic and bond modification pattern as follows (5'-3'):

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

or:

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 – Me,

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

wherein:

(s) is a phosphorothioate internucleoside linkage,

ia represents an inverted abasic nucleoside.

5. A nucleic acid according to any preceding claim, wherein said first strand comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 2.

6. A nucleic acid according to any preceding claim, wherein said first strand comprises at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the first strand sequences as listed in Table 3.

7. A nucleic acid according to claim 5 or 6, wherein the first strand comprises nucleosides 2-18 of any one of the sequences defined in claim 5 or 6.

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

9. A nucleic acid according to any preceding claim, wherein the second strand comprises a nucleoside sequence of at least 17 contiguous nucleosides differing by 0 or 1 nucleosides from any one of the second strand sequences as listed in Table 4, and wherein the second strand has a region of at least 85% complementarity over the 17 contiguous nucleosides to the first strand.

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

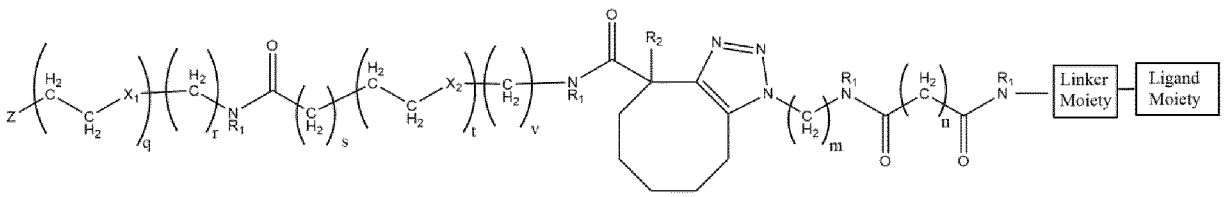
11. A nucleic acid according to any preceding claim, wherein the nucleic acid is conjugated directly or indirectly to one or more ligand moieties, optionally wherein said ligand moiety is present at a terminal region of the second strand, typically at the 3' terminal region thereof.

12. A nucleic acid according to claim 11, wherein the ligand moiety comprises:

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

13. A nucleic acid according to claim 12, wherein said one or more GalNAc ligands and / or GalNAc ligand derivatives are conjugated directly or indirectly to the 5' or 3' terminal region of the second strand of the nucleic acid, typically at the 3' terminal region thereof.

14. A nucleic acid according to any one of claims 11 to 13, 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;

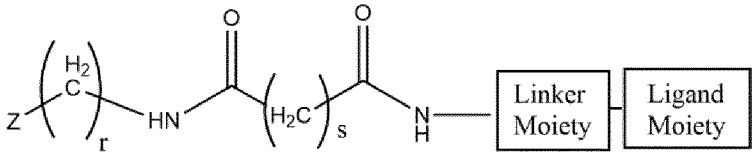
m is an integer of from 1 to 6;

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.

15. A nucleic acid according to any one of claims 11 to 13, having the structure:



wherein:

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

Z is an oligonucleoside.

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

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

18. 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.

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

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

Figure 1

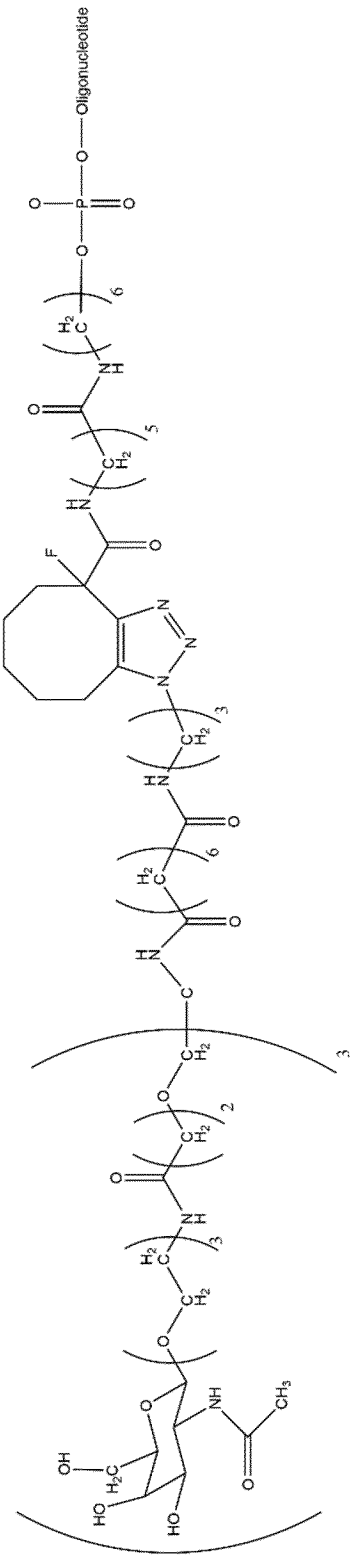


Figure 2

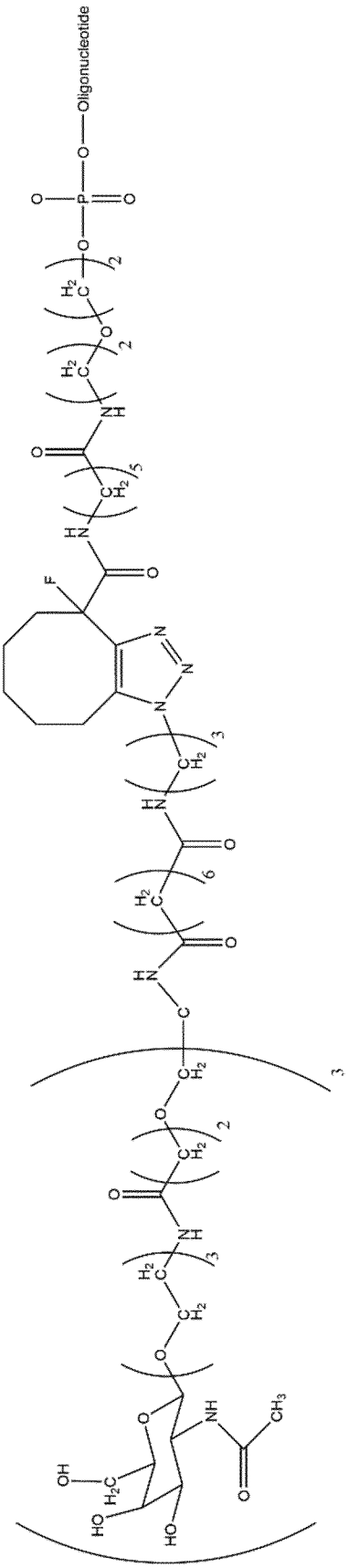
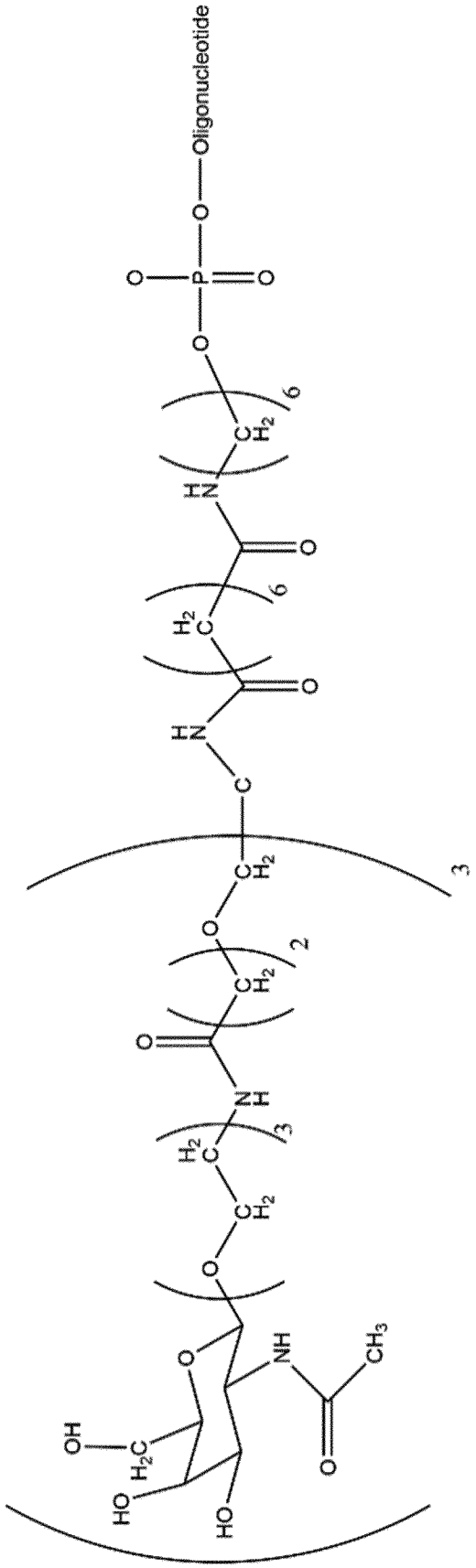


Figure 3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O
O
O
H2
C
6
N
H
O
6
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H2
C
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H2
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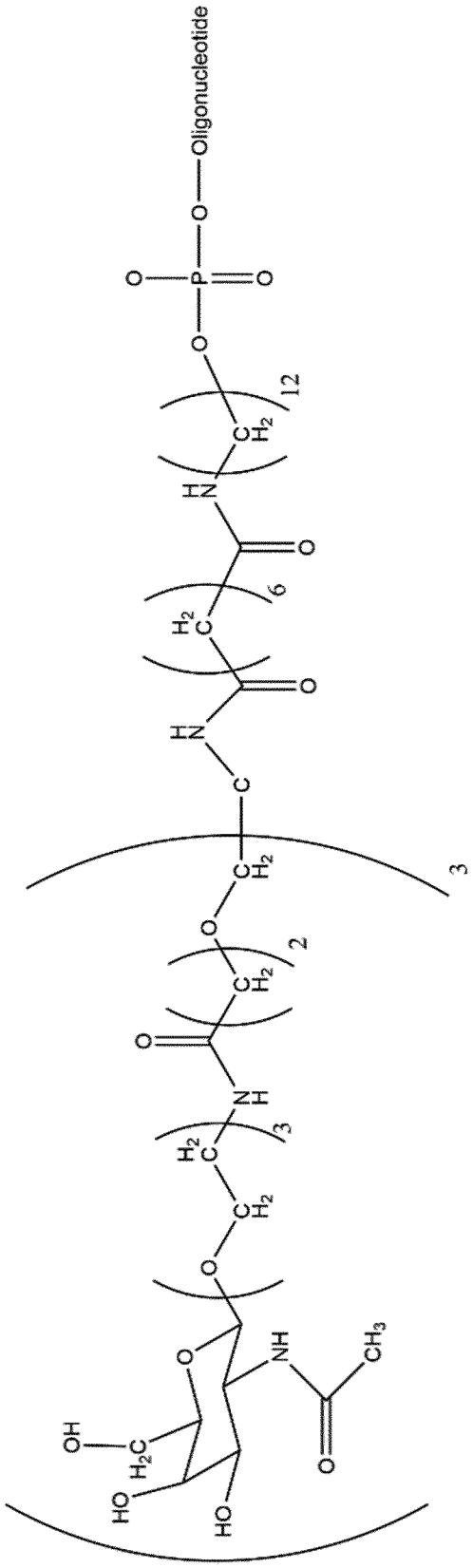
HO
HO

Figure 4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H2
C
O
N
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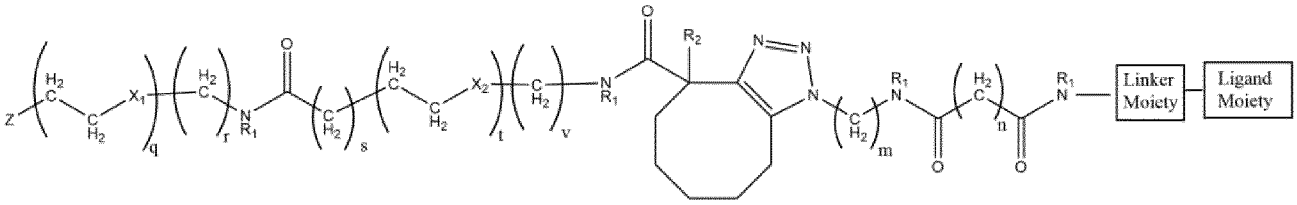
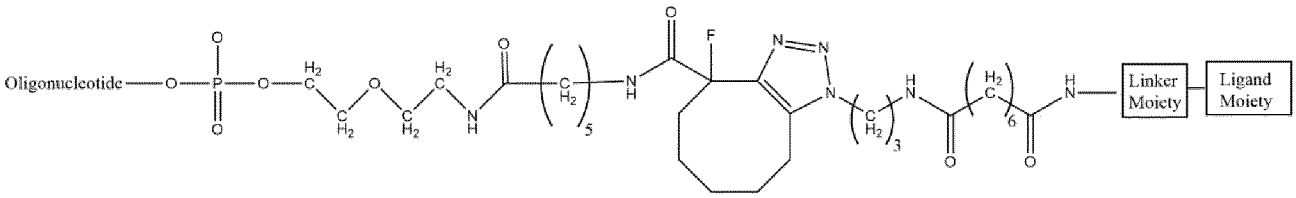
H2C
HO
HO

