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WO-A2-2005/000201
WO-A2-2009/073809
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US-A1- 2009 326 040
US-A1- 2011 039 910
US-A1- 2011 201 798
MAIER, MA ET AL.: 'Synthesis Of Antisense Oligonucleotides Conjugated To A Multivalent Carbohydrate Cluster For Cellular Targeting.' BIOCONJUGATE CHEM. vol. 14, 03 December 2002, pages 18 - 29, XP002510288
AKINC, A ET AL.: 'Targeted Delivery Of RNAi Therapeutics With Endogenous And Exogenous Ligand-Based Mechanisms.' MOLECULAR THERAPY. vol. 18, no. 7, 11 May 2010, pages 1357 - 1364, XP055016290
MAKINO, N ET AL.: 'Intravenous Injection With Intravenous Injection With Antisense Oligodeoxynucleotides Against Angiotensinogen Decreases Blood Pressure In Spontaneously Hypertensive Rats.' HYPERTENSION.

Fortsættes ...

vol. 31, 1998, pages 1166 - 1170, XP002336133
KANASTY, R ET AL.: 'Delivery Materials For siRNA Therapeutics.' NATURE MATERIALS. vol. 12, 23 October 2013, pages 967 - 977, XP055181421

DESCRIPTION

BACKGROUND OF THE INVENTION

[0001] The principle behind antisense technology is that an antisense compound hybridizes to a target nucleic acid and modulates the amount, activity, and/or function of the target nucleic acid. For example in certain instances, antisense compounds result in altered transcription or translation of a target. Such modulation of expression can be achieved by, for example, target mRNA degradation or occupancy-based inhibition. An example of modulation of RNA target function by degradation is RNase H-based degradation of the target RNA upon hybridization with a DNA-like antisense compound. Another example of modulation of gene expression by target degradation is RNA interference (RNAi). RNAi refers to antisense-mediated gene silencing through a mechanism that utilizes the RNA-induced siliencing complex (RISC). An additional example of modulation of RNA target function is by an occupancy-based mechanism such as is employed naturally by microRNA. MicroRNAs are small non-coding RNAs that regulate the expression of protein-coding RNAs. The binding of an antisense compound to a microRNA prevents that microRNA from binding to its messenger RNA targets, and thus interferes with the function of the microRNA. MicroRNA mimics can enhance native microRNA function. Certain antisense compounds alter splicing of pre-mRNA. Regardless of the specific mechanism, sequence-specificity makes antisense compounds attractive as tools for target validation and gene functionalization, as well as therapeutics to selectively modulate the expression of genes involved in the pathogenesis of diseases.

[0002] Antisense technology is an effective means for modulating the expression of one or more specific gene products and can therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications. Chemically modified nucleosides may be incorporated into antisense compounds to enhance one or more properties, such as nuclease resistance, pharmacokinetics or affinity for a target nucleic acid. In 1998, the antisense compound, Vitravene® (fomivirsen; developed by Isis Pharmaceuticals Inc., Carlsbad, CA) was the first antisense drug to achieve marketing clearance from the U.S. Food and Drug Administration (FDA), and is currently a treatment of cytomegalovirus (CMV)-induced retinitis in AIDS patients.

[0003] New chemical modifications have improved the potency and efficacy of antisense compounds, uncovering the potential for oral delivery as well as enhancing subcutaneous administration, decreasing potential for side effects, and leading to improvements in patient convenience. Chemical modifications increasing potency of antisense compounds allow administration of lower doses, which reduces the potential for toxicity, as well as decreasing overall cost of therapy. Modifications increasing the resistance to degradation result in slower clearance from the body, allowing for less frequent dosing. Different types of chemical modifications can be combined in one compound to further optimize the compound's efficacy.

[0004] Lipoproteins are globular, micelle-like particles that consist of a non-polar core of acylglycerols and cholesteryl esters surrounded by an amphiphilic coating of protein, phospholipid and cholesterol. Lipoproteins have been classified into five broad categories on the basis of their functional and physical properties: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Chylomicrons transport dietary lipids from intestine to tissues. VLDLs, IDLs and LDLs all transport triacylglycerols and cholesterol from the liver to tissues. HDLs transport endogenous cholesterol from tissues to the liver

[0005] Lipoprotein particles undergo continuous metabolic processing and have variable properties and compositions. Lipoprotein densities increase without increasing particle diameter because the density of their outer coatings is less than that of the inner core. The protein components of lipoproteins are known as apolipoproteins. At least nine apolipoproteins are distributed in significant amounts among the various human lipoproteins.

[0006] The lipoprotein(a) [Lp(a)] particle was identified nearly 50 years ago and is comprised of a highly unique LDL particle in which one apolipoprotein B (apoB) protein is linked via a disulfide bond to a single apolipoprotein(a) [apo(a)] protein. The apo(a) protein shares a high degree of homology with plasminogen particularly within the

kringle IV type 2 repetitive domain. Levels of circulating Lp(a) are inversely proportional to the number of kringle IV type 2 variable repeats present in the molecule and, as both alleles are co-expressed within individuals, can display heterozygous plasma isoform profiles (Kraft et al., Eur J Hum Genet, 1996; 4(2): 74-87). It is thought that this kringle repeat domain in apo(a) may be responsible for its pro-thrombotic and anti-fibrinolytic properties, potentially enhancing atherosclerotic progression.

[0007] Apo(a) is transcriptionally regulated by IL-6 and in studies in rheumatoid arthritis patients treated with an IL-6 inhibitor (tocilizumab), plasma levels were reduced by 30% after 3 month treatment (Schultz et al., PLoS One 2010; 5:e14328).

[0008] Apo(a) has been shown to preferentially bind oxidized phospholipids and potentiate vascular inflammation (Bergmark et al., J Lipid Res 2008; 49:2230-2239; Tsimikas et al., Circulation. 2009; 119(13):1711-1719).

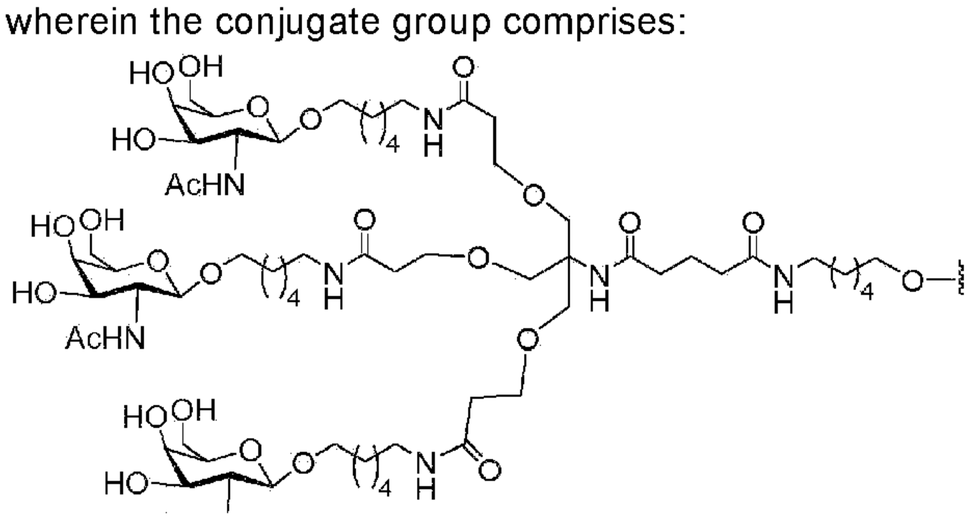
[0009] Further, studies suggest that the Lp(a) particle may also stimulate endothelial permeability, induce plasminogen activator inhibitor type-1 expression and activate macrophage interleukin-8 secretion (Koschinsky and Marcovina, Curr Opin Lipidol 2004; 15:167-174). Importantly, recent genetic association studies revealed that Lp(a) was an independent risk factor for myocardial infarction, stroke, peripheral vascular disease and abdominal aortic aneurysm (Rifai et al., Clin Chem 2004; 50:1364-71; Erqou et al., JAMA 2009;302:412-23; Kamstrup et al., Circulation 2008;117:176-84). Further, in the recent Precocious Coronary Artery Disease (PROCARDIS) study, Clarke *et al.* (Clarke et al., NEJM (2009)361; 2518-2528) described robust and independent associations between coronary heart disease and plasma Lp(a) concentrations. Additionally, Solfrizzi et al., suggested that increased serum Lp(a) may be linked to an increased risk for Alzheimer's Disease (AD) (Solfrizzi et al., J Neurol Neurosurg Psychiatry 2002, 72:732-736. Currently, in the clinic setting, examples of indirect apo(a) inhibitors for treating cardiovascular disease include aspirin, Niaspan, Mipomersen, Anacetrapib, Epirotirome and Lomitapide which reduce plasma Lp(a) levels by 18%, 39%, 32%, 36%, 43% and 17%, respectively. Additionally, Lp(a) apheresis has been used in the clinic to reduce apo(a) containing Lp(a) particles.

[0010] To date, therapeutic strategies to treat cardiovascular disease by directly targeting apo(a) levels have been limited. Ribozyme oligonucleotides (U.S. Patent 5,877,022) and antisense oligonucleotides (WO 2005/000201; WO 2003/014397; WO2013/177468; US20040242516; U.S. Patent Nos. 8,138,328, 8,673,632 and 7,259,150; Merki et al., J Am Coll Cardiol 2011; 57:1611-1621) have been developed but none have been approved for commercial use.

[0011] Thus, there remains a clear unmet medical need for novel agents which can potently and selectively reduce apo(a) levels in patients at enhanced risk for cardiovascular events due to chronically elevated plasma Lp(a) levels.

SUMMARY OF THE INVENTION

[0012] The present invention provides a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising 20 contiguous nucleobases complementary to an equal length portion of nucleobases 3901 to 3920 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to SEQ ID NO: 1; and wherein the conjugate group comprises:



AcHN

[0013] The present invention also provides a pharmaceutical composition comprising the compound of the invention and a pharmaceutically acceptable diluent or carrier.

[0014] The present invention also provides the compound of the invention for use in treating, preventing, or slowing progression of a disease related to elevated apo(a) and/or elevated Lp(a).

SUMMARY OF THE DISCLOSURE

[0015] Disclosed herein are compositions and methods for modulating expression of apo(a) mRNA and protein. In certain embodiments, the apo(a) specific inhibitor decreases expression of apo(a) mRNA and protein. Disclosed herein are compositions and methods for modulating expression of Lp(a) levels.

[0016] In certain embodiments, the composition is an apo(a) specific inhibitior. In certain embodiments, the apo(a) specific inhibitor is a nucleic acid, protein, or small molecule. In certain embodiments, the apo(a) specific inhibitor is an antisense oligonucleotide targeting apo(a) with a conjugate. In certain embodiments, the apo(a) specific inhibitor is a modified oligonucleotide and a conjugate, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases complementary to an equal length portion of nucleobases 3901 to 3920 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1. In certain embodiments, the apo(a) specific inhibitor is a modified oligonucleotide and a conjugate, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, least 9, least 10, least 11, at least 12, least 13, at least 14, at least 15, at least 16, least 17, least 18, least 19, or 20 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 1-130, 133, 134. In certain embodiments, the apo(a) specific inhibitor is a modified oligonucleotide and a conjugate, wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NO: 58, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein at least one internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0017] Certain embodiments of the present disclosure provide a composition comprising a conjugated antisense compound described herein, or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0018] In certain embodiments, the modulation of apo(a) expression occurs in a cell or tissue. In certain embodiments, the modulations occur in a cell or tissue in an animal. In certain embodiments, the animal is a human. In certain embodiments, the modulation is a reduction in apo(a) mRNA level. In certain embodiments, the modulation is a reduction in apo(a) protein level. In certain embodiments, both apo(a) mRNA and protein levels are reduced. In certain embodiments, the modulation is a reduction in Lp(a) level. Such reduction may occur in a time-dependent or in a dose-dependent manner.

[0019] Certain embodiments of the present disclosure provide conjugated antisense compositions and methods for use in therapy. Certain embodiments of the present disclosure provide compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating apo(a) related diseases, disorders, and conditions. Certain embodiments of the present disclosure provide compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating Lp(a) related diseases, disorders, and conditions. In certain embodiments, such diseases, disorders, and conditions are inflammatory, cardiovascular and/or metabolic diseases, disorders, and conditions. In certain embodiments, the compositions and methods for therapy include

administering an apo(a) specific inhibitor to an individual in need thereof. In certain embodiments, the apo(a) specific inhibitor is a nucleic acid. In certain embodiments, the nucleic acid is an antisense compound. In certain embodiments, the antisense compound is a modified oligonucleotide. In certain embodiments, the antisense compound is a modified oligonucleotide with a conjugate.

[0020] In certain embodiments, the present disclosure provides conjugated antisense compounds. In certain embodiments, the present disclosure provides conjugated antisense compounds comprising an antisense oligonucleotide complementary to a nucleic acid transcript. In certain embodiments, the present disclosure provides methods comprising contacting a cell with a conjugated antisense compound comprising an antisense oligonucleotide complementary to a nucleic acid transcript. In certain embodiments, the present disclosure provides methods comprising contacting a cell with a conjugated antisense compound comprising an antisense oligonucleotide and reducing the amount or activity of a nucleic acid transcript in a cell.

[0021] The asialoglycoprotein receptor (ASGP-R) has been described previously. See e.g., Park et al., PNAS vol. 102, No. 47, pp 17125-17129 (2005). Such receptors are expressed on liver cells, particularly hepatocytes. Further, it has been shown that compounds comprising clusters of three N-acetylgalactosamine (GalNAc) ligands are capable of binding to the ASGP-R, resulting in uptake of the compound into the cell. See e.g., Khorev et al., Bioorganic and Medicinal Chemistry, 16, 9, pp 5216-5231 (May 2008). Accordingly, conjugates comprising such GalNAc clusters have been used to facilitate uptake of certain compounds into liver cells, specifically hepatocytes. For example it has been shown that certain GalNAc-containing conjugates increase activity of duplex siRNA compounds in liver cells in vivo. In such instances, the GalNAc-containing conjugate is typically attached to the sense strand of the siRNA duplex. Since the sense strand is discarded before the antisense strand ultimately hybridizes with the target nucleic acid, there is little concern that the conjugate will interfere with activity. Typically, the conjugate is attached to the 3' end of the sense strand of the siRNA. See e.g., U.S. Patent 8,106,022. Certain conjugate groups described herein are more active and/or easier to synthesize than conjugate groups previously described.

[0022] In certain embodiments of the present disclosure, conjugates are attached to single-stranded antisense compounds, including, but not limited to RNase H based antisense compounds and antisense compounds that alter splicing of a pre-mRNA target nucleic acid. In such embodiments, the conjugate should remain attached to the antisense compound long enough to provide benefit (improved uptake into cells) but then should either be cleaved, or otherwise not interfere with the subsequent steps necessary for activity, such as hybridization to a target nucleic acid and interaction with RNase H or enzymes associated with splicing or splice modulation. This balance of properties is more important in the setting of single-stranded antisense compounds than in siRNA compounds, where the conjugate may simply be attached to the sense strand. Disclosed herein are conjugated single-stranded antisense compounds having improved potency in liver cells in vivo compared with the same antisense compound lacking the conjugate. Given the required balance of properties for these compounds such improved potency is surprising.

[0023] In certain embodiments, conjugate groups herein comprise a cleavable moiety. As noted, without wishing to be bound by mechanism, it is logical that the conjugate should remain on the compound long enough to provide enhancement in uptake, but after that, it is desirable for some portion or, ideally, all of the conjugate to be cleaved, releasing the parent compound (e.g., antisense compound) in its most active form. In certain embodiments, the cleavable moiety is a cleavable nucleoside. Such embodiments take advantage of endogenous nucleases in the cell by attaching the rest of the conjugate (the cluster) to the antisense oligonucleotide through a nucleoside via one or more cleavable bonds, such as those of a phosphodiester linkage. In certain embodiments, the cluster is bound to the cleavable nucleoside through a phosphodiester linkage. In certain embodiments, the cleavable nucleoside is attached to the antisense oligonucleotide (antisense compound) by a phosphodiester linkage. In certain embodiments, the conjugate group may comprise two or three cleavable nucleosides. In such embodiments, such cleavable nucleosides are linked to one another, to the antisense compound and/or to the cluster via cleavable bonds (such as those of a phosphodiester linkage). Certain conjugates herein do not comprise a cleavable nucleoside and instead comprise a cleavable bond. It is shown that that sufficient cleavage of the conjugate from the oligonucleotide is provided by at least one bond that is vulnerable to cleavage in the cell (a

cleavable bond).

[0024] In certain embodiments, conjugated antisense compounds are prodrugs. Such prodrugs are administered to an animal and are ultimately metabolized to a more active form. For example, conjugated antisense compounds are cleaved to remove all or part of the conjugate resulting in the active (or more active) form of the antisense compound lacking all or some of the conjugate.

[0025] In certain embodiments, conjugates are attached at the 5' end of an oligonucleotide. Certain such 5'-conjugates are cleaved more efficiently than counterparts having a similar conjugate group attached at the 3' end. In certain embodiments, improved activity may correlate with improved cleavage. In certain embodiments, oligonucleotides comprising a conjugate at the 5' end have greater efficacy than oligonucleotides comprising a conjugate at the 3' end (see, for example, Examples 56, 81, 83, and 84). Further, 5'-attachment allows simpler oligonucleotide synthesis. Typically, oligonucleotides are synthesized on a solid support in the 3' to 5' direction. To make a 3'-conjugated oligonucleotide, typically one attaches a pre-conjugated 3' nucleoside to the solid support and then builds the oligonucleotide as usual. However, attaching that conjugated nucleoside to the solid support adds complication to the synthesis. Further, using that approach, the conjugate is then present throughout the synthesis of the oligonucleotide and can become degraded during subsequent steps or may limit the sorts of reactions and reagents that can be used. Using the structures and techniques described herein for 5'-conjugated oligonucleotides, one can synthesize the oligonucleotide using standard automated techniques and introduce the conjugate with the final (5'-most) nucleoside or after the oligonucleotide has been cleaved from the solid support.

[0026] In view of the art and the present disclosure, one of ordinary skill can easily make any of the conjugates and conjugated oligonucleotides herein. Moreover, synthesis of certain such conjugates and conjugated oligonucleotides disclosed herein is easier and/or requires few steps, and is therefore less expensive than that of conjugates previously disclosed, providing advantages in manufacturing. For example, the synthesis of certain conjugate groups consists of fewer synthetic steps, resulting in increased yield, relative to conjugate groups previously described. Conjugate groups such as GalNAc3-10 in Example 46 and GalNAc3-7 in Example 48 are much simpler than previously described conjugates such as those described in U.S. 8,106,022 or U.S. 7,262,177 that require assembly of more chemical intermediates . Accordingly, these and other conjugates described herein have advantages over previously described compounds for use with any oligonucleotide, including single-stranded oligonucleotides and either strand of double-stranded oligonucleotides (e.g., siRNA).

[0027] Similarly, disclosed herein are conjugate groups having only one or two GalNAc ligands. As shown, such conjugates groups improve activity of antisense compounds. Such compounds are much easier to prepare than conjugates comprising three GalNAc ligands. Conjugate groups comprising one or two GalNAc ligands may be attached to any antisense compounds, including single-stranded oligonucleotides and either strand of double-stranded oligonucleotides (e.g., siRNA).

[0028] In certain embodiments, the conjugates herein do not substantially alter certain measures of tolerability. For example, it is shown herein that conjugated antisense compounds are not more immunogenic than unconjugated parent compounds. Since potency is improved, embodiments in which tolerability remains the same (or indeed even if tolerability worsens only slightly compared to the gains in potency) have improved properties for therapy.

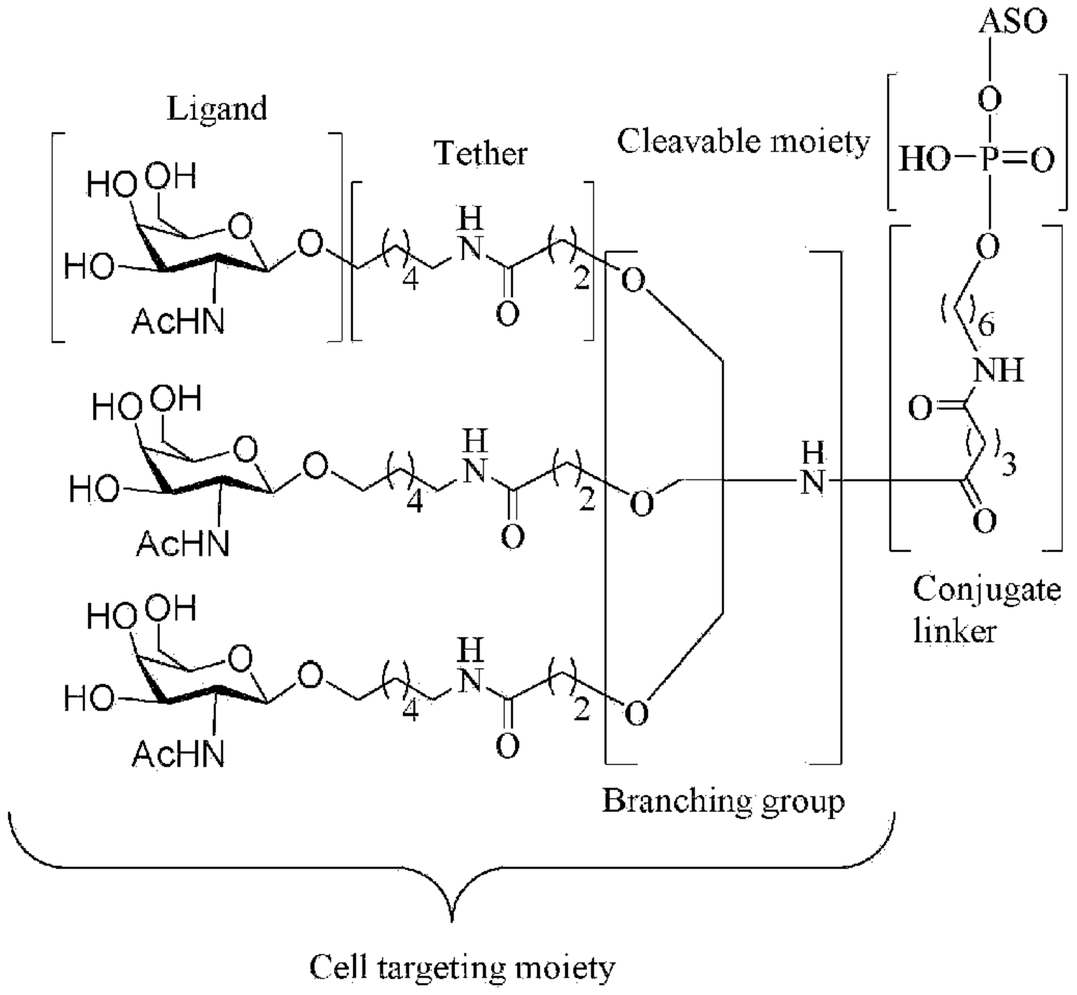
[0029] In certain embodiments, conjugation allows one to alter antisense compounds in ways that have less attractive consequences in the absence of conjugation. For example, in certain embodiments, replacing one or more phosphorothioate linkages of a fully phosphorothioate antisense compound with phosphodiester linkages results in improvement in some measures of tolerability. For example, in certain instances, such antisense compounds having one or more phosphodiester are less immunogenic than the same compound in which each linkage is a phosphorothioate. However, in certain instances, as shown in Example 26, that same replacement of one or more phosphorothioate linkages with phosphodiester linkages also results in reduced cellular uptake and/or loss in potency. In certain embodiments, conjugated antisense compounds described herein tolerate such change in linkages with little or no loss in uptake and potency when compared to the conjugated full-phosphorothioate counterpart. In fact, in certain embodiments, for example, in Examples 44, 57, 59, and 86, oligonucleotides

comprising a conjugate and at least one phosphodiester internucleoside linkage actually exhibit increased potency in vivo even relative to a full phosphorothioate counterpart also comprising the same conjugate. Moreover, since conjugation results in substantial increases in uptake/potency a small loss in that substantial gain may be acceptable to achieve improved tolerability. Accordingly, in certain embodiments, conjugated antisense compounds comprise at least one phosphodiester linkage.

[0030] In certain embodiments, conjugation of antisense compounds herein results in increased delivery, uptake and activity in hepatocytes. Thus, more compound is delivered to liver tissue. However, in certain embodiments, that increased delivery alone does not explain the entire increase in activity. In certain such embodiments, more compound enters hepatocytes. In certain embodiments, even that increased hepatocyte uptake does not explain the entire increase in activity. In such embodiments, productive uptake of the conjugated compound is increased. For example, as shown in Example 102, certain embodiments of GalNAc-containing conjugates increase enrichment of antisense oligonucleotides in hepatocytes versus non-parenchymal cells. This enrichment is beneficial for oligonucleotides that target genes that are expressed in hepatocytes.

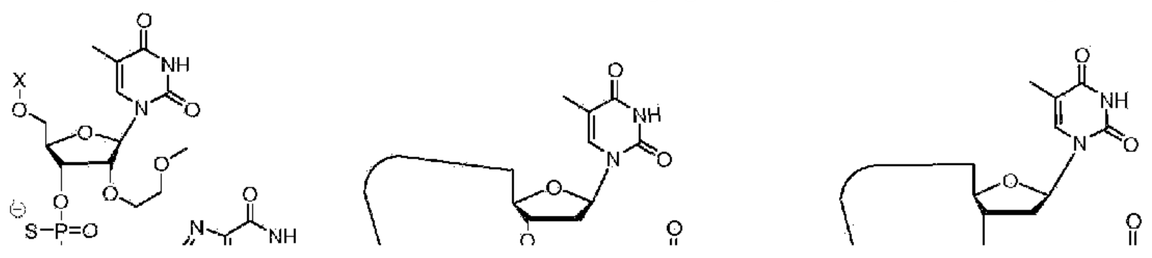
[0031] In certain embodiments, conjugated antisense compounds herein result in reduced kidney exposure. For example, as shown in Example 20, the concentrations of antisense oligonucleotides comprising certain embodiments of GalNAc-containing conjugates are lower in the kidney than that of antisense oligonucleotides lacking a GalNAc-containing conjugate. This has several beneficial therapeutic implications. For therapeutic indications where activity in the kidney is not sought, exposure to kidney risks kidney toxicity without corresponding benefit. Moreover, high concentration in kidney typically results in loss of compound to the urine resulting in faster clearance. Accordingly for non-kidney targets, kidney accumulation is undesired.

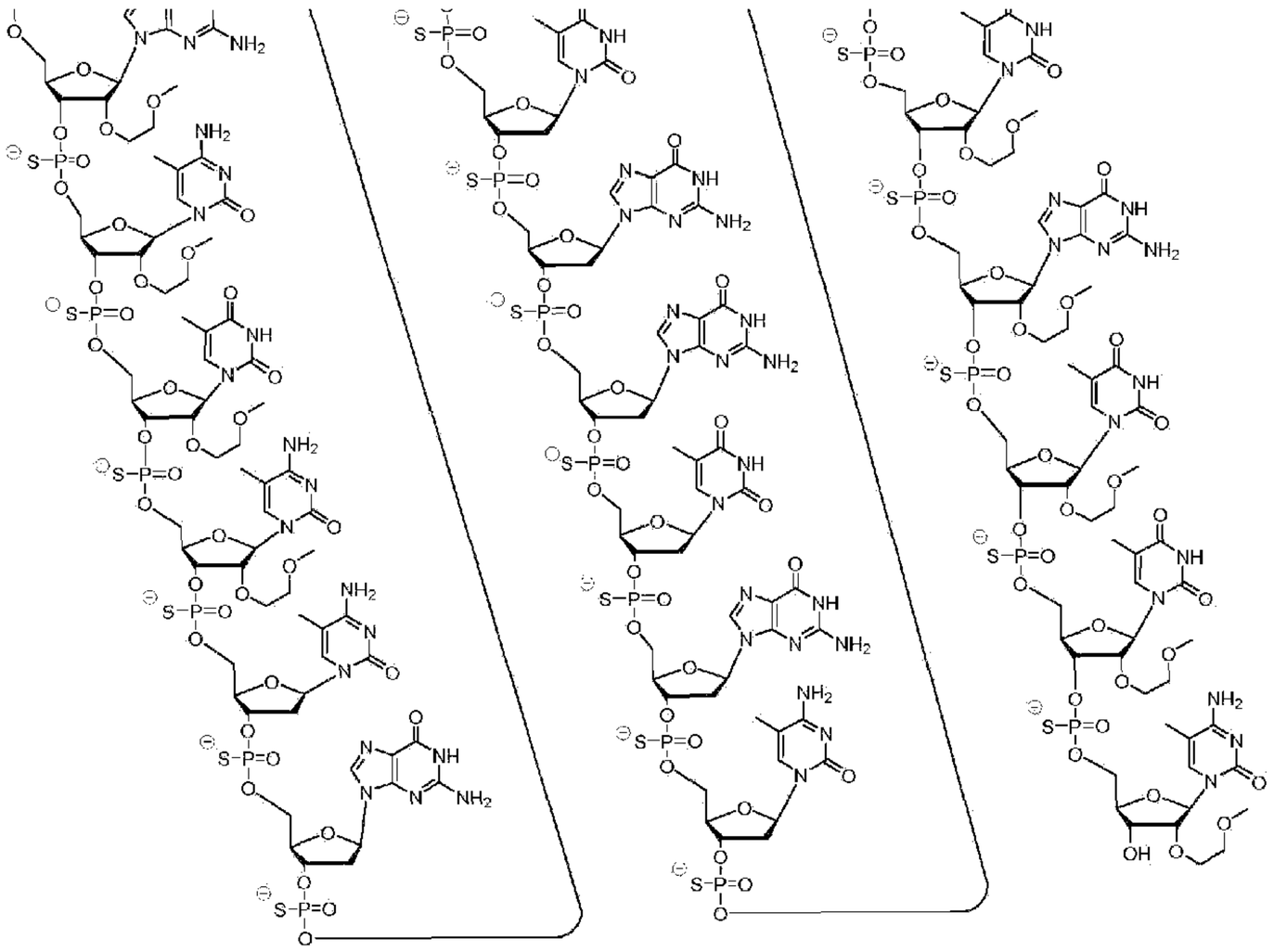
[0032] In certain embodiments, conjugated antisense compounds are provided having the structure:



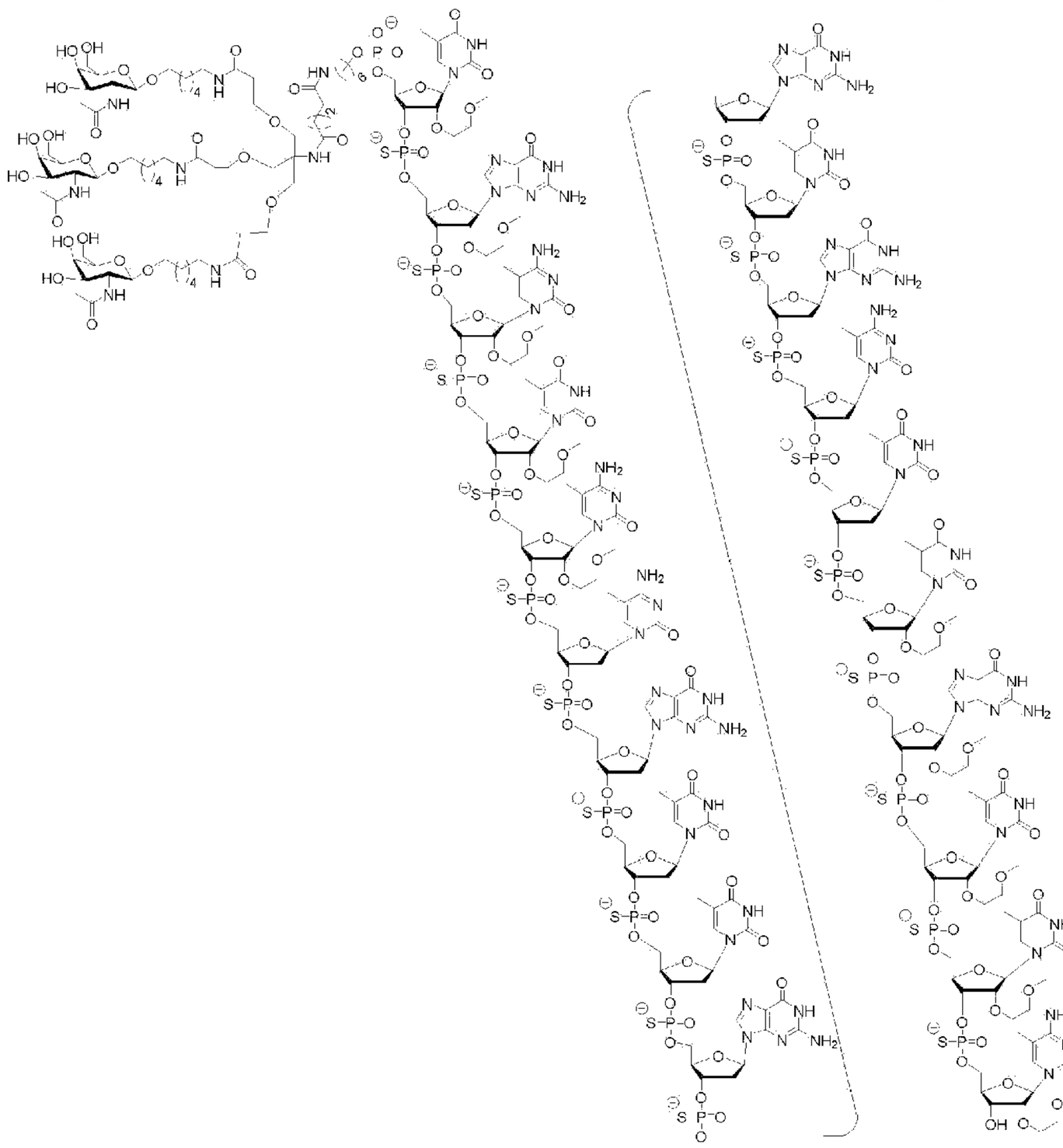
[0033] The present disclosure provides the following non-limiting numbered embodiments:

[0034] The conjugated antisense compound can be represented by the following structure. The antisense compound can comprise modified oligonucleotide ISIS 494372 with a 5'-X, wherein X is a conjugate group comprising GalNAc as defined in the claims. The antisense compound can consist of modified oligonucleotide ISIS 494372 with a 5'-X, wherein X is a conjugate group comprising GalNAc as defined in the claims.



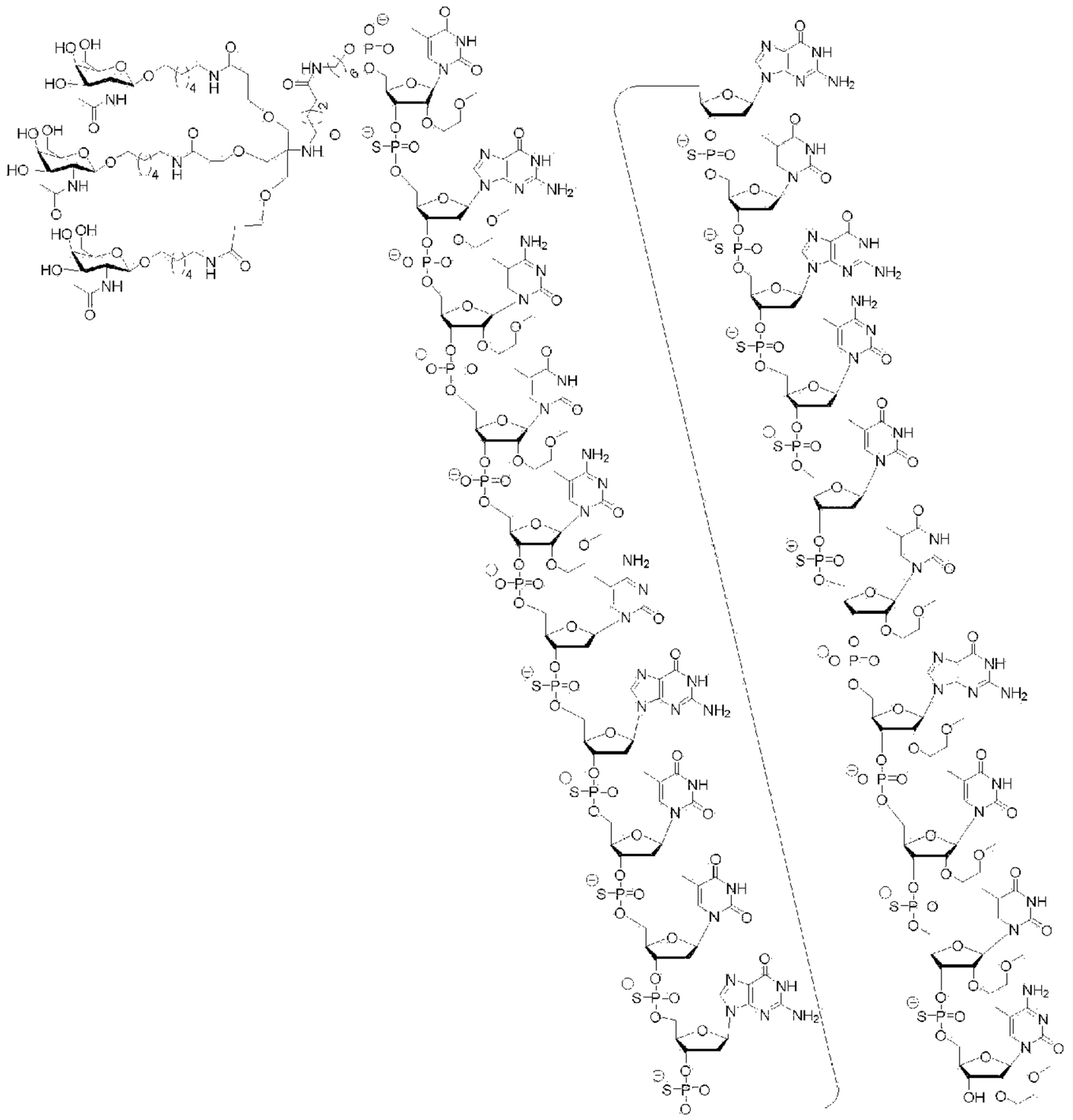


[0035] In certain embodiments, the conjugated antisense compound can be represented by the following structure. In certain embodiments, the antisense compound comprises the conjugated modified oligonucleotide ISIS 681251. In certain embodiments, the antisense compound consists of the conjugated modified oligonucleotide ISIS 681251.