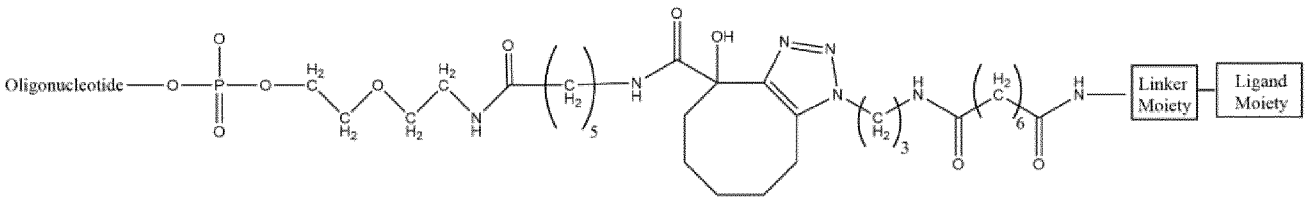
Figure 5 (from Sentences 1 – 101)



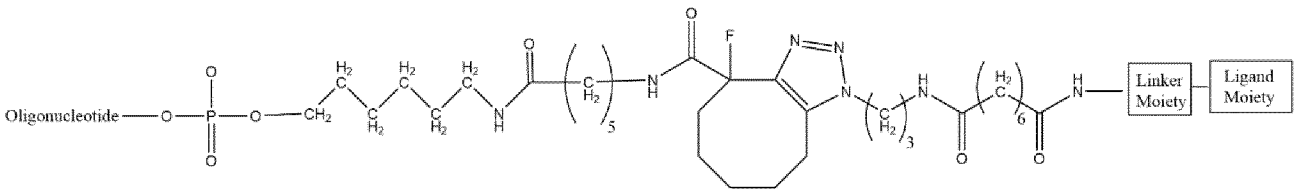
Formula (I)



Formula (II)

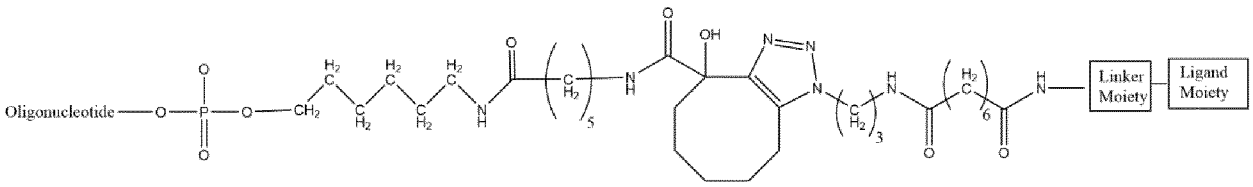


Formula (III)

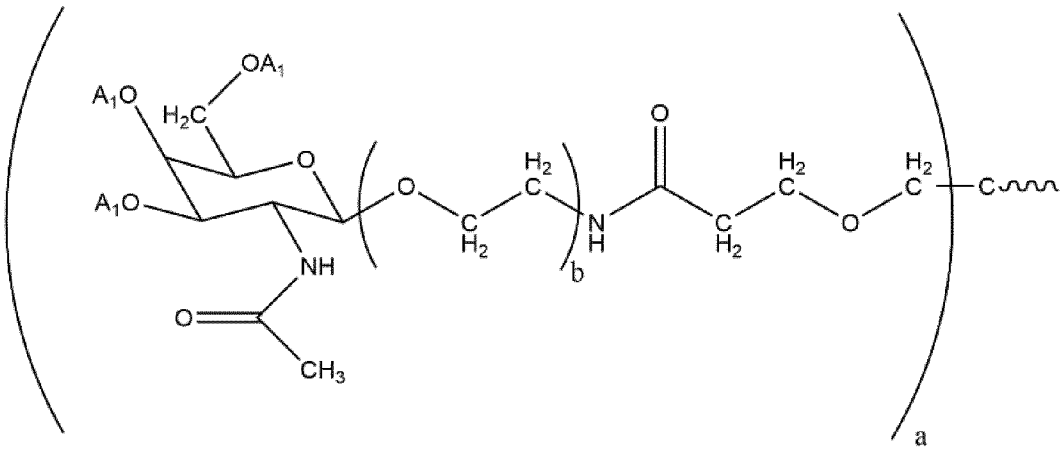


Formula (IV)

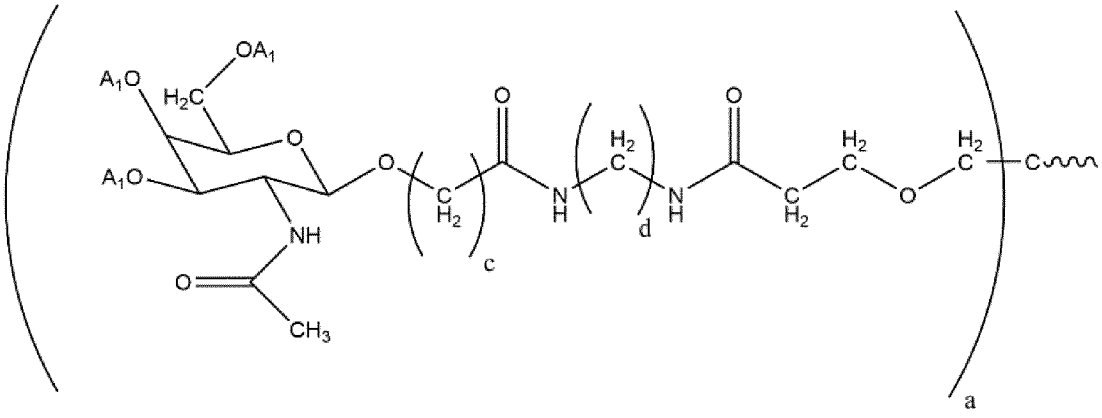
Figure 5 cont.



Formula (V)

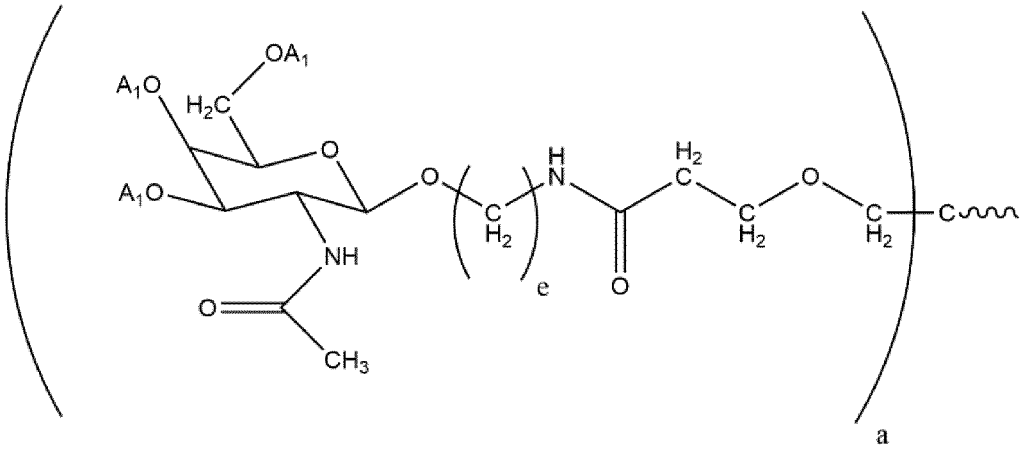


Formula (VIa)

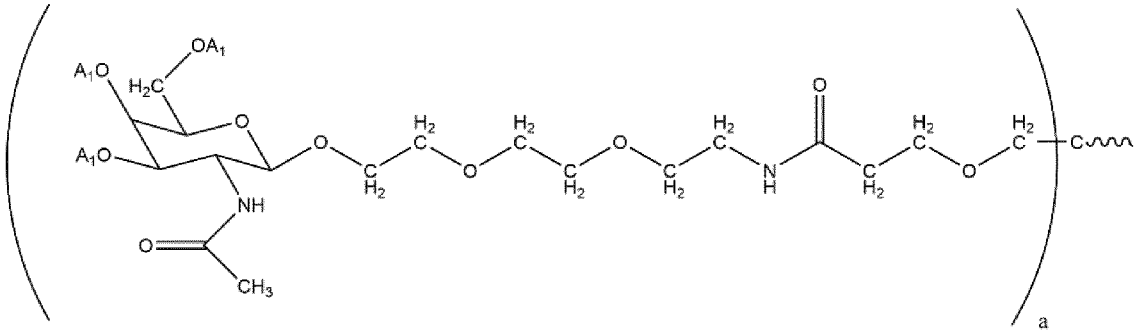


Formula (VIb)

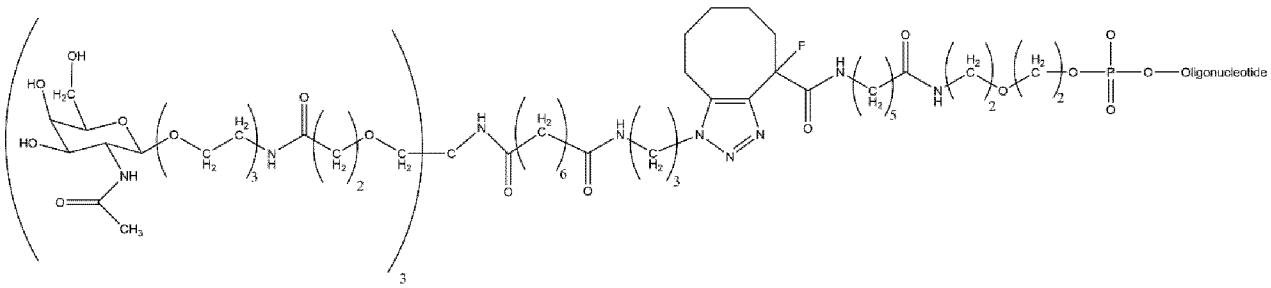
Figure 5 cont.



Formula (VIc)

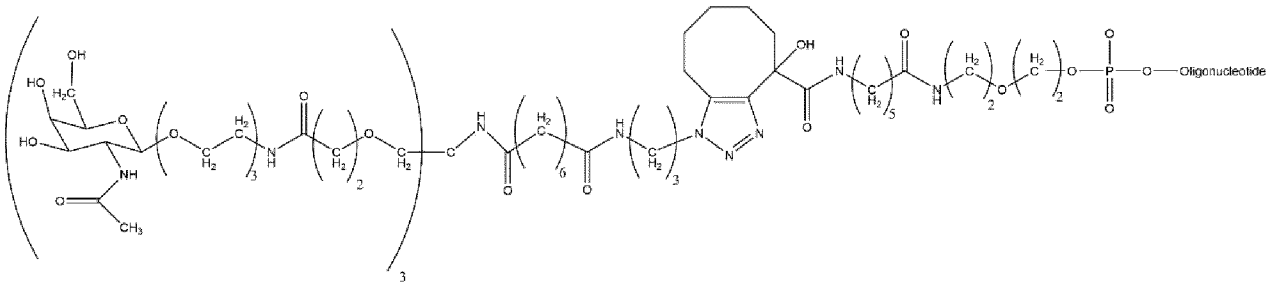


Formula (VII)

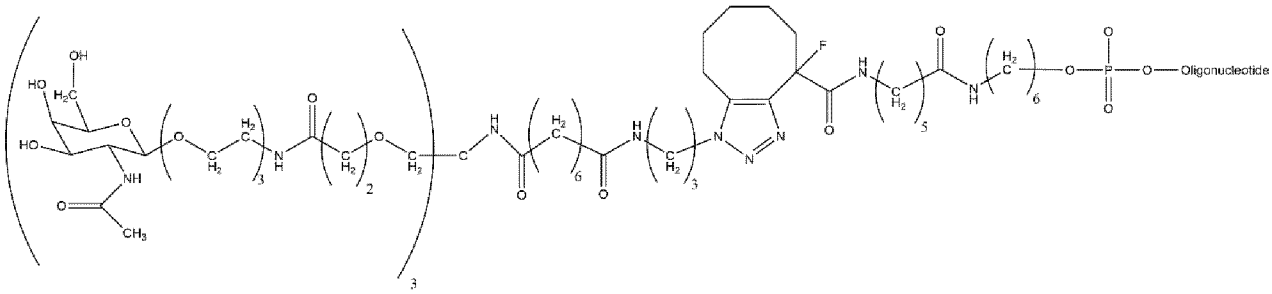


Formula (VIII)

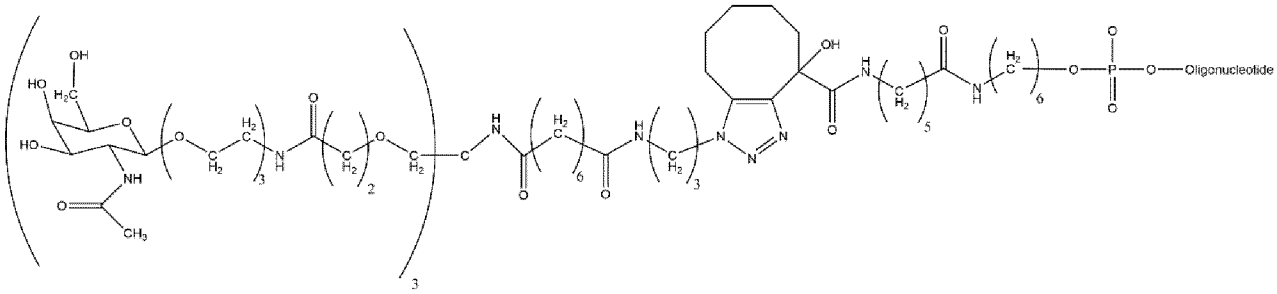
Figure 5 cont.



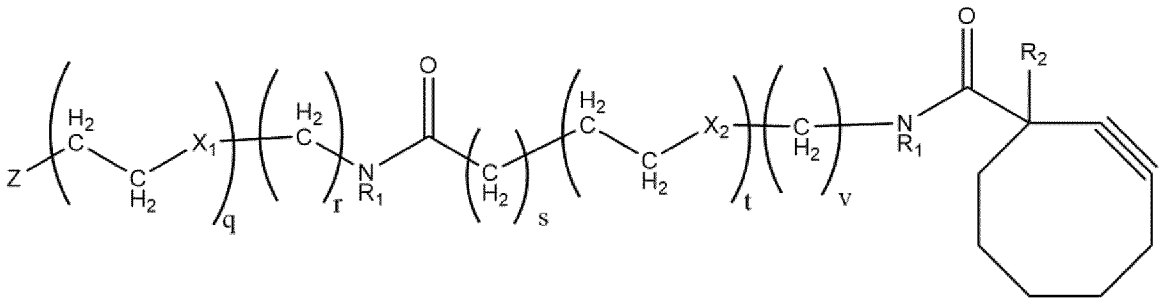
Formula (IX)



Formula (X)

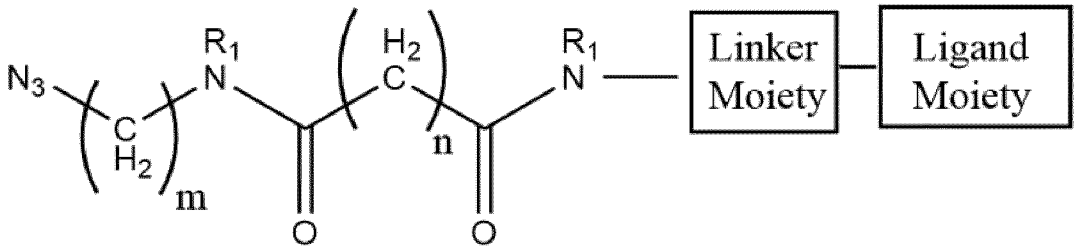


Formula (XI)

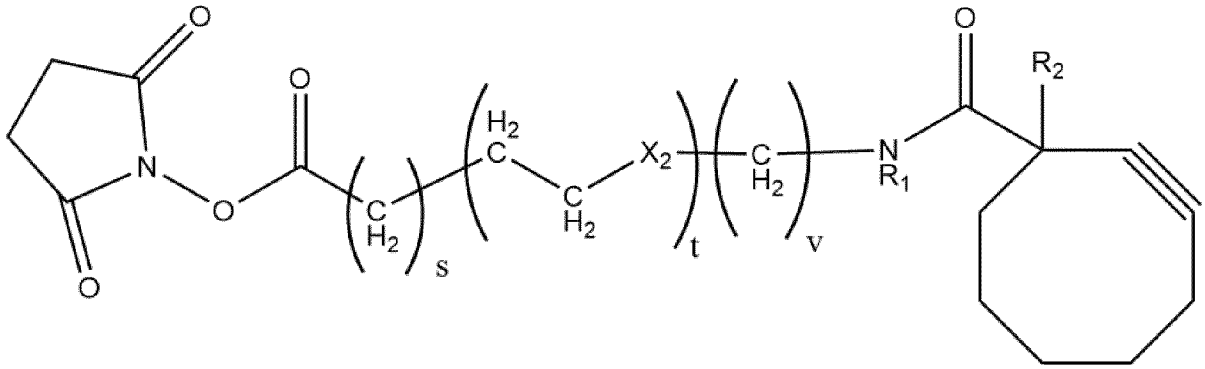


Formula (XII)

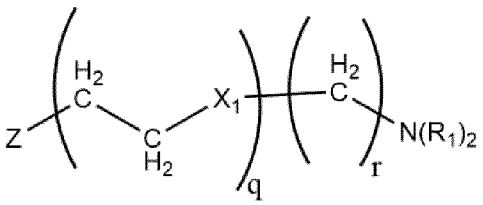
Figure 5 cont.



Formula (XIII)

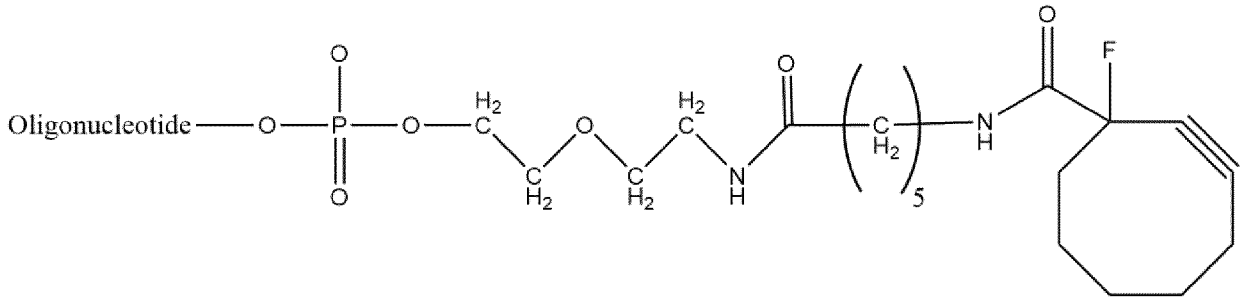


Formula (XIV)

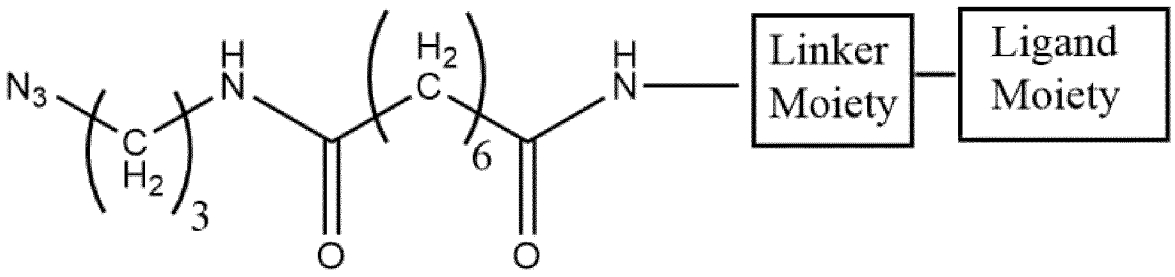


Formula (XV)

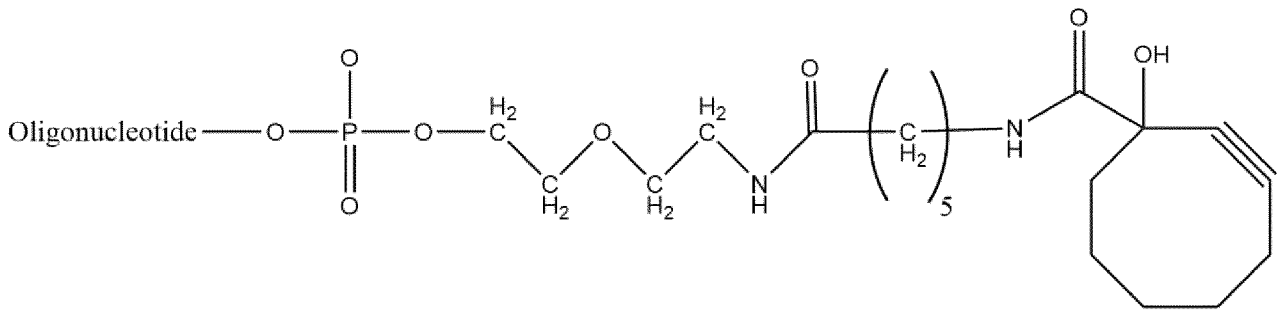
Figure 5 cont.



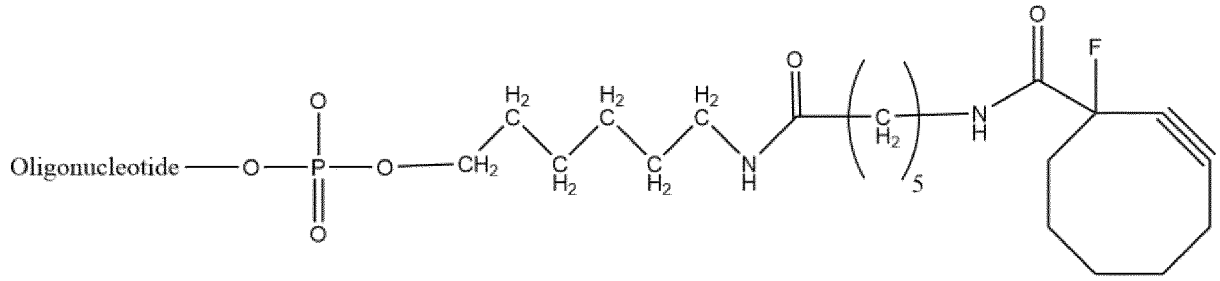
Formula (XIIa)



Formula (XIIIa)

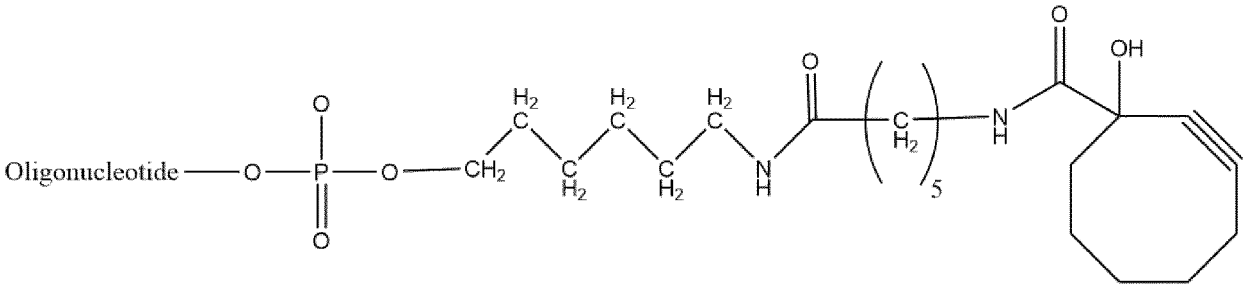


Formula (XIIb)

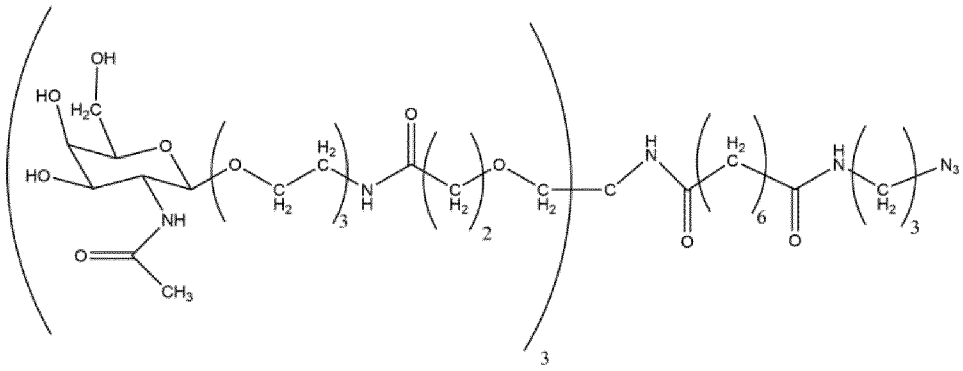


Formula (XIIc)

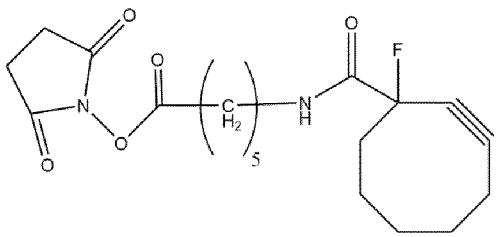
Figure 5 cont.