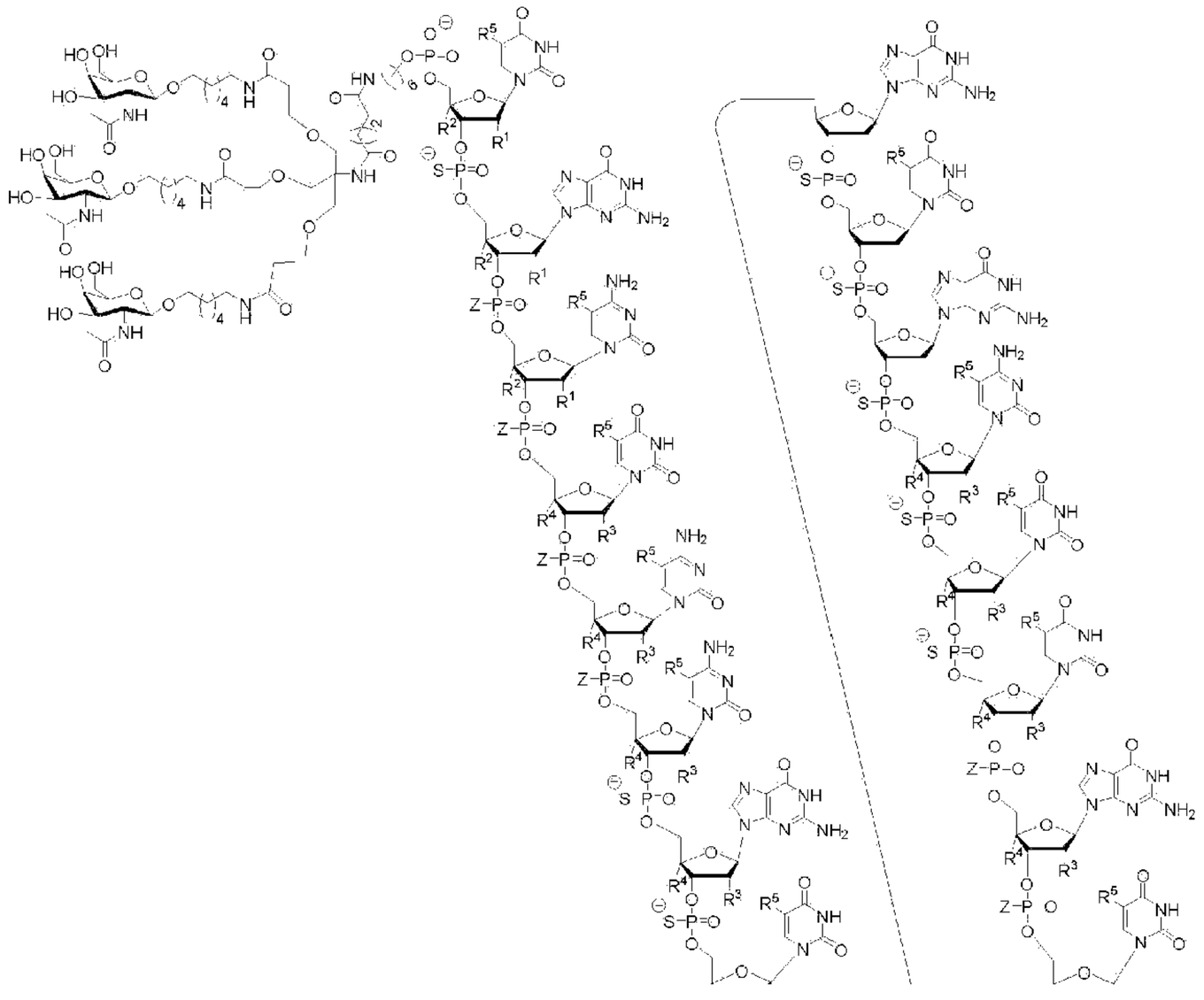


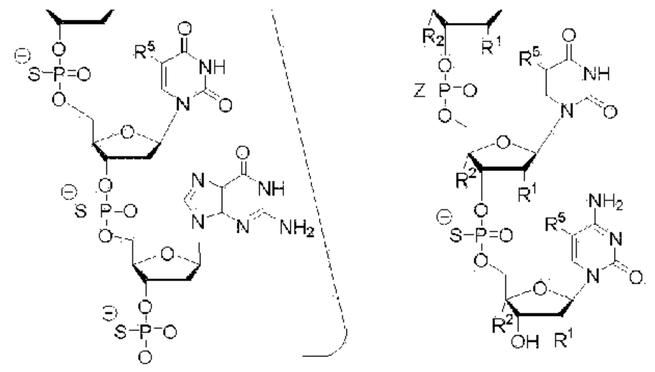
[0036] In certain embodiments, the conjugated antisense compound can be represented by the following structure. In certain embodiments, the antisense compound comprises the conjugated modified oligonucleotide ISIS 681257.

In certain embodiments, the antisense compound consists of the conjugated modified oligonucleotide ISIS 681257.



[0037] In certain embodiments, the conjugated antisense compound can be represented by the following structure. In certain embodiments, the antisense compound comprises a modified oligonucleotide with SEQ ID NO: 58 with a 5'-GalNAc, as defined in the claims, with variability in the sugar mods of the wings. In certain embodiments, the antisense compound consists of a modified oligonucleotide with SEQ ID NO: 58 with a 5'-GalNAc, as defined in the claims, with variability in the sugar mods of the wings.





[0038] Wherein either R^1 is $-OCH_2CH_2OCH_3$ (MOE)and R^2 is H; or R^1 and R^2 together form a bridge, wherein R^1 is -O- and R^2 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$, and R^1 and R^2 are directly connected such that the resulting bridge is selected from: $-O-CH_2-$, $-O-CH(CH_3)-$, and $-O-CH_2CH_2-$;

And for each pair of R^3 and R^4 on the same ring, independently for each ring: either R^3 is selected from H and $-OCH_2CH_2OCH_3$ and R^4 is H; or R^3 and R^4 together form a bridge, wherein R^3 is -O-, and R^4 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$and R^3 and R^4 are directly connected such that the resulting bridge is selected from: $-O-CH_2-$, $-O-CH(CH_3)-$, and $-O-CH_2CH_2-$;

And R^5 is selected from H and $-CH_3$;

And Z is selected from S^- and O^-.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0039] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosure. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit, unless specifically stated otherwise.

[0040] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

A. <u>Definitions</u>

[0041] Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, and chemical analysis. Certain such techniques and procedures may be found for example in "Carbohydrate Modifications in Antisense Research" Edited by Sangvi and Cook, American Chemical Society , Washington D.C., 1994; "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 21st edition, 2005; and "Antisense Drug Technology, Principles, Strategies, and Applications" Edited by Stanley T. Crooke, CRC Press, Boca Raton, Florida; and Sambrook et al., "Molecular Cloning, A laboratory Manual," 2nd Edition, Cold Spring Harbor Laboratory Press, 1989

[0042] Unless otherwise indicated, the following terms have the following meanings:
As used herein, "nucleoside" means a compound comprising a nucleobase moiety and a sugar moiety. Nucleosides include, but are not limited to, naturally occurring nucleosides (as found in DNA and RNA) and modified nucleosides. Nucleosides may be linked to a phosphate moiety.

[0043] As used herein, "chemical modification" means a chemical difference in a compound when compared to a

naturally occurring counterpart. Chemical modifications of oligonucleotides include nucleoside modifications (including sugar moiety modifications and nucleobase modifications) and internucleoside linkage modifications. In reference to an oligonucleotide, chemical modification does not include differences only in nucleobase sequence.

[0044] As used herein, "furanosyl" means a structure comprising a 5-membered ring comprising four carbon atoms and one oxygen atom.

[0045] As used herein, "naturally occurring sugar moiety" means a ribofuranosyl as found in naturally occurring RNA or a deoxyribofuranosyl as found in naturally occurring DNA.

[0046] As used herein, "sugar moiety" means a naturally occurring sugar moiety or a modified sugar moiety of a nucleoside.

[0047] As used herein, "modified sugar moiety" means a substituted sugar moiety or a sugar surrogate.

[0048] As used herein, "substituted sugar moiety" means a furanosyl that is not a naturally occurring sugar moiety. Substituted sugar moieties include, but are not limited to furanosyls comprising substituents at the 2'-position, the 3'-position, the 5'-position and/or the 4'-position. Certain substituted sugar moieties are bicyclic sugar moieties.

[0049] As used herein, "2'-substituted sugar moiety" means a furanosyl comprising a substituent at the 2'-position other than H or OH. Unless otherwise indicated, a 2'-substituted sugar moiety is not a bicyclic sugar moiety (i.e., the 2'-substituent of a 2'-substituted sugar moiety does not form a bridge to another atom of the furanosyl ring.

[0050] As used herein, "MOE" means $-OCH_2CH_2OCH_3$.

[0051] As used herein, "2'-F nucleoside" refers to a nucleoside comprising a sugar comprising fluorine at the 2' position. Unless otherwise indicated, the fluorine in a 2'-F nucleoside is in the ribo position (replacing the OH of a natural ribose).

[0052] As used herein the term "sugar surrogate" means a structure that does not comprise a furanosyl and that is capable of replacing the naturally occurring sugar moiety of a nucleoside, such that the resulting nucleoside sub-units are capable of linking together and/or linking to other nucleosides to form an oligomeric compound which is capable of hybridizing to a complementary oligomeric compound. Such structures include rings comprising a different number of atoms than furanosyl (e.g., 4, 6, or 7-membered rings); replacement of the oxygen of a furanosyl with a non-oxygen atom (e.g., carbon, sulfur, or nitrogen); or both a change in the number of atoms and a replacement of the oxygen. Such structures may also comprise substitutions corresponding to those described for substituted sugar moieties (e.g., 6-membered carbocyclic bicyclic sugar surrogates optionally comprising additional substituents). Sugar surrogates also include more complex sugar replacements (e.g., the non-ring systems of peptide nucleic acid). Sugar surrogates include without limitation morpholinos, cyclohexenyls and cyclohexitols.

[0053] As used herein, "bicyclic sugar moiety" means a modified sugar moiety comprising a 4 to 7 membered ring (including but not limited to a furanosyl) comprising a bridge connecting two atoms of the 4 to 7 membered ring to form a second ring, resulting in a bicyclic structure. In certain embodiments, the 4 to 7 membered ring is a sugar ring. In certain embodiments the 4 to 7 membered ring is a furanosyl. In certain such embodiments, the bridge connects the 2'-carbon and the 4'-carbon of the furanosyl.

[0054] As used herein, "nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids (ssDNA), double-stranded nucleic acids (dsDNA), small interfering ribonucleic acids (siRNA), and microRNAs (miRNA). A nucleic acid may also comprise any combination of these elements in a single molecule.

[0055] As used herein, "nucleotide" means a nucleoside further comprising a phosphate linking group. As used

herein, "linked nucleosides" may or may not be linked by phosphate linkages and thus includes, but is not limited to "linked nucleotides." As used herein, "linked nucleosides" are nucleosides that are connected in a continuous sequence (i.e. no additional nucleosides are present between those that are linked).

[0056] As used herein, "nucleobase" means a group of atoms that can be linked to a sugar moiety to create a nucleoside that is capable of incorporation into an oligonucleotide, and wherein the group of atoms is capable of bonding with a complementary naturally occurring nucleobase of another oligonucleotide or nucleic acid. Nucleobases may be naturally occurring or may be modified. As used herein, "nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, or nucleobase modification.

[0057] As used herein the terms, "unmodified nucleobase" or "naturally occurring nucleobase" means the naturally occurring heterocyclic nucleobases of RNA or DNA: the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) (including 5-methyl C), and uracil (U).

[0058] As used herein, "modified nucleobase" means any nucleobase that is not a naturally occurring nucleobase.

[0059] As used herein, "modified nucleoside" means a nucleoside comprising at least one chemical modification compared to naturally occurring RNA or DNA nucleosides. Modified nucleosides comprise a modified sugar moiety and/or a modified nucleobase.

[0060] As used herein, "bicyclic nucleoside" or "BNA" means a nucleoside comprising a bicyclic sugar moiety.

[0061] As used herein, "constrained ethyl nucleoside" or "cEt" means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-$CH(CH_3)$-O-2'bridge.

[0062] As used herein, "locked nucleic acid nucleoside" or "LNA" means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-CH_2-O-2'bridge.

[0063] As used herein, "2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position other than H or OH. Unless otherwise indicated, a 2'-substituted nucleoside is not a bicyclic nucleoside.

[0064] As used herein, "deoxynucleoside" means a nucleoside comprising 2'-H furanosyl sugar moiety, as found in naturally occurring deoxyribonucleosides (DNA). In certain embodiments, a 2'-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (e.g., uracil).

[0065] As used herein, "oligonucleotide" means a compound comprising a plurality of linked nucleosides. In certain embodiments, an oligonucleotide comprises one or more unmodified ribonucleosides (RNA) and/or unmodified deoxyribonucleosides (DNA) and/or one or more modified nucleosides.

[0066] As used herein "oligonucleoside" means an oligonucleotide in which none of the internucleoside linkages contains a phosphorus atom. As used herein, oligonucleotides include oligonucleosides.

[0067] As used herein, "modified oligonucleotide" means an oligonucleotide comprising at least one modified nucleoside and/or at least one modified internucleoside linkage.

[0068] As used herein, "linkage" or "linking group" means a group of atoms that link together two or more other groups of atoms.

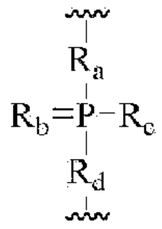
[0069] As used herein "internucleoside linkage" means a covalent linkage between adjacent nucleosides in an oligonucleotide.

[0070] As used herein "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

[0071] As used herein, "modified internucleoside linkage" means any internucleoside linkage other than a naturally occurring internucleoside linkage.

[0072] As used herein, "terminal internucleoside linkage" means the linkage between the last two nucleosides of an oligonucleotide or defined region thereof.

[0073] As used herein, "phosphorus linking group" means a linking group comprising a phosphorus atom. Phosphorus linking groups include without limitation groups having the formula:



wherein:

R_a and R_d are each, independently, O, S, CH_2, NH, or NJ_1 wherein J_1 is C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

R_b is O or S;

R_c is OH, SH, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, amino or substituted amino; and

J_1 is R_b is O or S.

[0074] Phosphorus linking groups include without limitation, phosphodiester, phosphorothioate, phosphorodithioate, phosphonate, phosphoramidate, phosphorothioamidate, thionoalkylphosphonate, phosphotriesters, thionoalkylphosphotriester and boranophosphate.

[0075] As used herein, "internucleoside phosphorus linking group" means a phosphorus linking group that directly links two nucleosides.

[0076] As used herein, "non-internucleoside phosphorus linking group" means a phosphorus linking group that does not directly link two nucleosides. In certain embodiments, a non-internucleoside phosphorus linking group links a nucleoside to a group other than a nucleoside. In certain embodiments, a non-internucleoside phosphorus linking group links two groups, neither of which is a nucleoside.

[0077] As used herein, "neutral linking group" means a linking group that is not charged. Neutral linking groups include without limitation phosphotriesters, methylphosphonates, MMI ($-CH_2-N(CH_3)-O-$), amide-3 ($-CH_2-C(=O)-N(H)-$), amide-4 ($-CH_2-N(H)-C(=O)-$), formacetal ($-O-CH_2-O-$), and thioformacetal ($-S-CH_2-O-$). Further neutral linking groups include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: Carbohydrate Modifications in Antisense Research; Y.S. Sanghvi and P.D. Cook Eds. ACS Symposium Series 580; Chapters 3 and 4, (pp. 40-65)). Further neutral linking groups include nonionic linkages comprising mixed N, O, S and CH_2 component parts.

[0078] As used herein, "internucleoside neutral linking group" means a neutral linking group that directly links two nucleosides.

[0079] As used herein, "non-internucleoside neutral linking group" means a neutral linking group that does not directly link two nucleosides. In certain embodiments, a non-internucleoside neutral linking group links a nucleoside to a group other than a nucleoside. In certain embodiments, a non-internucleoside neutral linking group links two groups, neither of which is a nucleoside.

[0080] As used herein, "oligomeric compound" means a polymeric structure comprising two or more substructures.

In certain embodiments, an oligomeric compound comprises an oligonucleotide. In certain embodiments, an oligomeric compound comprises one or more conjugate groups and/or terminal groups. In certain embodiments, an oligomeric compound consists of an oligonucleotide. Oligomeric compounds also include naturally occurring nucleic acids. In certain embodiments, an oligomeric compound comprises a backbone of one or more linked monomeric subunits where each linked monomeric subunit is directly or indirectly attached to a heterocyclic base moiety. In certain embodiments, oligomeric compounds may also include monomeric subunits that are not linked to a heterocyclic base moiety, thereby providing abasic sites. In certain embodiments, the linkages joining the monomeric subunits, the sugar moieties or surrogates and the heterocyclic base moieties can be independently modified. In certain embodiments, the linkage-sugar unit, which may or may not include a heterocyclic base, may be substituted with a mimetic such as the monomers in peptide nucleic acids.

[0081] As used herein, "terminal group" means one or more atom attached to either, or both, the 3' end or the 5' end of an oligonucleotide. In certain embodiments a terminal group is a conjugate group. In certain embodiments, a terminal group comprises one or more terminal group nucleosides.

[0082] As used herein, "conjugate" or "conjugate group" means an atom or group of atoms bound to an oligonucleotide or oligomeric compound. In general, conjugate groups modify one or more properties of the compound to which they are attached, including, but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and/or clearance properties.

[0083] As used herein, "conjugate linker" or "linker" in the context of a conjugate group means a portion of a conjugate group comprising any atom or group of atoms and which covalently link (1) an oligonucleotide to another portion of the conjugate group or (2) two or more portions of the conjugate group.

[0084] Conjugate groups are shown herein as radicals, providing a bond for forming covalent attachment to an oligomeric compound such as an antisense oligonucleotide. In certain embodiments, the point of attachment on the oligomeric compound is the 3'-oxygen atom of the 3'-hydroxyl group of the 3' terminal nucleoside of the oligomeric compound. In certain embodiments the point of attachment on the oligomeric compound is the 5'-oxygen atom of the 5'-hydroxyl group of the 5' terminal nucleoside of the oligomeric compound. In certain embodiments, the bond for forming attachment to the oligomeric compound is a cleavable bond. In certain such embodiments, such cleavable bond constitutes all or part of a cleavable moiety.

[0085] In certain embodiments, conjugate groups comprise a cleavable moiety (e.g., a cleavable bond or cleavable nucleoside) and a carbohydrate cluster portion, such as a GalNAc cluster portion. Such carbohydrate cluster portion comprises: a targeting moiety and, optionally, a conjugate linker. In certain embodiments, the carbohydrate cluster portion is identified by the number and identity of the ligand. For example, in certain embodiments, the carbohydrate cluster portion comprises 3 GalNAc groups and is designated "$GalNAc_3$". In certain embodiments, the carbohydrate cluster portion comprises 4 GalNAc groups and is designated "$GalNAc_4$". Specific carbohydrate cluster portions (having specific tether, branching and conjugate linker groups) are described herein and designated by Roman numeral followed by subscript "a". Accordingly "GalNac3-1_a" refers to a specific carbohydrate cluster portion of a conjugate group having 3 GalNac groups and specifically identified tether, branching and linking groups. Such carbohydrate cluster fragment is attached to an oligomeric compound via a cleavable moiety, such as a cleavable bond or cleavable nucleoside.

[0086] As used herein, "cleavable moiety" means a bond or group that is capable of being split under physiological conditions. In certain embodiments, a cleavable moiety is cleaved inside a cell or sub-cellular compartments, such as a lysosome. In certain embodiments, a cleavable moiety is cleaved by endogenous enzymes, such as nucleases. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds.

[0087] As used herein, "cleavable bond" means any chemical bond capable of being split. In certain embodiments, a cleavable bond is selected from among: an amide, a polyamide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, a di-sulfide, or a peptide.

[0088] As used herein, "carbohydrate cluster" means a compound having one or more carbohydrate residues attached to a scaffold or linker group. (*see,* e.g., Maier et al., "Synthesis of Antisense Oligonucleotides Conjugated to a Multivalent Carbohydrate Cluster for Cellular Targeting," Bioconjugate Chemistry, 2003, (14): 18-29, or Rensen et al., "Design and Synthesis of Novel N-Acetylgalactosamine-Terminated Glycolipids for Targeting of Lipoproteins to the Hepatic Asiaglycoprotein Receptor," J. Med. Chem. 2004, (47): 5798-5808, for examples of carbohydrate conjugate clusters).

[0089] As used herein, "modified carbohydrate" means any carbohydrate having one or more chemical modifications relative to naturally occurring carbohydrates.

[0090] As used herein, "carbohydrate derivative" means any compound which may be synthesized using a carbohydrate as a starting material or intermediate.

[0091] As used herein, "carbohydrate" means a naturally occurring carbohydrate, a modified carbohydrate, or a carbohydrate derivative.

[0092] As used herein "protecting group" means any compound or protecting group known to those having skill in the art. Non-limiting examples of protecting groups may be found in "Protective Groups in Organic Chemistry", T. W. Greene, P. G. M. Wuts, ISBN 0-471-62301-6, John Wiley & Sons, Inc, New York.

[0093] As used herein, "single-stranded" means an oligomeric compound that is not hybridized to its complement and which lacks sufficient self-complementarity to form a stable self-duplex.

[0094] As used herein, "double stranded" means a pair of oligomeric compounds that are hybridized to one another or a single self-complementary oligomeric compound that forms a hairpin structure. In certain embodiments, a double-stranded oligomeric compound comprises a first and a second oligomeric compound.

[0095] As used herein, "antisense compound" means a compound comprising or consisting of an oligonucleotide at least a portion of which is complementary to a target nucleic acid to which it is capable of hybridizing, resulting in at least one antisense activity.

[0096] As used herein, "antisense activity" means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity includes modulation of the amount or activity of a target nucleic acid transcript (e.g. mRNA). In certain embodiments, antisense activity includes modulation of the splicing of pre-mRNA.

[0097] As used herein, "RNase H based antisense compound" means an antisense compound wherein at least some of the antisense activity of the antisense compound is attributable to hybridization of the antisense compound to a target nucleic acid and subsequent cleavage of the target nucleic acid by RNase H.

[0098] As used herein, "RISC based antisense compound" means an antisense compound wherein at least some of the antisense activity of the antisense compound is attributable to the RNA Induced Silencing Complex (RISC).

[0099] As used herein, "detecting" or "measuring" means that a test or assay for detecting or measuring is performed. Such detection and/or measuring may result in a value of zero. Thus, if a test for detection or measuring results in a finding of no activity (activity of zero), the step of detecting or measuring the activity has nevertheless been performed.

[0100] As used herein, "detectable and/or measureable activity" means a statistically significant activity that is not zero.

[0101] As used herein, "essentially unchanged" means little or no change in a particular parameter, particularly

relative to another parameter which changes much more. In certain embodiments, a parameter is essentially unchanged when it changes less than 5%. In certain embodiments, a parameter is essentially unchanged if it changes less than two-fold while another parameter changes at least ten-fold. For example, in certain embodiments, an antisense activity is a change in the amount of a target nucleic acid. In certain such embodiments, the amount of a non-target nucleic acid is essentially unchanged if it changes much less than the target nucleic acid does, but the change need not be zero.

[0102] As used herein, "expression" means the process by which a gene ultimately results in a protein. Expression includes, but is not limited to, transcription, post-transcriptional modification (e.g., splicing, polyadenlyation, addition of 5'-cap), and translation.

[0103] As used herein, "target nucleic acid" means a nucleic acid molecule to which an antisense compound is intended to hybridize to result in a desired antisense activity. Antisense oligonucleotides have sufficient complementarity to their target nucleic acids to allow hybridization under physiological conditions.

[0104] As used herein, "nucleobase complementarity" or "complementarity" when in reference to nucleobases means a nucleobase that is capable of base pairing with another nucleobase. For example, in DNA, adenine (A) is complementary to thymine (T). For example, in RNA, adenine (A) is complementary to uracil (U). In certain embodiments, complementary nucleobase means a nucleobase of an antisense compound that is capable of base pairing with a nucleobase of its target nucleic acid. For example, if a nucleobase at a certain position of an antisense compound is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid, then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be complementary at that nucleobase pair. Nucleobases comprising certain modifications may maintain the ability to pair with a counterpart nucleobase and thus, are still capable of nucleobase complementarity.

[0105] As used herein, "non-complementary" in reference to nucleobases means a pair of nucleobases that do not form hydrogen bonds with one another.

[0106] As used herein, "complementary" in reference to oligomeric compounds (e.g., linked nucleosides, oligonucleotides, or nucleic acids) means the capacity of such oligomeric compounds or regions thereof to hybridize to another oligomeric compound or region thereof through nucleobase complementarity. Complementary oligomeric compounds need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. In certain embodiments, complementary oligomeric compounds or regions are complementary at 70% of the nucleobases (70% complementary). In certain embodiments, complementary oligomeric compounds or regions are 80% complementary. In certain embodiments, complementary oligomeric compounds or regions are 90% complementary. In certain embodiments, complementary oligomeric compounds or regions are 95% complementary. In certain embodiments, complementary oligomeric compounds or regions are 100% complementary.

[0107] As used herein, "mismatch" means a nucleobase of a first oligomeric compound that is not capable of pairing with a nucleobase at a corresponding position of a second oligomeric compound, when the first and second oligomeric compound are aligned. Either or both of the first and second oligomeric compounds may be oligonucleotides.

[0108] As used herein, "hybridization" means the pairing of complementary oligomeric compounds (e.g., an antisense compound and its target nucleic acid). While not limited to a particular mechanism, the most common mechanism of pairing involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases.

[0109] As used herein, "specifically hybridizes" means the ability of an oligomeric compound to hybridize to one nucleic acid site with greater affinity than it hybridizes to another nucleic acid site.

[0110] As used herein, "fully complementary" in reference to an oligonucleotide or portion thereof means that each

nucleobase of the oligonucleotide or portion thereof is capable of pairing with a nucleobase of a complementary nucleic acid or contiguous portion thereof. Thus, a fully complementary region comprises no mismatches or unhybridized nucleobases in either strand.

[0111] As used herein, "percent complementarity" means the percentage of nucleobases of an oligomeric compound that are complementary to an equal-length portion of a target nucleic acid. Percent complementarity is calculated by dividing the number of nucleobases of the oligomeric compound that are complementary to nucleobases at corresponding positions in the target nucleic acid by the total length of the oligomeric compound.

[0112] As used herein, "percent identity" means the number of nucleobases in a first nucleic acid that are the same type (independent of chemical modification) as nucleobases at corresponding positions in a second nucleic acid, divided by the total number of nucleobases in the first nucleic acid.

[0113] As used herein, "modulation" means a change of amount or quality of a molecule, function, or activity when compared to the amount or quality of a molecule, function, or activity prior to modulation. For example, modulation includes the change, either an increase (stimulation or induction) or a decrease (inhibition or reduction) in gene expression. As a further example, modulation of expression can include a change in splice site selection of pre-mRNA processing, resulting in a change in the absolute or relative amount of a particular splice-variant compared to the amount in the absence of modulation.

[0114] As used herein, "chemical motif" means a pattern of chemical modifications in an oligonucleotide or a region thereof. Motifs may be defined by modifications at certain nucleosides and/or at certain linking groups of an oligonucleotide.

[0115] As used herein, "nucleoside motif" means a pattern of nucleoside modifications in an oligonucleotide or a region thereof. The linkages of such an oligonucleotide may be modified or unmodified. Unless otherwise indicated, motifs herein describing only nucleosides are intended to be nucleoside motifs. Thus, in such instances, the linkages are not limited.

[0116] As used herein, "sugar motif" means a pattern of sugar modifications in an oligonucleotide or a region thereof.

[0117] As used herein, "linkage motif" means a pattern of linkage modifications in an oligonucleotide or region thereof. The nucleosides of such an oligonucleotide may be modified or unmodified. Unless otherwise indicated, motifs herein describing only linkages are intended to be linkage motifs. Thus, in such instances, the nucleosides are not limited.

[0118] As used herein, "nucleobase modification motif" means a pattern of modifications to nucleobases along an oligonucleotide. Unless otherwise indicated, a nucleobase modification motif is independent of the nucleobase sequence.

[0119] As used herein, "sequence motif" means a pattern of nucleobases arranged along an oligonucleotide or portion thereof. Unless otherwise indicated, a sequence motif is independent of chemical modifications and thus may have any combination of chemical modifications, including no chemical modifications.

[0120] As used herein, "type of modification" in reference to a nucleoside or a nucleoside of a "type" means the chemical modification of a nucleoside and includes modified and unmodified nucleosides. Accordingly, unless otherwise indicated, a "nucleoside having a modification of a first type" may be an unmodified nucleoside.

[0121] As used herein, "differently modified" mean chemical modifications or chemical substituents that are different from one another, including absence of modifications. Thus, for example, a MOE nucleoside and an unmodified DNA nucleoside are "differently modified," even though the DNA nucleoside is unmodified. Likewise, DNA and RNA are "differently modified," even though both are naturally-occurring unmodified nucleosides.

Nucleosides that are the same but for comprising different nucleobases are not differently modified. For example, a nucleoside comprising a 2'-OMe modified sugar and an unmodified adenine nucleobase and a nucleoside comprising a 2'-OMe modified sugar and an unmodified thymine nucleobase are not differently modified.

[0122] As used herein, "the same type of modifications" refers to modifications that are the same as one another, including absence of modifications. Thus, for example, two unmodified DNA nucleosides have "the same type of modification," even though the DNA nucleoside is unmodified. Such nucleosides having the same type modification may comprise different nucleobases.

[0123] As used herein, "separate regions" means portions of an oligonucleotide wherein the chemical modifications or the motif of chemical modifications of any neighboring portions include at least one difference to allow the separate regions to be distinguished from one another.

[0124] As used herein, "pharmaceutically acceptable carrier or diluent" means any substance suitable for use in administering to an animal. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile saline. In certain embodiments, such sterile saline is pharmaceutical grade saline.

[0125] As used herein the term "metabolic disorder" means a disease or condition principally characterized by dysregulation of metabolism - the complex set of chemical reactions associated with breakdown of food to produce energy.

[0126] As used herein, the term "cardiovascular disorder" means a disease or condition principally characterized by impaired function of the heart or blood vessels.

[0127] As used herein the term "mono or polycyclic ring system" is meant to include all ring systems selected from single or polycyclic radical ring systems wherein the rings are fused or linked and is meant to be inclusive of single and mixed ring systems individually selected from aliphatic, alicyclic, aryl, heteroaryl, aralkyl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic and heteroarylalkyl. Such mono and poly cyclic structures can contain rings that each have the same level of saturation or each, independently, have varying degrees of saturation including fully saturated, partially saturated or fully unsaturated. Each ring can comprise ring atoms selected from C, N, O and S to give rise to heterocyclic rings as well as rings comprising only C ring atoms which can be present in a mixed motif such as for example benzimidazole wherein one ring has only carbon ring atoms and the fused ring has two nitrogen atoms. The mono or polycyclic ring system can be further substituted with substituent groups such as for example phthalimide which has two =0 groups attached to one of the rings. Mono or polycyclic ring systems can be attached to parent molecules using various strategies such as directly through a ring atom, fused through multiple ring atoms, through a substituent group or through a bifunctional linking moiety.

[0128] As used herein, "prodrug" means an inactive or less active form of a compound which, when administered to a subject, is metabolized to form the active, or more active, compound (e.g., drug).

[0129] As used herein, "substituent" and "substituent group," means an atom or group that replaces the atom or group of a named parent compound. For example a substituent of a modified nucleoside is any atom or group that differs from the atom or group found in a naturally occurring nucleoside (e.g., a modified 2'-substuent is any atom or group at the 2'-position of a nucleoside other than H or OH). Substituent groups can be protected or unprotected. In certain embodiments, compounds of the present disclosure have substituents at one or at more than one position of the parent compound. Substituents may also be further substituted with other substituent groups and may be attached directly or via a linking group such as an alkyl or hydrocarbyl group to a parent compound.

[0130] Likewise, as used herein, "substituent" in reference to a chemical functional group means an atom or group of atoms that differs from the atom or a group of atoms normally present in the named functional group. In certain embodiments, a substituent replaces a hydrogen atom of the functional group (e.g., in certain embodiments, the substituent of a substituted methyl group is an atom or group other than hydrogen which replaces one of the

hydrogen atoms of an unsubstituted methyl group). Unless otherwise indicated, groups amenable for use as substituents include without limitation, halogen, hydroxyl, alkyl, alkenyl, alkynyl, acyl (-C(O)R_{aa}), carboxyl (-C(O)O-R_{aa}), aliphatic groups, alicyclic groups, alkoxy, substituted oxy (-O-R_{aa}), aryl, aralkyl, heterocyclic radical, heteroaryl, heteroarylalkyl, amino (-N(R_{bb})(R_{cc})), imino(=NR_{bb}), amido (-C(O)N-(Rbb)(R_{cc}) or -N(Rbb)C(O)R_{aa}), azido (-N_3), nitro (-NO_2), cyano (-CN), carbamido (-OC(O)N(R_{bb})(R_{cc}) or -N(R_{bb})C(O)OR_{aa}), ureido (-N(R_{bb})C(O)N(R_{bb})(R_{cc})), thioureido (-N(R_{bb})C(S)N(R_{bb})(R_{cc})), guanidinyl (-N(R_{bb})C(=NR_{bb})N(R_{bb})(R_{cc})), amidinyl (-C(=NRbb)N(Rbb)(Rcc) or -N(R_{bb})C(=NR_{bb})(R_{aa})), thiol (-SRbb), sulfinyl (-S(O)R_{bb}), sulfonyl (-$S(O)_2R_{bb}$) and sulfonamidyl (-$S(O)_2$N(R_{bb})(R_{cc}) or -N(R_{bb})$S(O)_2R_{bb}$). Wherein each R_{aa}, R_{bb} and R_{cc} is, independently, H, an optionally linked chemical functional group or a further substituent group with a preferred list including without limitation, alkyl, alkenyl, alkynyl, aliphatic, alkoxy, acyl, aryl, aralkyl, heteroaryl, alicyclic, heterocyclic and heteroarylalkyl. Selected substituents within the compounds described herein are present to a recursive degree.

[0131] As used herein, "alkyl," as used herein, means a saturated straight or branched hydrocarbon radical containing up to twenty four carbon atoms. Examples of alkyl groups include without limitation, methyl, ethyl, propyl, butyl, isopropyl, n-hexyl, octyl, decyl, dodecyl and the like. Alkyl groups typically include from 1 to about 24 carbon atoms, more typically from 1 to about 12 carbon atoms (C_1-C_{12} alkyl) with from 1 to about 6 carbon atoms being more preferred.

[0132] As used herein, "alkenyl," means a straight or branched hydrocarbon chain radical containing up to twenty four carbon atoms and having at least one carbon-carbon double bond. Examples of alkenyl groups include without limitation, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, dienes such as 1,3-butadiene and the like. Alkenyl groups typically include from 2 to about 24 carbon atoms, more typically from 2 to about 12 carbon atoms with from 2 to about 6 carbon atoms being more preferred. Alkenyl groups as used herein may optionally include one or more further substituent groups.

[0133] As used herein, "alkynyl," means a straight or branched hydrocarbon radical containing up to twenty four carbon atoms and having at least one carbon-carbon triple bond. Examples of alkynyl groups include, without limitation, ethynyl, 1 -propynyl, 1 -butynyl, and the like. Alkynyl groups typically include from 2 to about 24 carbon atoms, more typically from 2 to about 12 carbon atoms with from 2 to about 6 carbon atoms being more preferred. Alkynyl groups as used herein may optionally include one or more further substituent groups.

[0134] As used herein, "acyl," means a radical formed by removal of a hydroxyl group from an organic acid and has the general Formula -C(O)-X where X is typically aliphatic, alicyclic or aromatic. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates, aliphatic phosphates and the like. Acyl groups as used herein may optionally include further substituent groups.

[0135] As used herein, "alicyclic" means a cyclic ring system wherein the ring is aliphatic. The ring system can comprise one or more rings wherein at least one ring is aliphatic. Preferred alicyclics include rings having from about 5 to about 9 carbon atoms in the ring. Alicyclic as used herein may optionally include further substituent groups.

[0136] As used herein, "aliphatic" means a straight or branched hydrocarbon radical containing up to twenty four carbon atoms wherein the saturation between any two carbon atoms is a single, double or triple bond. An aliphatic group preferably contains from 1 to about 24 carbon atoms, more typically from 1 to about 12 carbon atoms with from 1 to about 6 carbon atoms being more preferred. The straight or branched chain of an aliphatic group may be interrupted with one or more heteroatoms that include nitrogen, oxygen, sulfur and phosphorus. Such aliphatic groups interrupted by heteroatoms include without limitation, polyalkoxys, such as polyalkylene glycols, polyamines, and polyimines. Aliphatic groups as used herein may optionally include further substituent groups.

[0137] As used herein, "alkoxy" means a radical formed between an alkyl group and an oxygen atom wherein the oxygen atom is used to attach the alkoxy group to a parent molecule. Examples of alkoxy groups include without limitation, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, sec-butoxy, *tert*-butoxy, n-pentoxy, neopentoxy, n-

hexoxy and the like. Alkoxy groups as used herein may optionally include further substituent groups.

[0138] As used herein, "aminoalkyl" means an amino substituted C_1-C_{12}alkyl radical. The alkyl portion of the radical forms a covalent bond with a parent molecule. The amino group can be located at any position and the aminoalkyl group can be substituted with a further substituent group at the alkyl and/or amino portions.

[0139] As used herein, "aralkyl" and "arylalkyl" mean an aromatic group that is covalently linked to a C_1-C_{12} alkyl radical. The alkyl radical portion of the resulting aralkyl (or arylalkyl) group forms a covalent bond with a parent molecule. Examples include without limitation, benzyl, phenethyl and the like. Aralkyl groups as used herein may optionally include further substituent groups attached to the alkyl, the aryl or both groups that form the radical group.

[0140] As used herein, "aryl" and "aromatic" mean a mono- or polycyclic carbocyclic ring system radicals having one or more aromatic rings. Examples of aryl groups include without limitation, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl and the like. Preferred aryl ring systems have from about 5 to about 20 carbon atoms in one or more rings. Aryl groups as used herein may optionally include further substituent groups.

[0141] As used herein, "halo" and "halogen," mean an atom selected from fluorine, chlorine, bromine and iodine.

[0142] As used herein, "heteroaryl," and "heteroaromatic," mean a radical comprising a mono- or poly-cyclic aromatic ring, ring system or fused ring system wherein at least one of the rings is aromatic and includes one or more heteroatoms. Heteroaryl is also meant to include fused ring systems including systems where one or more of the fused rings contain no heteroatoms. Heteroaryl groups typically include one ring atom selected from sulfur, nitrogen or oxygen. Examples of heteroaryl groups include without limitation, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl and the like. Heteroaryl radicals can be attached to a parent molecule directly or through a linking moiety such as an aliphatic group or hetero atom. Heteroaryl groups as used herein may optionally include further substituent groups.

[0143] As used herein, "conjugate compound" means any atoms, group of atoms, or group of linked atoms suitable for use as a conjugate group. In certain embodiments, conjugate compounds may possess or impart one or more properties, including, but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and/or clearance properties.

[0144] As used herein, unless otherwise indicated or modified, the term "double-stranded" refers to two separate oligomeric compounds that are hybridized to one another. Such double stranded compounds may have one or more or non-hybridizing nucleosides at one or both ends of one or both strands (overhangs) and/or one or more internal non-hybridizing nucleosides (mismatches) provided there is sufficient complementarity to maintain hybridization under physiologically relevant conditions.

[0145] As used herein, "5' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 5'-most nucleotide of a particular antisense compound.

[0146] As used herein, "About" means within ±10% of a value. For example, if it is stated, "a marker may be increased by about 50%", it is implied that the marker may be increased between 45%-55%.

[0147] As used herein, "administered concomitantly" refers to the co-administration of two agents in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Concomitant administration does not require that both agents be administered in a single pharmaceutical composition, in the same dosage form, or by the same route of administration. The effects of both agents need not manifest themselves at the same time. The effects need only be overlapping for a period of time and need not be coextensive.

[0148] As used herein, "administering" or "administration" means providing a pharmaceutical agent to an

individual, and includes, but is not limited to, administering by a medical professional and self-administering. Administration of a pharmaceutical agent to an individual can be continuous, chronic, short or intermittent. Administration can parenteral or non-parenteral.

[0149] As used herein, "agent" means an active substance that can provide a therapeutic benefit when administered to an animal. "First agent" means a therapeutic compound of the invention. For example, a first agent can be an antisense oligonucleotide targeting apo(a). "Second agent" means a second therapeutic compound of the invention (e.g. a second antisense oligonucleotide targeting apo(a)) and/or a non-apo(a) therapeutic compound.

[0150] As used herein, "amelioration" or "ameliorate" or "ameliorating" refers to a lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. The severity of indicators can be determined by subjective or objective measures, which are known to those skilled in the art.

[0151] As used herein, "animal" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

[0152] As used herein, "apo(a)" means any nucleic acid or protein sequence encoding apo(a). For example, in certain embodiments, apo(a) includes a DNA sequence encoding apo(a), a RNA sequence transcribed from DNA encoding apo(a) (including genomic DNA comprising introns and exons), a mRNA sequence encoding apo(a), or a peptide sequence encoding apo(a).