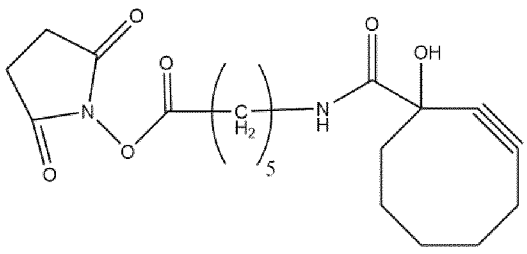
Formula (XIId)



Formula (XIIIb)

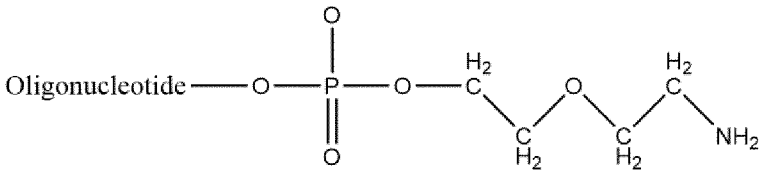


Formula (XIVa)

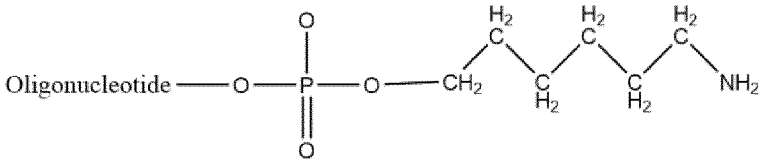


Formula (XIVb)

Figure 5 cont.

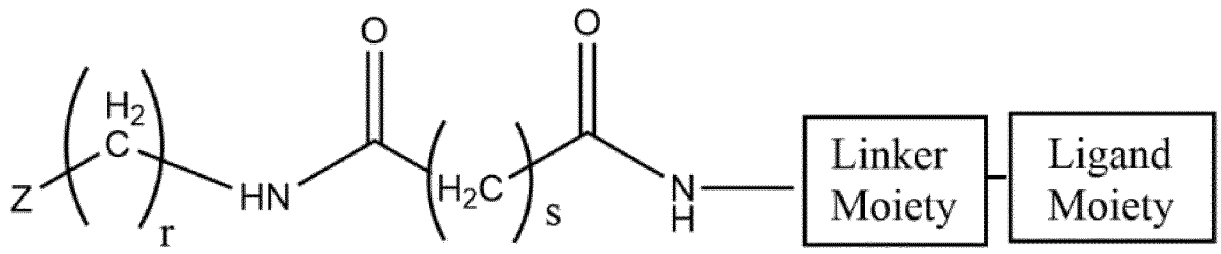


Formula (XVa)

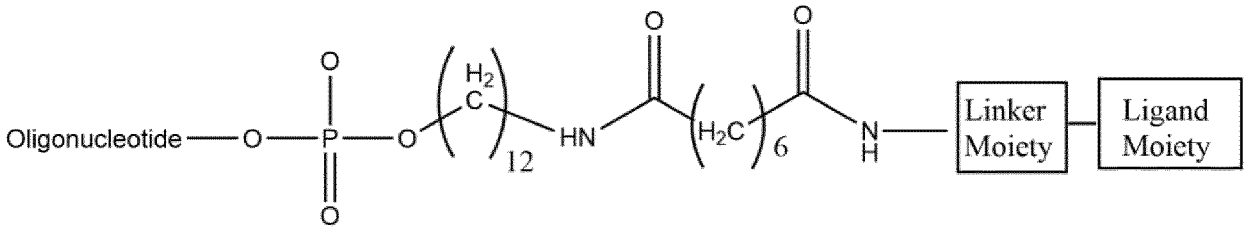


Formula (XVb)

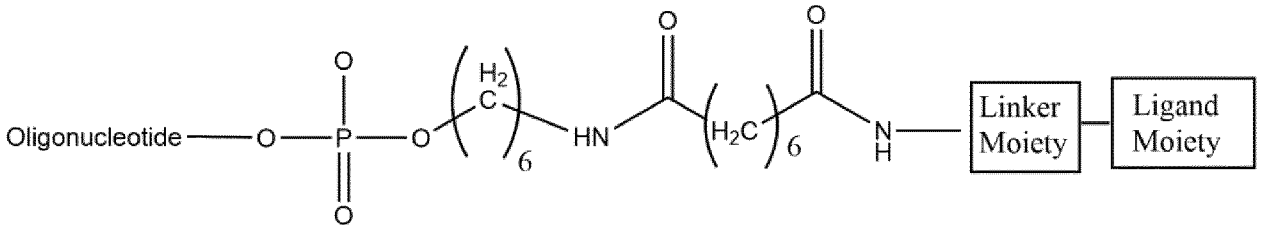
Figure 6 (Formulae from Clauses 1- 56)



Formula (I)

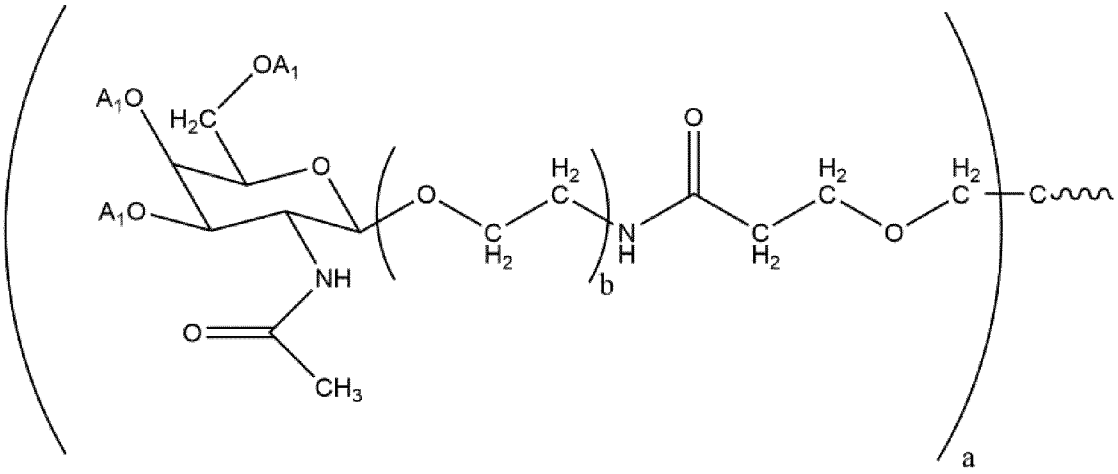


Formula (II)

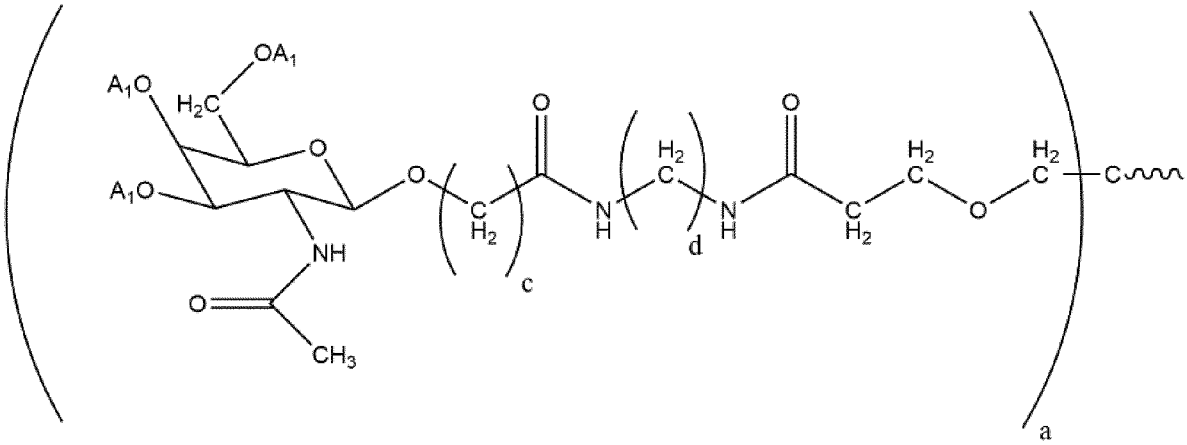


Formula (III)

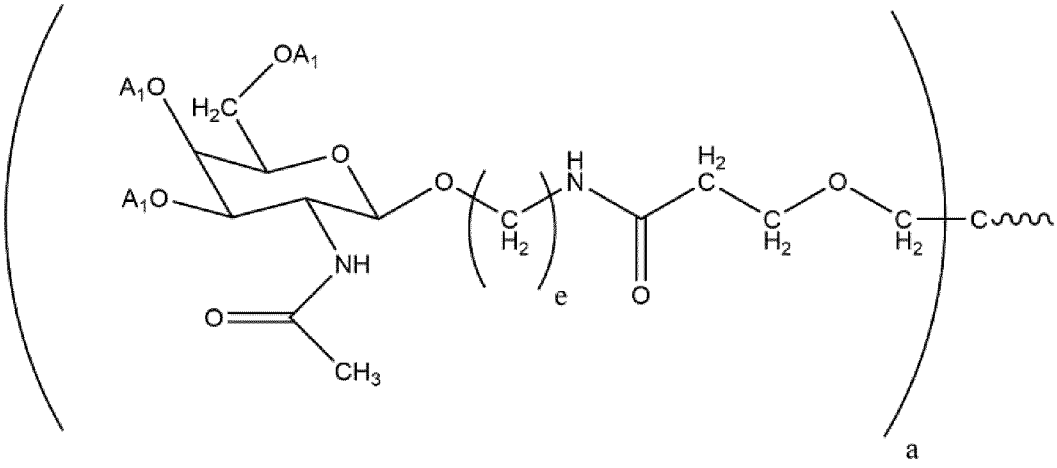
Figure 6 cont.



Formula (IV)

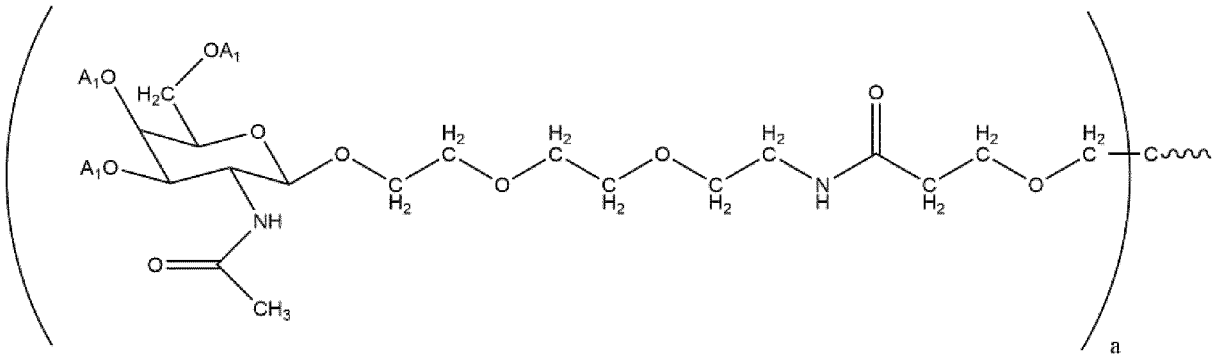


Formula (V)

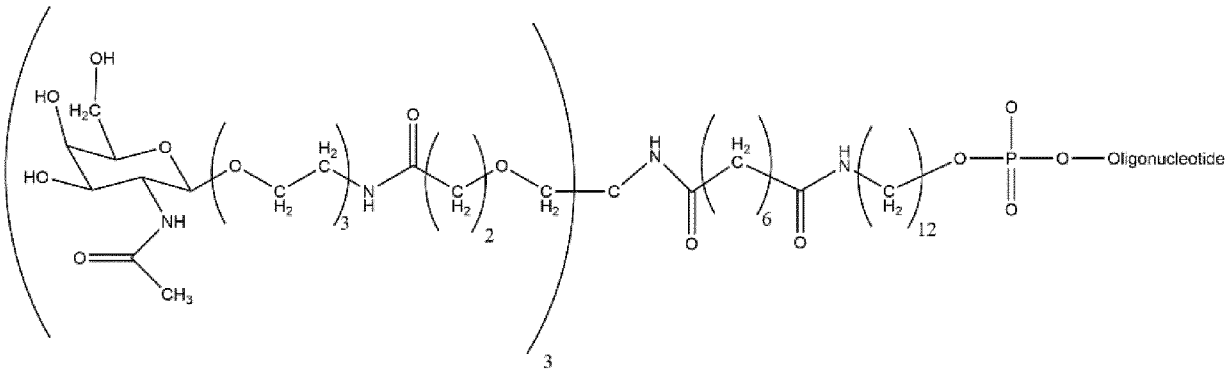


Formula (VI)

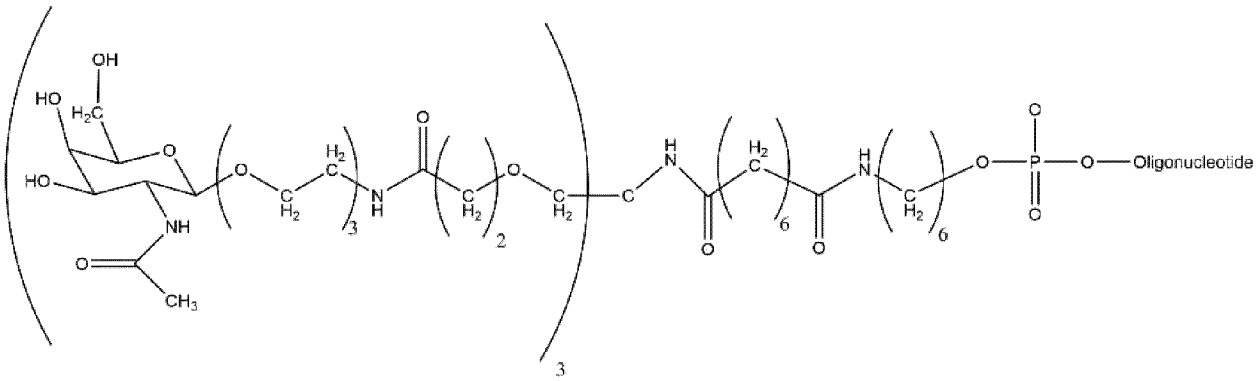
Figure 6 cont.



Formula (VII)

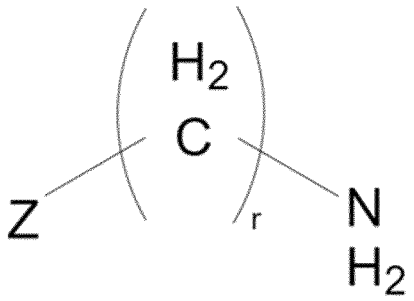


Formula (VIII)

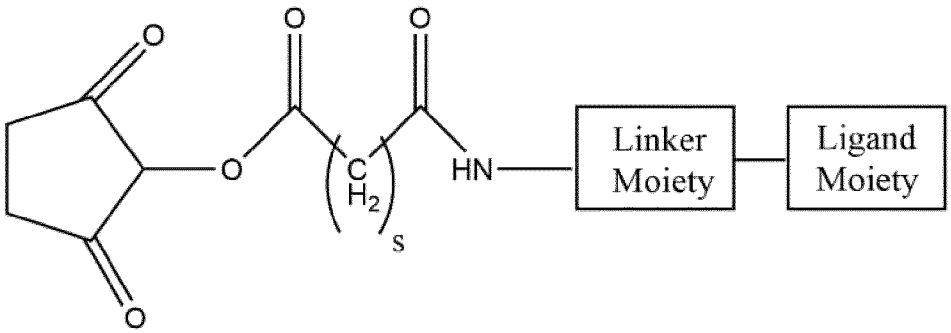


Formula (IX)

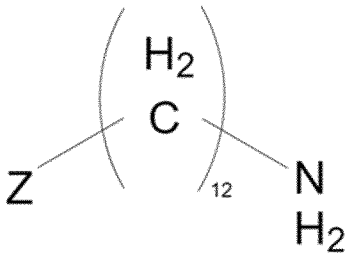
Figure 6 cont.



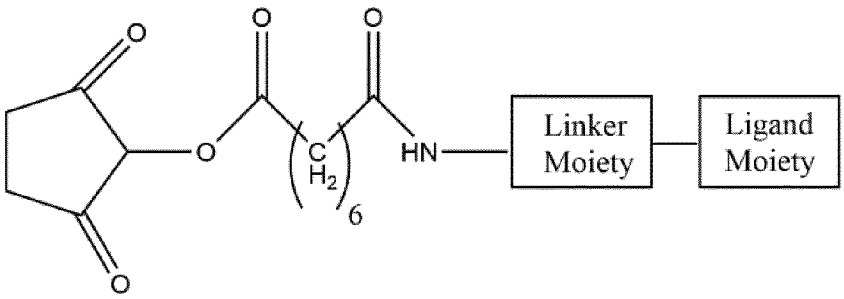
Formula (X)



Formula (XI)

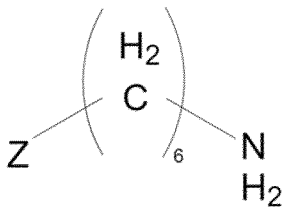


Formula (Xa)

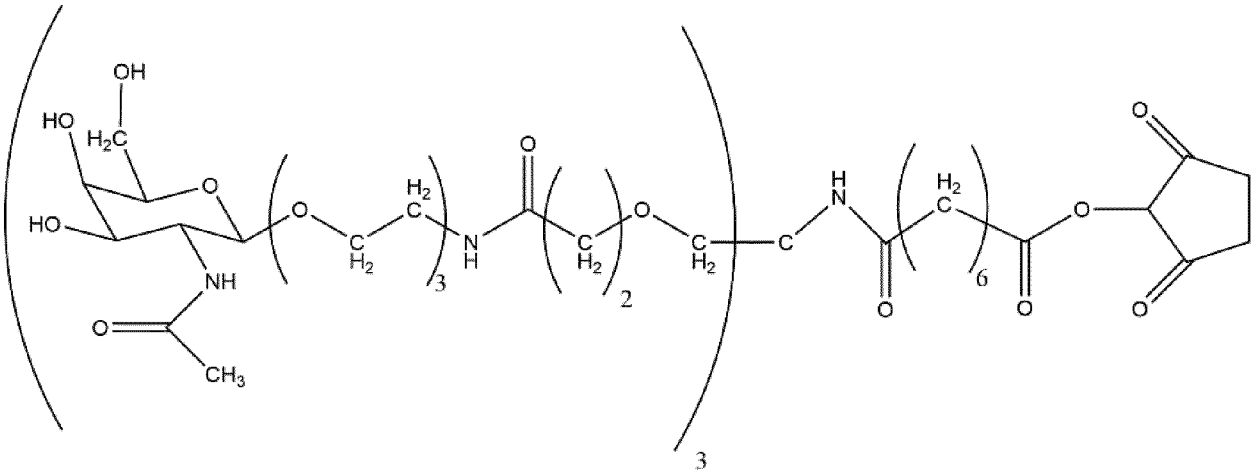


Formula (XIa)

Figure 6 cont.



Formula (Xb)



Formula (XIb)

Figure 7

Figure 7a:

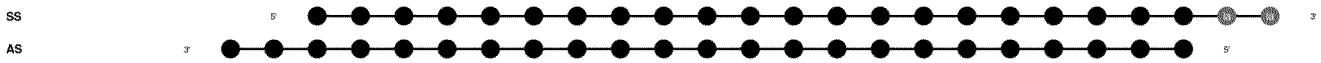


Figure 7b:

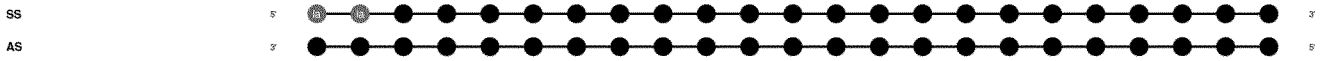


Figure 8:

Figure 8a:

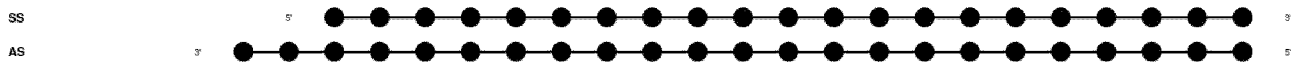


Figure 8b:

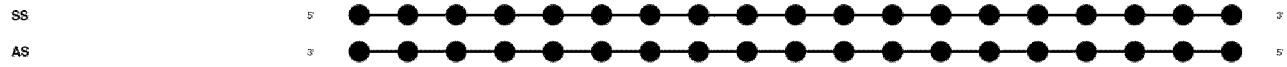


Figure 9a

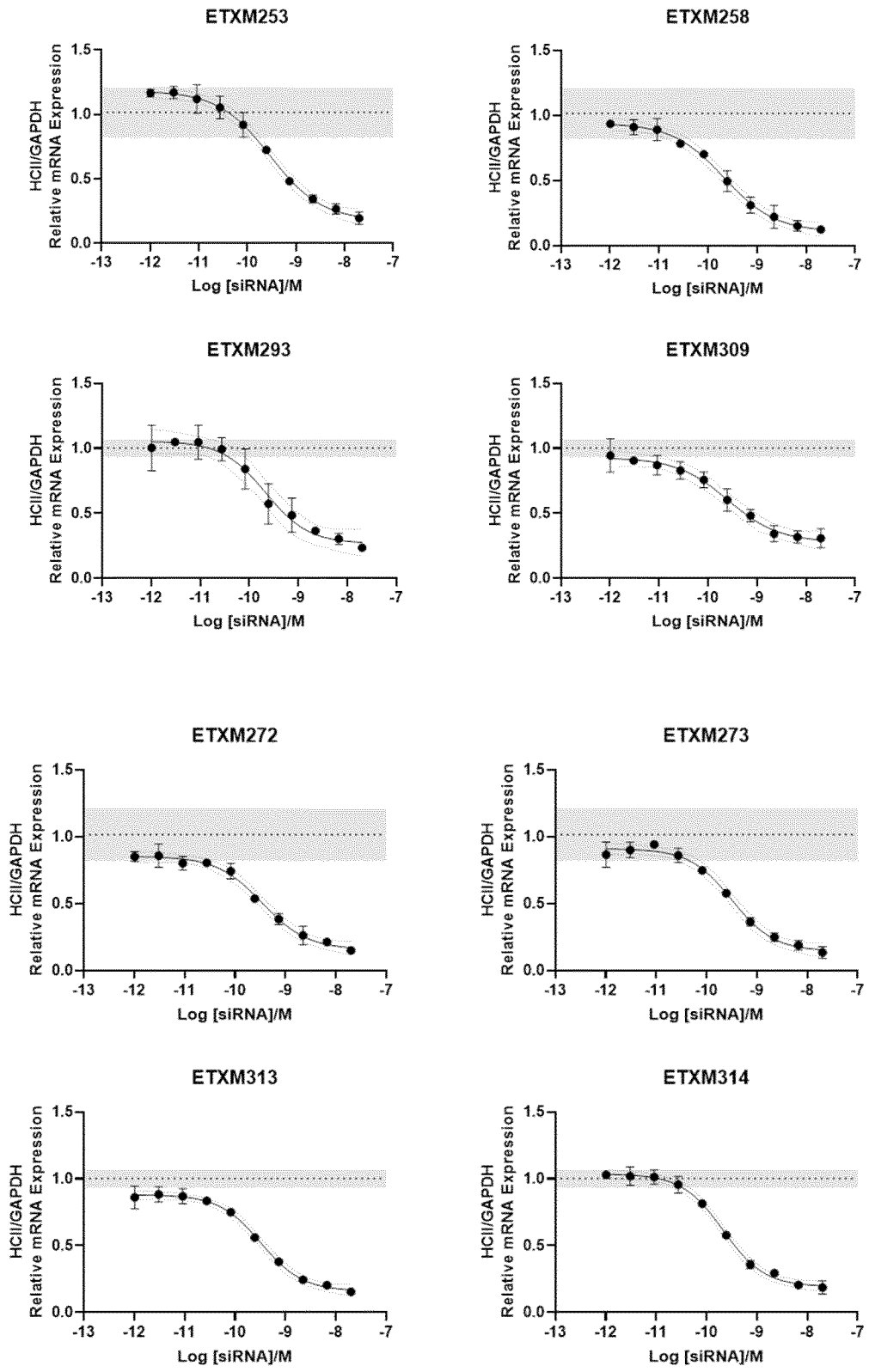

ETXM253
ETXM258
ETXM293
ETXM309
ETXM272
ETXM273
ETXM313
ETXM314
HCII/GAPDH
Relative mRNA Expression
Log [siRNA]/M
1.5
1.0
0.5
0.0
-13
-12
-11
-10
-9
-8
-7