[0153] As used herein, "apo(a) nucleic acid" means any nucleic acid encoding apo(a). For example, in certain embodiments, an apo(a) nucleic acid includes a DNA sequence encoding apo(a), a RNA sequence transcribed from DNA encoding apo(a) (including genomic DNA comprising introns and exons), and a mRNA sequence encoding apo(a).

[0154] As used herein, "apo(a) mRNA" means a mRNA encoding an apo(a) protein.

[0155] As used herein, "apo(a) protein" means any protein sequence encoding Apo(a).

[0156] As used herein, "apo(a) specific inhibitor" refers to any agent capable of specifically inhibiting the expression of an apo(a) nucleic acid and/or apo(a) protein. For example, apo(a) specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of apo(a) nucleic acid and/or apo(a) protein. In certain embodiments, by specifically modulating apo(a) nucleic acid expression and/or apo(a) protein expression, apo(a) specific inhibitors can affect other components of the lipid transport system including downstream components. Similarly, in certain embodiments, apo(a) specific inhibitors can affect other molecular processes in an animal.

[0157] As used herein, "atherosclerosis" means a hardening of the arteries affecting large and medium-sized arteries and is characterized by the presence of fatty deposits. The fatty deposits are called "atheromas" or "plaques," which consist mainly of cholesterol and other fats, calcium and scar tissue, and damage the lining of arteries.

[0158] As used herein, "coronary heart disease (CHD)" means a narrowing of the small blood vessels that supply blood and oxygen to the heart, which is often a result of atherosclerosis.

[0159] As used herein, "diabetes mellitus" or "diabetes" is a syndrome characterized by disordered metabolism and abnormally high blood sugar (hyperglycemia) resulting from insufficient levels of insulin or reduced insulin sensitivity. The characteristic symptoms are excessive urine production (polyuria) due to high blood glucose levels, excessive thirst and increased fluid intake (polydipsia) attempting to compensate for increased urination, blurred vision due to high blood glucose effects on the eye's optics, unexplained weight loss, and lethargy.

[0160] As used herein, "diabetic dyslipidemia" or "type 2 diabetes with dyslipidemia" means a condition characterized by Type 2 diabetes, reduced HDL-C, elevated triglycerides (TG), and elevated small, dense LDL particles.

[0161] As used herein, "diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, the diluent in an injected composition can be a liquid, e.g. saline solution.

[0162] As used herein, "dyslipidemia" refers to a disorder of lipid and/or lipoprotein metabolism, including lipid and/or lipoprotein overproduction or deficiency. Dyslipidemias can be manifested by elevation of lipids such as chylomicron, cholesterol and triglycerides as well as lipoproteins such as low-density lipoprotein (LDL) cholesterol.

[0163] As used herein, "dosage unit" means a form in which a pharmaceutical agent is provided, e.g. pill, tablet, or other dosage unit known in the art. In certain embodiments, a dosage unit is a vial containing lyophilized antisense oligonucleotide. In certain embodiments, a dosage unit is a vial containing reconstituted antisense oligonucleotide.

[0164] As used herein, "dose" means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose can be administered in one, two, or more boluses, tablets, or injections. For example, in certain embodiments where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection, therefore, two or more injections can be used to achieve the desired dose. In certain embodiments, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses can be stated as the amount of pharmaceutical agent per hour, day, week, or month. Doses can also be stated as mg/kg or g/kg.

[0165] As used herein, "effective amount" or "therapeutically effective amount" means the amount of active pharmaceutical agent sufficient to effectuate a desired physiological outcome in an individual in need of the agent. The effective amount can vary among individuals depending on the health and physical condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual's medical condition, and other relevant factors.

[0166] As used herein, "fully complementary" or "100% complementary" means each nucleobase of a nucleobase sequence of a first nucleic acid has a complementary nucleobase in a second nucleobase sequence of a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a second nucleic acid is a target nucleic acid.

[0167] As used herein, "glucose" is a monosaccharide used by cells as a source of energy and inflammatory intermediate. "Plasma glucose" refers to glucose present in the plasma.

[0168] As used herein, "high density lipoprotein-C" or "HDL-C" means cholesterol associated with high density lipoprotein particles. Concentration of HDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum HDL-C" and "plasma HDL-C" mean HDL-C in serum and plasma, respectively.

[0169] As used herein, "HMG-CoA reductase inhibitor" means an agent that acts through the inhibition of the enzyme HMG-CoA reductase, such as atorvastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

[0170] As used herein, "hypercholesterolemia" means a condition characterized by elevated cholesterol or circulating (plasma) cholesterol, LDL-cholesterol and VLDL-cholesterol, as per the guidelines of the Expert Panel Report of the National Cholesterol Educational Program (NCEP) of Detection, Evaluation of Treatment of high cholesterol in adults (see, Arch. Int. Med. (1988) 148, 36-39).

[0171] As used herein, "hyperlipidemia" or "hyperlipemia" is a condition characterized by elevated serum lipids or circulating (plasma) lipids. This condition manifests an abnormally high concentration of fats. The lipid fractions in

the circulating blood are cholesterol, low density lipoproteins, very low density lipoproteins, chylomicrons and triglycerides. The Fredrickson classification of hyperlipidemias is based on the pattern of TG and cholesterol-rich lipoprotein particles, as measured by electrophoresis or ultracentrifugation and is commonly used to characterize primary causes of hyperlipidemias such as hypertriglyceridemia (Fredrickson and Lee, Circulation, 1965, 31:321-327; Fredrickson et al., New Eng J Med, 1967, 276 (1): 34-42).

[0172] As used herein, "hypertriglyceridemia" means a condition characterized by elevated triglyceride levels. Its etiology includes primary (i.e. genetic causes) and secondary (other underlying causes such as diabetes, metabolic syndrome/insulin resistance, obesity, physical inactivity, cigarette smoking, excess alcohol and a diet very high in carbohydrates) factors or, most often, a combination of both (Yuan et al. CMAJ, 2007, 176:1113-1120).

[0173] As used herein, "identifying" or "selecting an animal with metabolic or cardiovascular disease" means identifying or selecting a subject prone to or having been diagnosed with a metabolic disease, a cardiovascular disease, or a metabolic syndrome; or, identifying or selecting a subject having any symptom of a metabolic disease, cardiovascular disease, or metabolic syndrome including, but not limited to, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypertension increased insulin resistance, decreased insulin sensitivity, above normal body weight, and/or above normal body fat content or any combination thereof. Such identification can be accomplished by any method, including but not limited to, standard clinical tests or assessments, such as measuring serum or circulating (plasma) cholesterol, measuring serum or circulating (plasma) blood-glucose, measuring serum or circulating (plasma) triglycerides, measuring blood-pressure, measuring body fat content, measuring body weight, and the like.

[0174] As used herein, "improved cardiovascular outcome" means a reduction in the occurrence of adverse cardiovascular events, or the risk thereof. Examples of adverse cardiovascular events include, without limitation, death, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia.

[0175] As used herein, "immediately adjacent" means there are no intervening elements between the immediately adjacent elements, for example, between regions, segments, nucleotides and/or nucleosides.

[0176] As used herein, "increasing HDL" or "raising HDL" means increasing the level of HDL in an animal after administration of at least one compound of the invention, compared to the HDL level in an animal not administered any compound.

[0177] As used herein, "individual" or "subject" or "animal" means a human or non-human animal selected for treatment or therapy.

[0178] As used herein, "individual in need thereof" refers to a human or non-human animal selected for treatment or therapy that is in need of such treatment or therapy.

[0179] As used herein, "induce", "inhibit", "potentiate", "elevate", "increase", "decrease", "reduce" or the like denote quantitative differences between two states. For example, "an amount effective to inhibit the activity or expression of apo(a)" means that the level of activity or expression of apo(a) in a treated sample will differ from the level of apo(a) activity or expression in an untreated sample. Such terms are applied to, for example, levels of expression, and levels of activity.

[0180] As used herein, "inflammatory condition" refers to a disease, disease state, syndrome, or other condition resulting in inflammation. For example, rheumatoid arthritis and liver fibrosis are inflammatory conditions. Other examples of inflammatory conditions include sepsis, myocardial ischemia/reperfusion injury, adult respiratory distress syndrome, nephritis, graft rejection, inflammatory bowel disease, multiple sclerosis, arteriosclerosis, atherosclerosis and vasculitis.

[0181] As used herein, "inhibiting the expression or activity" refers to a reduction or blockade of the expression or activity of a RNA or protein and does not necessarily indicate a total elimination of expression or activity.

[0182] As used herein, "insulin resistance" is defined as the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to metabolic syndrome and type 2 diabetes.

[0183] As used herein, "insulin sensitivity" is a measure of how effectively an individual processes glucose. An individual having high insulin sensitivity effectively processes glucose whereas an individual with low insulin sensitivity does not effectively process glucose.

[0184] As used herein, "lipid-lowering" means a reduction in one or more lipids (e.g., LDL, VLDL) in a subject. "Lipid-raising" means an increase in a lipid (e.g., HDL) in a subject. Lipid-lowering or lipid-raising can occur with one or more doses over time.

[0185] As used herein, "lipid-lowering therapy" or "lipid lowering agent" means a therapeutic regimen provided to a subject to reduce one or more lipids in a subject. In certain embodiments, a lipid-lowering therapy is provided to reduce one or more of apo(a), CETP, apoB, total cholesterol, LDL-C, VLDL-C, IDL-C, non-HDL-C, triglycerides, small dense LDL particles, and Lp(a) in a subject. Examples of lipid-lowering therapy include, but are not limited to, apoB inhibitors, statins, fibrates and MTP inhibitors.

[0186] As used herein, "lipoprotein", such as VLDL, LDL and HDL, refers to a group of proteins found in the serum, plasma and lymph and are important for lipid transport. The chemical composition of each lipoprotein differs, for example, in that the HDL has a higher proportion of protein versus lipid, whereas the VLDL has a lower proportion of protein versus lipid.

[0187] As used herein, "Lp(a)" comprises apo(a) and a LDL like particle containing apoB. The apo(a) is linked to the apoB by a disulfide bond.

[0188] As used herein, "low density lipoprotein-cholesterol (LDL-C)" means cholesterol carried in low density lipoprotein particles. Concentration of LDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum LDL-C" and "plasma LDL-C" mean LDL-C in the serum and plasma, respectively.

[0189] As used herein, "major risk factors" refers to factors that contribute to a high risk for a particular disease or condition. In certain embodiments, major risk factors for coronary heart disease include, without limitation, cigarette smoking, hypertension, high LDL, low HDL-C, family history of coronary heart disease, age, and other factors disclosed herein.

[0190] As used herein, "metabolic disorder" or "metabolic disease" refers to a condition characterized by an alteration or disturbance in metabolic function. "Metabolic" and "metabolism" are terms well known in the art and generally include the whole range of biochemical processes that occur within a living organism. Metabolic disorders include, but are not limited to, hyperglycemia, prediabetes, diabetes (type 1 and type 2), obesity, insulin resistance, metabolic syndrome and dyslipidemia due to type 2 diabetes.

[0191] As used herein, "metabolic syndrome" means a condition characterized by a clustering of lipid and non-lipid cardiovascular risk factors of metabolic origin. In certain embodiments, metabolic syndrome is identified by the presence of any 3 of the following factors: waist circumference of greater than 102 cm in men or greater than 88 cm in women; serum triglyceride of at least 150 mg/dL; HDL-C less than 40 mg/dL in men or less than 50 mg/dL in women; blood pressure of at least 130/85 mmHg; and fasting glucose of at least 110 mg/dL. These determinants can be readily measured in clinical practice (JAMA, 2001, 285: 2486-2497).

[0192] "Parenteral administration" means administration through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular administration, intraarterial

administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration. Administration can be continuous, chronic, short or intermittent.

[0193] As used herein, "peptide" means a molecule formed by linking at least two amino acids by amide bonds. Peptide refers to polypeptides and proteins.

[0194] As used herein, "pharmaceutical agent" means a substance that provides a therapeutic benefit when administered to an individual. For example, in certain embodiments, an antisense oligonucleotide targeted to apo(a) is a pharmaceutical agent.

[0195] As used herein, "pharmaceutical composition" or "composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition can comprise one or more active agents and a pharmaceutical carrier e.g., a sterile aqueous solution.

[0196] As used herein, "pharmaceutically acceptable derivative" encompasses derivatives of the compounds described herein such as solvates, hydrates, esters, prodrugs, polymorphs, isomers, isotopically labelled variants, pharmaceutically acceptable salts and other derivatives known in the art.

[0197] As used herein, "pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. The term "pharmaceutically acceptable salt" or "salt" includes a salt prepared from pharmaceutically acceptable non-toxic acids or bases, including inorganic or organic acids and bases. "Pharmaceutically acceptable salts" of the compounds described herein may be prepared by methods well-known in the art. For a review of pharmaceutically acceptable salts, see Stahl and Wermuth, Handbook of Pharmaceutical Salts: Properties, Selection and Use (Wiley-VCH, Weinheim, Germany, 2002). Sodium salts of antisense oligonucleotides are useful and are well accepted for therapeutic administration to humans. Accordingly, in one embodiment the compounds described herein are in the form of a sodium salt.

[0198] As used herein, "portion" means a defined number of contiguous (i.e. linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an antisense compound.

[0199] As used herein, "prevent"or "preventing" refers to delaying or forestalling the onset or development of a disease, disorder, or condition for a period of time from minutes to indefinitely. Prevent also means reducing risk of developing a disease, disorder, or condition.

[0200] As used herein, "raise" means to increase in amount. For example, to raise plasma HDL levels means to increase the amount of HDL in the plasma.

[0201] As used herein, "reduce" means to bring down to a smaller extent, size, amount, or number. For example, to reduce plasma triglyceride levels means to bring down the amount of triglyceride in the plasma.

[0202] As used herein, "region" or "target region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. The structurally defined regions for apo(a) can be obtained by accession number from sequence databases such as NCBI. In certain embodiments, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the target region.

[0203] As used herein, "second agent" or "second therapeutic agent" means an agent that can be used in combination with a "first agent". A second therapeutic agent can include, but is not limited to, antisense oligonucleotides targeting apo(a) or apoB. A second agent can also include anti- apo(a) antibodies, apo(a) peptide

inhibitors, cholesterol lowering agents, lipid lowering agents, glucose lowering agents and anti-inflammatory agents.

[0204] As used herein, "segments" are defined as smaller, sub-portions of regions within a nucleic acid. For example, a "target segment" means the sequence of nucleotides of a target nucleic acid to which one or more antisense compounds is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment. Alternatively, a "start site" can refer to the 5'-most nucleotide of a target segment and a "stop site" refers to the 3'-most nucleotide of a target segment. A target segment can also begin at the "start site" of one sequence and end at the "stop site" of another sequence.

[0205] As used herein, "statin" means an agent that inhibits the activity of HMG-CoA reductase.

[0206] As used herein, "subcutaneous administration" means administration just below the skin.

[0207] As used herein, "subject" means a human or non-human animal selected for treatment or therapy.

[0208] As used herein, "symptom of cardiovascular disease or disorder" means a phenomenon that arises from and accompanies the cardiovascular disease or disorder and serves as an indication of it. For example, angina; chest pain; shortness of breath; palpitations; weakness; dizziness; nausea; sweating; tachycardia; bradycardia; arrhythmia; atrial fibrillation; swelling in the lower extremities; cyanosis; fatigue; fainting; numbness of the face; numbness of the limbs; claudication or cramping of muscles; bloating of the abdomen; or fever are symptoms of cardiovascular disease or disorder.

[0209] As used herein, "targeting" or "targeted" means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

[0210] As used herein, "therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

[0211] As used herein, "therapeutic lifestyle change" means dietary and lifestyle changes intended to lower fat/adipose tissue mass and/or cholesterol. Such change can reduce the risk of developing heart disease, and may includes recommendations for dietary intake of total daily calories, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, carbohydrate, protein, cholesterol, insoluble fiber, as well as recommendations for physical activity.

[0212] As used herein, "treat" or "treating" refers to administering a compound described herein to effect an alteration or improvement of a disease, disorder, or condition.

[0213] As used herein, "triglyceride" or "TG" means a lipid or neutral fat consisting of glycerol combined with three fatty acid molecules.

[0214] As used herein, "type 2 diabetes," (also known as "type 2 diabetes mellitus", "diabetes mellitus, type 2", "non-insulin-dependent diabetes", "NIDDM", "obesity related diabetes", or "adult-onset diabetes") is a metabolic disorder that is primarily characterized by insulin resistance, relative insulin deficiency, and hyperglycemia.

Certain Embodiments of the Disclosure

[0215] In certain embodiments, a compound comprises a siRNA or antisense oligonucleotide targeted to apolipoprotein(a) (apo(a)) known in the art and a conjugate group described herein. Examples of antisense oligonucleotides targeted to apo(a) suitable for conjugation include but are not limited to those disclosed in WO 2013/177468; US 8,673,632; US 7,259,150; and US Patent Application Publication No. US 2004/0242516. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any

of SEQ ID NOs 12-130, 133, 134 disclosed in WO 2013/177468 and a conjugate group described herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 11-45 and 85-96 disclosed in US 8,673,632 and a conjugate group described herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 11-45 disclosed in US 7,259,150 and a conjugate group described herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 7-41 disclosed in US Patent Application Publication No. US 2004/0242516 and a conjugate group described herein.

[0216] Certain embodiments of the present disclosure provide a compounds and methods for decreasing apo(a) mRNA and protein expression. In certain embodiments, the compound is an apo(a) specific inhibitor for treating, preventing, or ameliorating an apo(a) associated disease. In certain embodiments, the compound is an antisense oligonucleotide targeting apo(a). In certain embodiments, the compound is an antisense oligonucleotide targeting apo(a) and a conjugate group.

[0217] Certain embodiments of the present disclosure provide a compounds and methods for decreasing Lp(a) levels. In certain embodiments, the compound is an apo(a) specific inhibitor for treating, preventing, or ameliorating an Lp(a) associated disease. In certain embodiments, the compound is an antisense oligonucleotide targeting apo(a). In certain embodiments, the compound is an antisense oligonucleotide targeting apo(a) and a conjugate group.

[0218] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides. In certain embodiments, the modified oligonucleotide with the conjugate group consists of 15 to 30, 18 to 24, 19 to 22, 13 to 25, 14 to 25, 15 to 25 linked nucleosides. In certain embodiments, the modified oligonucleotide with the conjugate group comprises at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29 or 30 linked nucleosides. In certain embodiments, the modified oligonucleotide with the conjugate group consists of 20 linked nucleosides.

[0219] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to an equal length portion of any of SEQ ID NOs: 1-4.

[0220] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting an apo(a) segment and a conjugate group, wherein the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to an equal length portion of any of the target segments shown in, for example, Examples 114 and 117. In the tables, the "Start Site" refers to the 5'-most nucleotide of a target segment and "Stop Site" refers to the 3'-most nucleotide of a target segment. A target segment can range from the start site to the stop site of each sequence listed in the tables. Alternatively, the target segment can range from the start site of one sequence and end at the stop site of another sequence. For example, as shown in Table 125, a target segment can range from 3901-3920, the start site to the stop site of SEQ ID NO: 58. In another example, as shown in Table 125, a target segment can range from 3900-3923, the start site of SEQ ID NO: 57 to the stop site of SEQ ID NO: 61.

[0221] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the nucleobase sequence of the modified oligonucleotide is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of SEQ ID NOs: 1-4. Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the nucleobase sequence of the modified oligonucleotide is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to any of the target segments shown in, for example, Examples 114 and 117.

[0222] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising a portion of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases complementary to an equal length portion of nucleobases 3901 to 3920 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1.

[0223] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29 or 30 contiguous nucleobases complementary to an equal length portion of nucleobases 3900 to 3923 of SEQ ID NO: 1, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to SEQ ID NO: 1.

[0224] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-130,133, 134. In certain embodiments, the modified oligonucleotide has a nucleobase sequence comprising at least 8 contiguous nucleobases of any one of the nucleobase sequences of SEQ ID NOs: 12-130, 133, 134. In certain embodiments, the compound consists of any one of SEQ ID NOs: 12-130, 133, 134 and a conjugate group.

[0225] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-20, 22-33, 35-44, 47-50, 51, 53, 57-62, 65-66, 68, 70-79, 81, 85-86, 89-90, 92-94, 97, 105-110, 103-104, 133-134. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 12-20, 22-33, 35-44, 47-50, 51, 53, 57-62, 65-66, 68, 70-79, 81, 85-86, 89-90, 92-94, 97, 105-110, 103-104, 133-134 and a conjugate group.

[0226] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-19, 26-30, 32, 35, 38-44, 46-47, 50, 57-58, 61, 64-66, 68, 72-74, 76-77, 92-94, 103-110. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 12-19, 26-30, 32, 35, 38-44, 46-47, 50, 57-58, 61, 64-66, 68, 72-74, 76-77, 92-94, 103-110 and a conjugate group.

[0227] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 111, 114-121, 123-129. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 111, 114-121, 123-129 and a conjugate group.

[0228] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of

any of the nucleobase sequences of SEQ ID NOs: 14, 17, 18, 26-28, 39, 71, 106-107. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 14, 17, 18, 26-28, 39, 71, 106-107 and a conjugate group.

[0229] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 14, 26-29, 39-40, 82. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 14, 26-29, 39-40, 82 and a conjugate group.

[0230] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 14, 16-18. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 14, 16-18 and a conjugate group.

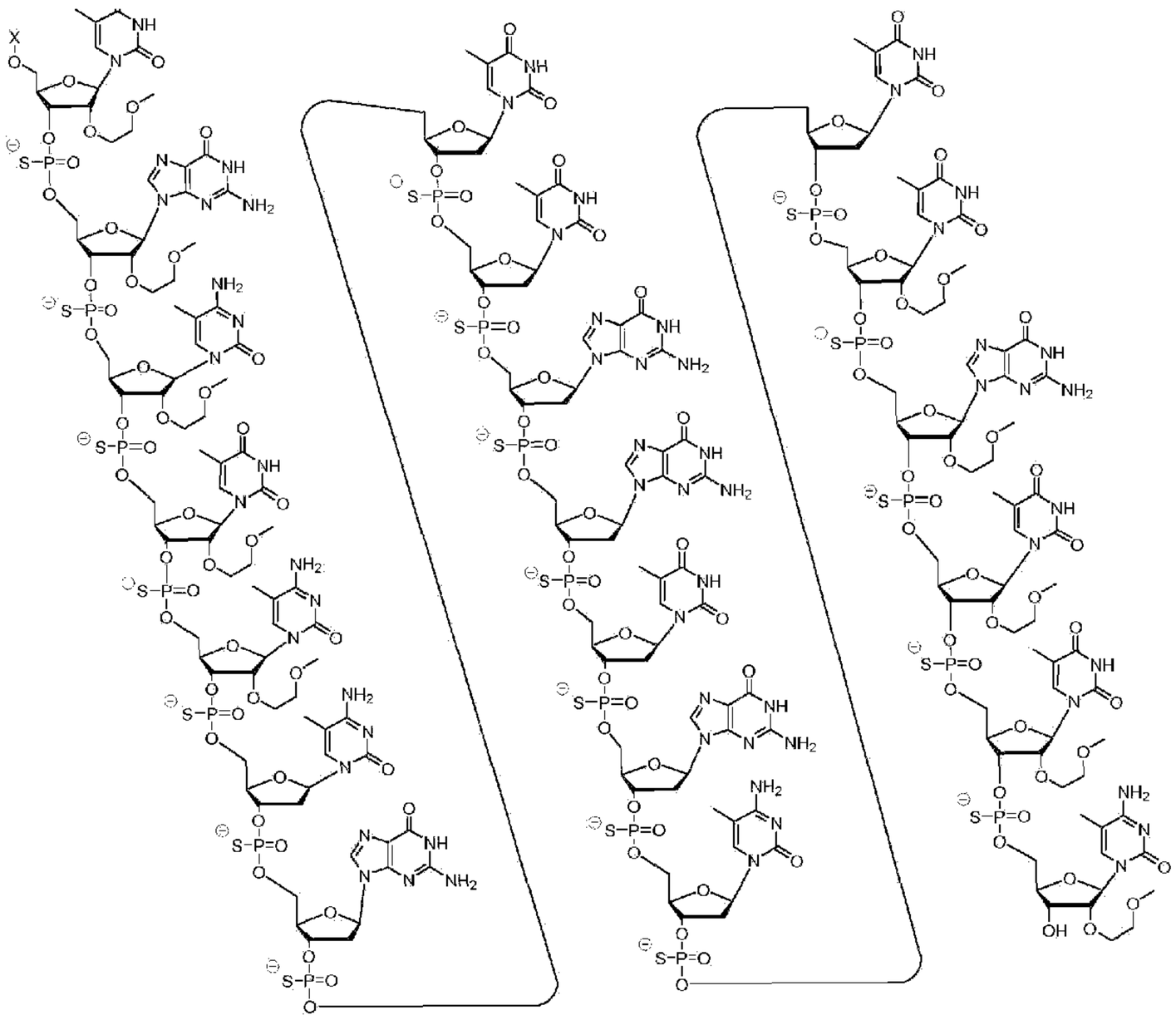
[0231] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 26-27, 107. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 26-27, 107 and a conjugate group.

[0232] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 28-29, 39-40, 47. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: : 28-29, 39-40, 47 and a conjugate group.

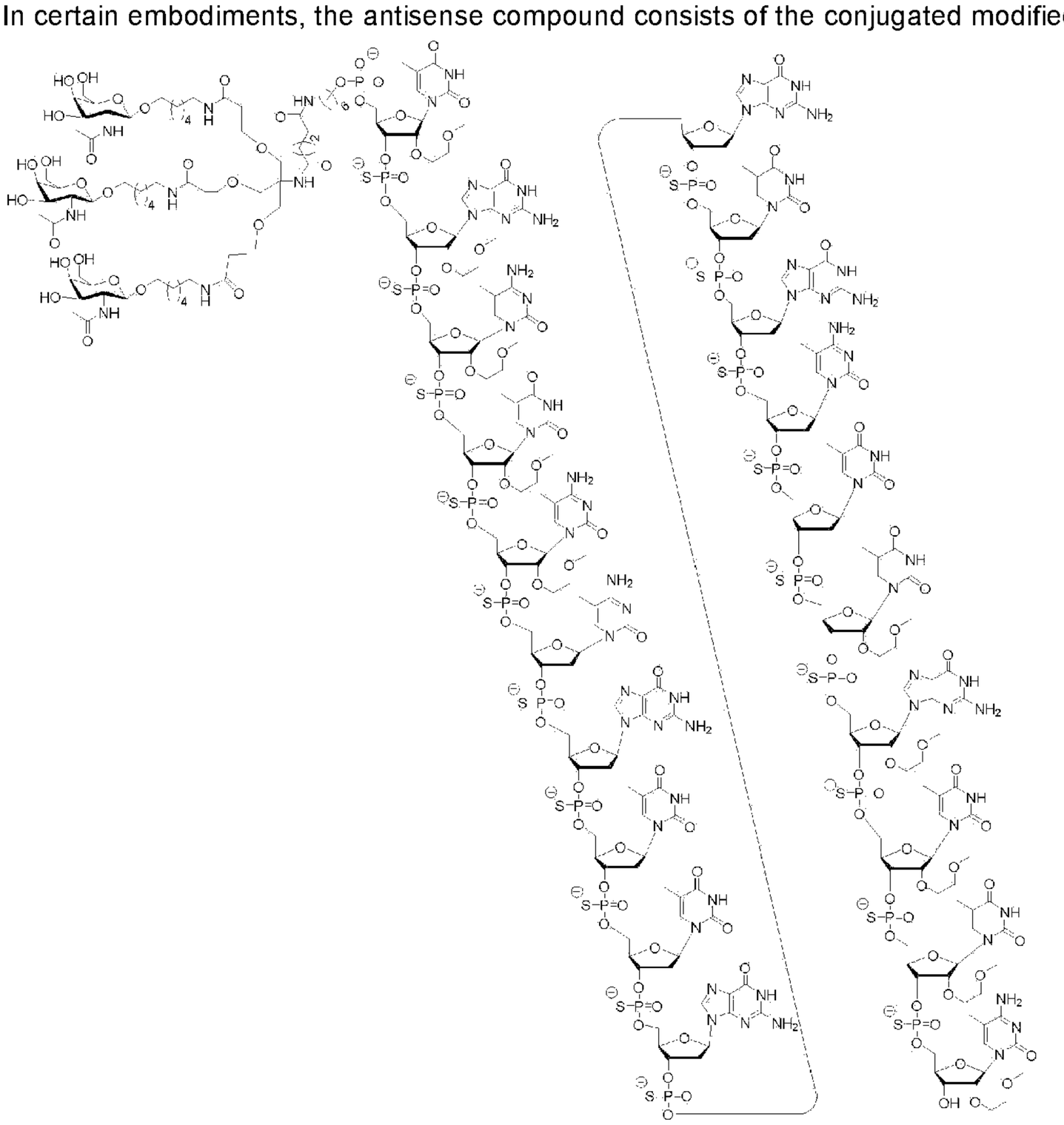
[0233] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 28, 93, 104, 134. In certain embodiments, the compound consists of any of the nucleobase sequences of SEQ ID NOs: 28, 93, 104, 134 and a conjugate group.

[0234] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 58. In certain embodiments, the modified oligonucleotide with the conjugate group has a nucleobase sequence comprising at least 8 contiguous nucleobases of the nucleobase sequence of SEQ ID NO: 58. In certain embodiments, the compound consists of SEQ ID NO: 58 and a conjugate group.

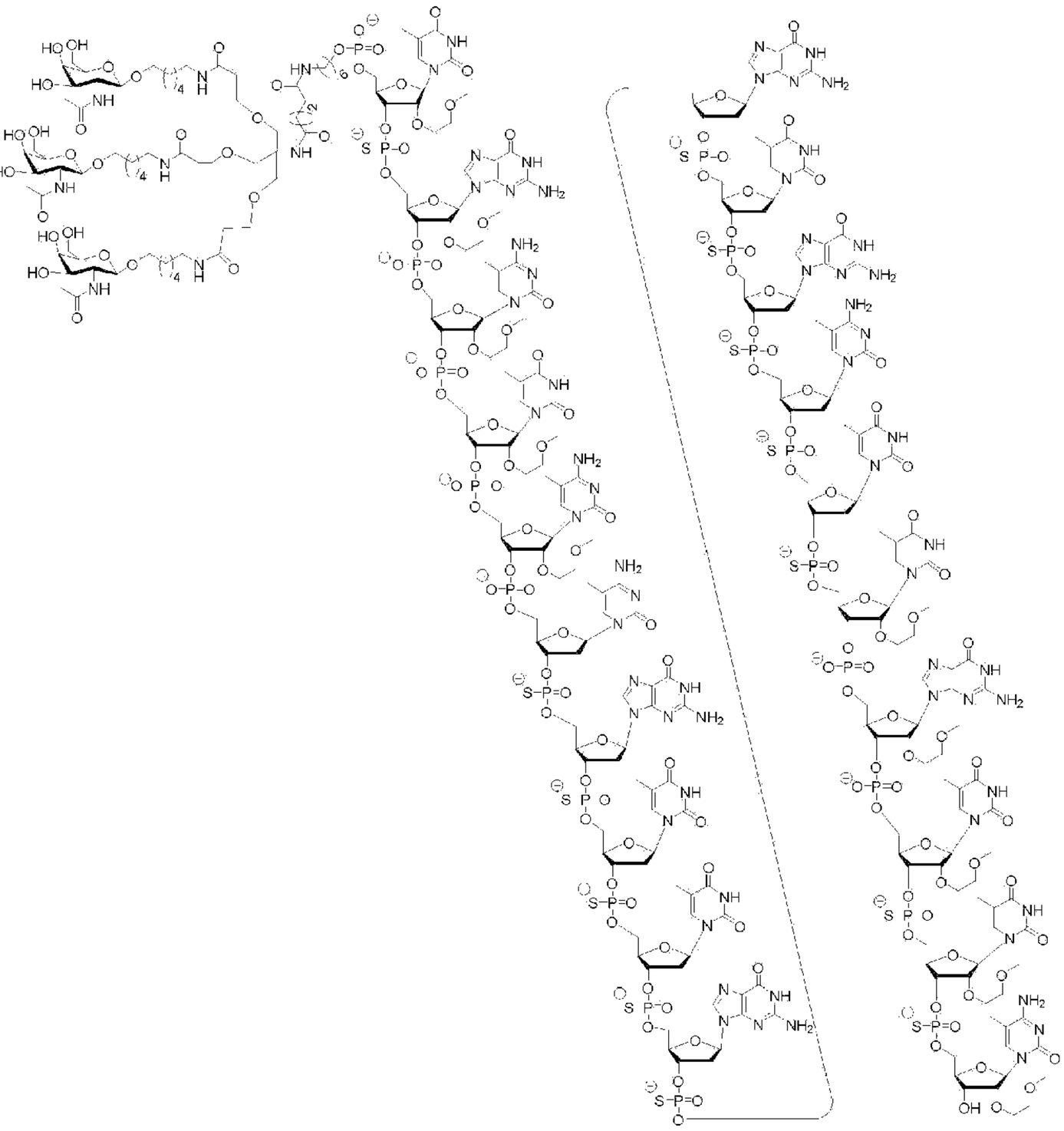
[0235] In certain embodiments, the conjugated antisense compounds can be represented by the following structure. In certain embodiments, the antisense compound comprises the modified oligonucleotide ISIS 494372 with a 5'-X, wherein X is a conjugate group comprising GalNAc as defined in the claims. In certain embodiments, the antisense compound consists of the modified oligonucleotide ISIS 494372 with a 5'-X, wherein X is a conjugate group comprising GalNAc as defined in the claims.



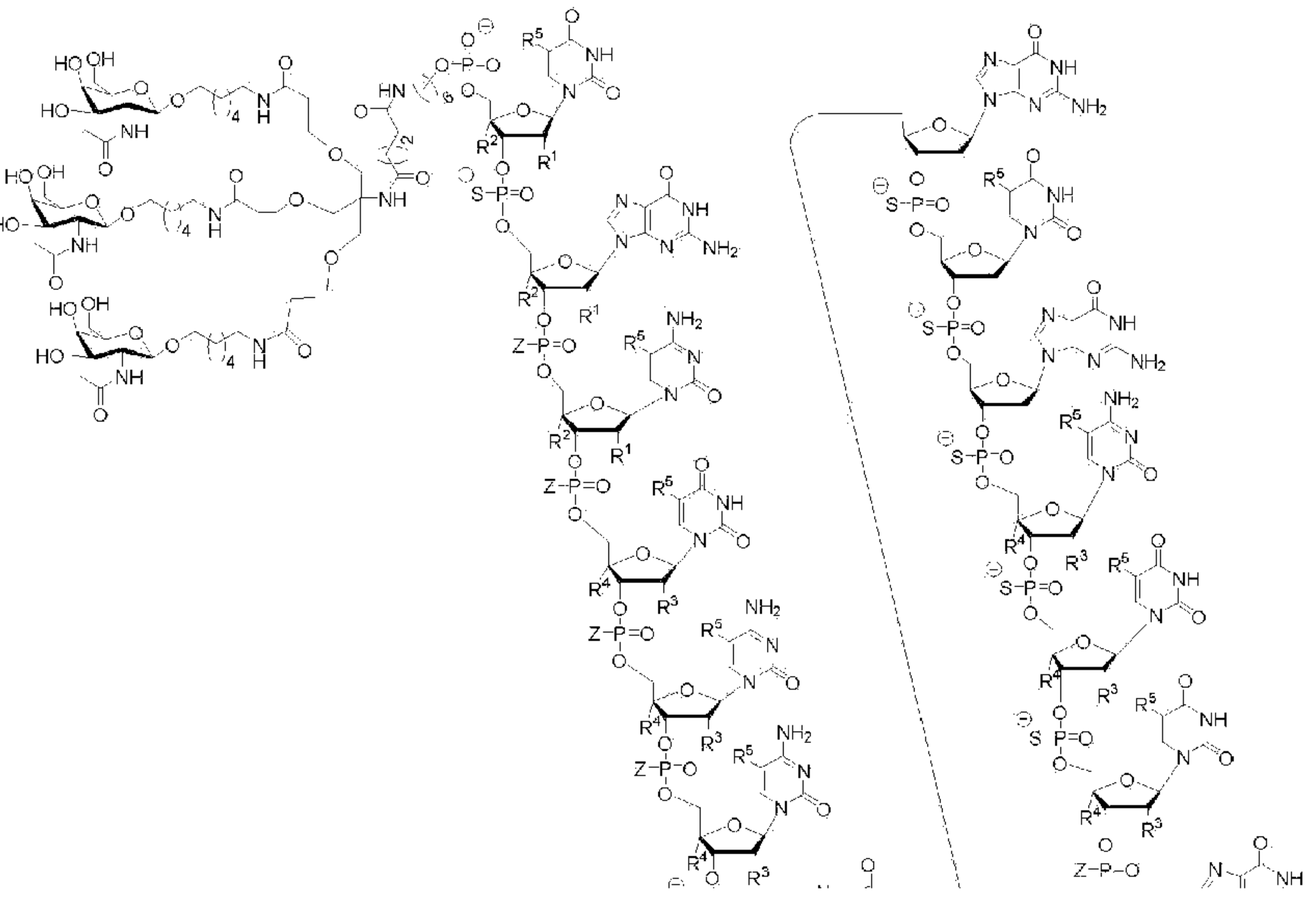
[0236] In certain embodiments, the conjugated antisense compound can be represented by the following structure. In certain embodiments, the antisense compound comprises the conjugated modified oligonucleotide ISIS 681251. In certain embodiments, the antisense compound consists of the conjugated modified oligonucleotide ISIS 681251.

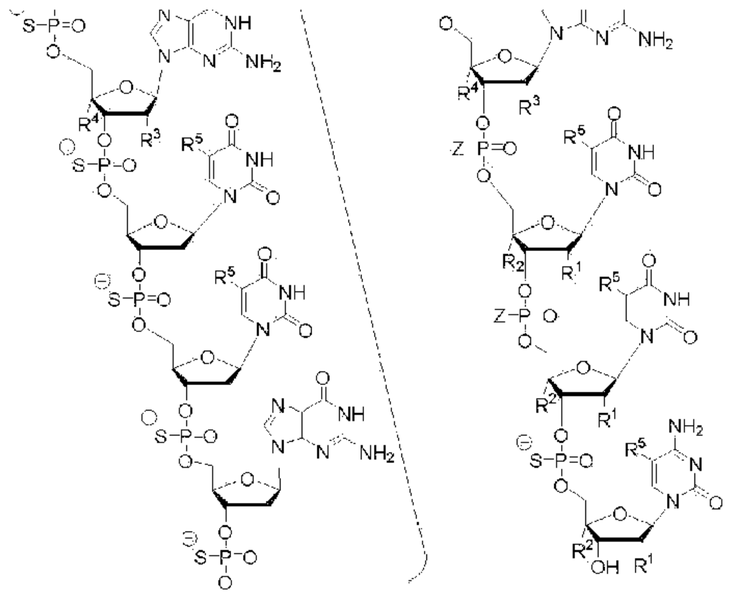


[0237] In certain embodiments, the conjugated antisense compound can be represented by the following structure. In certain embodiments, the antisense compound comprises the conjugated modified oligonucleotide ISIS 681257. In certain embodiments, the antisense compound consists of the conjugated modified oligonucleotide ISIS 681257.



[0238] In certain embodiments, the conjugated antisense compound can be represented by the following structure. In certain embodiments, the antisense compound comprises a modified oligonucleotide with the nucleobase sequence of SEQ ID NO: 58 with a 5'-GalNAc, as defined in the claims, with variability in the sugar mods of the wings. In certain embodiments, the antisense compound consists of a modified oligonucleotide with the nucleobase seuquence of SEQ ID NO: 58 with a 5'-GalNAc, as defined in the claims, with variability in the sugar mods of the wings.