Figure 9b

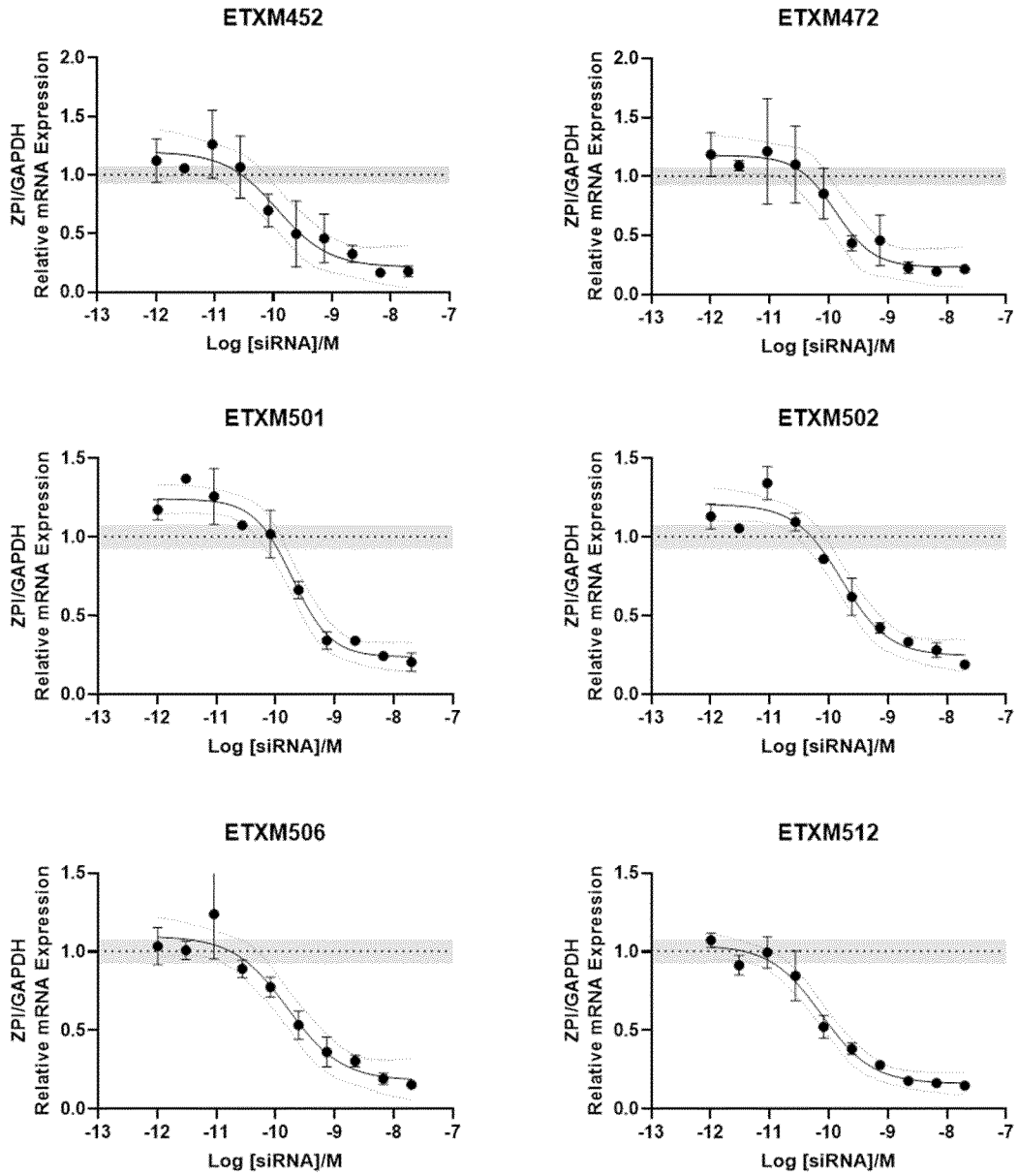

ETXM452
ETXM472
ETXM501
ETXM502
ETXM506
ETXM512
ZPI/GAPDH Relative mRNA Expression
Log [siRNA]/M

Figure 9b cont.

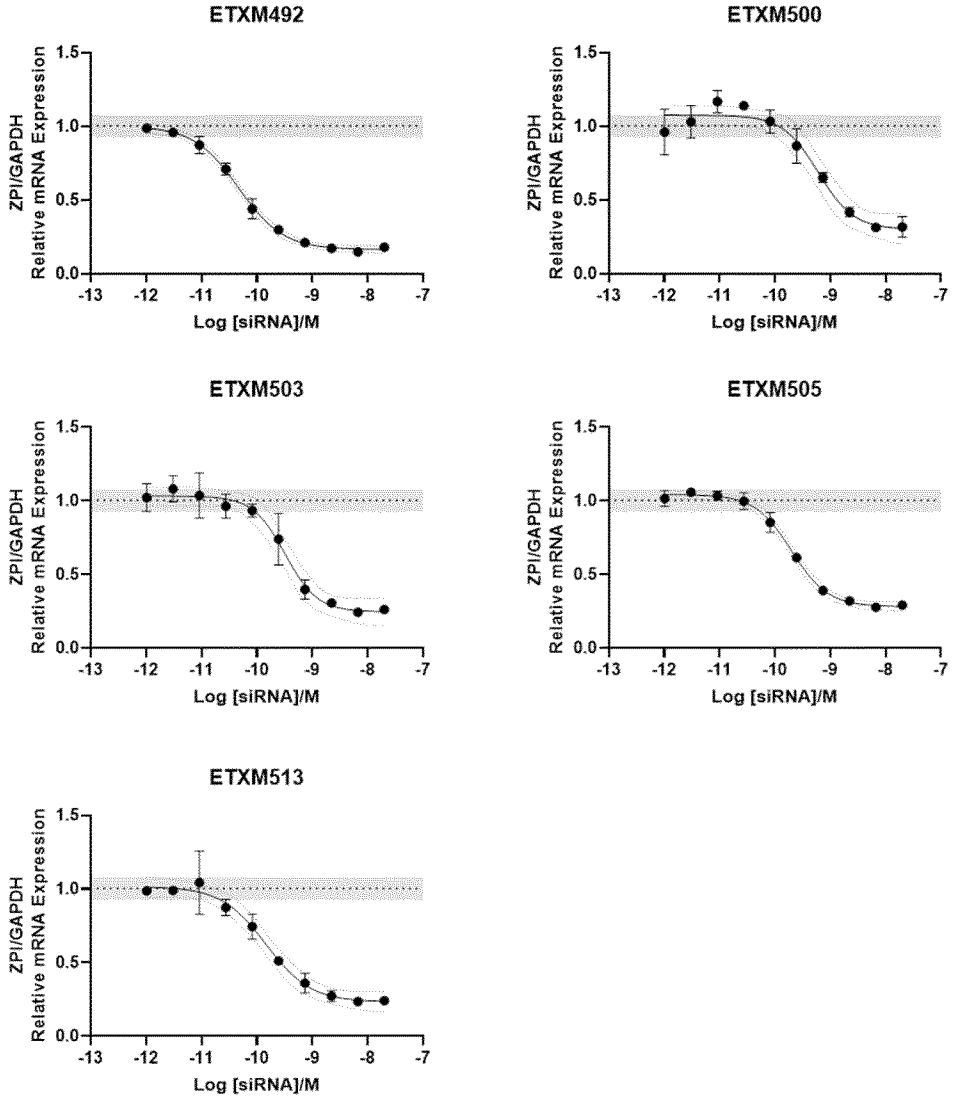


Figure 10

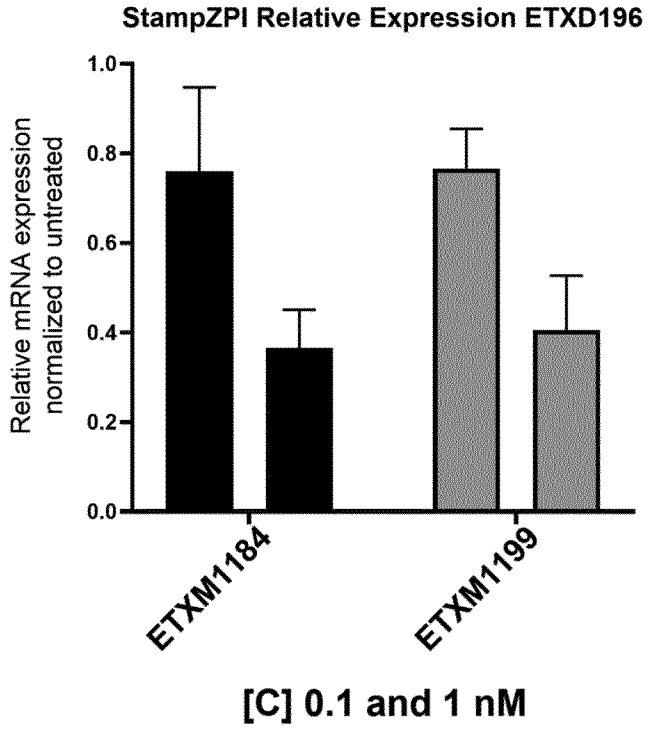


Figure 11

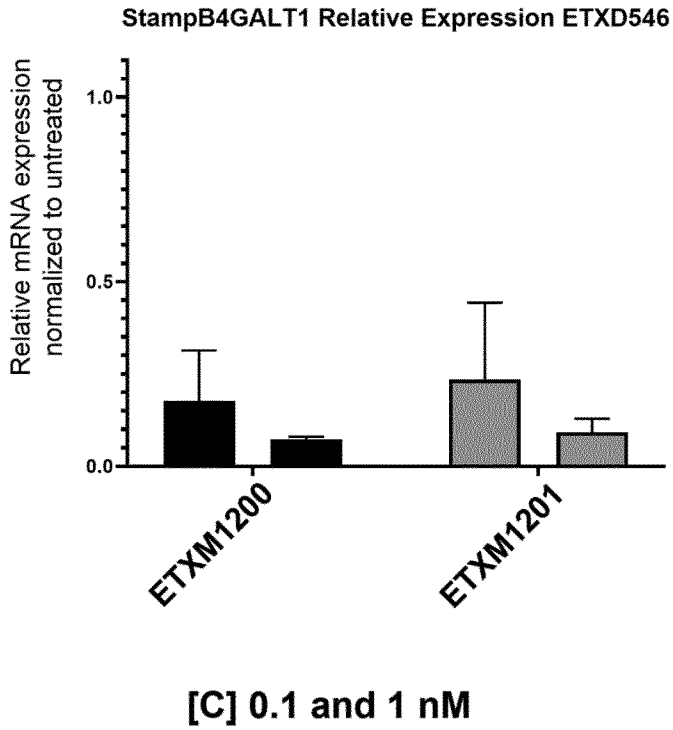


Figure 12

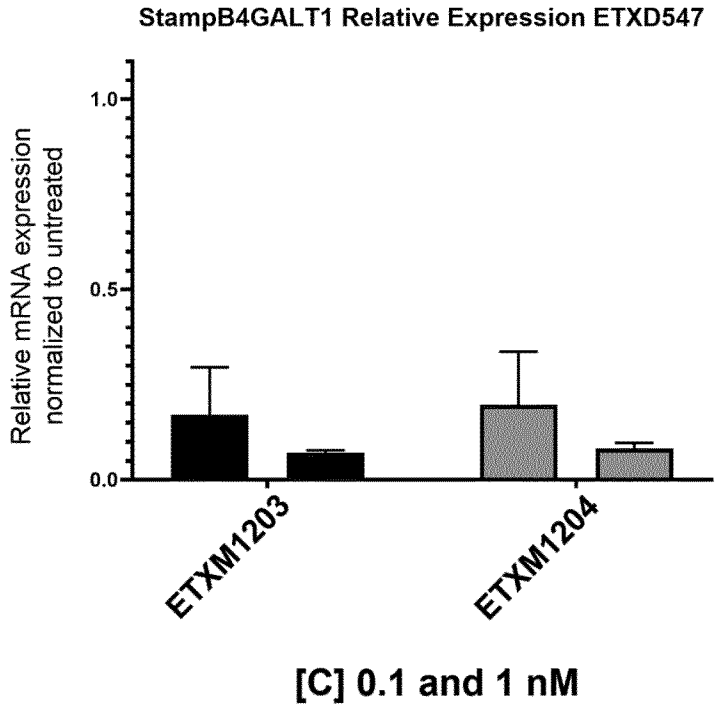

StampB4GALT1 Relative Expression ETXD547
Relative mRNA expression normalized to untreated
1.0
0.5
0.0
ETXM1203
ETXM1204
[C] 0.1 and 1 nM