[0239] Wherein either R^1 is $-OCH_2CH_2OCH_3$ (MOE) and R^2 is H; or R^1 and R^2 together form a bridge, wherein R^1 is -O- and R^2 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$, and R^1 and R^2 are directly connected such that the resulting bridge is selected from: $-O-CH_2-$, $-O-CH(CH_3)-$, and $-O-CH_2CH_2-$;

And for each pair of R^3 and R^4 on the same ring, independently for each ring: either R^3 is selected from H and $-OCH_2CH_2OCH_3$ and R^4 is H; or R^3 and R^4 together form a bridge, wherein R^3 is -O-, and R^4 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$and R^3 and R^4 are directly connected such that the resulting bridge is selected from: $-O-CH_2-$, $-O-CH(CH_3)-$, and $-O-CH_2CH_2-$;

And R^5 is selected from H and $-CH_3$;

And Z is selected from S^- and O^-.

[0240] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide is single-stranded.

[0241] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein at least one internucleoside linkage is a modified internucleoside linkage. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 or at least 10 internucleoside linkages of said modified oligonucleotide are phosphorothioate internucleoside linkages. In certain embodiments, each internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, the modified oligonucleotide comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 or at least 10 phosphodiester internucleoside linkages. In certain embodiments, each internucleoside linkage of the modified oligonucleotide is selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

[0242] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein at least one nucleoside comprises a modified nucleobase. In certain embodiments, the modified nucleobase is a 5-methylcytosine.

[0243] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide comprises at least one modified sugar. In certain embodiments, the modified sugar is a bicyclic sugar. In certain embodiments, the modified sugar comprises a 2'-O-methoxyethyl, a constrained ethyl, a 3'-fluoro-HNA or a 4'- $(CH_2)_n$-O-2' bridge, wherein n is 1 or 2.

[0244] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises: (a) a gap segment consisting of linked deoxynucleosides; (b) a 5' wing segment consisting of linked nucleosides; (c) a 3' wing segment consisting of linked nucleosides; and wherein the gap

segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

[0245] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein at least one internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0246] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising at least 8 contiguous nucleobases of any of SEQ ID NOs: 12-130, 133, 134, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein at least one internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

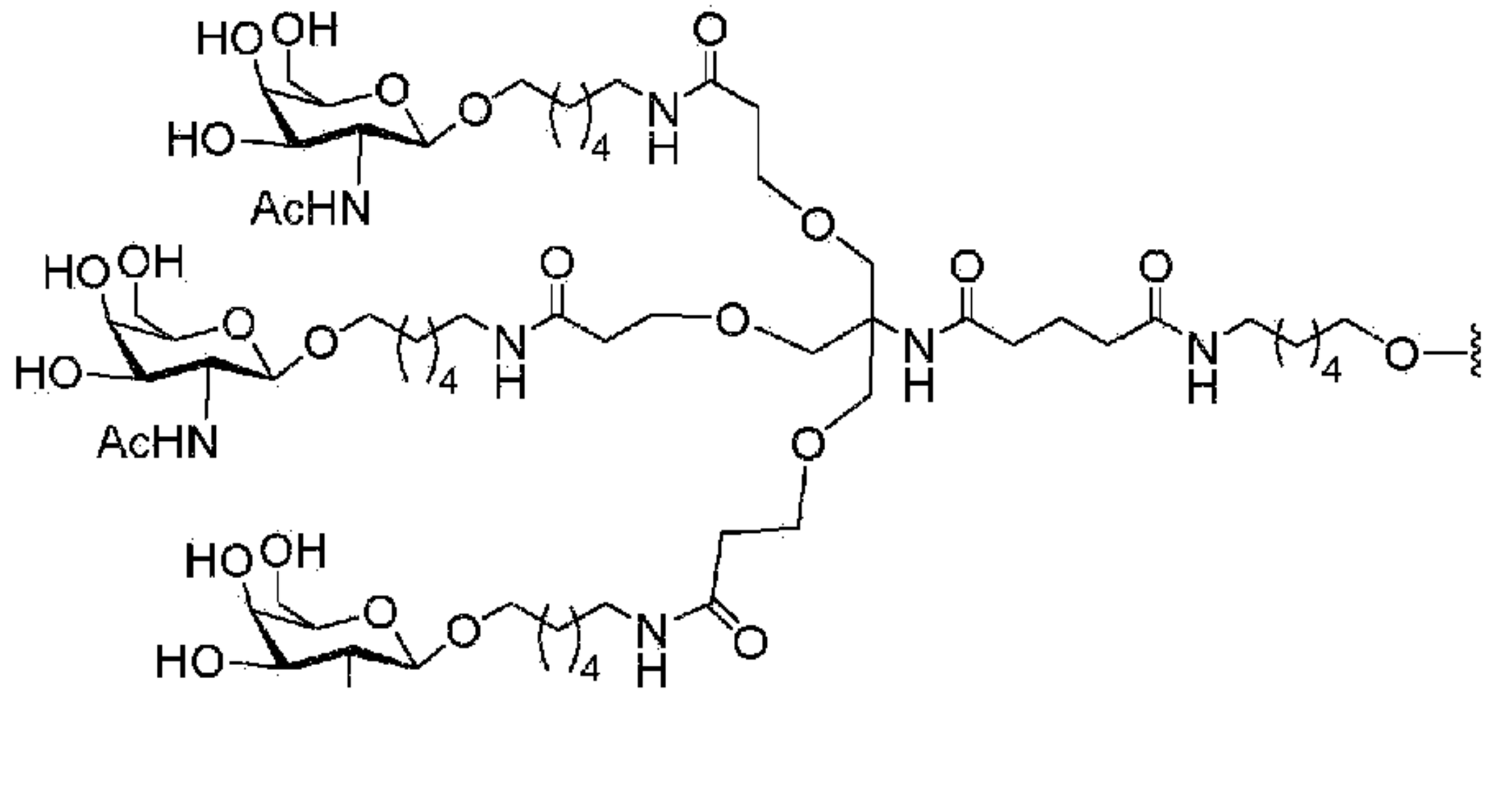
[0247] Certain embodiments of the present disclosure provide a compound comprising a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising at least 8 contiguous nucleobases of SEQ ID NO: 58, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-0-methoxyethyl sugar, wherein at least one internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0248] Certain embodiments of the present disclosure provide a modified oligonucleotide targeting apo(a) and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides with the nucleobase sequence of SEQ ID NO: 58, wherein the modified oligonucleotide comprises: (a) a gap segment consisting of ten linked deoxynucleosides; (b) a 5' wing segment consisting of five linked nucleosides; (c) a 3' wing segment consisting of five linked nucleosides; and wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar, wherein at least one internucleoside linkage is a phosphorothioate linkage and wherein each cytosine residue is a 5-methylcytosine.

[0249] In certain embodiments, the conjugate group is linked to the modified oligonucleotide at the 5' end of the modified oligonucleotide. In certain embodiments, the conjugate group is linked to the modified oligonucleotide at the 3' end of the modified oligonucleotide.

[0250] The conjugate group of the present invention comprises three ligands, wherein each ligand is N-acetyl galactosamine.

[0251] The conjugate group of the present invention comprises:



AcHN

[0252] The conjugate group is covalently attached to the modified oligonucleotide.

[0253] The compound can be represented by the formula:

$$A\text{-}B\text{-}C\text{-}D(E\text{-}F)_q$$

wherein

A is the modified oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0254] In certain embodiments of the present disclosure, the compound has a structure represented by the formula:

$$A\text{-}C\text{-}D(E\text{-}F)_q$$

wherein

A is the modified oligonucleotide;

C is the conjugate linker;

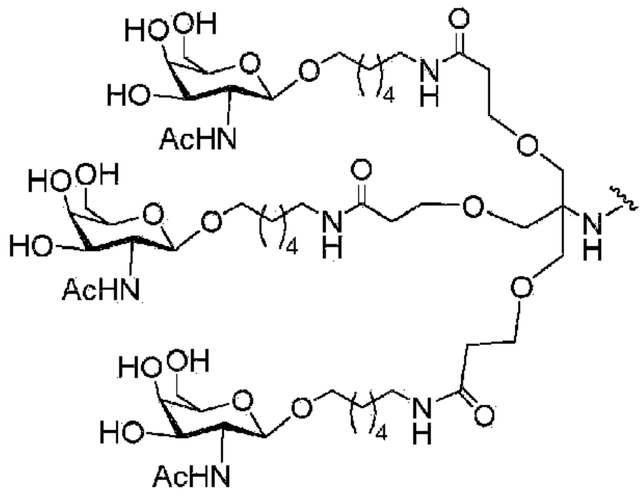
D is the branching group;

each E is a tether;

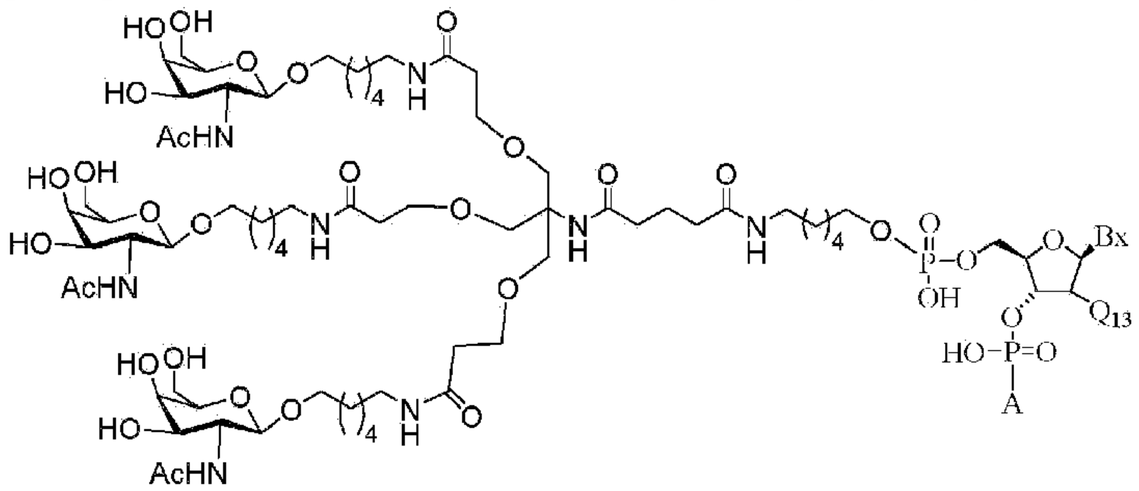
each F is a ligand; and

q is an integer between 1 and 5.

[0255] The conjugate group of the present invention comprises a cell-targeting moiety comprising:



[0256] In certain embodiments, the conjugate group comprises:



wherein Q13 is H or O(CH2)2-OCH3;

A is the modified oligonucleotide; and

Bx is a heterocyclic base moiety.

[0257] In certain embodiments, Bx is selected from among from adenine, guanine, thymine, uracil, or cytosine, or 5-methyl cytosine. In certain embodiments, Bx is adenine. In certain embodiments, Bx is thymine. In certain embodiments, Q13 is O(CH2)2-OCH3. In certain embodiments, Q13 is H.

[0258] In certain embodiments, the compound is in a salt form. In further embodiments, the compound further comprises of a pharmaceutically acceptable carrier or diluent. In certain embodiments, the compound comprises a modified oligonucleotide targeting apo(a) and a conjugate group, or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

[0259] Certain embodiments of the present disclosure provide a composition comprising a conjugated antisense compound as described herein, wherein the viscosity level of the compound is less than 40 centipoise (cP). In certain embodiments, the conjugated antisense compounds as described herein are efficacious by virtue of having a viscosity of less than 40 cP, less than 35 cP, less than 30 cP, less than 25 cP, less than 20 cP or less than 15 cP when measured by the parameters as described in Example 125.

[0260] Certain embodiments of the present disclosure provide compositions and methods comprising administering to an animal a conjugated antisense compound or composition disclosed herein. In certain embodiments, administering the conjugated antisense compound prevents, treats, ameliorates, or slows progression of a cardiovascular, metabolic and/or inflammatory disease

[0261] Certain embodiments of the present disclosure provide compositions and methods for use in therapy to treat an apo(a) related disease, disorder or condition. Certain embodiments of the present disclosure provide compositions and methods for use in therapy to treat an Lp(a) related disease, disorder or condition. In certain embodiments, apo(a) and/or Lp(a) levels are elevated in an animal. In certain embodiments, the composition is a compound comprising an apo(a) specific inhibitor. In certain embodiments, the apo(a) specific inhibitor is a nucleic acid. In certain embodiments, the nucleic acid is an antisense compound. In certain embodiments, the antisense compound is a modified oligonucleotide targeting apo(a). In certain embodiments, the antisense compound is a modified oligonucleotide targeting apo(a) and a conjugate group. In certain embodiments, the modified oligonucleotide targeting apo(a) with the conjugate group, is used in treating, preventing, slowing progression, ameliorating a cardiovascular and/or metabolic disease, disorder or condition. In certain embodiments, the compositions and methods for therapy include administering an apo(a) specific inhibitor to an individual in need thereof.

[0262] Certain embodiments of the present disclosure provide compositions and methods for reducing apo(a) levels. Certain embodiments of the present disclosure provide compositions and methods for reducing Lp(a) levels.

In certain embodiments, reducing apo(a) levels in a tissue, organ or subject improves the ratio of LDL to HDL or the ratio of TG to HDL. Certain embodiments of the present disclosure provide compositions and methods to reduce apo(a) mRNA or protein expression in an animal comprising administering to the animal a conjugated antisense compound or composition disclosed herein to reduce apo(a) mRNA or protein expression in the animal. Certain embodiments of the present disclosure provide compositions and methods to reduce Lp(a) levels in an animal comprising administering to the animal a conjugated antisense compound or composition disclosed herein to reduce apo(a) mRNA or protein expression in the animal.

[0263] Certain embodiments of the present disclosure provide compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating apo(a) related diseases, disorders, and conditions in a subject in need thereof. Certain embodiments of the present disclosure provide compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating Lp(a) related diseases, disorders, and conditions in a subject in need thereof. In certain embodiments, such diseases, disorders, and conditions include inflammatory, cardiovascular and/or metabolic diseases, disorders, and conditions. Certain such cardiovascular diseases, disorders or conditions include, but are not limited to, aortic stenosis, aneurysm (e.g., abdominal aortic aneurysm), angina, arrhythmia, atherosclerosis, cerebrovascular disease, coronary artery disease, coronary heart disease, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, myocardial infarction, peripheral vascular disease (e.g., peripheral artery disease, peripheral artery occlusive disease), retinal vascular occlusion, or stroke. Certain such metabolic diseases, disorders or conditions include, but are not limited to, hyperglycemia, prediabetes, diabetes (type I and type II), obesity, insulin resistance, metabolic syndrome and diabetic dyslipidemia. Certain such inflammatory diseases, disorders or conditions include, but are not limited to, aortic stenosis, coronary artey disease (CAD), Alzheimer's Disease and thromboembolic diseases, disorder or conditions. Certain thromboembolic diseases, disorders or conditions include, but are not limited to, stroke, thrombosis (e.g., venous thromboembolism), myocardial infarction and peripheral vascular disease. Certain embodiments of the present disclosure provide compositions and methods for preventing, treating, delaying, slowing the progression and/or ameliorating aortic stenosis.

[0264] Certain embodiments of the present disclosure provide a method of reducing at least one symptom of a cardiovascular disease, disorder or condition. In certain embodiments, the symptoms include, but are not limited to, angina, chest pain, shortness of breath, palpitations, weakness, dizziness, nausea, sweating, tachycardia, bradycardia, arrhythmia, atrial fibrillation, swelling in the lower extremities, cyanosis, fatigue, fainting, numbness of the face, numbness of the limbs, claudication or cramping of muscles, bloating of the abdomen, and fever. Certain embodiments of the present disclosure provide a method of reducing at least one symptom of aortic stenosis.

[0265] In certain embodiments, the modulation of apo(a) or Lp(a) expression occurs in a cell, tissue or organ. In certain embodiments, the modulations occur in a cell, tissue or organ in an animal. In certain embodiments, the modulation is a reduction in apo(a) mRNA level. In certain embodiments, the modulation is a reduction in apo(a) protein level. In certain embodiments, both apo(a) mRNA and protein levels are reduced. In certain embodiments, the modulation is a reduction in Lp(a) level. Such reduction may occur in a time-dependent or in a dose-dependent manner.

[0266] In certain embodiments, the subject or animal is human.

[0267] In certain embodiments, the conjugated antisense compound is parenterally administered. In further embodiments, the parenteral administration is subcutaneous.

[0268] In certain embodiments, the conjugated antisense compound or composition is co-administered with a second agent or therapy. In certain embodiments, the conjugated antisense compound or composition and the second agent are administered concomitantly.

[0269] In certain embodiments, the second agent is a glucose-lowering agent. In certain embodiments, the second agent is a LDL, TG or cholesterol lowering agent. In certain embodiments, the second agent is an anti-inflammatory agent. In certain embodiments, the second agent is an Alzheimer Disease drug. In certain

embodiments, the second agent can be, but is not limited to, a non-steroidal anti-inflammatory drug (NSAID e.g., aspirin), niacin (e.g., Niaspan), nicotinic acid, an apoB inhibitor (e.g., Mipomersen), a CETP inhibitor (e.g., Anacetrapib), an apo(a) inhibitor, a thyroid hormone analog (e.g., Eprotirome), a HMG-CoA reductase inhibitor (e.g., a statin), a fibrate (e.g., Gemfibrozil) and an microsomal triglyceride transfer protein inhibitor (e.g., Lomitapide). The therapy can be, but is not limited to, Lp(a) apheresis. Agents or therapies can be co-administered or administered concomitantly. Agents or therapies can be sequentially or subsequently administered.

[0270] Certain embodiments of the present disclosure provide use of a conjugated antisense compound targeted to apo(a) for decreasing apo(a) levels in an animal. Certain embodiments of the present disclosure provide use of a conjugated antisense compound targeted to apo(a) for decreasing Lp(a) levels in an animal. Certain embodiments of the present disclosure provide use of a conjugated antisense compounds targeted to apo(a) for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with apo(a). Certain embodiments of the present disclosure provide use of a conjugated antisense compounds targeted to apo(a) for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with Lp(a).

[0271] Certain embodiments of the present disclosure provide use of a conjugated antisense compound targeted to apo(a) in the preparation of a medicament for decreasing apo(a) levels in an animal. Certain embodiments of the present disclosure provide use of a conjugated antisense compound targeted to apo(a) in the preparation of a medicament for decreasing Lp(a) levels in an animal. Certain embodiments of the present disclosure provide use of a conjugated antisense compound for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with apo(a). Certain embodiments of the present disclosure provide use of a conjugated antisense compound for the preparation of a medicament for the treatment, prevention, or amelioration of a disease, disorder, or condition associated with Lp(a).

[0272] Certain embodiments of the present disclosure provide the use of a conjugated antisense compound as described herein in the manufacture of a medicament for treating, ameliorating, delaying or preventing one or more of a disease related to apo(a) and/or Lp(a).

[0273] Certain embodiments of the present disclosure provide a kit for treating, preventing, or ameliorating a disease, disorder or condition as described herein wherein the kit comprises: (i) an apo(a) specific inhibitor as described herein; and optionally (ii) a second agent or therapy as described herein.

[0274] A kit can further include instructions for using the kit to treat, prevent, or ameliorate a disease, disorder or condition as described herein by combination therapy as described herein.

B. Certain Compounds

[0275] In certain embodiments, the present disclosure provides conjugated antisense compounds comprising antisense oligonucleoitdes and a conjugate.

a. Certain Antisense Oligonucleotides

[0276] In certain embodiments, the present disclosure provides antisense oligonucleotides. Such antisense oligonucleotides comprise linked nucleosides, each nucleoside comprising a sugar moiety and a nucleobase. The structure of such antisense oligonucleotides may be considered in terms of chemical features (e.g., modifications and patterns of modifications) and nucleobase sequence (e.g., sequence of antisense oligonucleotide, idenity and sequence of target nucleic acid).

i. Certain Chemistry Features

[0277] The antisense oligonucleotide comprises one or more modifications. In certain such embodiments, antisense oligonucleotides comprise one or more modified nucleosides and/or modified internucleoside linkages. In certain embodiments, modified nucleosides comprise a modifed sugar moirty and/or modifed nucleobase.

1. <u>Certain Sugar Moieties</u>

[0278] In certain embodiments, compounds of the disclosure comprise one or more modifed nucleosides comprising a modifed sugar moiety. Such compounds comprising one or more sugar-modified nucleosides may have desirable properties, such as enhanced nuclease stability or increased binding affinity with a target nucleic acid relative to an oligonucleotide comprising only nucleosides comprising naturally occurring sugar moieties. In certain embodiments, modified sugar moieties are substitued sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of substituted sugar moieties.

[0279] In certain embodiments, modified sugar moieties are substituted sugar moieties comprising one or more non-bridging sugar substituent, including but not limited to substituents at the 2' and/or 5' positions. Examples of sugar substituents suitable for the 2'-position, include, but are not limited to: 2'-F, 2'-OCH_3 ("OMe" or "O-methyl"), and 2'-$O(CH_2)_2OCH_3$ ("MOE"). In certain embodiments, sugar substituents at the 2' position is selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, O-C_1-C_{10} substituted alkyl; OCF_3, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-N(Rm)(Rn), and O-CH_2-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl. Examples of sugar substituents at the 5'-position, include, but are not limited to:, 5'-methyl (R or S); 5'-vinyl, and 5'-methoxy. In certain embodiments, substituted sugars comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties (*see,e.g.,* PCT International Application WO 2008/101157, for additional 5', 2'-bis substituted sugar moieties and nucleosides).

[0280] Nucleosides comprising 2'-substituted sugar moieties are referred to as 2'-substituted nucleosides. In certain embodiments, a 2'- substituted nucleoside comprises a 2'-substituent group selected from halo, allyl, amino, azido, SH, CN, OCN, CF_3, OCF_3, O, S, or N(R_m)-alkyl; O, S, or N(R_m)-alkenyl; O, S or N(R_m)-alkynyl; O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, $O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n) or O-CH_2-C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl. These 2'-substituent groups can be further substituted with one or more substituent groups independently selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

[0281] In certain embodiments, a 2'- substituted nucleoside comprises a 2'-substituent group selected from F, NH_2, N_3, OCF_3, O-CH_3, $O(CH_2)_3NH_2$, CH_2-CH=CH_2, O-CH_2-CH=CH_2, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-N(R_m)(R_n), $O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and N-substituted acetamide (O-CH_2-C(=O)-N(R_m)(R_n) where each R_m and R_n is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl.

[0282] In certain embodiments, a 2'- substituted nucleoside comprises a sugar moiety comprising a 2'-substituent group selected from F, OCF_3, O-CH_3, $OCH_2CH_2OCH_3$, $O(CH_2)_2SCH_3$, O-$(CH_2)_2$-ON$(CH_3)_2$, -$O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and O-$CH_2$-C(=O)-N(H)$CH_3$.

[0283] In certain embodiments, a 2'- substituted nucleoside comprises a sugar moiety comprising a 2'-substituent group selected from F, O-CH_3, and $OCH_2CH_2OCH_3$.

[0284] Certain modifed sugar moieties comprise a bridging sugar substituent that forms a second ring resulting in a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. Examples of such 4' to 2' sugar substituents, include, but are not limited to: -[C(R_a)

$(R_b)]_n$-, -$[C(R_a)(R_b)]_n$-O-, -$C(R_aR_b)$-N(R)-O- or, -$C(R_aR_b)$-O-N(R)-; 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2',. 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)-S-2'; 4'-$(CH_2)_2$-O-2' (ENA); 4'-$CH(CH_3)$-O-2' (cEt) and 4'-$CH(CH_2OCH_3)$-O-2',and analogs thereof (*see, e.g.,* U.S. Patent 7,399,845, issued on July 15, 2008); 4'-$C(CH_3)(CH_3)$-O-2'and analogs thereof, (*see, e.g.,* WO2009/006478, published January 8, 2009); 4'-CH_2-$N(OCH_3)$-2' and analogs thereof (*see, e.g.,* WO2008/150729, published December 11, 2008); 4'-CH_2-$ON(CH_3)$-2' (*see, e.g.,* US2004/0171570, published September 2, 2004); 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-0-2'-, wherein each R is, independently, H, a protecting group, or C_1-C_{12} alkyl; 4'-CH_2-N(R)-O-2', wherein R is H, C_1-C_{12} alkyl, or a protecting group (*see,* U.S. Patent 7,427,672, issued on September 23, 2008); 4'-CH_2-C(H)(CH_3)-2' (*see, e.g.,* Chattopadhyaya, et al., J. Org. Chem.,2009, 74, 118-134); and 4'-CH_2-$C(=CH_2)$-2' and analogs thereof (*see,* published PCT International Application WO 2008/154401, published on December 8, 2008).

[0285] In certain embodiments, such 4' to 2' bridges independently comprise from 1 to 4 linked groups independently selected from -$[C(R_a)(R_b)]_n$-, -$C(R_a)$=$C(R_b)$-, -$C(R_a)$=N-, -$C(=NR_a)$-, -C(=O)-, -C(=S)-, -O-, - $Si(R_a)_2$-, -$S(=O)_x$-, and -$N(R_a)$-;
wherein:

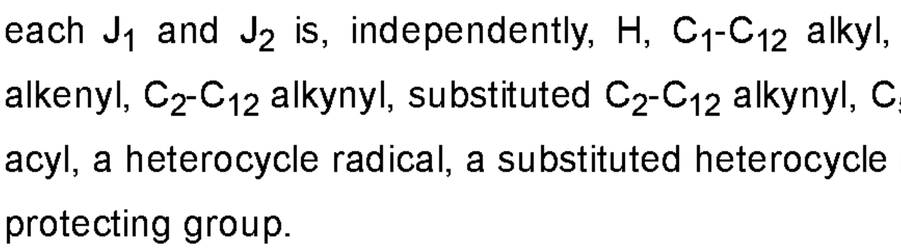
x is 0, 1, or 2;

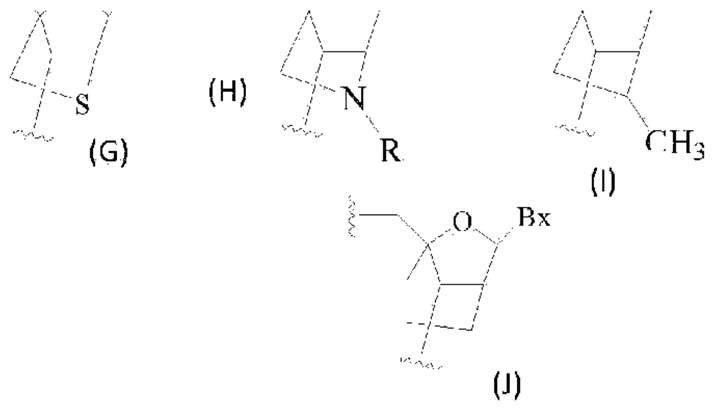
n is 1, 2, 3, or 4;

each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C_5-C_7 alicyclic radical, substituted C_5-C_7 alicyclic radical, halogen, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, acyl (C(=O)-H), substituted acyl, CN, sulfonyl ($S(=O)_2$-J_1), or sulfoxyl (S(=O)-J_1); and

each J_1 and J_2 is, independently, H, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C_1-C_{12} aminoalkyl, substituted C_1-C_{12} aminoalkyl, or a protecting group.

[0286] Nucleosides comprising bicyclic sugar moieties are referred to as bicyclic nucleosides or BNAs. Bicyclic nucleosides include, but are not limited to, (A) α-L-Methyleneoxy (4'-CH_2-O-2') BNA , (B) β-D-Methyleneoxy (4'-CH_2-O-2') BNA (also referred to as locked nucleic acid or LNA), (C) Ethyleneoxy (4'-$(CH_2)_2$-O-2') BNA, (D) Aminooxy (4'-CH_2-O-N(R)-2') BNA, (E) Oxyamino (4'-CH_2-N(R)-O-2') BNA, (F) Methyl(methyleneoxy) (4'-$CH(CH_3)$-O-2') BNA (also referred to as constrained ethyl or cEt), (G) methylenethio (4'-CH_2-S-2') BNA, (H) methylene-amino (4'-CH2-N(R)-2') BNA, (I) methyl carbocyclic (4'-CH_2-$CH(CH_3)$-2') BNA, and (J) propylene carbocyclic (4'-$(CH_2)_3$-2') BNA as depicted below.





wherein Bx is a nucleobase moiety and R is, independently, H, a protecting group, or C_1-C_{12} alkyl.

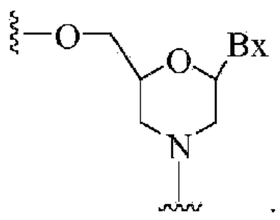
[0287] Additional bicyclic sugar moieties are known in the art, for example: Singh et al., Chem. Commun., 1998, 4, 455-456; Koshkin et al., Tetrahedron, 1998, 54, 3607-3630; Wahlestedt et al., Proc. Natl. Acad. Sci. U. S. A., 2000, 97, 5633-5638; Kumar et al., Bioorg. Med. Chem. Lett., 1998, 8, 2219-2222; Singh et al., J. Org. Chem., 1998, 63, 10035-10039; Srivastava et al., J. Am. Chem. Soc., 129(26) 8362-8379 (Jul. 4, 2007); Elayadi et al., Curr. Opinion Invens. Drugs, 2001, 2, 558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; U.S. Patent Nos. 7,053,207, 6,268,490, 6,770,748, 6,794,499, 7,034,133, 6,525,191, 6,670,461, and 7,399,845; WO 2004/106356, WO 1994/14226, WO 2005/021570, and WO 2007/134181; U.S. Patent Publication Nos. US2004/0171570, US2007/0287831, and US2008/0039618; U.S. Patent Serial Nos. 12/129,154, 60/989,574, 61/026,995, 61/026,998, 61/056,564, 61/086,231, 61/097,787, and 61/099,844; and PCT International Publication Nos. WO/2008/150729, WO/2008/154401, and WO/2009/006478.

[0288] In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2-O-2') bicyclic nucleosides have been incorporated into antisense oligonucleotides that showed antisense activity (Frieden et al., Nucleic Acids Research, 2003, 21, 6365-6372).

[0289] In certain embodiments, substituted sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (e.g., 5'-substituted and 4'-2' bridged sugars), (*see,* PCT International Publication WO 2007/134181, published on 11/22/07, wherein LNA is substituted with, for example, a 5'-methyl or a 5'-vinyl group).

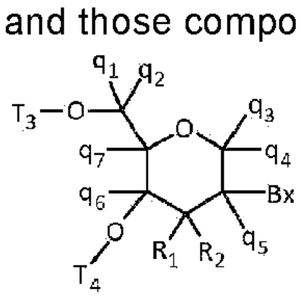
[0290] In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the naturally occuring sugar is substituted, e.g., with a sulfer, carbon or nitrogen atom. In certain such embodiments, such modified sugar moiety also comprises bridging and/or non-bridging substituents as described above. For example, certain sugar surrogates comprise a 4'-sulfer atom and a substitution at the 2'-position (*see,e.g.,* published U.S. Patent Application US2005/0130923, published on June 16, 2005) and/or the 5' position. By way of additional example, carbocyclic bicyclic nucleosides having a 4'-2' bridge have been described *(see, e.g.,* Freier et al., Nucleic Acids Research, 1997, 25(22), 4429-4443 and Albaek et al., J. Org. Chem., 2006, 71, 7731-7740).

[0291] In certain embodiments, sugar surrogates comprise rings having other than 5-atoms. For example, in certain embodiments, a sugar surrogate comprises a morphlino. Morpholino compounds and their use in oligomeric compounds has been reported in numerous patents and published articles (see for example: Braasch et al., Biochemistry, 2002, 41, 4503-4510; and U.S. Patents 5,698,685; 5,166,315; 5,185,444; and 5,034,506). As used here, the term "morpholino" means a sugar surrogate having the following structure:



In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are refered to herein as "modifed morpholinos."

[0292] For another example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran. Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include, but are not limited to, hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (*see* Leumann, CJ. Bioorg. & Med. Chem. (2002) 10:841-854), fluoro HNA (F-HNA), and those compounds having Formula VI:



VI

wherein independently for each of said at least one tetrahydropyran nucleoside analog of Formula VI:

Bx is a nucleobase moiety;

T_3 and T_4 are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_3 and T_4 is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_3 and T_4 is H, a hydroxyl protecting group, a linked conjugate group, or a 5' or 3'-terminal group;

q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, or substituted C_2-C_6 alkynyl; and

each of R_1 and R_2 is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$, and CN, wherein X is O, S or NJ_1, and each J_1, J_2, and J_3 is, independently, H or C_1-C_6 alkyl.

[0293] In certain embodiments, the modified THP nucleosides of Formula VI are provided wherein q_1, q_2, q_3, q_4, q_5, q_6 and q_7 are each H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is other than H. In certain embodiments, at least one of q_1, q_2, q_3, q_4, q_5, q_6 and q_7 is methyl. In certain embodiments, THP nucleosides of Formula VI are provided wherein one of R_1 and R_2 is F. In certain embodiments, R_1 is fluoro and R_2 is H, R_1 is methoxy and R_2 is H, and R_1 is methoxyethoxy and R_2 is H.

[0294] Many other bicyclo and tricyclo sugar surrogate ring systems are also known in the art that can be used to modify nucleosides for incorporation into antisense compounds (*see, e.g.,* review article: Leumann, J. C, Bioorganic & Medicinal Chemistry, 2002, 10, 841-854).

[0295] Combinations of modifications are also provided without limitation, such as 2'-F-5'-methyl substituted nucleosides (see PCT International Application WO 2008/101157 Published on 8/21/08 for other disclosed 5', 2'-bis substituted nucleosides) and replacement of the ribosyl ring oxygen atom with S and further substitution at the 2'-position (see published U.S. Patent Application US2005-0130923, published on June 16, 2005) or alternatively 5'-substitution of a bicyclic nucleic acid (see PCT International Application WO 2007/134181, published on 11/22/07 wherein a 4'-CH_2-O-2' bicyclic nucleoside is further substituted at the 5' position with a 5'-methyl or a 5'-vinyl group). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (*see, e.g.,* Srivastava et al., J. Am. Chem. Soc. 2007, 129(26), 8362-8379).

[0296] In certain embodiments, the present disclosure provides oligonucleotides comprising modified nucleosides. Those modified nucleotides may include modified sugars, modified nucleobases, and/or modified linkages. The specific modifications are selected such that the resulting oligonucleotides possess desireable characteristics. In certain embodmiments, oligonucleotides comprise one or more RNA-like nucleosides. In certain embodiments,

oligonucleotides comprise one or more DNA-like nucleotides.

2. <u>Certain Nucleobase Modifications</u>

[0297] In certain embodiments, nucleosides of the present disclosure comprise one or more unmodified nucleobases. In certain embodiments, nucleosides of the present disclosure comprise one or more modifed nucleobases.

[0298] In certain embodiments, modified nucleobases are selected from: universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases as defined herein. 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil; 5-propynylcytosine; 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH_3) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine, 3-deazaguanine and 3-deazaadenine, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases as defined herein. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine([5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in United States Patent No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613; and those disclosed by Sanghvi, Y.S., Chapter 15, Antisense Research and Applications, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993,273-288.

[0299] Representative United States patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, U.S. 3,687,808; 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,645,985; 5,681,941; 5,750,692; 5,763,588; 5,830,653 and 6,005,096.

3. <u>Certain Internucleoside Linkages</u>

[0300] In certain embodiments, the present disclosure provides oligonucleotides comprising linked nucleosides. In such embodiments, nucleosides may be linked together using any internucleoside linkage. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters (PO), phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates (PS). Representative non-phosphorus containing internucleoside linking groups include, but are not limited to, methylenemethylimino (-CH_2-$N(CH_3)$-O-CH_2-), thiodiester (-O-C(O)-S-), thionocarbamate (-O-C(O)(NH)-S-); siloxane (-O-$Si(H)_2$-O-); and N,N'-dimethylhydrazine (-CH_2-$N(CH_3)$-$N(CH_3)$-). Modified linkages, compared to natural phosphodiester linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Representative chiral linkages include, but are not limited to, alkylphosphonates and phosphorothioates. Methods

of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

[0301] The oligonucleotides described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of absolute stereochemistry, as (R) or (S), a or b such as for sugar anomers, or as (D) or (L) such as for amino acids etc. Included in the antisense compounds provided herein are all such possible isomers, as well as their racemic and optically pure forms.

[0302] Neutral internucleoside linkages include without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH_2-N(CH_3)-O-5'), amide-3 (3'-CH_2-C(=O)-N(H)-5'), amide-4 (3'-CH_2-N(H)-C(=O)-5'), formacetal (3'-O-CH_2-O-5'), and thioformacetal (3'-S-CH_2-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: Carbohydrate Modifications in Antisense Research; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH_2 component parts.

4. <u>Certain Motifs</u>

[0303] In certain embodiments, antisense oligonucleotides comprise one or more modified nucleoside (e.g., nucleoside comprising a modified sugar and/or modified nucleobase) and/or one or more modified internucleoside linkage. The pattern of such modifications on an oligonucleotide is referred to herein as a motif. In certain embodiments, sugar, nucleobase, and linkage motifs are independent of one another.

a. <u>Certain sugar motifs</u>

[0304] In certain embodiments, oligonucleotides comprise one or more type of modified sugar moieties and/or naturally occurring sugar moieties arranged along an oligonucleotide or region thereof in a defined pattern or sugar modification motif. Such motifs may include any of the sugar modifications discussed herein and/or other known sugar modifications.

[0305] In certain embodiments, the oligonucleotides comprise or consist of a region having a gapmer sugar motif, which comprises two external regions or "wings" and a central or internal region or "gap." The three regions of a gapmer sugar motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap. In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric sugar gapmer). In certain embodiments, the sugar motifs of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric sugar gapmer).

i. Certain 5'-wings

[0306] In certain embodiments, the 5'- wing of a gapmer consists of 1 to 8 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 1 to 7 linked nucleosides. In certain embodiments, the 5'-wing of a gapmer consists of 1 to 6 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 1 to

5 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 2 to 5 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 3 to 5 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 4 or 5 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 1 to 4 linked nucleosides. In certain embodiments, the 5'-wing of a gapmer consists of 1 to 3 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 1 or 2 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 2 to 4 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 2 or 3 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 3 or 4 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 1 nucleoside. In certain embodiments, the 5'- wing of a gapmer consists of 2 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 3 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 4 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 5 linked nucleosides. In certain embodiments, the 5'- wing of a gapmer consists of 6 linked nucleosides.

[0307] In certain embodiments, the 5'- wing of a gapmer comprises at least one bicyclic nucleoside. In certain embodiments, the 5'- wing of a gapmer comprises at least two bicyclic nucleosides. In certain embodiments, the 5'- wing of a gapmer comprises at least three bicyclic nucleosides. In certain embodiments, the 5'- wing of a gapmer comprises at least four bicyclic nucleosides. In certain embodiments, the 5'- wing of a gapmer comprises at least one constrained ethyl nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one LNA nucleoside. In certain embodiments, each nucleoside of the 5'-wing of a gapmer is a bicyclic nucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a constrained ethyl nucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a LNA nucleoside.

[0308] In certain embodiments, the 5'- wing of a gapmer comprises at least one non-bicyclic modified nucleoside. In certain embodiments, the 5'- wing of a gapmer comprises at least one 2'-substituted nucleoside. In certain embodiments, the 5'- wing of a gapmer comprises at least one 2'-MOE nucleoside. In certain embodiments, the 5'- wing of a gapmer comprises at least one 2'-OMe nucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a non-bicyclic modified nucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a 2'-substituted nucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a 2'-MOE nucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a 2'-OMe nucleoside.

[0309] In certain embodiments, the 5'- wing of a gapmer comprises at least one 2'-deoxynucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a 2'-deoxynucleoside. In a certain embodiments, the 5'- wing of a gapmer comprises at least one ribonucleoside. In certain embodiments, each nucleoside of the 5'- wing of a gapmer is a ribonucleoside. In certain embodiments, one, more than one, or each of the nucleosides of the 5'- wing is an RNA-like nucleoside.

[0310] In certain embodiments, the 5'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one non-bicyclic modified nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-substituted nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-MOE nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-OMe nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-deoxynucleoside.

[0311] In certain embodiments, the 5'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one non-bicyclic modified nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-substituted nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-MOE nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-OMe nucleoside. In certain embodiments, the 5'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-deoxynucleoside.

ii. Certain 3'-wings

[0312] In certain embodiments, the 3'- wing of a gapmer consists of 1 to 8 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 1 to 7 linked nucleosides. In certain embodiments, the 3'-wing of a gapmer consists of 1 to 6 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 1 to 5 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 2 to 5 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 3 to 5 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 4 or 5 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 1 to 4 linked nucleosides. In certain embodiments, the 3'-wing of a gapmer consists of 1 to 3 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 1 or 2 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 2 to 4 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 2 or 3 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 3 or 4 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 1 nucleoside. In certain embodiments, the 3'- wing of a gapmer consists of 2 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 3linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 4 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 5 linked nucleosides. In certain embodiments, the 3'- wing of a gapmer consists of 6 linked nucleosides.

[0313] In certain embodiments, the 3'- wing of a gapmer comprises at least one bicyclic nucleoside. In certain embodiments, the 3'- wing of a gapmer comprises at least one constrained ethyl nucleoside. In certain embodiments, the 3'- wing of a gapmer comprises at least one LNA nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a bicyclic nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a constrained ethyl nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a LNA nucleoside.

[0314] In certain embodiments, the 3'- wing of a gapmer comprises at least one non-bicyclic modified nucleoside. In certain embodiments, the 3'- wing of a gapmer comprises at least two non-bicyclic modified nucleosides. In certain embodiments, the 3'- wing of a gapmer comprises at least three non-bicyclic modified nucleosides. In certain embodiments, the 3'- wing of a gapmer comprises at least four non-bicyclic modified nucleosides. In certain embodiments, the 3'- wing of a gapmer comprises at least one 2'-substituted nucleoside. In certain embodiments, the 3'- wing of a gapmer comprises at least one 2'-MOE nucleoside. In certain embodiments, the 3'- wing of a gapmer comprises at least one 2'-OMe nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a non-bicyclic modified nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a 2'-substituted nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a 2'-MOE nucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a 2'-OMe nucleoside.

[0315] In certain embodiments, the 3'- wing of a gapmer comprises at least one 2'-deoxynucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a 2'-deoxynucleoside. In a certain embodiments, the 3'- wing of a gapmer comprises at least one ribonucleoside. In certain embodiments, each nucleoside of the 3'- wing of a gapmer is a ribonucleoside. In certain embodiments, one, more than one, or each of the nucleosides of the 5'- wing is an RNA-like nucleoside.

[0316] In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one non-bicyclic modified nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-substituted nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-MOE nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-OMe nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside and at least one 2'-deoxynucleoside.

[0317] In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one non-bicyclic modified nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-substituted nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-MOE nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside and at least one 2'-OMe nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl

nucleoside and at least one 2'-deoxynucleoside.

[0318] In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside and at least one non-bicyclic modified nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside and at least one 2'-substituted nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside and at least one 2'-MOE nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside and at least one 2'-OMe nucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside and at least one 2'-deoxynucleoside.

[0319] In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside, at least one non-bicyclic modified nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside, at least one non-bicyclic modified nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside, at least one non-bicyclic modified nucleoside, and at least one 2'-deoxynucleoside.

[0320] In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside, at least one 2'-substituted nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside, at least one 2'-substituted nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside, at least one 2'-substituted nucleoside, and at least one 2'-deoxynucleoside.

[0321] In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside, at least one 2'-MOE nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside, at least one 2'-MOE nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside, at least one 2'-MOE nucleoside, and at least one 2'-deoxynucleoside.

[0322] In certain embodiments, the 3'-wing of a gapmer comprises at least one bicyclic nucleoside, at least one 2'-OMe nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one constrained ethyl nucleoside, at least one 2'-OMe nucleoside, and at least one 2'-deoxynucleoside. In certain embodiments, the 3'-wing of a gapmer comprises at least one LNA nucleoside, at least one 2'-OMe nucleoside, and at least one 2'-deoxynucleoside.

iii. Certain Central Regions (gaps)

[0323] In certain embodiments, the gap of a gapmer consists of 6 to 20 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 to 15 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 to 12 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 to 10 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 to 9 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 to 8 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 or 7 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 7 to 10 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 7 to 9 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 7 or 8 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 8 to 10 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 8 or 9 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 6 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 7 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 8 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 9 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 10 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 11 linked nucleosides. In certain embodiments, the gap of a gapmer consists of 12 linked nucleosides.

[0324] In certain embodiments, each nucleoside of the gap of a gapmer is a 2'-deoxynucleoside. In certain

embodiments, the gap comprises one or more modified nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer is a 2'-deoxynucleoside or is a modified nucleoside that is "DNA-like." In such embodiments, "DNA-like" means that the nucleoside has similar characteristics to DNA, such that a duplex comprising the gapmer and an RNA molecule is capable of activating RNase H. For example, under certain conditions, 2'-(ara)-F have been shown to support RNase H activation, and thus is DNA-like. In certain embodiments, one or more nucleosides of the gap of a gapmer is not a 2'-deoxynucleoside and is not DNA-like. In certain such embodiments, the gapmer nonetheless supports RNase H activation (e.g., by virtue of the number or placement of the non-DNA nucleosides).

[0325] In certain embodiments, gaps comprise a stretch of unmodified 2'-deoxynucleoside interrupted by one or more modified nucleosides, thus resulting in three sub-regions (two stretches of one or more 2'-deoxynucleosides and a stretch of one or more interrupting modified nucleosides). In certain embodiments, no stretch of unmodified 2'-deoxynucleosides is longer than 5, 6, or 7 nucleosides. In certain embodiments, such short stretches is achieved by using short gap regions. In certain embodiments, short stretches are achieved by interrupting a longer gap region.

[0326] In certain embodiments, the gap comprises one or more modified nucleosides. In certain embodiments, the gap comprises one or more modified nucleosides selected from among cEt, FHNA, LNA, and 2-thio-thymidine. In certain embodiments, the gap comprises one modified nucleoside. In certain embodiments, the gap comprises a 5'-substituted sugar moiety selected from among 5'-Me, and 5'-*(R)*-Me. In certain embodiments, the gap comprises two modified nucleosides. In certain embodiments, the gap comprises three modified nucleosides. In certain embodiments, the gap comprises four modified nucleosides. In certain embodiments, the gap comprises two or more modified nucleosides and each modified nucleoside is the same. In certain embodiments, the gap comprises two or more modified nucleosides and each modified nucleoside is different.

[0327] In certain embodiments, the gap comprises one or more modified linkages. In certain embodiments, the gap comprises one or more methyl phosphonate linkages. In certain embodiments the gap comprises two or more modified linkages. In certain embodiments, the gap comprises one or more modified linkages and one or more modified nucleosides. In certain embodiments, the gap comprises one modified linkage and one modified nucleoside. In certain embodiments, the gap comprises two modified linkages and two or more modified nucleosides.

b. <u>Certain Internucleoside Linkage Motifs</u>

[0328] In certain embodiments, oligonucleotides comprise modified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or modified internucleoside linkage motif. In certain embodiments, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides of the present disclosure comprise a region of uniformly modified internucleoside linkages. In certain such embodiments, the oligonucleotide comprises a region that is uniformly linked by phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide is uniformly linked by phosphorothioate internucleoside linkages. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate. In certain embodiments, each internucleoside linkage of the oligonucleotide is selected from phosphodiester and phosphorothioate and at least one internucleoside linkage is phosphorothioate.

[0329] In certain embodiments, the oligonucleotide comprises at least 6 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 7 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 9 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 11 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 12 phosphorothioate internucleoside

linkages. In certain embodiments, the oligonucleotide comprises at least 13 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 14 phosphorothioate internucleoside linkages.

[0330] In certain embodiments, the oligonucleotide comprises at least one block of at least 6 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 7 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 8 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 9 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least one block of at least 10 consecutive phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least block of at least one 12 consecutive phosphorothioate internucleoside linkages. In certain such embodiments, at least one such block is located at the 3' end of the oligonucleotide. In certain such embodiments, at least one such block is located within 3 nucleosides of the 3' end of the oligonucleotide. In certain embodiments, the oligonucleotide comprises less than 15 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 14 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 13 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 12 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 11 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 10 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 9 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 7 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 6 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises less than 5 phosphorothioate internucleoside linkages.

c. <u>Certain Nucleobase Modification Motifs</u>

[0331] In certain embodiments, oligonucleotides comprise chemical modifications to nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or nucleobases modification motif. In certain such embodiments, nucleobase modifications are arranged in a gapped motif. In certain embodiments, nucleobase modifications are arranged in an alternating motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases is chemically modified.

[0332] In certain embodiments, oligonucleotides comprise a block of modified nucleobases. In certain such embodiments, the block is at the 3'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleotides of the 3'-end of the oligonucleotide. In certain such embodiments, the block is at the 5'-end of the oligonucleotide. In certain embodiments the block is within 3 nucleotides of the 5'-end of the oligonucleotide.

[0333] In certain embodiments, nucleobase modifications are a function of the natural base at a particular position of an oligonucleotide. For example, in certain embodiments each purine or each pyrimidine in an oligonucleotide is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each cytosine is modified. In certain embodiments, each uracil is modified.

[0334] In certain embodiments, some, all, or none of the cytosine moieties in an oligonucleotide are 5-methyl cytosine moieties. Herein, 5-methyl cytosine is not a "modified nucleobase." Accordingly, unless otherwise indicated, unmodified nucleobases include both cytosine residues having a 5-methyl and those lacking a 5 methyl. In certain embodiments, the methylation state of all or some cytosine nucleobases is specified.

[0335] In certain embodiments, chemical modifications to nucleobases comprise attachment of certain conjugate groups to nucleobases. In certain embodiments, each purine or each pyrimidine in an oligonucleotide may be

optionally modified to comprise a conjugate group.

d. Certain Overall Lengths

[0336] In certain embodiments, the present disclosure provides oligonucleotides of any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number of nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that X≤Y. For example, in certain embodiments, the oligonucleotide may consist of 8 to 9, 8 to 10, 8 to 11, 8 to 12, 8 to 13, 8 to 14, 8 to 15, 8 to 16, 8 to 17, 8 to 18, 8 to 19, 8 to 20, 8 to 21, 8 to 22, 8 to 23, 8 to 24, 8 to 25, 8 to 26, 8 to 27, 8 to 28, 8 to 29, 8 to 30, 9 to 10, 9 to 11, 9 to 12, 9 to 13, 9 to 14, 9 to 15, 9 to 16, 9 to 17, 9 to 18, 9 to 19, 9 to 20, 9 to 21, 9 to 22, 9 to 23, 9 to 24, 9 to 25, 9 to 26, 9 to 27, 9 to 28, 9 to 29, 9 to 30, 10 to 11, 10 to 12, 10 to 13, 10 to 14, 10 to 15, 10 to 16, 10 to 17, 10 to 18, 10 to 19, 10 to 20, 10 to 21, 10 to 22, 10 to 23, 10 to 24, 10 to 25, 10 to 26, 10 to 27, 10 to 28, 10 to 29, 10 to 30, 11 to 12, 11 to 13, 11 to 14, 11 to 15, 11 to 16, 11 to 17, 11 to 18, 11 to 19, 11 to 20, 11 to 21, 11 to 22, 11 to 23, 11 to 24, 11 to 25, 11 to 26, 11 to 27, 11 to 28, 11 to 29, 11 to 30, 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 29, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides. In embodiments where the number of nucleosides of an oligonucleotide of a compound is limited, whether to a range or to a specific number, the compound may, nonetheless further comprise additional other substituents. For example, an oligonucleotide comprising 8-30 nucleosides excludes oligonucleotides having 31 nucleosides, but, unless otherwise indicated, such an oligonucleotide may further comprise, for example one or more conjugate groups, terminal groups, or other substituents.

[0337] Further, where an oligonucleotide is described by an overall length range and by regions having specified lengths, and where the sum of specified lengths of the regions is less than the upper limit of the overall length range, the oligonucleotide may have additional nucleosides, beyond those of the specified regions, provided that the total number of nucleosides does not exceed the upper limit of the overall length range.

5. Certain Antisense Oligonucleotide Chemistry Motifs

[0338] In certain embodiments, the chemical structural features of antisense oligonucleotides are characterized by their sugar motif, internucleoside linkage motif, nucleobase modification motif and overall length. In certain embodiments, such parameters are each independent of one another. Thus, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. Thus, the internucleoside linkages within the wing regions of a sugar-gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region. Likewise, such sugar-gapmer oligonucleotides may comprise one or

more modified nucleobase independent of the gapmer pattern of the sugar modifications. One of skill in the art will appreciate that such motifs may be combined to create a variety of oligonucleotides.

[0339] In certain embodiments, the selection of internucleoside linkage and nucleoside modification are not independent of one another.

i. Certain Sequences and Targets

[0340] In certain embodiments, the present disclosure provides antisense oligonucleotides having a sequence complementary to a target nucleic acid. Such antisense compounds are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity. In certain embodiments, antisense compounds specifically hybridize to one or more target nucleic acid. In certain embodiments, a specifically hybridizing antisense compound has a nucleobase sequence comprising a region having sufficient complementarity to a target nucleic acid to allow hybridization and result in antisense activity and insufficient complementarity to any non-target so as to avoid or reduce non-specific hybridization to non-target nucleic acid sequences under conditions in which specific hybridization is desired (e.g., under physiological conditions for *in vivo* or therapeutic uses, and under conditions in which assays are performed in the case of *in vitro* assays). In certain embodiments, oligonucleotides are selective between a target and non-target, even though both target and non-target comprise the target sequence. In such embodiments, selectivity may result from relative accessibility of the target region of one nucleic acid molecule compared to the other.

[0341] In certain embodiments, the present disclosure provides antisense compounds comprising oligonucleotides that are fully complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are 95% complementary to the target nucleic acid. In certain embodiments, such oligonucleotides are 90% complementary to the target nucleic acid.

[0342] In certain embodiments, such oligonucleotides are 85% complementary to the target nucleic acid. In certain embodiments, such oligonucleotides are 80% complementary to the target nucleic acid. In certain embodiments, an antisense compound comprises a region that is fully complementary to a target nucleic acid and is at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain such embodiments, the region of full complementarity is from 6 to 14 nucleobases in length.

[0343] In certain embodiments, oligonucleotides comprise a hybridizing region and a terminal region. In certain such embodiments, the hybridizing region consists of 12-30 linked nucleosides and is fully complementary to the target nucleic acid. In certain embodiments, the hybridizing region includes one mismatch relative to the target nucleic acid. In certain embodiments, the hybridizing region includes two mismatches relative to the target nucleic acid. In certain embodiments, the hybridizing region includes three mismatches relative to the target nucleic acid. In certain embodiments, the terminal region consists of 1-4 terminal nucleosides. In certain embodiments, the terminal nucleosides are at the 3' end. In certain embodiments, one or more of the terminal nucleosides are not complementary to the target nucleic acid.

[0344] Antisense mechanisms include any mechanism involving the hybridization of an oligonucleotide with target nucleic acid, wherein the hybridization results in a biological effect. In certain embodiments, such hybridization results in either target nucleic acid degradation or occupancy with concomitant inhibition or stimulation of the cellular machinery involving, for example, translation, transcription, or splicing of the target nucleic acid.

[0345] One type of antisense mechanism involving degradation of target RNA is RNase H mediated antisense. RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-stranded antisense compounds which are "DNA-like" elicit RNase H activity in mammalian cells. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of DNA-like oligonucleotide-mediated inhibition of gene expression.

[0346] In certain embodiments, a conjugate group comprises a cleavable moiety. In certain embodiments, a conjugate group comprises one or more cleavable bond. In certain embodiments, a conjugate group comprises a linker. In certain embodiments, a linker comprises a protein binding moiety. In certain embodiments, a conjugate group comprises a cell-targeting moiety (also referred to as a cell-targeting group). In certain embodiments a cell-targeting moiety comprises a branching group. In certain embodiments, a cell-targeting moiety comprises one or more tethers. In certain embodiments, a cell-targeting moiety comprises a carbohydrate or carbohydrate cluster.

ii. <u>Certain Cleavable Moieties</u>

[0347] In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety comprises a cleavable bond. In certain embodiments, the conjugate group comprises a cleavable moiety. In certain such embodiments, the cleavable moiety attaches to the antisense oligonucleotide. In certain such embodiments, the cleavable moiety attaches directly to the cell-targeting moiety. In certain such embodiments, the cleavable moiety attaches to the conjugate linker. In certain embodiments, the cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a cleavable nucleoside or nucleoside analog. In certain embodiments, the nucleoside or nucleoside analog comprises an optionally protected heterocyclic base selected from a purine, substituted purine, pyrimidine or substituted pyrimidine. In certain embodiments, the cleavable moiety is a nucleoside comprising an optionally protected heterocyclic base selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methylcytosine, 4-N-benzoyl-5-methylcytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. In certain embodiments, the cleavable moiety is 2'-deoxy nucleoside that is attached to the 3' position of the antisense oligonucleotide by a phosphodiester linkage and is attached to the linker by a phosphodiester or phosphorothioate linkage. In certain embodiments, the cleavable moiety is 2'-deoxy adenosine that is attached to the 3' position of the antisense oligonucleotide by a phosphodiester linkage and is attached to the linker by a phosphodiester or phosphorothioate linkage. In certain embodiments, the cleavable moiety is 2'-deoxy adenosine that is attached to the 3' position of the antisense oligonucleotide by a phosphodiester linkage and is attached to the linker by a phosphodiester linkage.

[0348] In certain embodiments, the cleavable moiety is attached to the 3' position of the antisense oligonucleotide. In certain embodiments, the cleavable moiety is attached to the 5' position of the antisense oligonucleotide. In certain embodiments, the cleavable moiety is attached to a 2' position of the antisense oligonucleotide. In certain embodiments, the cleavable moiety is attached to the antisense oligonucleotide by a phosphodiester linkage. In certain embodiments, the cleavable moiety is attached to the linker by either a phosphodiester or a phosphorothioate linkage. In certain embodiments, the cleavable moiety is attached to the linker by a phosphodiester linkage. In certain embodiments, the conjugate group does not include a cleavable moiety.

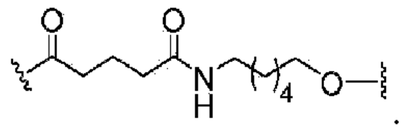
[0349] In certain embodiments, the cleavable moiety is cleaved after the complex has been administered to an animal only after being internalized by a targeted cell. Inside the cell the cleavable moiety is cleaved thereby releasing the active antisense oligonucleotide. While not wanting to be bound by theory it is believed that the cleavable moiety is cleaved by one or more nucleases within the cell. In certain embodiments, the one or more nucleases cleave the phosphodiester linkage between the cleavable moiety and the linker.

iii. <u>Certain Linkers</u>

[0350] The conjugate group of the invention comprises a linker. In certain such embodiments, the linker is covalently bound to the cleavable moiety. In certain such embodiments, the linker is covalently bound to the antisense oligonucleotide. The linker is covalently bound to a cell-targeting moiety.

[0351] The linker is a linear group comprising alkyl, amide and ether groups. In certain embodiments, the linear group is covalently attached to the cell-targeting moiety and the cleavable moiety. In certain embodiments, the linear group is covalently attached to the cell-targeting moiety and the antisense oligonucleotide.

[0352] The conjugate linker of the present invention has the structure:



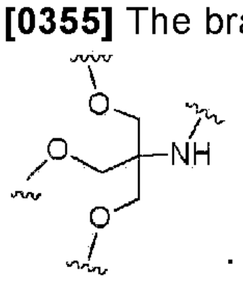
iv. **Certain Cell-Targeting Moieties**

[0353] The conjugate group of the present invention comprises cell-targeting moieties. Certain such cell-targeting moieties increase cellular uptake of antisense compounds. The cell-targeting moieties comprise a branching group, three tethers, and three ligands.

1. **Certain Branching Groups**

[0354] The conjugate group of the present invention comprises a targeting moiety comprising a branching group and three tethered ligands. The branching group attaches to the conjugate linker.. The branching group is covalently attached to the linker and each of the tethered ligands.

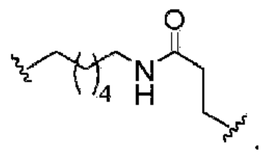
[0355] The branching group of the present invention has the structure:



2. **Certain Tethers**

[0356] The conjugate group of the present invention comprises three tethers covalently attached to the branching group. The tether is attached to the branching group through an ether group. The tether is attached to the ligand through an ether group.

[0357] The tether of the present invention has the structure:

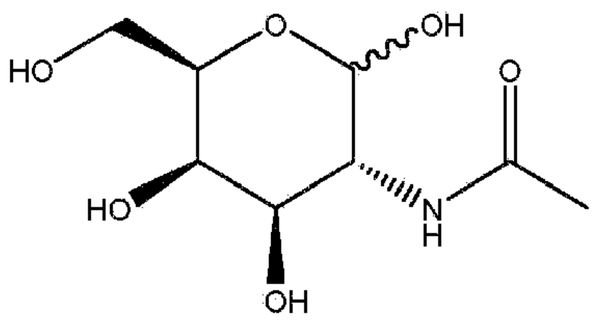


3. **Certain Ligands**

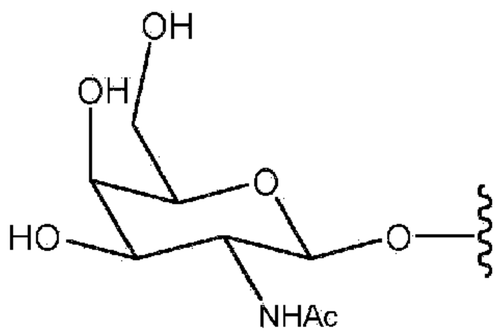
[0358] Each ligand of the present invention is covalently attached to a tether. In certain embodiments, each ligand is selected to have an affinity for at least one type of receptor on a target cell. In certain embodiments, ligands are selected that have an affinity for at least one type of receptor on the surface of a mammalian liver cell. In certain embodiments, ligands are selected that have an affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments of the present disclosure, each ligand is a carbohydrate. Each ligand of the invention is N-acetyl galactoseamine (GalNAc). In certain embodiments of the present disclosure, the targeting moiety comprises 3 ligands. The targeting moiety of the present invention comprises 3 N-acetyl galactoseamine ligands.

[0359] In certain embodiments, "GalNac" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose,

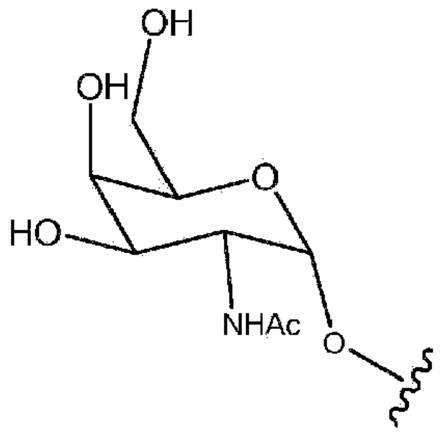
commonly referred to in the literature as N-acetyl galactosamine. In certain embodiments, "N-acetyl galactosamine" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose. "GalNac" or "Gal-NAc" of the present invention refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose, which is in the β-form: 2-(Acetylamino)-2-deoxy-β-D-galactopyranose. In adition to the present invention, disclosed herein is the α-form: 2-(Acetylamino)-2-deoxy-D-galactopyranose, which is depicted for reference below.



2-(Acetylamino)-2-deoxy-D-galactopyranose



2-(Acetylamino)-2-deoxy-β-D-galactopyranose

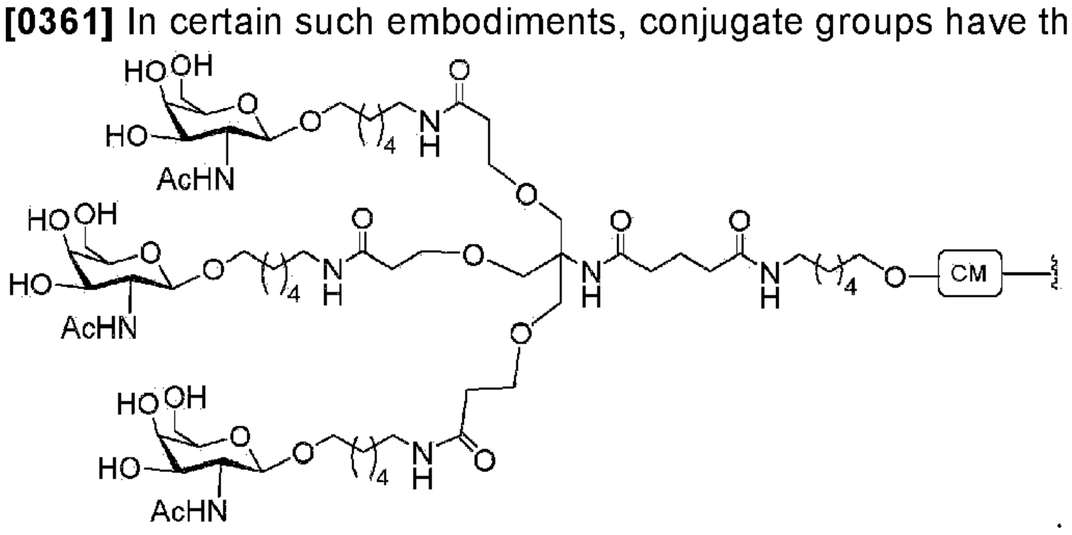


2-(Acetylamino)-2-deoxy-α-D-galactopyranose

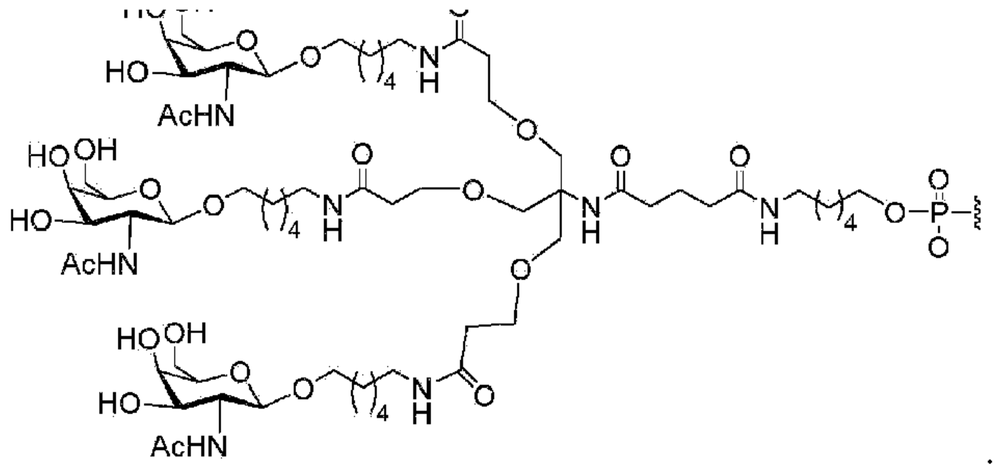
i. <u>Certain Conjugates</u>

[0360] In certain embodiments, conjugate groups comprise the structural features above that are consistent with the appended claims.

[0361] In certain such embodiments, conjugate groups have the following structure:



[0362] In certain such embodiments, conjugate groups have the following structure:



b.Certain conjugated antisense compounds

[0363] In certain embodiments, the conjugates are bound to a nucleoside of the antisense oligonucleotide at the 2', 3', of 5' position of the nucleoside. The conjugated antisense compound can have the following structure:

$$A\text{-}B\text{-}C\text{-}D(\text{-}E\text{-}F)_q$$

wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0364] In certain embodiments of the present disclosure, a conjugated antisense compound has the following structure:

$$A\text{-}C\text{-}D(\text{-}E\text{-}F)_q$$

wherein

A is the antisense oligonucleotide;

C is the conjugate linker

D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0365] In certain such embodiments, the conjugate linker comprises at least one cleavable bond.

[0366] In certain such embodiments, the branching group comprises at least one cleavable bond.

[0367] In certain embodiments each tether comprises at least one cleavable bond.

[0368] In certain embodiments, the conjugates are bound to a nucleoside of the antisense oligonucleotide at the 2', 3', of 5' position of the nucleoside.

[0369] In certain embodiments of the present disclosure, a conjugated antisense compound has the following structure:

wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

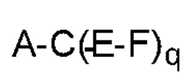
C is the conjugate linker

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0370] In certain embodiments, the conjugates are bound to a nucleoside of the antisense oligonucleotide at the 2', 3', of 5' position of the nucleoside. In certain embodiments of the present disclosure, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

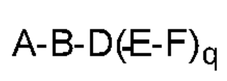
C is the conjugate linker

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0371] In certain embodiments of the present disclosure, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0372] In certain embodiments of the present disclosure, a conjugated antisense compound has the following structure:

$$A\text{-}D(\text{-}E\text{-}F)_q$$

wherein

A is the antisense oligonucleotide;

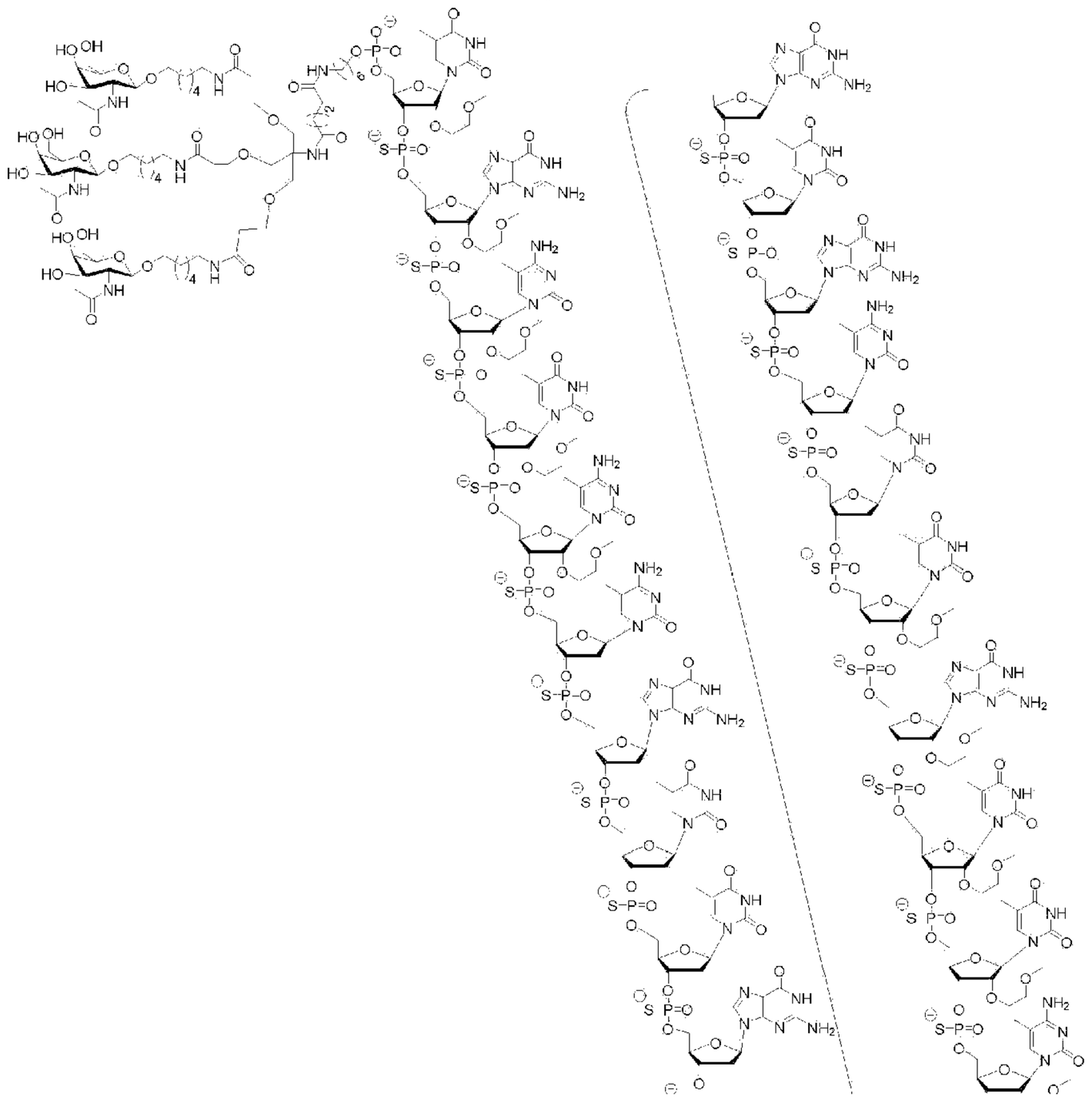
D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

[0373] In certain embodiments, the conjugated antisense compound has the following structure:



[0374] Representative United States patents, United States patent application publications, and international patent application publications that teach the preparation of certain of the above noted conjugates, conjugated antisense compounds, tethers, linkers, branching groups, ligands, cleavable moieties as well as other modifications include without limitation, US 5,994,517, US 6,300,319, US 6,660,720, US 6,906,182, US 7,262,177, US 7,491,805, US 8,106,022, US 7,723,509, US 2006/0148740, US 2011/0123520, WO 2013/033230 and WO 2012/037254.Representative publications that teach the preparation of certain of the above noted conjugates, conjugated antisense compounds, tethers, linkers, branching groups, ligands, cleavable moieties as well as other modifications include without limitation, BIESSEN et al., "The Cholesterol Derivative of a Triantennary Galactoside with High Affinity for the Hepatic Asialoglycoprotein Receptor: a Potent Cholesterol Lowering Agent" J. Med. Chem. (1995) 38:1846-1852, BIESSEN et al., "Synthesis of Cluster Galactosides with High Affinity for the Hepatic Asialoglycoprotein Receptor" J. Med. Chem. (1995) 38:1538-1546, LEE et al., "New and more efficient multivalent glyco-ligands for asialoglycoprotein receptor of mammalian hepatocytes" Bioorganic & Medicinal Chemistry (2011) 19:2494-2500, RENSEN et al., "Determination of the Upper Size Limit for Uptake and Processing of Ligands by the Asialoglycoprotein Receptor on Hepatocytes in Vitro and in Vivo" J. Biol. Chem. (2001) 276(40):37577-37584, RENSEN et al., "Design and Synthesis of Novel N-Acetylgalactosamine-Terminated Glycolipids for Targeting of Lipoproteins to the Hepatic Asialoglycoprotein Receptor" J. Med. Chem. (2004) 47:5798-5808, SLIEDREGT et al., "Design and Synthesis of Novel Amphiphilic Dendritic Galactosides for Selective Targeting of Liposomes to the Hepatic Asialoglycoprotein Receptor" J. Med. Chem. (1999) 42:609-618, and Valentijn et al., "Solid-phase synthesis of lysine-based cluster galactosides with high affinity for the Asialoglycoprotein Receptor" Tetrahedron, 1997, 53(2), 759-770.

[0375] In certain embodiments, conjugated antisense compounds comprise an RNase H based oligonucleotide (such as a gapmer) or a splice modulating oligonucleotide (such as a fully modified oligonucleotide) and any conjugate group comprising at least one, two, or three GalNAc groups. In certain embodiments a conjugated antisense compound comprises any conjugate group found in any of the following references: Lee, Carbohydr Res, 1978, 67, 509-514; Connolly et al., J Biol Chem, 1982,257, 939-945; Pavia et al., Int J Pep Protein Res, 1983, 22, 539-548; Lee et al., Biochem, 1984, 23, 4255-4261; Lee et al., Glycoconjugate J, 1987, 4, 317-328; Toyokuni et al., Tetrahedron Lett, 1990, 31, 2673-2676; Biessen et al., J Med Chem, 1995, 38, 1538-1546; Valentijn et al., Tetrahedron, 1997, 53, 759-770; Kim et al., Tetrahedron Lett, 1997, 38, 3487-3490; Lee et al., Bioconjug Chem, 1997, 8, 762-765; Kato et al., Glycobiol, 2001, 11, 821-829; Rensen et al., J Biol Chem, 2001, 276, 37577-37584; Lee et al., Methods Enzymol, 2003, 362, 38-43; Westerlind et al., Glycoconj J, 2004, 21, 227-241; Lee et al., Bioorg Med Chem Lett, 2006, 16(19), 5132-5135; Maierhofer et al., Bioorg Med Chem, 2007, 15, 7661-7676; Khorev et al., Bioorg Med Chem, 2008, 16, 5216-5231; Lee et al., Bioorg Med Chem, 2011, 19, 2494-2500; Kornilova et al., Analyt Biochem, 2012, 425, 43-46; Pujol et al., Angew Chemie Int Ed Engl, 2012, 51, 7445-7448; Biessen et al., J Med Chem, 1995, 38, 1846-1852; Sliedregt et al., J Med Chem, 1999, 42, 609-618; Rensen et al., J Med Chem, 2004, 47, 5798-5808; Rensen et al., Arterioscler Thromb Vasc Biol, 2006, 26, 169-175; van Rossenberg et al., Gene Ther, 2004, 11, 457-464; Sato et al., J Am Chem Soc, 2004, 126, 14013-14022; Lee et al., J Org Chem, 2012, 77, 7564-7571; Biessen et al., FASEB J, 2000, 14, 1784-1792; Rajur et al., Bioconjug Chem, 1997, 8, 935-940; Duff et al., Methods Enzymol, 2000, 313, 297-321; Maier et al., Bioconjug Chem, 2003, 14, 18-29; Jayaprakash et al., Org Lett, 2010, 12, 5410-5413; Manoharan, Antisense Nucleic Acid Drug Dev, 2002, 12, 103-128; Merwin et al., Bioconjug Chem, 1994, 5, 612-620; Tomiya et al., Bioorg Med Chem, 2013, 21, 5275-5281; International applications WO1998/013381; WO2011/038356; WO1997/046098; WO2008/098788; WO2004/101619; WO2012/037254; WO2011/120053; WO2011/100131; WO2011/163121; WO2012/177947; WO2013/033230; WO2013/075035; WO2012/083185; WO2012/083046; WO2009/082607; WO2009/134487; WO2010/144740; WO2010/148013; WO1997/020563; WO2010/088537; WO2002/043771; WO2010/129709; WO2012/068187; WO2009/126933; WO2004/024757; WO2010/054406; WO2012/089352; WO2012/089602; WO2013/166121; WO2013/165816; U.S. Patents 4,751,219; 8,552,163; 6,908,903; 7,262,177; 5,994,517; 6,300,319; 8,106,022; 7,491,805; 7,491,805; 7,582,744; 8,137,695; 6,383,812; 6,525,031; 6,660,720; 7,723,509; 8,541,548; 8,344,125; 8,313,772; 8,349,308; 8,450,467; 8,501,930; 8,158,601; 7,262,177; 6,906,182; 6,620,916; 8,435,491; 8,404,862; 7,851,615; Published U.S. Patent Application Publications US2011/0097264;

US2011/0097265; US2013/0004427; US2005/0164235; US2006/0148740; US2008/0281044; US2010/0240730; US2003/0119724; US2006/0183886; US2008/0206869; US2011/0269814; US2009/0286973; US2011/0207799; US2012/0136042; US2012/0165393; US2008/0281041; US2009/0203135; US2012/0035115; US2012/0095075; US2012/0101148; US2012/0128760; US2012/0157509; US2012/0230938; US2013/0109817; US2013/0121954; US2013/0178512; US2013/0236968; US2011/0123520; US2003/0077829; US2008/0108801; and US2009/0203132.