Figure 13

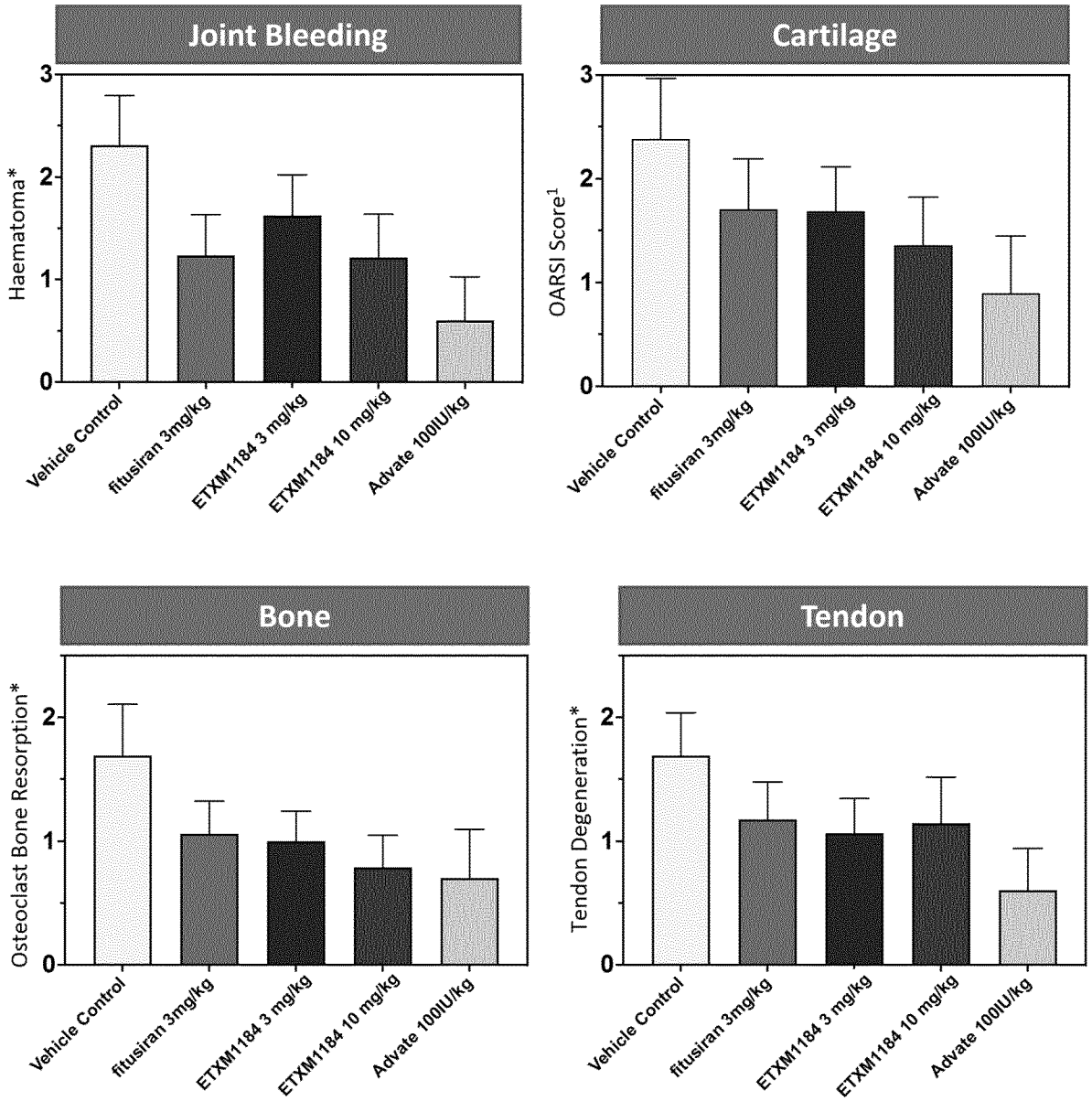

Joint Bleeding
Haematoma*
Cartilage
OARSI Score[1]
Bone
Osteoclast Bone Resorption*
Tendon
Tendon Degeneration*
Vehicle Control
fitusiran 3mg/kg
ETXM1184 3 mg/kg
ETXM1184 10 mg/kg
Advate 100IU/kg

Figure 14

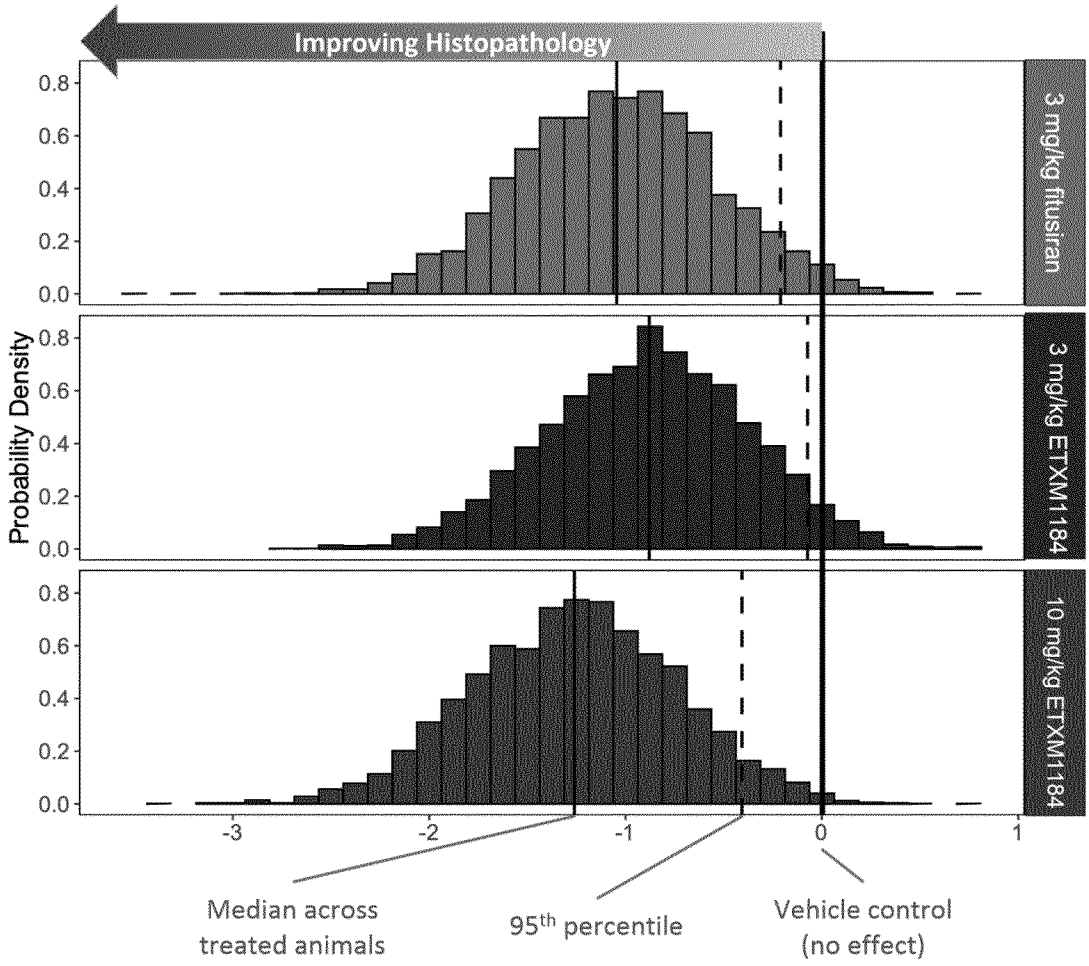

Improving Histopathology
Probability Density
0.0
0.2
0.4
0.6
0.8
3 mg/kg fitusiran
3 mg/kg ETXM1184
10 mg/kg ETXM1184
-3
-2
-1
0
1
Median across treated animals
95th percentile
Vehicle control (no effect)

Figure 15

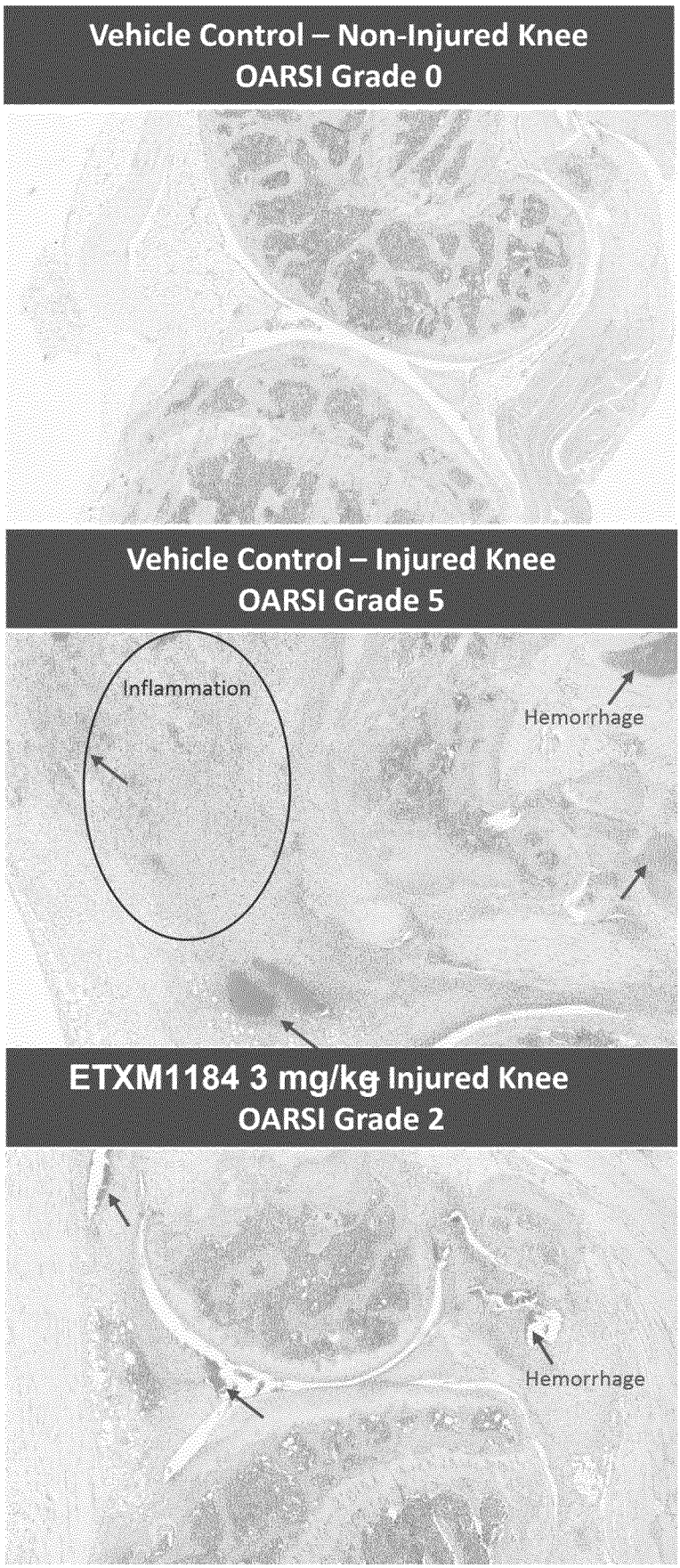

Vehicle Control – Non-Injured Knee
OARSI Grade 0
Vehicle Control – Injured Knee
OARSI Grade 5
Inflammation
Hemorrhage
ETXM1184 3 mg/kg Injured Knee
OARSI Grade 2
Hemorrhage

Figure 16

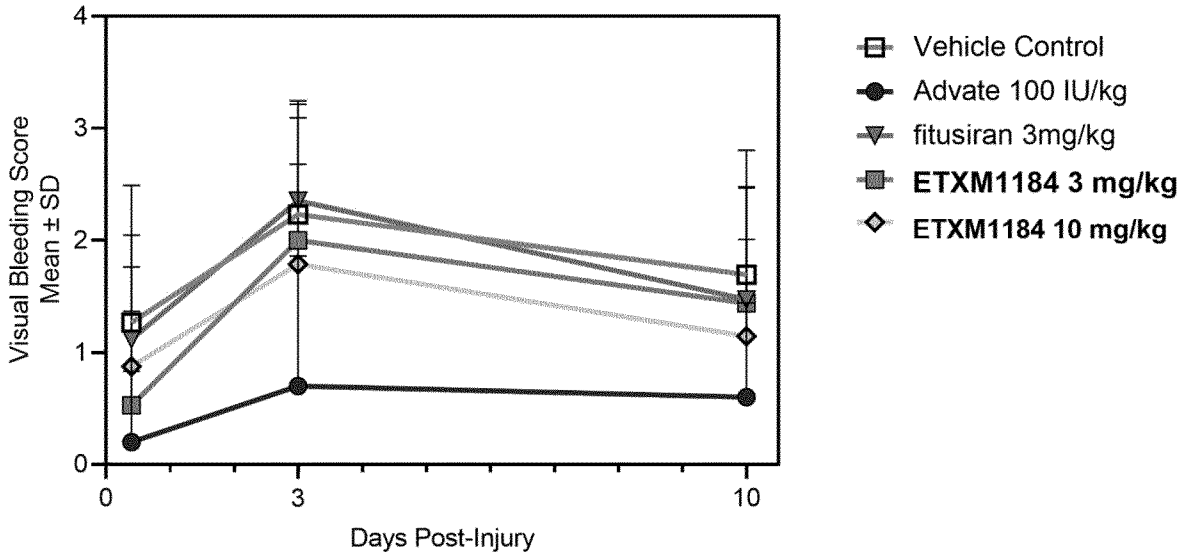

Visual Bleeding Score
Mean ± SD
4
3
2
1
0
0
3
10
Days Post-Injury
Vehicle Control
Advate 100 IU/kg
fitusiran 3mg/kg
ETXM1184 3 mg/kg
ETXM1184 10 mg/kg

Figure 16 cont.