C. Certain Uses and Features

[0376] In certain embodiments, conjugated antisense compounds exhibit potent Apo(a) RNA reduction *in vivo*. In certain embodiments, unconjugated antisense compounds accumulate in the kidney. In certain embodiments, conjugated antisense compounds accumulate in the liver. In certain embodiments, conjugated antisense compounds are well tolerated. Such properties render conjugated antisense compounds particularly useful for inhibition of many target RNAs, including, but not limited to those involved in metabolic, cardiovascular and other diseases, disorders or conditions. Thus, provided herein are methods of treating such diseases, disorders or conditions by contacting liver tissues with the conjugated antisense compounds targeted to RNAs associated with such diseases, disorders or conditions. Thus, also disclosed are methods for ameliorating any of a variety of metabolic, cardiovascular and other diseases, disorders or conditions with the conjugated antisense compounds of the present disclosure.

[0377] In certain embodiments, conjugated antisense compounds are more potent than unconjugated counterpart at a particular tissue concentration. Without wishing to be bound by any theory or mechanism, in certain embodiemtns, the conjugate may allow the conjugated antisense compound to enter the cell more efficiently or to enter the cell more productively. For example, in certain embodiments conjugated antisense compounds may exhibit greater target reduction as compared to its unconjugated counterpart wherein both the conjugated antisense compound and its unconjugated counterpart are present in the tissue at the same concentrations. For example, in certain embodiments conjugated antisense compounds may exhibit greater target reduction as compared to its unconjugated counterpart wherein both the conjugated antisense compound and its unconjugated counterpart are present in the liver at the same concentrations.

[0378] Productive and non-productive uptake of oligonucleotides has beed discussed previously (*See* e.g. Geary, R. S., E. Wancewicz, et al. (2009). "Effect of Dose and Plasma Concentration on Liver Uptake and Pharmacologic Activity of a 2'-Methoxyethyl Modified Chimeric Antisense Oligonucleotide Targeting PTEN." Biochem. Pharmacol. 78(3): 284-91; & Koller, E., T. M. Vincent, et al. (2011). "Mechanisms of single-stranded phosphorothioate modified antisense oligonucleotide accumulation in hepatocytes." Nucleic Acids Res. 39(11): 4795-807). Conjugate groups described herein may improve productive uptake.

[0379] In certain embodiments, the conjugate groups described herein may further improve potency by increasing the affinity of the conjugated antisense compound for a particular type of cell or tissue. In certain embodiments, the conjugate groups described herein may further improve potency by increasing recognition of the conjugated antisense compound by one or more cell-surface receptors.. In certain embodiments, the conjugate groups described herein may further improve potency by facilitating endocytosis of the conjugated antisense compound.

[0380] In certain embodiments, the cleavable moiety may further improve potency by allowing the conjugate to be cleaved from the antisense oligonucleotide after the conjugated antisense compound has entered the cell. Accordingly, in certain embodiments, conjugated antisense compounds can be administed at doses lower than would be necessary for unconjugated antisense oligonucleotides.

[0381] Phosphorothioate linkages have been incorporated into antisense oligonucleotides previously. Such phosphorothioate linkages are resistant to nucleases and so improve stability of the oligonucleotide. Further, phosphorothioate linkages also bind certain proteins, which results in accumulation of antisense oligonucleotide in the liver. Oligonucleotides with fewer phosphorothioate linkages accumulate less in the liver and more in the kidney

(see, for example, Geary, R., "Pharmacokinetic Properties of 2'-O-(2-Methoxyethyl)-Modified Oligonucleotide Analogs in Rats," Journal of Pharmacology and Experimental Therapeutics, Vol. 296, No. 3, 890-897; & Pharmacological Properties of 2'-O-Methoxyethyl Modified Oligonucleotides in Antisense a Drug Technology, Chapter 10, Crooke, S.T., ed., 2008) In certain embodiments, oligonucleotides with fewer phosphorothioate internculeoside linkages and more phosphodiester internucleoside linkages accumulate less in the liver and more in the kidney. When treating diseases in the liver, this is undesibable for several reasons (1) less drug is getting to the site of desired action (liver); (2) drug is escaping into the urine; and (3) the kidney is exposed to relatively high concentration of drug which can result in toxicities in the kidney. Thus, for liver diseases, phosphorothioate linkages provide important benefits.

[0382] In certain embodiments, however, administration of oligonucleotides uniformly linked by phosphorothioate internucleoside linkages induces one or more proinflammatory reactions. (see for example: J Lab Clin Med. 1996 Sep; 128(3):329-38. "Amplification of antibody production by phosphorothioate oligodeoxynucleotides". Branda et al.; and see also for example: Toxicologic Properties in Antisense a Drug Technology, Chapter 12, pages 342-351, Crooke, S.T., ed., 2008). In certain embodiments, administration of oligonucleotides wherein most of the internucleoside linkages comprise phosphorothioate internucleoside linkages induces one or more proinflammatory reactions.

[0383] In certain embodiments, the degree of proinflammatory effect may depend on several variables (e.g. backbone modification, off-target effects, nucleobase modifications, and/or nucleoside modifications) see for example: Toxicologic Properties in Antisense a Drug Technology, Chapter 12, pages 342-351, Crooke, S.T., ed., 2008). In certain embodiments, the degree of proinflammatory effect may be mitigated by adjusting one or more variables. For example the degree of proinflammatory effect of a given oligonucleotide may be mitigated by replacing any number of phosphorothioate internucleoside linkages with phosphodiester internucleoside linkages and thereby reducing the total number of phosphorothioate internucleoside linkages.

[0384] In certain embodiments, it would be desirable to reduce the number of phosphorothioate linkages, if doing so could be done without losing stability and without shifting the distribution from liver to kidney. For example, in certain embodiments, the number of phosphorothioate linkages may be reduced by replacing phosphorothioate linkages with phosphodiester linkages. In such an embodiment, the antisense compound having fewer phosphorothioate linkages and more phosphodiester linkages may induce less proinflammatory reactions or no proinflammatory reaction. Although the the antisense compound having fewer phosphorothioate linkages and more phosphodiester linkages may induce fewer proinflammatory reactions, the antisense compound having fewer phosphorothioate linkages and more phosphodiester linkages may not accumulate in the liver and may be less efficacious at the same or similar dose as compared to an antisense compound having more phosphorothioate linkages. In certain embodiments, it is therefore desirable to design an antisense compound that has a plurality of phosphodiester bonds and a plurality of phosphorothioate bonds but which also possesses stability and good distribution to the liver.

[0385] In certain embodiments, conjugated antisense compounds accumulate more in the liver and less in the kidney than unconjugated counterparts, even when some of the phosporothioate linkages are replaced with less proinflammatory phosphodiester internucleoside linkages. In certain embodiments, conjugated antisense compounds accumulate more in the liver and are not excreted as much in the urine compared to its unonjugated counterparts, even when some of the phosporothioate linkages are replaced with less proinflammatory phosphodiester internucleoside linkages. In certain embodiments, the use of a conjugate allows one to design more potent and better tolerated antisense drugs. Indeed, in certain emobidments, conjugated antisense compounds have larger therapeutic indexes than unconjugated counterparts. This allows the conjugated antisense compound to be administered at a higher absolute dose, because there is less risk of proinflammatory response and less risk of kidney toxicity. This higher dose, allows one to dose less frequently, since the clearance (metabolism) is expected to be similar. Further, because the compound is more potent, as described above, one can allow the concentration to go lower before the next dose without losing therapeutic activity, allowing for even longer periods between dosing.

[0386] In certain embodiments, the inclusion of some phosphorothioate linkages remains desirable. For example, the terminal linkages are vulnerable to exonucleoases and so in certain embodiments, those linkages are phosphorothioate or other modified linkage. Internucleoside linkages linking two deoxynucleosides are vulnerable to endonucleases and so in certain embodiments those those linkages are phosphorothioate or other modified linkage. Internucleoside linkages between a modified nucleoside and a deoxynucleoside where the deoxynucleoside is on the 5' side of the linkage deoxynucleosides are vulnerable to endonucleases and so in certain embodiments those those linkages are phosphorothioate or other modified linkage. Internucleoside linkages between two modified nucleosides of certain types and between a deoxynucleoside and a modified nucleoside of certain typ where the modified nucleoside is at the 5' side of the linkage are sufficiently resistant to nuclease digestion, that the linkage can be phosphodiester.

[0387] In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 16 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 15 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 14 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 13 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 12 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 11 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 10 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 9 phosphorthioate linkages. In certain embodiments, the antisense oligonucleotide of a conjugated antisense compound comprises fewer than 8 phosphorthioate linkages.

[0388] In certain embodiments, antisense compounds comprsing one or more conjugae group described herein has increased activity and/or potency and/or tolerability compared to a parent antisense compound lacking such one or more conjugate group. Accordingly, in certain embodiments, attachment of such conjugate groups to an oligonucleotide is desirable. Such conjugate groups may be attached at the 5'-, and/or 3'- end of an oligonucleotide. In certain instances, attachment at the 5'-end is synthetically desireable. Typically, oligonucleietides are synthesized by attachment of the 3' terminal nucleoside to a solid support and sequential coupling of nucleosides from 3' to 5' using techniques that are well known in the art. Accordingly if a conjugate group is desred at the 3'-terminus, one may (1) attach the conjugate group to the 3 '-terminal nucleoside and attach that conjugated nucleoside to the solid support for subsequent preparation of the oligonucleotide or (2) attach the conjugate group to the 3'-terminal nucleoside of a completed oligonucleotide after synthesis. Niether of these approaches is very efficient and thus both are costly. In particular, attachment of the conjugated nucleoside to the solid support, while demonstrated in the Examples herein, is an inefficient process. In certain embodiments, attaching a conjugate group to the 5'-terminal nucleoside is synthetically easier than attachment at the 3'-end. One may attach a non-conjugated 3' terminal nucleoside to the solid support and prepare the oligonucleotide using standard and well characterized reastions. One then needs only to attach a 5'nucleoside having a conjugate group at the final coupling step. In certain embodiments, this is more efficient than attaching a conjugated nucleoside directly to the solid support as is typically done to prepare a 3'-conjugated oligonucleotide. The Examples herein demonstrate attachment at the 5'-end. In addition, certain conjugate groups have synthetic advantages. For Example, certain conjugate groups comprising phosphorus linkage groups are synthetically simpler and more efficiently prepared than other conjugate groups, including conjugate groups reported previously (e.g., WO/2012/037254).

[0389] In certain embodiments, conjugated antisense compounds are administered to a subject. In such embodiments, antisense compounds comprsing one or more conjugae group described herein has increased activity and/or potency and/or tolerability compared to a parent antisense compound lacking such one or more conjugate group. Without being bound by mechanism, it is believed that the conjugate group helps with distribution, delivery, and/or uptake into a target cell or tissue. In certain embodiments, once inside the target cell or tissue, it is desirable that all or part of the conjugate group to be cleaved to releas the active oligonucleitde. In certain embodiments, it is not necessary that the entire conjugate group be cleaved from the oligonucleotide. For

example, in Example 20 a conjugated oligonucleotide was administered to mice and a number of different chemical species, each comprising a different portion of the conjugate group remaining on the oligonucleotide, were detected (Table 23a). Thisconjugated antisense compound demonstrated good potency (Table 23). Thus, in certain embodiments, such metabolite profile of multiple partial cleavage of the conjugate group does not interfere with activity/potency. Nevertheless, in certain embodiments it is desirable that a prodrug (conjugated oligonucleotide) yield a single active compound. In certain instances, if multiple forms of the active compound are found, it may be necessary to determine relative amounts and activities for each one. In certain embodiments where regulatory review is required (e.g., USFDA or counterpart) it is desirable to have a single (or predominantly single) active species. In certain such embodiments, it is desirable that such single active species be the antisense oligonucleotide lacking any portion of the conjugate group. In certain embodiments, conjugate groups at the 5'-end are more likely to result in complete metabolism of the conjugate group. Without being bound by mechanism it may be that endogenous enzymes responsible for metabolism at the 5' end (e.g., 5' nucleases) are more active/efficient than the 3' counterparts. In certain embodiments, the specific conjugate groups are more amenable to metabolism to a single active species. In certain embodiments, certain conjugate groups are more amenable to metabolism to the oligonucleotide.

D. Antisense

[0390] In certain embodiments, oligomeric compounds of the present disclosure are antisense compounds. In such embodiments, the oligomeric compound is complementary to a target nucleic acid. In certain embodiments, a target nucleic acid is an RNA. In certain embodiments, a target nucleic acid is a non-coding RNA. In certain embodiments, a target nucleic acid encodes a protein. In certain embodiments, a target nucleic acid is selected from a mRNA, a pre-mRNA, a microRNA, a non-coding RNA, including small non-coding RNA, and a promoter-directed RNA. In certain embodiments, oligomeric compounds are at least partially complementary to more than one target nucleic acid. For example, oligomeric compounds may be microRNA mimics, which typically bind to multiple targets.

[0391] In certain embodiments, antisense compounds comprise a portion having a nucleobase sequence at least 70% complementary to the nucleobase sequence of a target nucleic acid. In certain embodiments, antisense compounds comprise a portion having a nucleobase sequence at least 80% complementary to the nucleobase sequence of a target nucleic acid. In certain embodiments, antisense compounds comprise a portion having a nucleobase sequence at least 90% complementary to the nucleobase sequence of a target nucleic acid. In certain embodiments, antisense compounds comprise a portion having a nucleobase sequence at least 95% complementary to the nucleobase sequence of a target nucleic acid. In certain embodiments, antisense compounds comprise a portion having a nucleobase sequence at least 98% complementary to the nucleobase sequence of a target nucleic acid. In certain embodiments, antisense compounds comprise a portion having a nucleobase sequence that is 100% complementary to the nucleobase sequence of a target nucleic acid. In certain embodiments, antisense compounds are at least 70%, 80%, 90%, 95%, 98%, or 100% complementary to the nucleobase sequence of a target nucleic acid over the entire length of the antisense compound.

[0392] Antisense mechanisms include any mechanism involving the hybridization of an oligomeric compound with target nucleic acid, wherein the hybridization results in a biological effect. In certain embodiments, such hybridization results in either target nucleic acid degradation or occupancy with concomitant inhibition or stimulation of the cellular machinery involving, for example, translation, transcription, or polyadenylation of the target nucleic acid or of a nucleic acid with which the target nucleic acid may otherwise interact.

[0393] One type of antisense mechanism involving degradation of target RNA is RNase H mediated antisense. RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. It is known in the art that single-stranded antisense compounds which are "DNA-like" elicit RNase H activity in mammalian cells. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of DNA-like oligonucleotide-mediated inhibition of gene expression.

[0394] Antisense mechanisms also include, without limitation RNAi mechanisms, which utilize the RISC pathway. Such RNAi mechanisms include, without limitation siRNA, ssRNA and microRNA mechanisms. Such mechanisms include creation of a microRNA mimic and/or an anti-microRNA.

[0395] Antisense mechanisms also include, without limitation, mechanisms that hybridize or mimic non-coding RNA other than microRNA or mRNA. Such non-coding RNA includes, but is not limited to promoter-directed RNA and short and long RNA that effects transcription or translation of one or more nucleic acids.

[0396] In certain embodiments, oligonucleotides comprising conjugates described herein are RNAi compounds. In certain embodiments, oligomeric oligonucleotides comprising conjugates described herein are ssRNA compounds. In certain embodiments, oligonucleotides comprising conjugates described herein are paired with a second oligomeric compound to form an siRNA. In certain such embodiments, the second oligomeric compound also comprises a conjugate. In certain embodiments, the second oligomeric compound is any modified or unmodified nucleic acid. In certain embodiments, the oligonucleotides comprising conjugates described herein is the antisense strand in an siRNA compound. In certain embodiments, the oligonucleotides comprising conjugates described herein is the sense strand in an siRNA compound. In embodiments in which the conjugated oligomeric compound is double-stranded siRnA, the conjugate may be on the sense strand, the antisense strand or both the sense strand and the antisense strand.

C. <u>Apolipoprotein (a) (apo(a))</u>

[0397] In certain embodiments, conjugated antisense compounds target any apo(a) nucleic acid. In certain embodiments, the target nucleic acid encodes an apo(a) target protein that is clinically relevant. In such embodiments, modulation of the target nucleic acid results in clinical benefit.

[0398] The targeting process usually includes determination of at least one target region, segment, or site within the target nucleic acid for the antisense interaction to occur such that the desired effect will result.

[0399] In certain embodiments, a target region is a structurally defined region of the nucleic acid. For example, in certain such embodiments, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region or target segment.

[0400] In certain embodiments, a target segment is at least about an 8-nucleobase portion of a target region to which a conjugated antisense compound is targeted. Target segments can include DNA or RNA sequences that comprise at least 8 consecutive nucleobases from the 5'-terminus of one of the target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately upstream of the 5'-terminus of the target segment and continuing until the DNA or RNA comprises about 8 to about 30 nucleobases). Target segments are also represented by DNA or RNA sequences that comprise at least 8 consecutive nucleobases from the 3'-terminus of one of the target segments (the remaining nucleobases being a consecutive stretch of the same DNA or RNA beginning immediately downstream of the 3'-terminus of the target segment and continuing until the DNA or RNA comprises about 8 to about 30 nucleobases). Target segments can also be represented by DNA or RNA sequences that comprise at least 8 consecutive nucleobases from an internal portion of the sequence of a target segment, and may extend in either or both directions until the conjugated antisense compound comprises about 8 to about 30 nucleobases.

[0401] In certain embodiments, antisense compounds targeted to an apo(a) nucleic acid can be modified as described herein. In certain embodiments, the antisense compounds can have a modified sugar moiety, an unmodified sugar moiety or a mixture of modified and unmodified sugar moieties as described herein. In certain embodiments, the antisense compounds can have a modified internucleoside linkage, an unmodified internucleoside linkage or a mixture of modified and unmodified internucleoside linkages as described herein. In certain embodiments, the antisense compounds can have a modified nucleobase, an unmodified nucleobase or a

mixture of modified and unmodified nucleobases as described herein. In certain embodiments, the antisense compounds can have a motif as described herein.

[0402] In certain embodiments, antisense compounds targeted to apo(a) nucleic acids can be conjugated as described herein.

[0403] One apo(a) protein is linked via a disulfide bond to a single apolipoprotein B (apoB) protein to form a lipoprotein(a) (Lp(a)) particle. The apo(a) protein shares a high degree of homology with plasminogen particularly within the kringle IV type 2 repetitive domain. It is thought that the kringle repeat domain in apo(a) may be responsible for its pro-thrombotic and anti-fibrinolytic properties, potentially enhancing atherosclerotic progression. Apo(a) is transcriptionally regulated by IL-6 and in studies in rheumatoid arthritis patients treated with an IL-6 inhibitor (tocilizumab), plasma levels were reduced by 30% after 3 month treatment. Apo(a) has been shown to preferentially bind oxidized phospholipids and potentiate vascular inflammation. Further, studies suggest that the Lp(a) particle may also stimulate endothelial permeability, induce plasminogen activator inhibitor type-1 expression and activate macrophage interleukin-8 secretion. Importantly, recent genetic association studies revealed that Lp(a) was an independent risk factor for myocardial infarction, stroke, peripheral vascular disease and abdominal aortic aneurysm. Further, in the Precocious Coronary Artery Disease (PROCARDIS) study, Clarke *et al.* described robust and independent associations between coronary heart disease and plasma Lp(a) concentrations. Additionally, Solfrizzi et al., suggested that increased serum Lp(a) may be linked to an increased risk for Alzheimer's Disease (AD). Antisense compounds targeting apo(a) have been previously disclosed in WO2005/000201 and US2010-0331390. An antisense oligonucleobase targeting Apo(a), ISIS-APOA$_{Rx}$, was assessed in a Phase I clinical trial to study it's safety profile.

Certain Conjugated Antisense Compounds Targeted to an Apo(a) Nucleic Acid

[0404] In certain embodiments, conjugated antisense compounds are targeted to an Apo(a) nucleic acid having the sequence of GENBANK® Accession No. NM_005577.2, incorporated herein as SEQ ID NO: 1; GENBANK Accession No. NT_007422.12 truncated from nucleotides 3230000 to 3380000, incorporated herein as SEQ ID NO: 2; GENBANK Accession No. NT_025741.15 truncated from nucleotides 65120000 to 65258000, designated herein as SEQ ID NO: 3; and GENBANK Accession No. NM_005577.1, incorporated herein as SEQ ID NO: **4**. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to any of the nucleobase sequences of SEQ ID NOs: 1-**4**.

[0405] In certain embodiments, a conjugated antisense compound targeted to any of the nucleobase sequences of SEQ ID NOs: 1-**4** comprises an at least 8 consecutive nucleobase sequence selected from the nucleobase sequence of any of SEQ ID NOs: 12-130, 133, 134. In certain embodiments, a conjugated antisense compound targeted to any of SEQ ID NOs: 1-**4** comprises a nucleobase sequence selected from the nucleobase sequence of any of SEQ ID NOs: 12-130, 133, 134.

Table A: Antisense Compounds targeted to Apo(a) SEQ ID NO: 1

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
494372	3901	TGCTCCGTTGGTGCTTGTTC	eeeeeddddddddddeeeee	58
494283	584	TCTTCCTGTGACAGTGGTGG	eeeeeddddddddddeeeee	26
	926			
	1610			
	1952			
	2294			
	3320			
	585			
	927			

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
494284	1611 1953 2295 3321	TTCTTCCTGTGACAGTGGTG	eeeeeddddddddddeeeee	27
494286	587 929 1613 1955 2297	GGTTCTTCCTGTGACAGTGG	eeeeeddddddddddeeeee	29
494301	628 970 1312 1654 1996 2338 2680 3022	CGACTATGCGAGTGTGGTGT	eeeeeddddddddddeeeee	38
494302	629 971 1313 1655 1997 2339 2681 3023	CCGACTATGCGAGTGTGGTG	eeeeeddddddddddeeeee	39

Apo(a) Therapeutic Indications

[0406] In certain embodiments, the present disclosure provides methods for using a conjugated antisense compound targeted to an apo(a) nucleic acid for modulating the expression of apo(a) in a subject. In certain embodiments, the expression of apo(a) is reduced.

[0407] In certain embodiments, disclosed herein are methods of treating a subject comprising administering one or more pharmaceutical compositions as described herein. In certain embodiments, disclosed herein are methods for using a conjugated antisense compound targeted to an apo(a) nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the individual has an apo(a) related disease. In certain embodiments, the individual has an Lp(a) related disease. In certain embodiments, the individual has an inflammatory, cardiovascular and/or a metabolic disease, disorder or condition.

[0408] In certain embodiments, the subject has an inflammatory, cardiovascular and/or metabolic disease, disorder or condition.

[0409] In certain embodiments, the cardiovascular diseases, disorders or conditions include, but are not limited to, aortic stenosis, aneurysm (e.g., abdominal aortic aneurysm), angina, arrhythmia, atherosclerosis, cerebrovascular

disease, coronary artery disease, coronary heart disease, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, myocardial infarction, peripheral vascular disease (e.g., peripheral artery disease), stroke and the like.

[0410] In certain embodiments, the compounds targeted to apo(a) described herein modulate physiological markers or phenotypes of the cardiovascular disease, disorder or condition. For example, administration of the compounds to animals can decrease LDL and cholesterol levels in those animals compared to untreated animals. In certain embodiments, the modulation of the physiological markers or phenotypes can be associated with inhibition of apo(a) by the compounds.

[0411] In certain embodiments, the physiological markers of the cardiovascular disease, disorder or condition can be quantifiable. For example, LDL or cholesterol levels can be measured and quantified by, for example, standard lipid tests. For such markers, in certain embodiments, the marker can be decreased by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0412] Also, disclosed herein are methods for preventing, treating or ameliorating a symptom associated with the cardiovascular disease, disorder or condition in a subject in need thereof. In certain embodiments, provided is a method for reducing the rate of onset of a symptom associated with the cardiovascular disease, disorder or condition. In certain embodiments, provided is a method for reducing the severity of a symptom associated with the cardiovascular disease, disorder or condition. In such embodiments, the methods comprise administering a therapeutically effective amount of a compound targeted to an apo(a) nucleic acid to an individual in need thereof.

[0413] The cardiovascular disease, disorder or condition can be characterized by numerous physical symptoms. Any symptom known to one of skill in the art to be associated with the cardiovascular disease, disorder or condition can be prevented, treated, ameliorated or otherwise modulated with the compounds and methods described herein. In certain embodiments, the symptom can be any of, but not limited to, angina, chest pain, shortness of breath, palpitations, weakness, dizziness, nausea, sweating, tachycardia, bradycardia, arrhythmia, atrial fibrillation, swelling in the lower extremities, cyanosis, fatigue, fainting, numbness of the face, numbness of the limbs, claudication or cramping of muscles, bloating of the abdomen or fever.

[0414] In certain embodiments, the metabolic diseases, disorders or conditions include, but are not limited to, hyperglycemia, prediabetes, diabetes (type I and type II), obesity, insulin resistance, metabolic syndrome and diabetic dyslipidemia.

[0415] In certain embodiments, compounds targeted to apo(a) as described herein modulate physiological markers or phenotypes of the metabolic disease, disorder or condition. For example, administrion of the compounds to animals can decrease glucose and insulin resistance levels in those animals compared to untreated animals. In certain embodiments, the modulation of the physiological markers or phenotypes can be associated with inhibition of apo(a) by the compounds.

[0416] In certain embodiments, physiological markers of the metabolic disease, disorder or condition can be quantifiable. For example, glucose levels or insulin resistance can be measured and quantified by standard tests known in the art. For such markers, in certain embodiments, the marker can be decreased by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values. In another example, insulin sensitivity can be measured and quantified by standard tests known in the art. For such markers, in certain embodiments, the marker can be increase by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%, or a range defined by any two of these values.

[0417] Also, disclosed herein are methods for preventing, treating or ameliorating a symptom associated with the metabolic disease, disorder or condition in a subject in need thereof. In certain embodiments, provided is a method for reducing the rate of onset of a symptom associated with the metabolic disease, disorder or condition. In certain embodiments, provided is a method for reducing the severity of a symptom associated with the metabolic disease, disorder or condition. In such embodiments, the methods comprise administering a therapeutically effective

amount of a compound targeted to an apo(a) nucleic acid to an individual in need thereof.

[0418] The metabolic disease, disorder or condition can be characterized by numerous physical symptoms. Any symptom known to one of skill in the art to be associated with the metabolic disease, disorder or condition can be prevented, treated, ameliorated or otherwise modulated with the compounds and methods described herein. In certain embodiments, the symptom can be any of, but not limited to, excessive urine production (polyuria), excessive thirst and increased fluid intake (polydipsia), blurred vision, unexplained weight loss and lethargy.

[0419] In certain embodiments, the inflammatory diseases, disorders or conditions include, but are not limited to, aortic stenosis, coronary artey disease (CAD), Alzheimer's Disease and thromboembolic diseases, disorder or conditions. Certain thromboembolic diseases, disorders or conditions include, but are not limited to, stroke, thrombosis, myocardial infarction and peripheral vascular disease.

[0420] In certain embodiments, the compounds targeted to apo(a) described herein modulate physiological markers or phenotypes of the inflammatory disease, disorder or condition. For example, administration of the compounds to animals can decrease inflammatory cytokine or other inflammatory markers levels in those animals compared to untreated animals. In certain embodiments, the modulation of the physiological markers or phenotypes can be associated with inhibition of apo(a) by the compounds.

[0421] In certain embodiments, the physiological markers of the inflammatory disease, disorder or condition can be quantifiable. For example, cytokine levels can be measured and quantified by standard tests known in the art. For such markers, in certain embodiments, the marker can be decreased by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99%, or a range defined by any two of these values.

[0422] Also, disclosed herein are methods for preventing, treating or ameliorating a symptom associated with the inflammatory disease, disorder or condition in a subject in need thereof. In certain embodiments, provided is a method for reducing the rate of onset of a symptom associated with the inflammatory disease, disorder or condition. In certain embodiments, provided is a method for reducing the severity of a symptom associated with the inflammatory disease, disorder or condition. In such embodiments, the methods comprise administering a therapeutically effective amount of a compound targeted to an apo(a) nucleic acid to an individual in need thereof.

[0423] In certain embodiments, provided are methods of treating an individual with an apo(a) related disease, disorder or condition comprising administering a therapeutically effective amount of one or more pharmaceutical compositions as described herein. In certain embodiments, the individual has elevated apo(a) levels. In certain embodiments, provided are methods of treating an individual with an Lp(a) related disease, disorder or condition comprising administering a therapeutically effective amount of one or more pharmaceutical compositions as described herein. In certain embodiments, the individual has elevated Lp(a) levels. In certain embodiments, the individual has an inflammatory, cardiovascular and/or metabolic disease, disorder or condition. In certain embodiments, administration of a therapeutically effective amount of an antisense compound targeted to an apo(a) nucleic acid is accompanied by monitoring of apo(a) or Lp(a) levels. In certain embodiments, administration of a therapeutically effective amount of an antisense compound targeted to an apo(a) nucleic acid is accompanied by monitoring of markers of inflammatory, cardiovascular and/or metabolic disease, or other disease process associated with the expression of apo(a), to determine an individual's response to the antisense compound. An individual's response to administration of the antisense compound targeting apo(a) can be used by a physician to determine the amount and duration of therapeutic intervention with the compound.

[0424] In certain embodiments, administration of an antisense compound targeted to an apo(a) nucleic acid results in reduction of apo(a) expression by at least about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99%, or a range defined by any two of these values. In certain embodiments, apo(a) expression is reduced to at least ≤ 100 mg/dL, ≤ 90 mg/dL, ≤ 80 mg/dL, ≤ 70 mg/dL, ≤ 60 mg/dL, ≤ 50 mg/dL, ≤ 40 mg/dL, ≤ 30 mg/dL, ≤20 mg/dL or ≤ 10 mg/dL.

[0425] In certain embodiments, administration of an antisense compound targeted to an apo(a) nucleic acid results in reduction of Lp(a) expression by at least about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99%, or a range defined by any two of these values. In certain embodiments, Lp(a) expression is reduced to at least ≤ 200 mg/dL, ≤ 190 mg/dL, ≤ 180 mg/dL, ≤ 175 mg/dL, ≤ 170 mg/dL, ≤ 160 mg/dL, ≤ 150 mg/dL, ≤ 140 mg/dL, ≤ 130 mg/dL, ≤ 120 mg/dL, ≤ 110 mg/dL, ≤ 100 mg/dL, ≤ 90 mg/dL, ≤ 80 mg/dL, ≤ 70 mg/dL, ≤ 60 mg/dL, ≤ 55 mg/dL, ≤ 50 mg/dL, ≤ 45 mg/dL, ≤ 40 mg/dL, ≤ 35 mg/dL, ≤ 30 mg/dL, ≤ 25 mg/dL, ≤ 20 mg/dL, ≤ 15 mg/dL, or ≤ 10 mg/dL.

[0426] In certain embodiments, herein disclosed are methods for using a conjugated antisense compound targeted to an apo(a) nucleic acid in the preparation of a medicament. In certain embodiments, pharmaceutical compositions comprising a conjugated antisense compound targeted to apo(a) are used for the preparation of a medicament for treating a patient suffering or susceptible to an inflammatory, cardiovascular and/or a metabolic disease, disorder or condition.

Apo(a) Treatment Populations

[0427] Certain subjects with high Lp(a) levels are at a significant risk of various diseases (Lippi et al., Clinica Chimica Acta, 2011, 412:797-801; Solfrizz et al.). In many subjects with high Lp(a) levels, current treatments cannot reduce their Lp(a) levels to safe levels. Apo(a) plays an important role in the formation of Lp(a), hence reducing apo(a) can reduce Lp(a) and prevent, treat or ameliorate a disease associated with Lp(a).

[0428] In certain embodiments, treatment with the compounds and methods disclosed herein is indicated for a human animal with elevated apo(a) levels and/or Lp(a) levels. In certain embodiments, the human has apo(a) levels ≥ 10 mg/dL, ≥ 20 mg/dL, ≥ 30 mg/dL, ≥ 40 mg/dL, ≥ 50 mg/dL, ≥ 60 mg/dL, ≥ 70 mg/dL, ≥ 80 mg/dL, ≥ 90 mg/dL or ≥ 100 mg/dL. In certain embodiments, the human has Lp(a) levels ≥ 10 mg/dL, ≥ 15 mg/dL, ≥ 20 mg/dL, ≥ 25 mg/dL, ≥ 30 mg/dL, ≥ 35 mg/dL, ≥ 40 mg/dL, ≥ 50 mg/dL, ≥ 60 mg/dL, ≥ 70 mg/dL, ≥ 80 mg/dL, ≥ 90 mg/dL, ≥ 100 mg/dL, ≥ 110 mg/dL, ≥ 120 mg/dL, ≥ 130 mg/dL, ≥ 140 mg/dL, ≥ 150 mg/dL, ≥ 160 mg/dL, ≥ 170 mg/dL, ≥ 175 mg/dL, ≥ 180 mg/dL, ≥ 190 mg/dL, ≥ 200 mg/dL.

D. <u>Certain Pharmaceutical Compositions</u>

[0429] In certain embodiments, the present invention provides pharmaceutical compositions comprising one or more antisense compounds according to the invention. In certain embodiments, such pharmaceutical composition comprises a suitable pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises a sterile saline solution and one or more antisense compound. In certain embodiments, such pharmaceutical composition consists of a sterile saline solution and one or more antisense compound. In certain embodiments, the sterile saline is pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition comprises one or more antisense compound and sterile water. In certain embodiments, a pharmaceutical composition consists of one or more antisense compound and sterile water. In certain embodiments, the sterile saline is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises one or more antisense compound and phosphate-buffered saline (PBS). In certain embodiments, a pharmaceutical composition consists of one or more antisense compound and sterile phosphate-buffered saline (PBS). In certain embodiments, the sterile saline is pharmaceutical grade PBS.

[0430] In certain embodiments, antisense compounds may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

[0431] Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters. In certain embodiments, pharmaceutical compositions comprising

antisense compounds comprise one or more oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of antisense compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

[0432] A prodrug can include the incorporation of additional nucleosides at one or both ends of an oligonucleotide which are cleaved by endogenous nucleases within the body, to form the active antisense oligonucleotide.

[0433] Lipid moieties have been used in nucleic acid therapies in a variety of methods. In certain such methods, the nucleic acid is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, DNA complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to a particular cell or tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to fat tissue. In certain embodiments, a lipid moiety is selected to increase distribution of a pharmaceutical agent to muscle tissue.

[0434] In certain embodiments, pharmaceutical compositions provided herein comprise one or more modified oligonucleotides and one or more excipients. In certain such embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

[0435] In certain embodiments, a pharmaceutical composition provided herein comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0436] In certain embodiments, a pharmaceutical composition provided herein comprises one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present disclosure to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

[0437] In certain embodiments, a pharmaceutical composition provided herein comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0438] In certain embodiments, a pharmaceutical composition provided herein is prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration.

[0439] In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose

containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the pharmaceutical agents to allow for the preparation of highly concentrated solutions.

[0440] In certain embodiments, a pharmaceutical composition is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0441] In certain embodiments, a pharmaceutical composition provided herein comprises an oligonucleotide in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[0442] In certain embodiments, one or more modified oligonucleotide provided herein is formulated as a prodrug. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active form of an oligonucleotide. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (e.g., through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, a prodrug is an ester. In certain such embodiments, the ester is metabolically hydrolyzed to carboxylic acid upon administration. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is cleaved upon administration to form the corresponding active form.

[0443] In certain embodiments, the present disclosure provides compositions and methods for reducing the amount or activity of a target nucleic acid in a cell. In certain embodiments, the cell is in an animal. In certain embodiments, the animal is a mammal. In certain embodiments, the animal is a rodent. In certain embodiments, the animal is a primate. In certain embodiments, the animal is a non-human primate. In certain embodiments, the animal is a human.

[0444] In certain embodiments, the present disclosure provides methods of administering a pharmaceutical composition comprising an oligonucleotide of the present disclosure to an animal. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intracerebroventricular, intraperitoneal, intranasal, intraocular, intratumoral, and parenteral (e.g., intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecals are administered to achieve local rather than systemic exposures. For example, pharmaceutical compositions may be injected directly in the area of desired effect (e.g., into the liver).

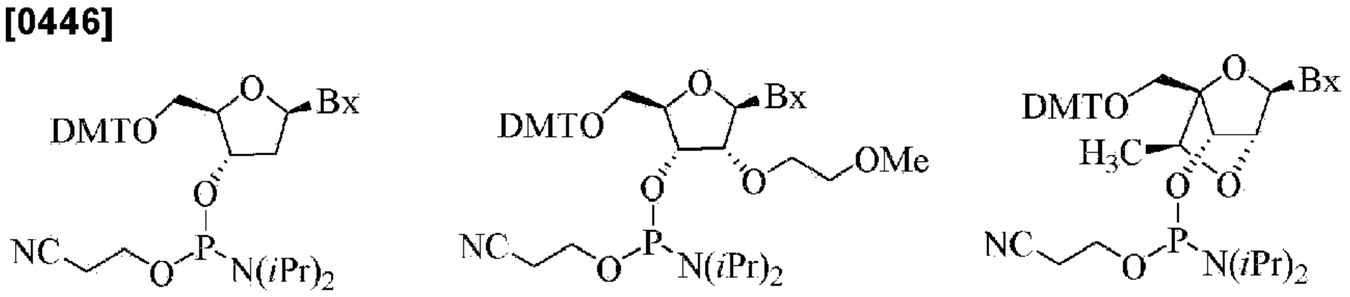
EXAMPLES

[0445] The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-

affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

Example 1: General Method for the Preparation of Phosphoramidites, Compounds 1, 1a and 2

[0446]



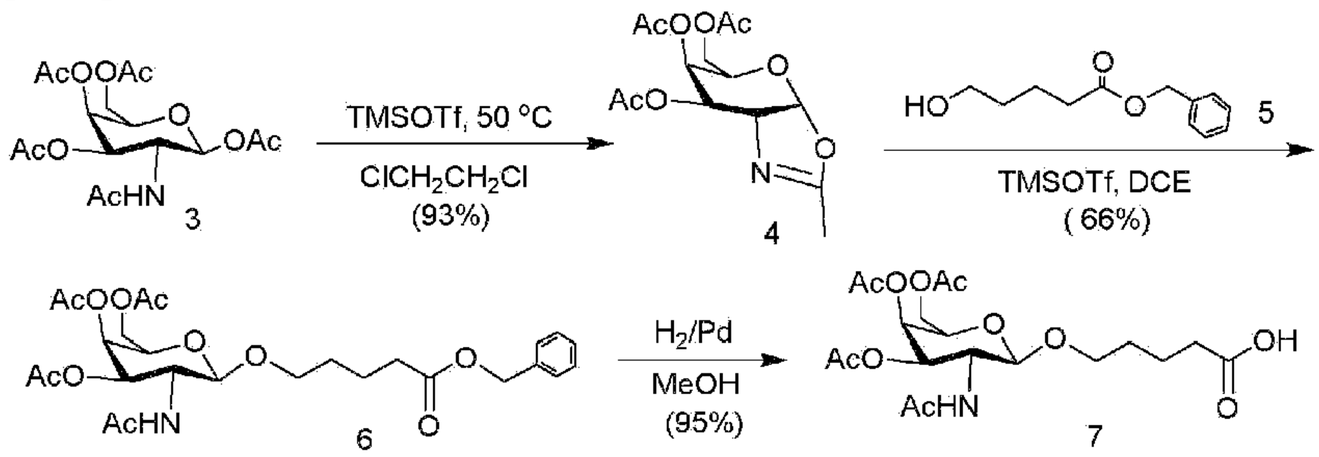
1 1a 2

Bx is a heterocyclic base;

[0447] Compounds 1, 1a and 2 were prepared as per the procedures well known in the art as described in the specification herein (see Seth et al., Bioorg. Med. Chem., 2011, 21(4), 1122-1125, J. Org. Chem., 2010, 75(5), 1569-1581, Nucleic Acids Symposium Series, 2008, 52(1), 553-554); and also see published PCT International Applications (WO 2011/115818, WO 2010/077578, WO2010/036698, WO2009/143369, WO 2009/006478, and WO 2007/090071), and US patent 7,569,686).

Example 2: Preparation of Compound 7

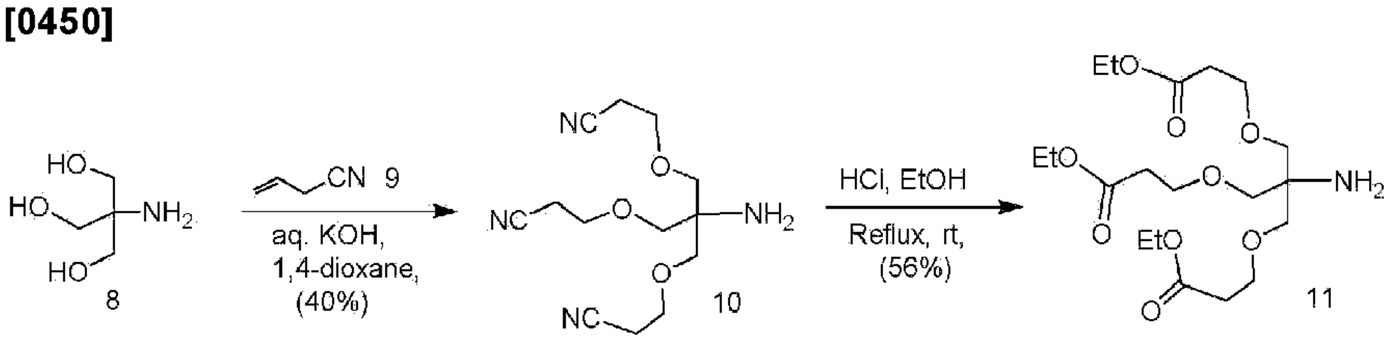
[0448]



[0449] Compounds 3 (2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-Dgalactopyranose or galactosamine pentaacetate) is commercially available. Compound 5 was prepared according to published procedures (Weber et al., J. Med. Chem., 1991, 34, 2692).

Example 3: Preparation of Compound 11

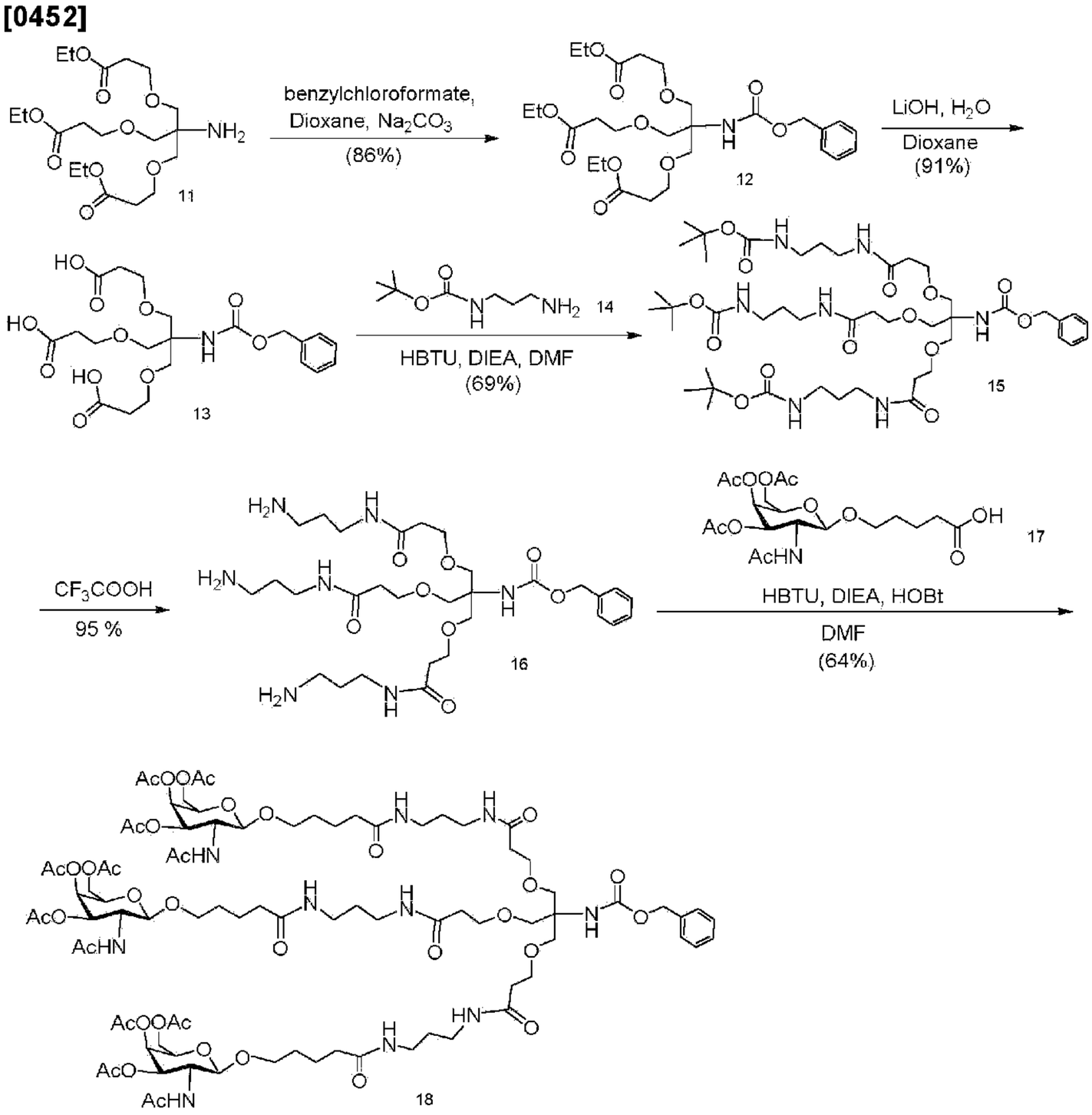
[0450]



[0451] Compounds 8 and 9 are commercially available.

Example 4: Preparation of Compound 18

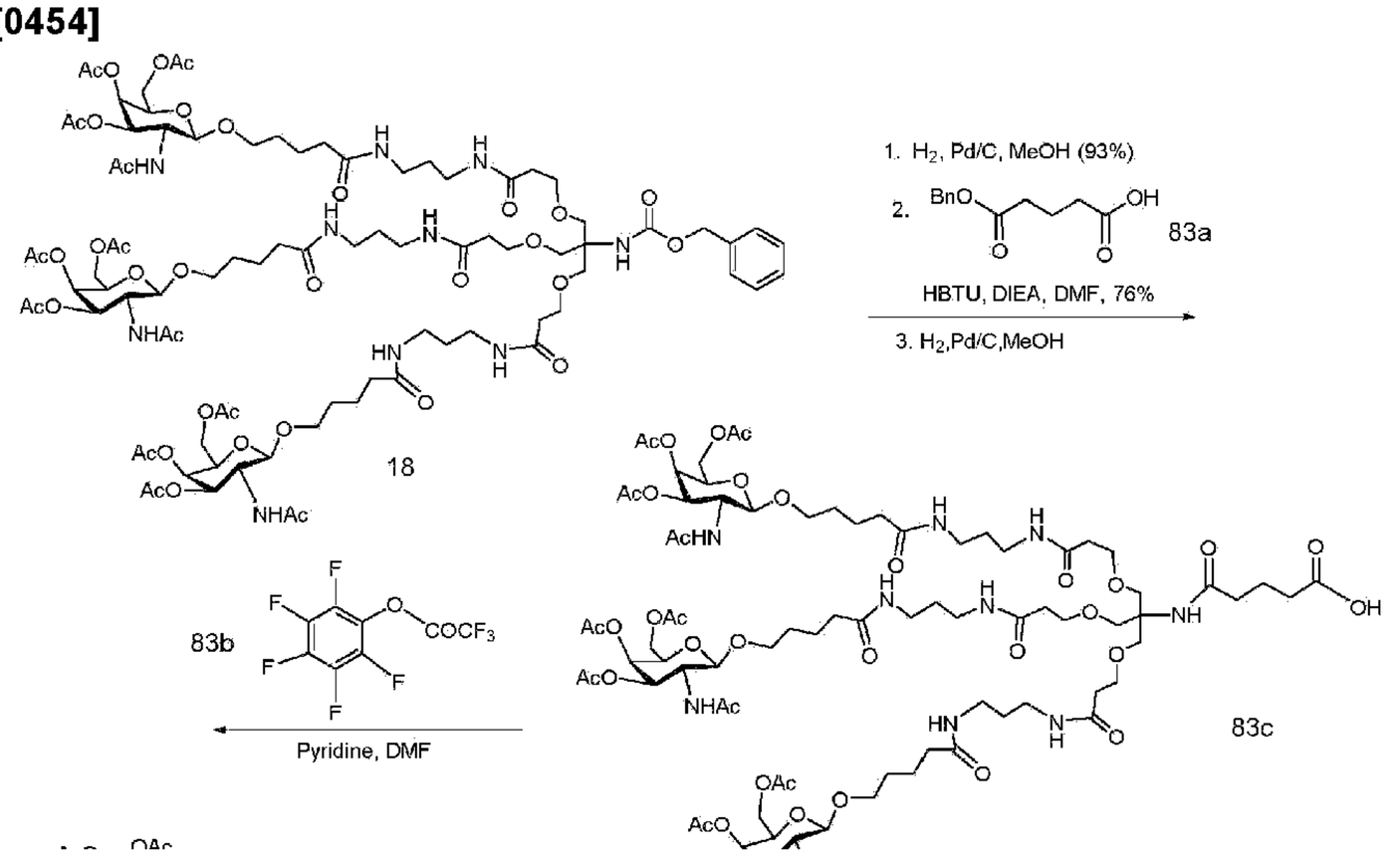
[0452]

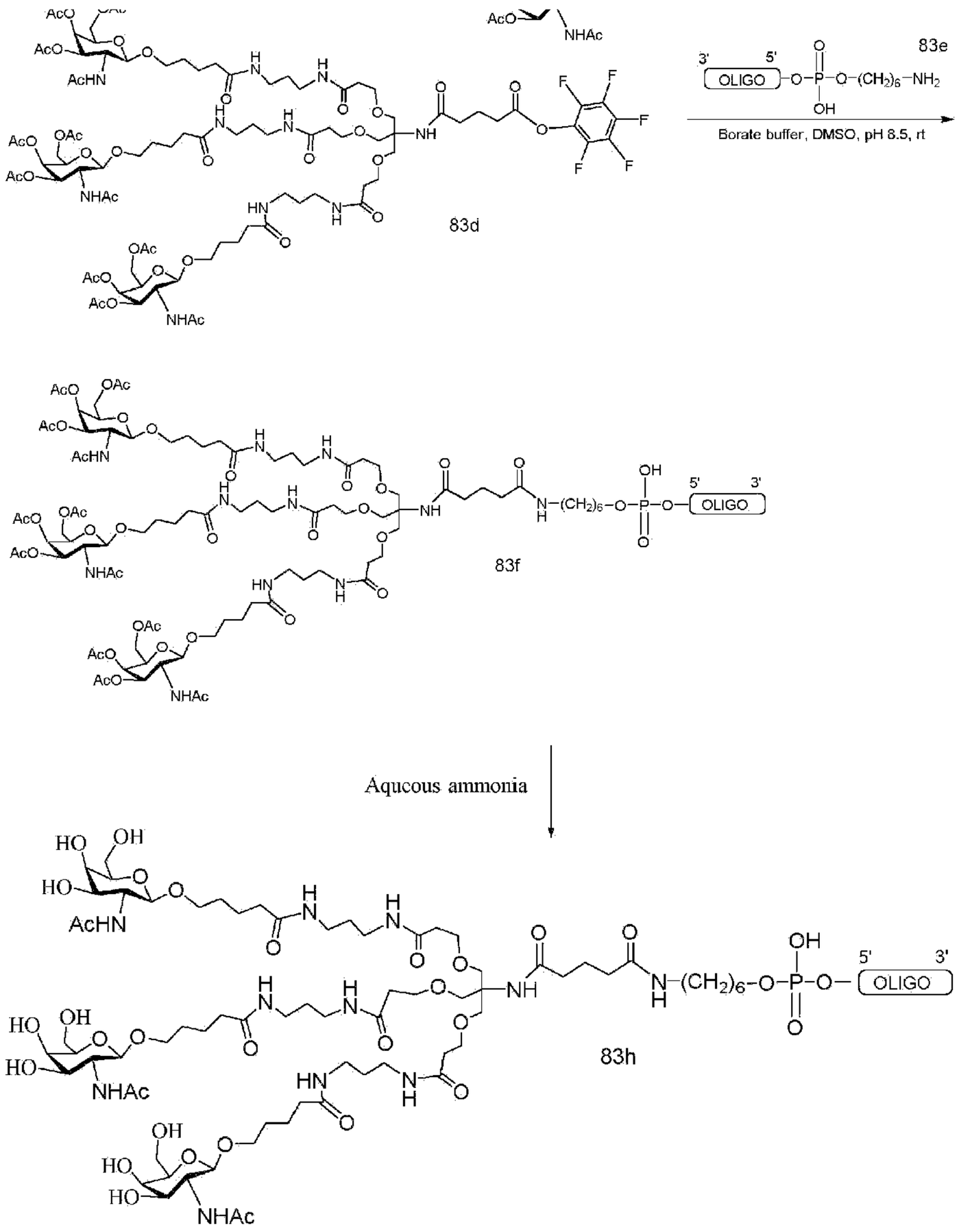


[0453] Compound 11 was prepared as per the procedures illustrated in Example 3. Compound 14 is commercially available. Compound 17 was prepared using similar procedures reported by Rensen et al., J. Med. Chem., 2004, 47, 5798-5808.

Example 39: General method for the preparation of oligomeric compound 83h comprising a $GalNAc_3$-3 Conjugate at the 5' Terminus ($GalNAc_3$-1 modified for 5' end attachment) *via* Solid Support

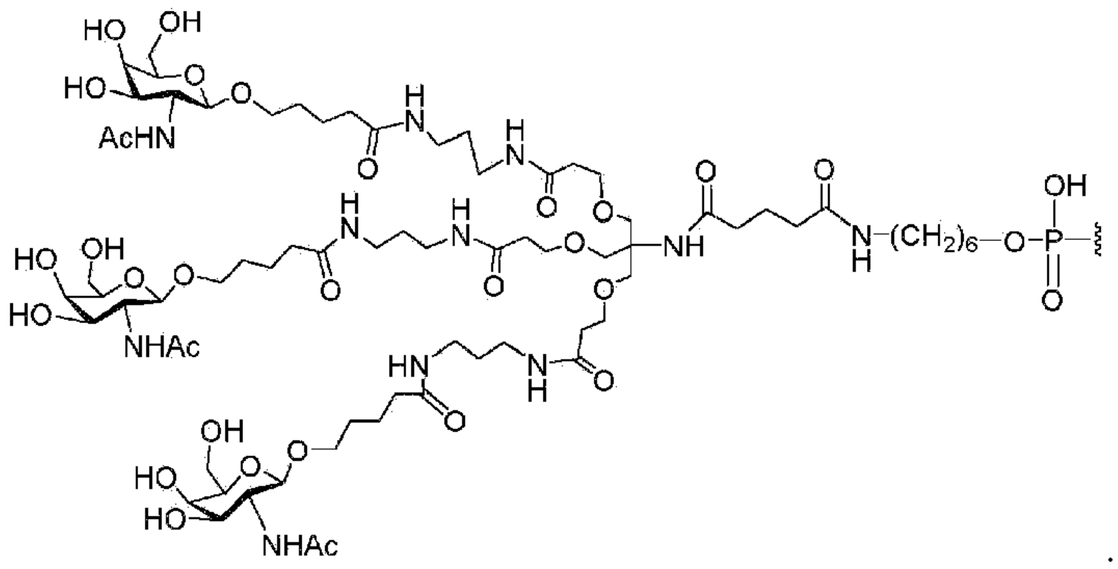
[0454]





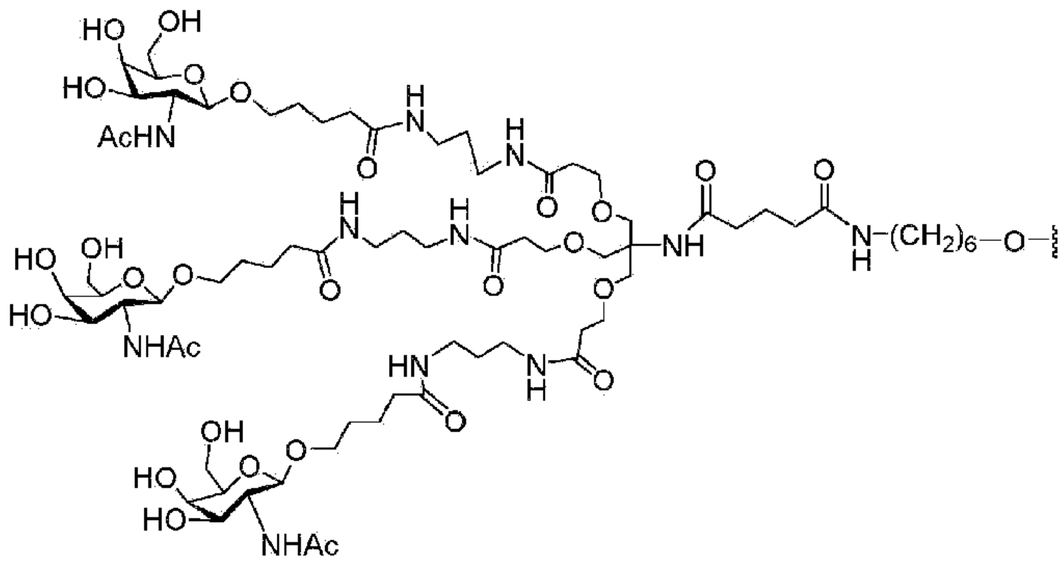
[0455] Compound 18 was prepared as per the procedures illustrated in Example **4**. Compounds 83a and 83b are commercially available. Oligomeric Compound 83e comprising a phosphodiester linked hexylamine was prepared using standard oligonucleotide synthesis procedures. Treatment of the protected oligomeric compound with aqueous ammonia provided the 5'-GalNAc$_3$-3 conjugated oligomeric compound (83h).

[0456] Wherein GalNAc$_3$-3 has the structure:



[0457] The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-3 (GalNAc$_3$-3$_a$) can be combined with any

cleavable moiety to provide a variety of conjugate groups. Wherein $GalNAc_3$-3_a has the formula:



Example 44: Effect of PO/PS linkages on antisense inhibition of ASOs comprising $GalNAc_3$-1 conjugate (see Example 9) at the 3' terminus targeting SRB-1

[0458] ISIS 655861 and 655862 comprising a $GalNAc_3$-1 conjugate at the 3' terminus each targeting SRB-1 were tested in a single administration study for their ability to inhibit SRB-1 in mice. The parent unconjugated compound, ISIS 353382 was included in the study for comparison.

[0459] The ASOs are 5-10-5 MOE gapmers, wherein the gap region comprises ten 2'-deoxyribonucleosides and each wing region comprises five 2'-MOE modified nucleosides. The ASOs were prepared using similar methods as illustrated previously in Example 19 and are described Table 36, below.

Table 36

Modified ASOs comprising $GalNAc_3$-1 conjugate at the 3' terminus targeting SRB-1

ISIS No.	Sequence (5' to 3')	Chemistry	SEQ ID No.
353382 (parent)	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	Full PS no conjugate	143
655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	Full PS with **$GalNAc_3$-1** conjugate	144
655862	$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	Mixed PS/PO with **$GalNAc_3$-1** conjugate	144

[0460] Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "s" indicates phosphorothioate internucleoside linkages (PS); "o" indicates phosphodiester internucleoside linkages (PO); and "o'" indicates -O-P(=O)(OH)-. Superscript "m" indicates 5-methylcytosines. The structure of "$GalNAc_3$-1" is shown in Example 9.

Treatment

[0461] Six week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 353382, 655861, 655862 or with PBS treated control. Each treatment group consisted of 4 animals. Prior to the treatment as well as after the last dose, blood was drawn from each mouse and

plasma samples were analyzed. The mice were sacrificed 72 hours following the final administration to determine the liver SRB-1 mRNA levels using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. SRB-1 mRNA levels were determined relative to total RNA (using Ribogreen), prior to normalization to PBS-treated control. The results below are presented as the average percent of SRB-1 mRNA levels for each treatment group, normalized to PB S-treated control and is denoted as "% PBS". The ED_{50}s were measured using similar methods as described previously and are reported below.

[0462] As illustrated in Table 37, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner compared to PBS treated control. Indeed, the antisense oligonucleotides comprising the $GalNAc_3$-1 conjugate at the 3' terminus (ISIS 655861 and 655862) showed substantial improvement in potency comparing to the unconjugated antisense oligonucleotide (ISIS 353382). Further, ISIS 655862 with mixed PS/PO linkages showed an improvement in potency relative to full PS (ISIS 655861).

Table 37

Effect of PO/PS linkages on antisense inhibition of ASOs comprising $GalNAc_3$-1 conjugate at 3' terminus targeting SRB-1

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA levels (% PBS)	ED_{50} (mg/kg)	Chemistry	SEQ ID No.
PBS	0	100	--	--	
353382 (parent)	3	76.65	10.4	Full PS without conjugate	143
	10	52.40			
	30	24.95			
655861	0.5	81.22	2.2	Full PS with $GalNAc_3$-1 conjugate	144
	1.5	63.51			
	5	24.61			
	15	14.80			
655862	0.5	69.57	1.3	Mixed PS/PO with $GalNAc_3$-1 conjugate	144
	1.5	45.78			
	5	19.70			
	15	12.90			

[0463] Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Organ weights were also evaluated. The results demonstrated that no elevation in transaminase levels (Table 38) or organ weights (data not shown) were observed in mice treated with ASOs compared to PBS control. Further, the ASO with mixed PS/PO linkages (ISIS 655862) showed similar transaminase levels compared to full PS (ISIS 655861).

Table 38

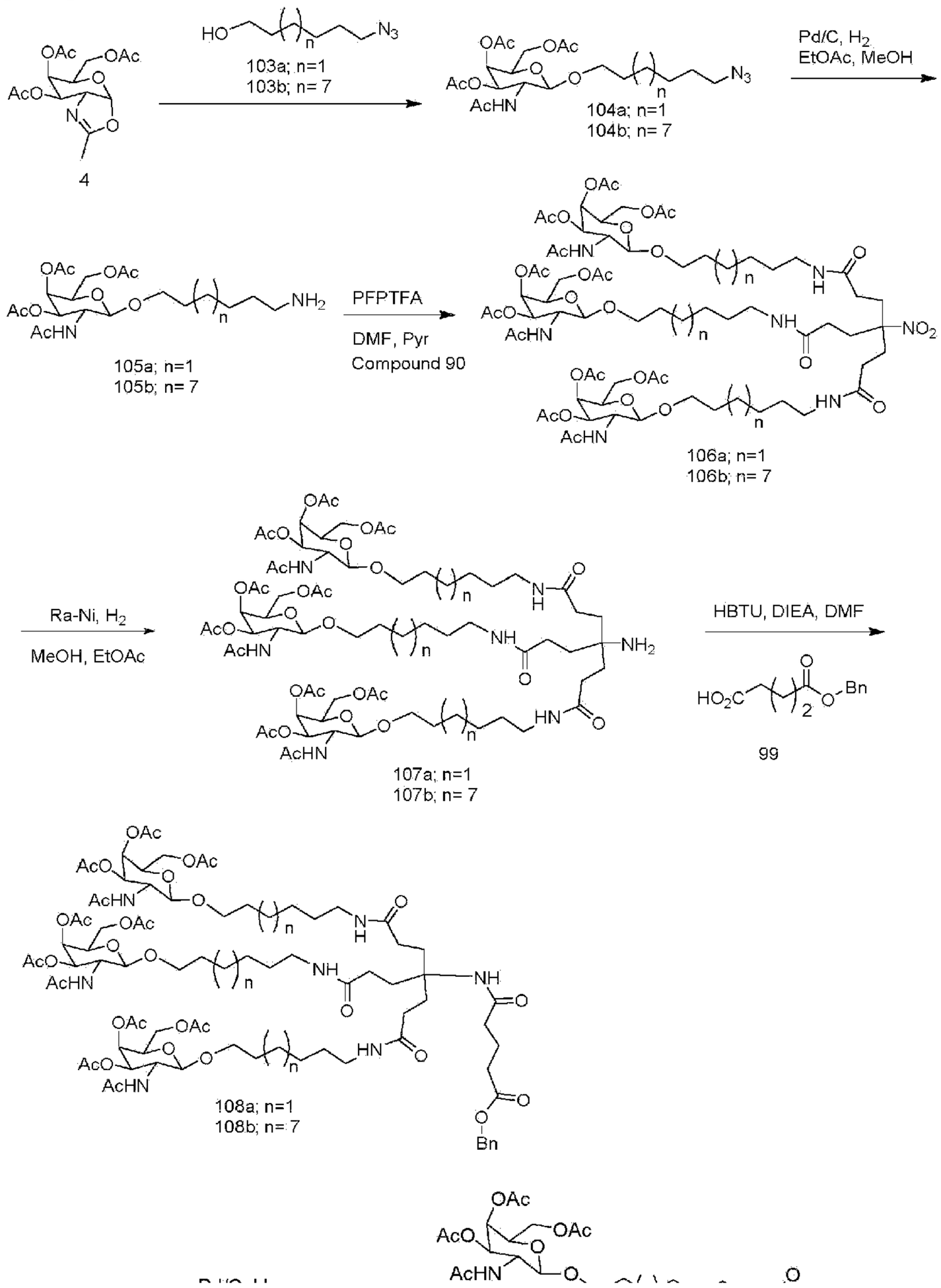
Effect of PO/PS linkages on transaminase levels of ASOs comprising $GalNAc_3$-1 conjugate at 3' terminus targeting SRB-1

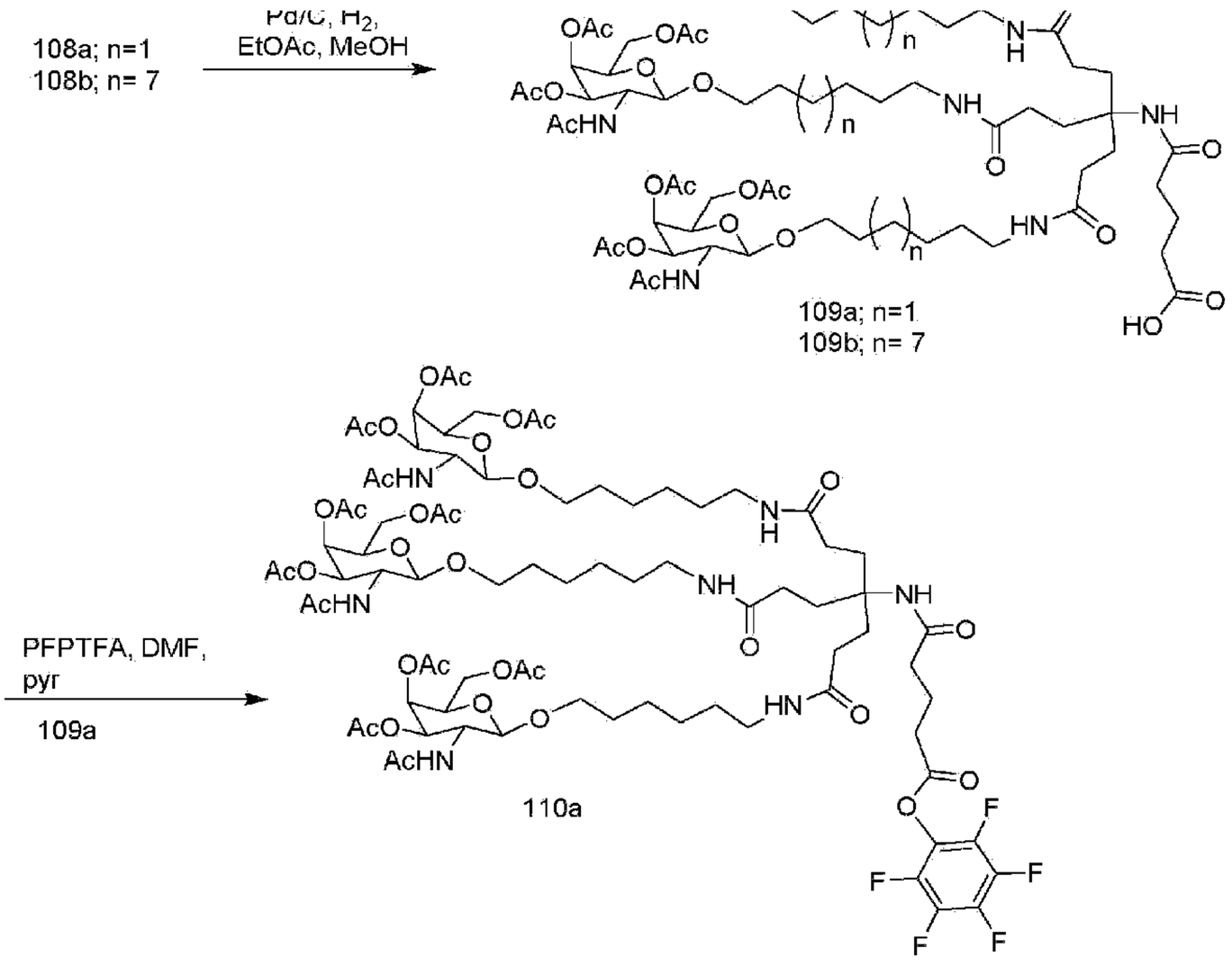
ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Chemistry	SEQ ID No.
PBS	0	28.5	65	--	
353382 (parent)	3	50.25	89	Full PS without conjugate	143
	10	27.5	79.3		
	30	27.3	97		
	0.5	28	55.7		

Effect of PO/PS linkages on transaminase levels of ASOs comprising GalNAc$_3$-1 conjugate at 3' terminus targeting SRB-1					
ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Chemistry	SEQ ID No.
655861	1.5	30	78	Full PS with **GalNAc$_3$-1**	144
	5	29	63.5		
	15	28.8	67.8		
655862	0.5	50	75.5	Mixed PS/PO with **GalNAc$_3$-1**	144
	1.5	21.7	58.5		
	5	29.3	69		
	15	22	61		

Example 45: Preparation of PFP Ester, Compound 110a

[0464]





[0465] Compound **4** (9.5g, 28.8 mmoles) was treated with compound 103a or 103b (38 mmoles), individually, and TMSOTf (0.5 eq.) and molecular sieves in dichloromethane (200 mL), and stirred for 16 hours at room temperature. At that time, the organic layer was filtered thru celite, then washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->10% methanol/dichloromethane) to give compounds 104a and 104b in >80% yield. LCMS and proton NMR was consistent with the structure.

[0466] Compounds 104a and 104b were treated to the same conditions as for compounds 100a-d (Example **47**), to give compounds 105a and 105b in >90% yield. LCMS and proton NMR was consistent with the structure.

[0467] Compounds 105a and 105b were treated, individually, with compound 90 under the same conditions as for compounds 901a-d, to give compounds 106a (80%) and 106b (20%). LCMS and proton NMR was consistent with the structure.

[0468] Compounds 106a and 106b were treated to the same conditions as for compounds 96a-d (Example **47**), to give 107a (60%) and 107b (20%). LCMS and proton NMR was consistent with the structure.

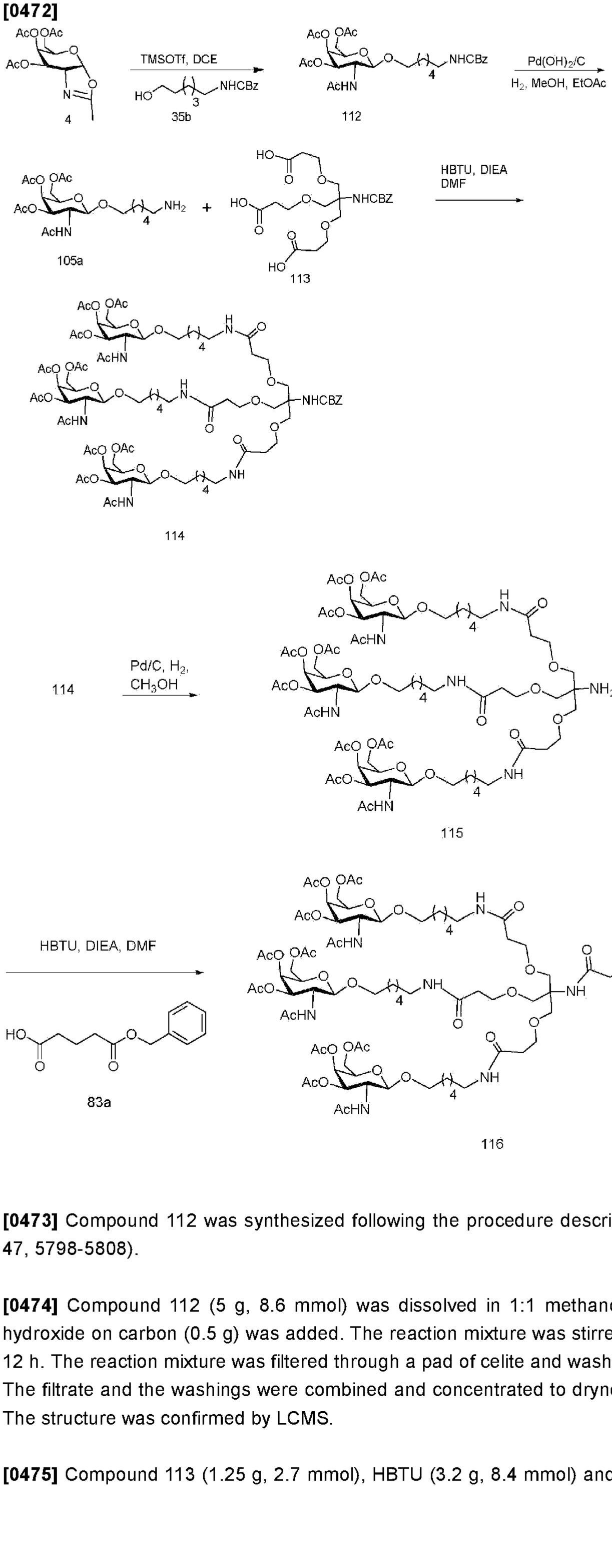
[0469] Compounds 107a and 107b were treated to the same conditions as for compounds 97a-d (Example **47**), to give compounds 108a and 108b in 40-60% yield. LCMS and proton NMR was consistent with the structure.

[0470] Compounds 108a (60%) and 108b (40%) were treated to the same conditions as for compounds 100a-d (Example **47**), to give compounds 109a and 109b in >80% yields. LCMS and proton NMR was consistent with the structure.

[0471] Compound 109a was treated to the same conditions as for compounds 101a-d (Example **47**), to give Compound 110a in 30-60% yield. LCMS and proton NMR was consistent with the structure. Alternatively, Compound 110b can be prepared in a similar manner starting with Compound 109b.

Example 48: Preparation of Oligonucleotide 119 Comprising GalNAc$_3$-7

[0472]



[0473] Compound 112 was synthesized following the procedure described in the literature (J. Med. Chem. 2004, 47, 5798-5808).

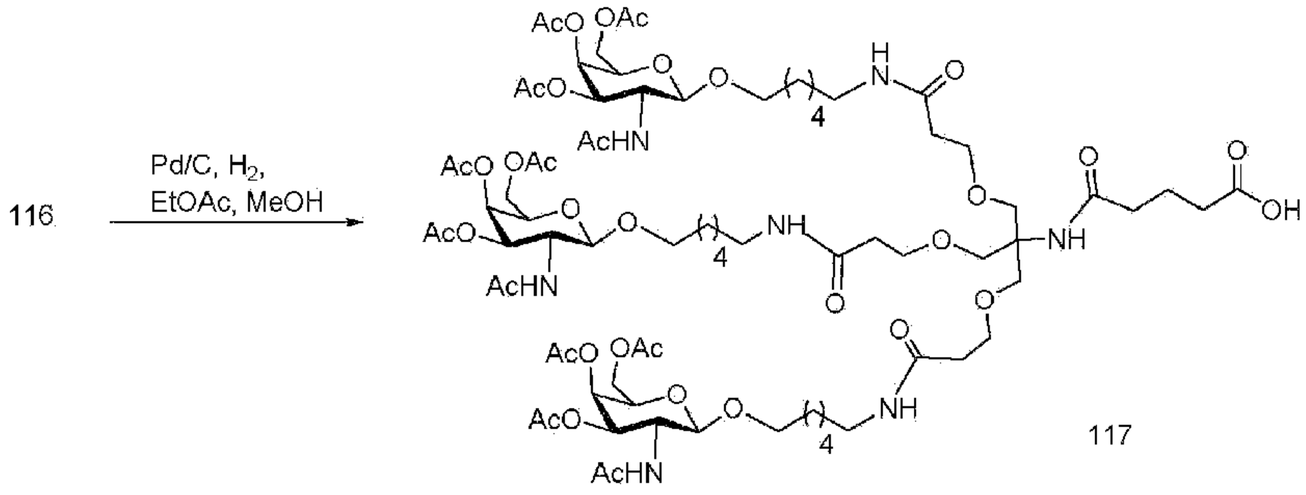
[0474] Compound 112 (5 g, 8.6 mmol) was dissolved in 1:1 methanol/ethyl acetate (22 mL/22 mL). Palladium hydroxide on carbon (0.5 g) was added. The reaction mixture was stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite and washed the pad with 1:1 methanol/ethyl acetate. The filtrate and the washings were combined and concentrated to dryness to yield Compound 105a (quantitative). The structure was confirmed by LCMS.

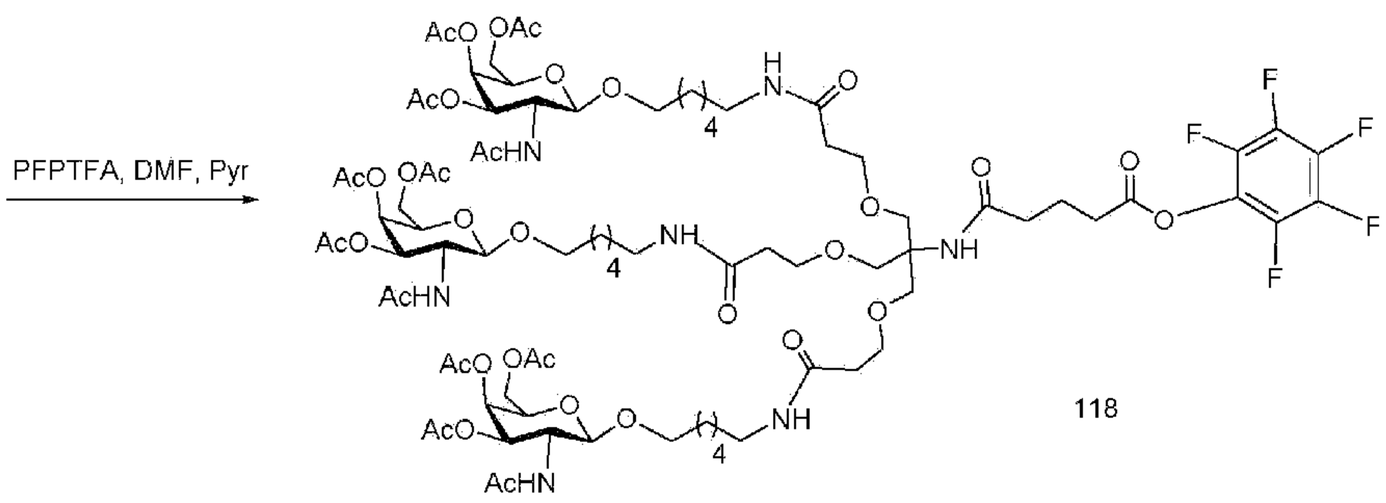
[0475] Compound 113 (1.25 g, 2.7 mmol), HBTU (3.2 g, 8.4 mmol) and DIEA (2.8 mL, 16.2 mmol) were dissolved

in anhydrous DMF (17 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 105a (3.77 g, 8.4 mmol) in anhydrous DMF (20 mL) was added. The reaction was stirred at room temperature for 6 h. Solvent was removed under reduced pressure to get an oil. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with aqueous saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography and eluted with 10 to 20 % MeOH in dichloromethane to yield Compound 114 (1.45 g, 30%). The structure was confirmed by LCMS and ^1H NMR analysis.