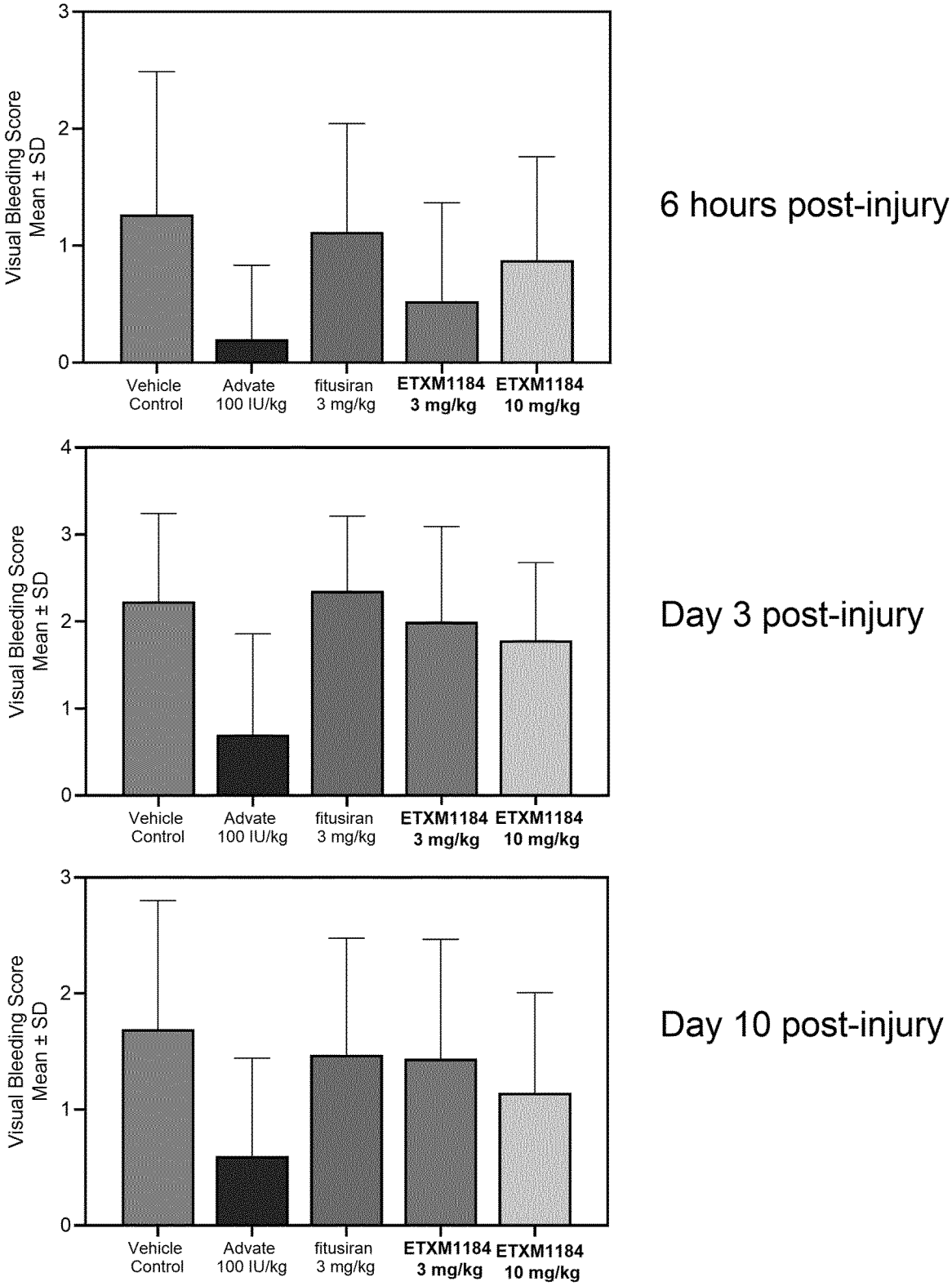
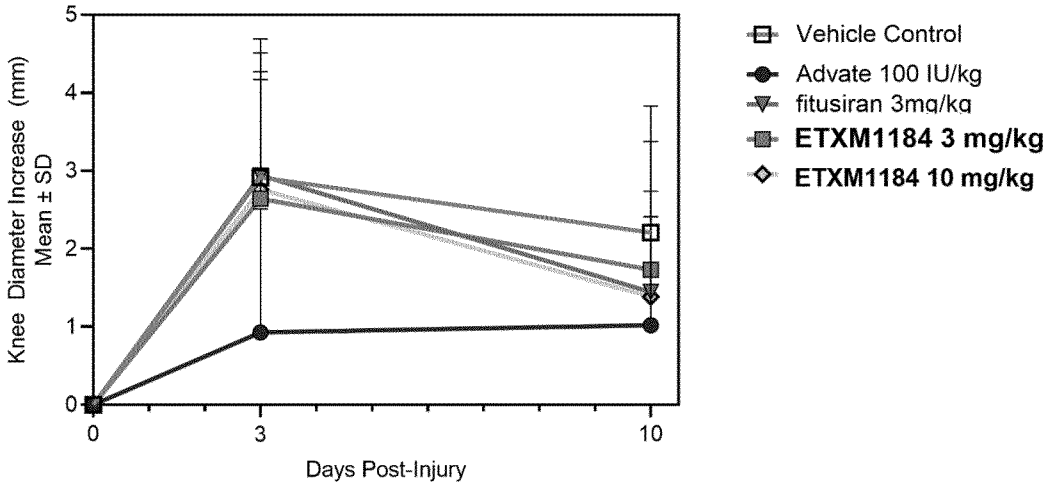
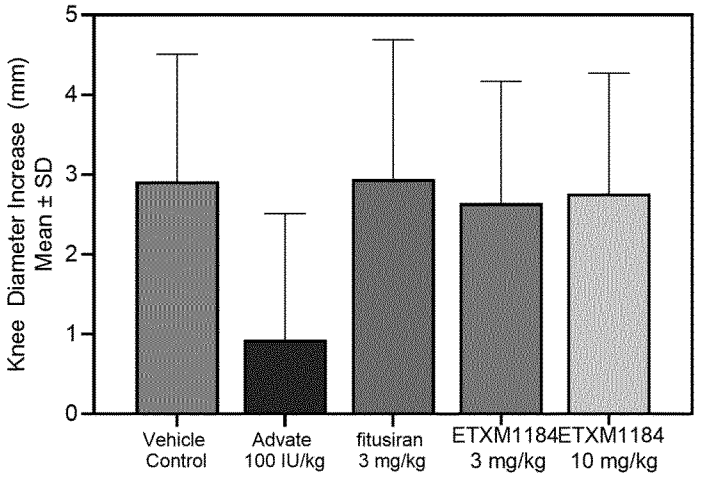
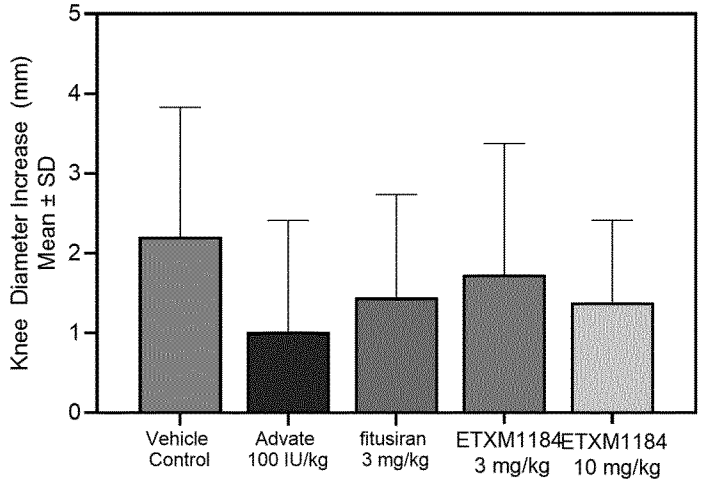


Figure 17



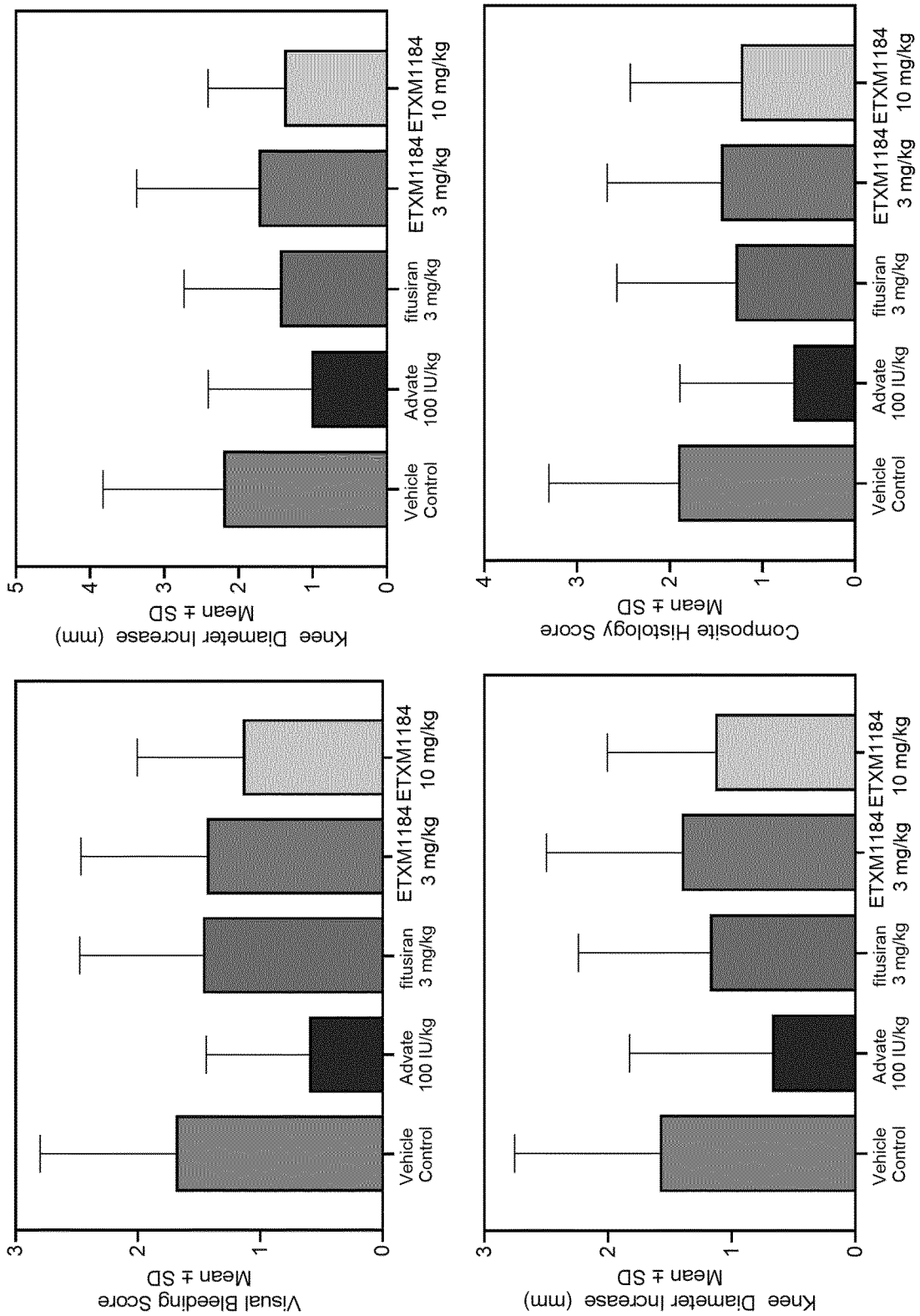


Day 3 post-injury



Day 10 post-injury

Figure 18


Knee Diameter Increase (mm)
Mean ± SD
0
1
2
3
4
5
Vehicle Control
Advate 100 IU/kg
fitusiran 3 mg/kg
ETXM1184 3 mg/kg
ETXM1184 10 mg/kg
Composite Histology Score
Mean ± SD
0
1
2
3
4
Vehicle Control
Advate 100 IU/kg
fitusiran 3 mg/kg
ETXM1184 3 mg/kg
ETXM1184 10 mg/kg
Visual Bleeding Score
Mean ± SD
0
1
2
3
Vehicle Control
Advate 100 IU/kg
fitusiran 3 mg/kg
ETXM1184 3 mg/kg
ETXM1184 10 mg/kg
Knee Diameter Increase (mm)
Mean ± SD
0
1
2
3
Vehicle Control
Advate 100 IU/kg
fitusiran 3 mg/kg
ETXM1184 3 mg/kg
ETXM1184 10 mg/kg