[0476] Compound 114 (1.43 g, 0.8 mmol) was dissolved in 1:1 methanol/ethyl acetate (4 mL/4 mL). Palladium on carbon (wet, 0.14 g) was added. The reaction mixture was flushed with hydrogen and stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite. The celite pad was washed with methanol/ethyl acetate (1:1). The filtrate and the washings were combined together and evaporated under reduced pressure to yield Compound 115 (quantitative). The structure was confirmed by LCMS and ^1H NMR analysis.

[0477] Compound 83a (0.17 g, 0.75 mmol), HBTU (0.31 g, 0.83 mmol) and DIEA (0.26 mL, 1.5 mmol) were dissolved in anhydrous DMF (5 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 115 (1.22 g, 0.75 mmol) in anhydrous DMF was added and the reaction was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The organic layer was washed aqueous saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4 and filtered. The organic layer was concentrated to dryness and the residue obtained was purified by silica gel column chromatography and eluted with 3 to 15 % MeOH in dichloromethane to yield Compound 116 (0.84 g, 61%). The structure was confirmed by LC MS and ^1H NMR analysis.

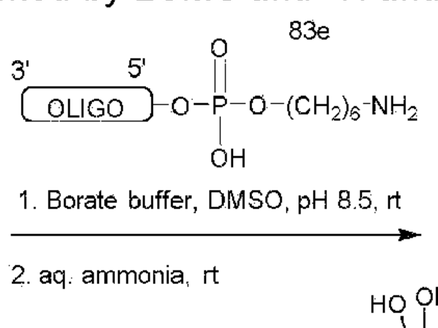




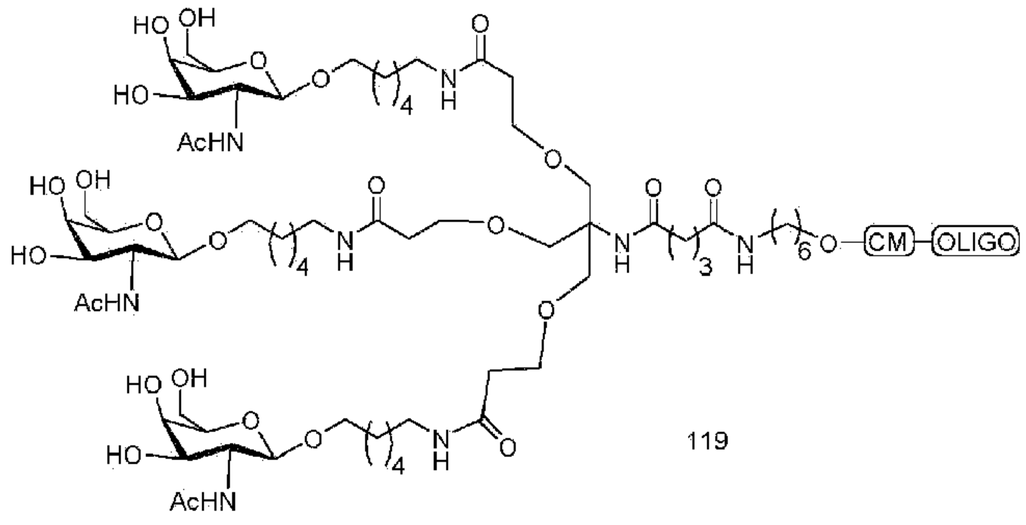
[0478] Compound 116 (0.74 g, 0.4 mmol) was dissolved in 1:1 methanol/ethyl acetate (5 mL/5 mL). Palladium on carbon (wet, 0.074 g) was added. The reaction mixture was flushed with hydrogen and stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite. The celite pad was washed with methanol/ethyl acetate (1:1). The filtrate and the washings were combined together and evaporated under reduced pressure to yield compound 117 (0.73 g, 98%). The structure was confirmed by LCMS and ^1H NMR analysis.

[0479] Compound 117 (0.63 g, 0.36 mmol) was dissolved in anhydrous DMF (3 mL). To this solution *N,N*-Diisopropylethylamine (70 µL, 0.4 mmol) and pentafluorophenyl trifluoroacetate (72 µL, 0.42 mmol) were added.

The reaction mixture was stirred at room temperature for 12 h and poured into a aqueous saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane, washed with brine and dried over anhydrous Na_2SO_4. The dichloromethane solution was concentrated to dryness and purified with silica gel column chromatography and eluted with 5 to 10 % MeOH in dichloromethane to yield compound 118 (0.51 g, 79%). The structure was confirmed by LCMS and ^1H and ^1H and ^{19}F NMR.



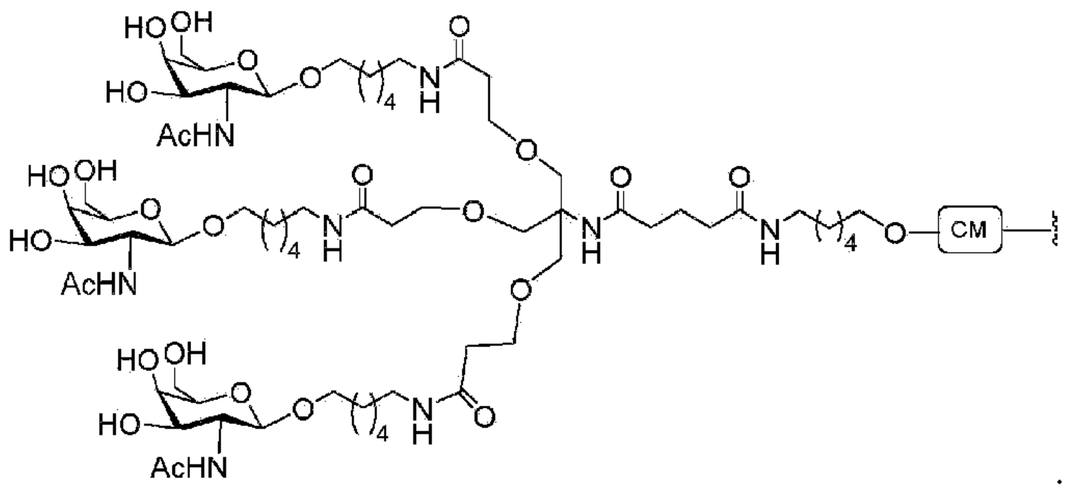
118



119

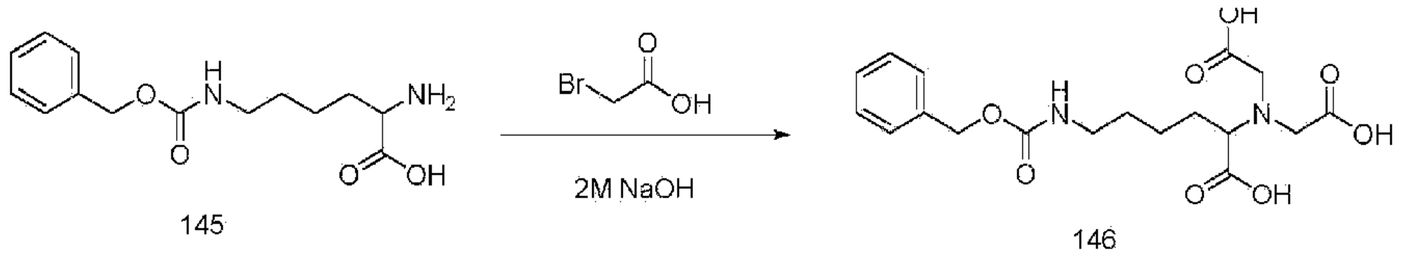
[0480] Oligomeric Compound 119, comprising a $GalNAc_3$-7 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-7 ($GalNAc_3$-7_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-.

[0481] The structure of $GalNAc_3$-7 ($GalNAc_3$-7_a-CM-) is shown below:



Example 51: Preparation of Oligonucleotide 155 Comprising $GalNAc_3$-6

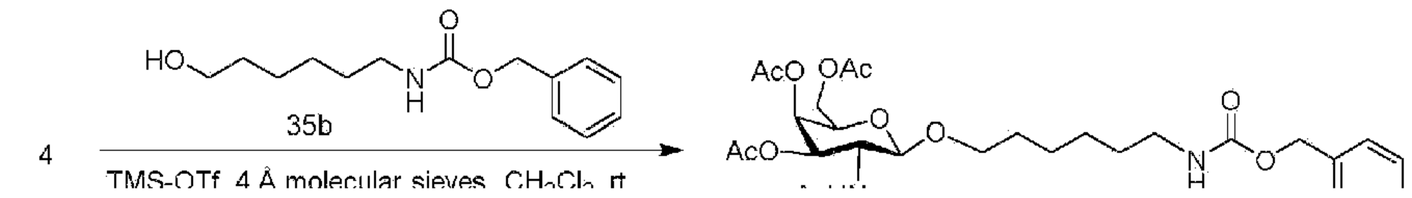
[0482]



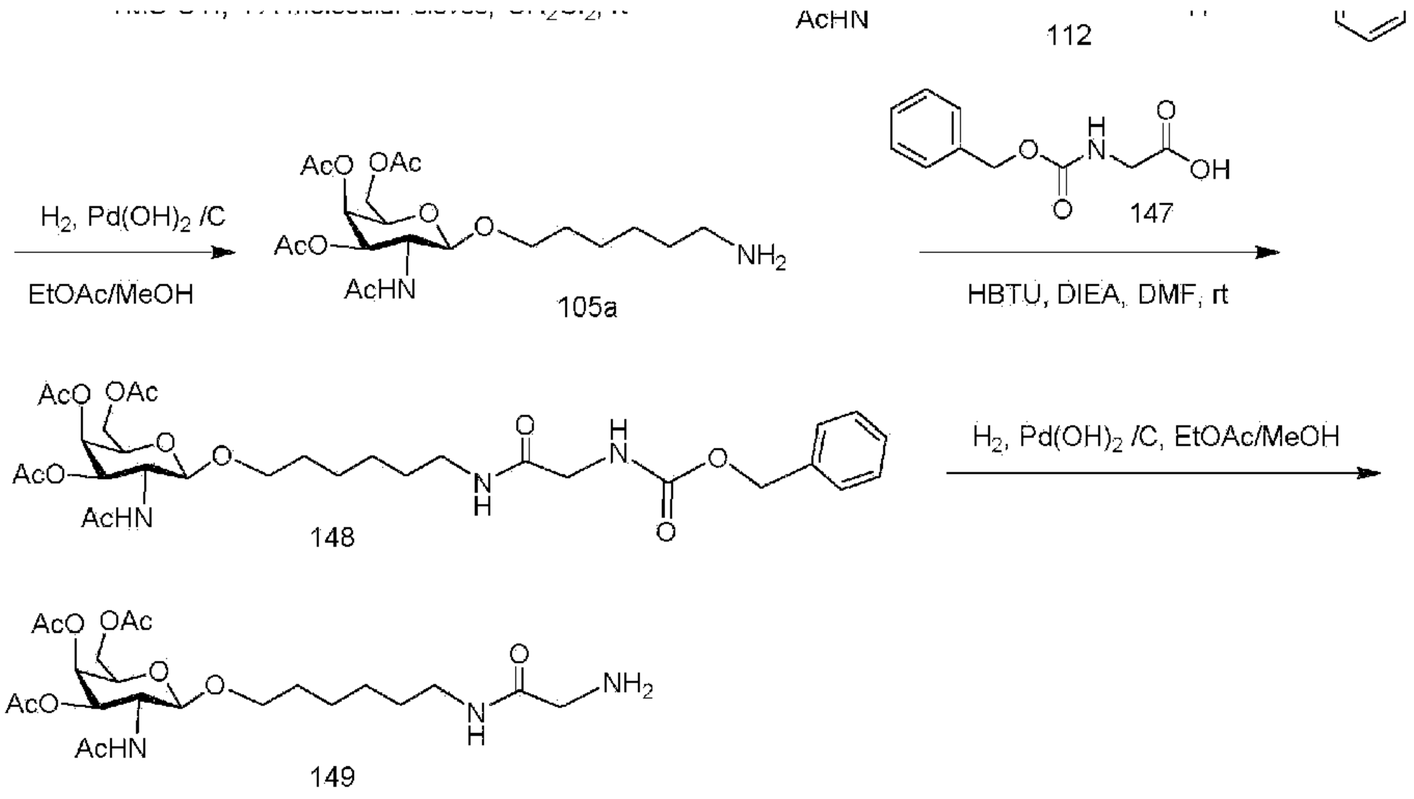
145

146

[0483] Compound 146 was synthesized as described in the literature (Analytical Biochemistry 1995, 229, 54-60).



4

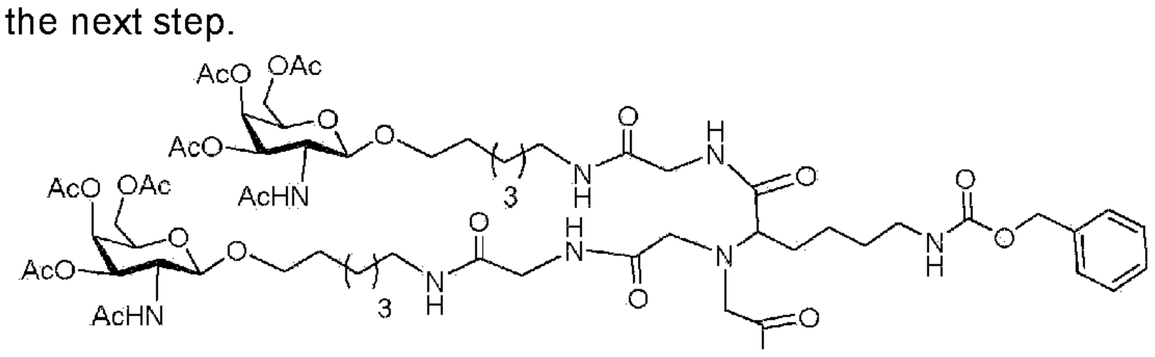


[0484] Compound **4** (15 g, **45.55** mmol) and compound 35b (**14.3** grams, 57 mmol) were dissolved in CH_2Cl_2 (200 ml). Activated molecular sieves (**4** Å. 2 g, powdered) were added, and the reaction was allowed to stir for 30 minutes under nitrogen atmosphere. TMS-OTf was added (**4**.1 ml, 22.77 mmol) and the reaction was allowed to stir at room temp overnight. Upon completion, the reaction was quenched by pouring into solution of saturated aqueous $NaHCO_3$ (500 ml) and crushed ice (~150 g). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and was concentrated to an orange oil under reduced pressure. The crude material was purified by silica gel column chromatography and eluted with 2-10 % MeOH in CH_2Cl_2 to yield Compound 112 (16.53 g, 63 %). LCMS and ^1H NMR were consistent with the expected compound.

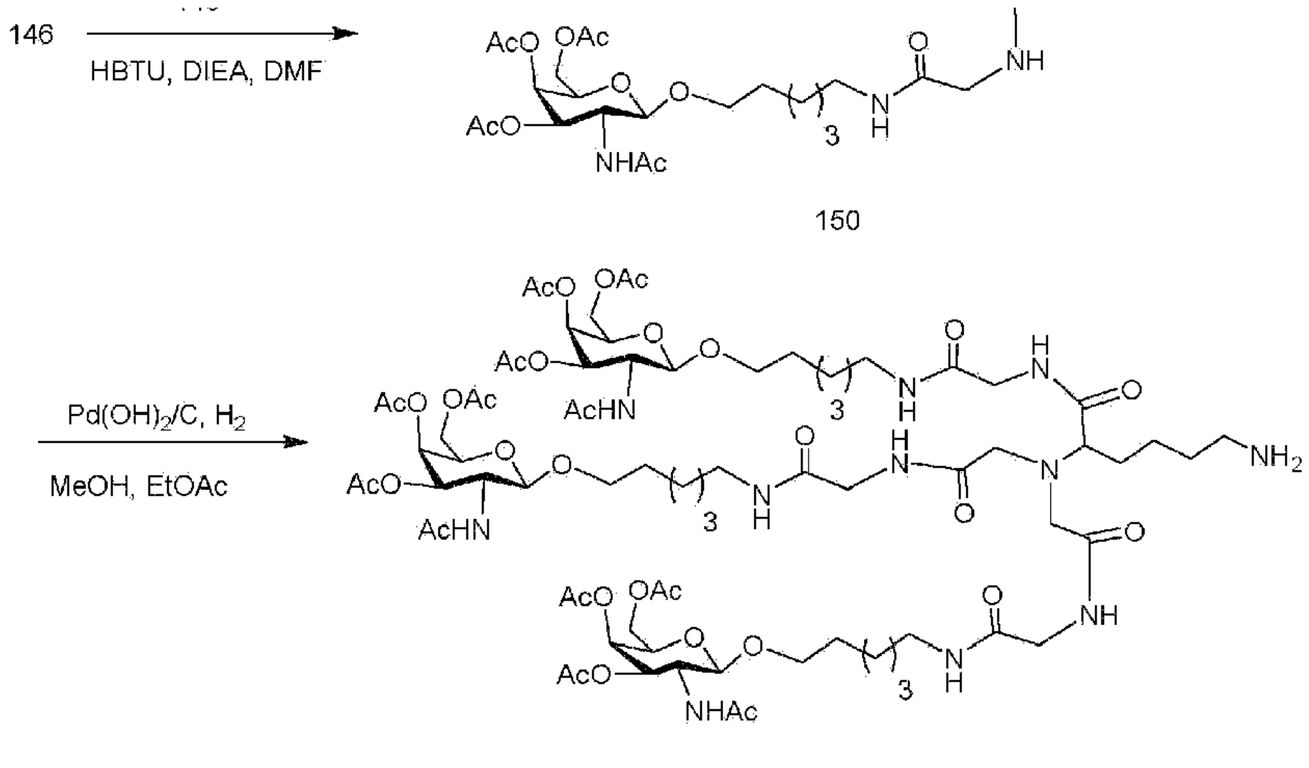
[0485] Compound 112 (**4**.27 g, 7.35 mmol) was dissolved in 1:1 MeOH/EtOAc (**40** ml). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon, **400** mg) was added, and hydrogen gas was bubbled through the solution for 30 minutes. Upon completion (TLC 10% MeOH in CH_2Cl_2, and LCMS), the catalyst was removed by filtration through a pad of celite. The filtrate was concentrated by rotary evaporation, and was dried briefly under high vacuum to yield Compound 105a (3.28 g). LCMS and 1H NMR were consistent with desired product.

[0486] Compound 147 (2.31 g, 11 mmol) was dissolved in anhydrous DMF (100 mL). *N,N*-Diisopropylethylamine (DIEA, 3.9 mL, 22 mmol) was added, followed by HBTU (**4** g, 10.5 mmol). The reaction mixture was allowed to stir for ~15 minutes under nitrogen. To this a solution of compound 105a (3.3 g, 7.**4** mmol) in dry DMF was added and stirred for 2 h under nitrogen atmosphere. The reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organics phase was separated, dried ($MgSO_4$), filtered, and concentrated to an orange syrup. The crude material was purified by column chromatography 2-5 % MeOH in CH_2Cl_2 to yield Compound 148 (3.**44** g, 73 %). LCMS and ^1H NMR were consistent with the expected product.

[0487] Compound 148 (3.3 g, 5.2 mmol) was dissolved in 1:1 MeOH/EtOAc (75 ml). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (350 mg). Hydrogen gas was bubbled through the solution for 30 minutes. Upon completion (TLC 10% MeOH in DCM, and LCMS), the catalyst was removed by filtration through a pad of celite. The filtrate was concentrated by rotary evaporation, and was dried briefly under high vacuum to yield Compound 149 (2.6 g). LCMS was consistent with desired product. The residue was dissolved in dry DMF (10 ml) was used immediately in the next step.



149

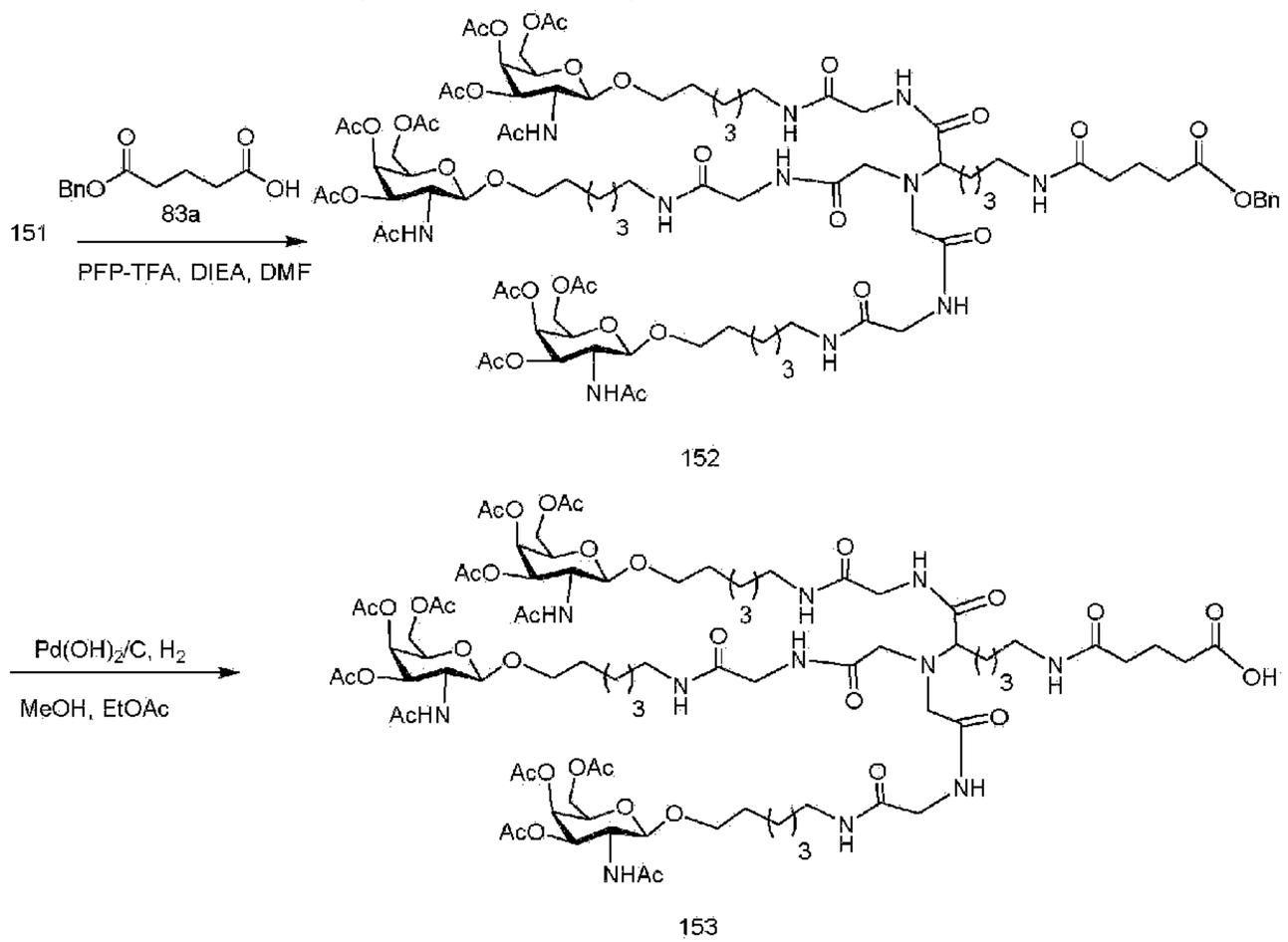


150

151

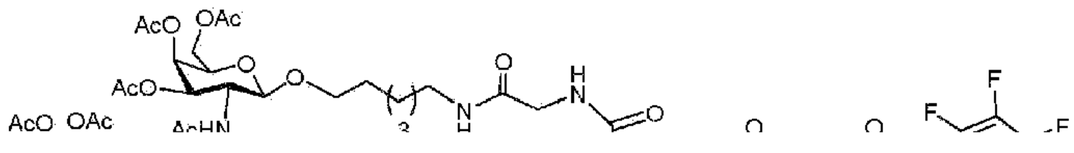
[0488] Compound 146 (0.68 g, 1.73 mmol) was dissolved in dry DMF (20 ml). To this DIEA (450 µL, 2.6 mmol, 1.5 eq.) and HBTU (1.96 g, 0.5.2 mmol) were added. The reaction mixture was allowed to stir for 15 minutes at room temperature under nitrogen. A solution of compound 149 (2.6 g) in anhydrous DMF (10 mL) was added. The pH of the reaction was adjusted to pH = 9-10 by addition of DIEA (if necessary). The reaction was allowed to stir at room temperature under nitrogen for 2 h. Upon completion the reaction was diluted with EtOAc (100 mL), and washed with aqueous saturated aqueous $NaHCO_3$, followed by brine. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography and eluted with 2-10 % MeOH in CH_2Cl_2 to yield Compound 150 (0.62 g, 20 %). LCMS and ^1H NMR were consistent with the desired product.

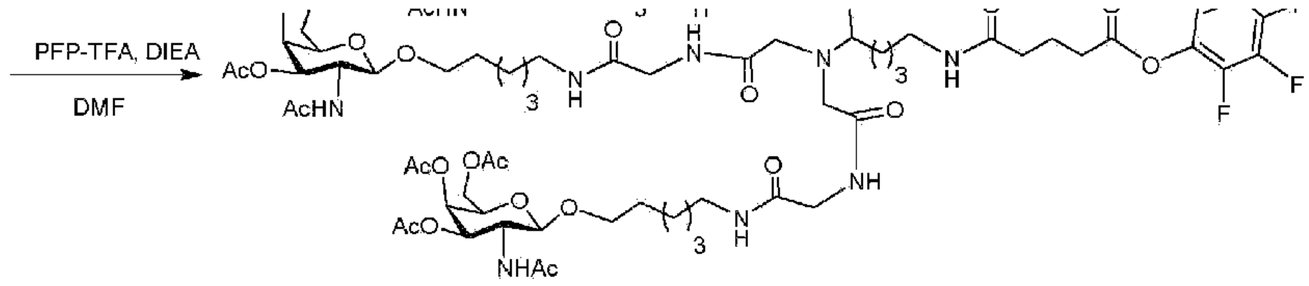
[0489] Compound 150 (0.62 g) was dissolved in 1:1 MeOH/ EtOAc (5 L). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (60 mg). Hydrogen gas was bubbled through the solution for 30 minutes. Upon completion (TLC 10% MeOH in DCM, and LCMS), the catalyst was removed by filtration (syringe-tip Teflon filter, 0.45 µm). The filtrate was concentrated by rotary evaporation, and was dried briefly under high vacuum to yield Compound 151 (0.57 g). The LCMS was consistent with the desired product. The product was dissolved in 4 mL dry DMF and was used immediately in the next step.



152

153



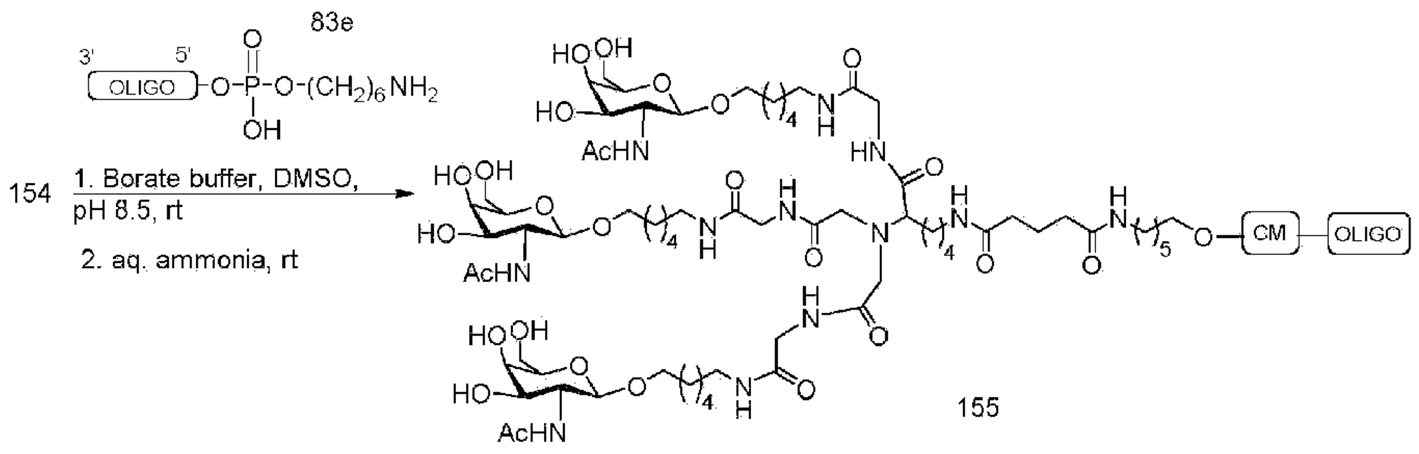


154

[0490] Compound 83a (0.11 g, 0.33 mmol) was dissolved in anhydrous DMF (5 mL) and *N,N*-Diisopropylethylamine (75 µL, 1 mmol) and PFP-TFA (90 µL, 0.76 mmol) were added. The reaction mixture turned magenta upon contact, and gradually turned orange over the next 30 minutes. Progress of reaction was monitored by TLC and LCMS. Upon completion (formation of the PFP ester), a solution of compound 151 (0.57 g, 0.33 mmol) in DMF was added. The pH of the reaction was adjusted to pH = 9-10 by addition of *N,N*-Diisopropylethylamine (if necessary). The reaction mixture was stirred under nitrogen for ~ 30 min. Upon completion, the majority of the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with aqueous saturated $NaHCO_3$, followed by brine. The organic phase separated, dried over $MgSO_4$, filtered, and concentrated to an orange syrup. The residue was purified by silica gel column chromatography (2-10 % MeOH in CH_2Cl_2) to yield Compound 152 (0.35 g, 55 %). LCMS and ^1H NMR were consistent with the desired product.

[0491] Compound 152 (0.35 g, 0.182 mmol) was dissolved in 1:1 MeOH/EtOAc (10 mL). The reaction mixture was purged by bubbling a stream of argon thru the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (35 mg). Hydrogen gas was bubbled thru the solution for 30 minutes. Upon completion (TLC 10% MeOH in DCM, and LCMS), the catalyst was removed by filtration (syringe-tip Teflon filter, 0.45 µm). The filtrate was concentrated by rotary evaporation, and was dried briefly under high vacuum to yield Compound 153 (0.33 g, quantitative). The LCMS was consistent with desired product.

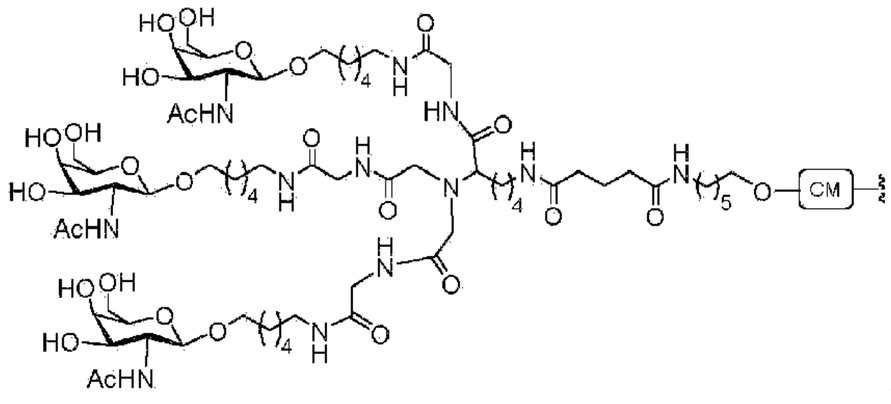
[0492] Compound 153 (0.33 g, 0.18 mmol) was dissolved in anhydrous DMF (5 mL) with stirring under nitrogen. To this *N,N*-Diisopropylethylamine (65 µL, 0.37 mmol) and PFP-TFA (35 µL, 0.28 mmol) were added. The reaction mixture was stirred under nitrogen for ~ 30 min. The reaction mixture turned magenta upon contact, and gradually turned orange. The pH of the reaction mixture was maintained at pH = 9-10 by adding more *N*,-Diisopropylethylamine. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the majority of the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL), and washed with saturated aqueous $NaHCO_3$, followed by brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to an orange syrup. The residue was purified by column chromatography and eluted with 2-10 % MeOH in CH_2Cl_2 to yield Compound 154 (0.29 g, 79 %). LCMS and ^1H NMR were consistent with the desired product.



155

[0493] Oligomeric Compound 155, comprising a $GalNAc_3$-6 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-6 ($GalNAc_3$-6_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-.

[0494] The structure of $GalNAc_3$-6 ($GalNAc_3$-6_a-CM-) is shown below:



Example 56: Dose-dependent study of oligonucleotides comprising either a 3' or 5'-conjugate group (comparison of $GalNAc_3$-1, 2, 3, 5, 6, 7 and 10) targeting SRB-1 *in vivo*

[0495] The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice. Unconjugated ISIS 353382 was included as a standard. Each of the various $GalNAc_3$ conjugate groups was attached at the 5' terminus of the respective oligonucleotide by a phosphodiester linked 2'-deoxyadenosine nucleoside (cleavable moiety) except for ISIS 655861 which had the $GalNAc_3$ conjugate group attached at the 3' terminus.

Table 42

Modified ASO targeting SRB-1				
ASO	Sequence (5' to 3')	Motif	**Conjugate**	SEQ ID No.
ISIS 353382 (parent)	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	no conjugate	143
ISIS 655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}\mathbf{A_{do}}$-$\mathbf{GalNAc_3\text{-}1_a}$	5/10/5	**$GalNAc_3$-1**	144
ISIS 664507	$\mathbf{GalNAc_3\text{-}2_{a\text{-}o}}\mathbf{A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-2**	145
ISIS 661161	$\mathbf{GalNAc_3\text{-}3_{a\text{-}o}}\mathbf{A_{do}}$ $G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-3**	145
ISIS 666224	$\mathbf{GalNAc_3\text{-}5_{a\text{-}o}}\mathbf{A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{cs}{}^{m}C_{cs}{}^{m}C_{cs}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-5**	145
ISIS 666961	$\mathbf{GalNAc_3\text{-}6_{a\text{-}o}}\mathbf{A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-6**	145
ISIS 666981	$\mathbf{GalNAc_3\text{-}7_{a\text{-}o}}\mathbf{A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-7**	145
ISIS 666881	$\mathbf{GalNAc_3\text{-}10_{a\text{-}o}}\mathbf{A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{cs}{}^{m}C_{cs}{}^{m}C_{cs}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-10**	145

[0496] Capital letters indicate the nucleobase for each nucleoside and ^{m}C indicates a 5-methyl cytosine. Subscripts: "e" indicates a 2'-MOE modified nucleoside; "d" indicates a P-D-2'-deoxyribonucleoside; "s" indicates a phosphorothioate internucleoside linkage (PS); "o" indicates a phosphodiester internucleoside linkage (PO); and "o'" indicates -O-P(=O)(OH)-. Conjugate groups are in bold.

[0497] The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9. The structure of GalNAc$_3$-2$_a$ was shown previously in Example 37. The structure of GalNAc$_3$-3$_a$ was shown previously in Example 39. The structure of GalNAc$_3$-5$_a$ was shown previously in Example 49. The structure of GalNAc$_3$-6$_a$ was shown previously in Example 51. The structure of GalNAc$_3$-7$_a$ was shown previously in Example 48. The structure of GalNAc$_3$-10$_a$ was shown previously in Example 46.

Treatment

[0498] Six week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 353382, 655861, 664507, 661161, 666224, 666961, 666981, 666881 or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration to determine the liver SRB-1 mRNA levels using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. The results below are presented as the average percent of SRB-1 mRNA levels for each treatment group, normalized to the saline control.

[0499] As illustrated in Table 43, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. Indeed, the conjugated antisense oligonucleotides showed substantial improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 353382). The 5' conjugated antisense oligonucleotides showed a slight increase in potency compared to the 3' conjugated antisense oligonucleotide.

Table 43

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	Conjugate
Saline	n/a	100.0	
353382	3	96.0	none
	10	73.1	
	30	36.1	
655861	0.5	99.4	**GalNac$_3$-1** (3')
	1.5	81.2	
	5	33.9	
	15	15.2	
664507	0.5	102.0	**GalNac$_3$-2** (5')
	1.5	73.2	
	5	31.3	
	15	10.8	
661161	0.5	90.7	**GalNac$_3$-3** (5')
	1.5	67.6	
	5	24.3	
	15	11.5	
666224	0.5	96.1	**GalNac$_3$-5** (5')
	1.5	61.6	
	5	25.6	

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	Conjugate
	15	11.7	
666961	0.5	85.5	**GalNAc$_3$-6** (5')
	1.5	56.3	
	5	34.2	
	15	13.1	
666981	0.5	84.7	**GalNAc$_3$-7** (5')
	1.5	59.9	
	5	24.9	
	15	8.5	
666881	0.5	100.0	**GalNAc$_3$-10** (5')
	1.5	65.8	
	5	26.0	
	15	13.0	

[0500] Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Total bilirubin and BUN were also evaluated. The change in body weights was evaluated with no significant change from the saline group. ALTs, ASTs, total bilirubin and BUN values are shown in Table **44** below.

Table 44

ISIS No.	Dosage mg/kg	ALT	AST	Total Bilirubin	BUN	Conjugate
Saline		26	57	0.2	27	
353382	3	25	92	0.2	27	none
	10	23	40	0.2	25	
	30	29	54	0.1	28	
655861	0.5	25	71	0.2	34	**GalNac$_3$-1** (3')
	1.5	28	60	0.2	26	
	5	26	63	0.2	28	
	15	25	61	0.2	28	
664507	0.5	25	62	0.2	25	**GalNac$_3$-2** (5')
	1.5	24	49	0.2	26	
	5	21	50	0.2	26	
	15	59	84	0.1	22	
661161	0.5	20	42	0.2	29	**GalNac$_3$-3** (5')
	1.5 g	37	74	0.2	25	
	5 g	28	61	0.2	29	
	15	21	41	0.2	25	
666224	0.5	34	48	0.2	21	**GalNac$_3$-5** (5')
	1.5	23	46	0.2	26	
	5	24	47	0.2	23	
	15	32	49	0.1	26	
	0.5	17	63	0.2	26	

ISIS No.	Dosage mg/kg	ALT	AST	Total Bilirubin	BUN	Conjugate
666961	1.5	23	68	0.2	26	**GalNAc$_3$-6** (5')
	5	25	66	0.2	26	
	15	29	107	0.2	28	
666981	0.5	24	48	0.2	26	**GalNAc$_3$-7** (5')
	1.5	30	55	0.2	24	
	5	46	74	0.1	24	
	15	29	58	0.1	26	
666881	0.5	20	65	0.2	27	**GalNAc$_3$-10** (5')
	1.5	23	59	0.2	24	
	5	45	70	0.2	26	
	15	21	57	0.2	24	

Example 80: Antisense inhibition *in vivo* by oligonucleotides targeting Alpha-1 Antitrypsin (A1AT) comprising a GalNAc$_3$ Conjugate

[0501] The oligonucleotides listed in Table 72 below were tested in a study for dose-dependent inhibition of A1AT in mice.

Table 72

Modified ASOs targeting A1AT

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No.
476366	$A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}$ $G_{es}G_{es}A_e$	n/a	n/a	152
656326	$A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}$ $G_{es}G_{es}A_{eo}\mathbf{A_{do}}$-**GalNAc$_3-1_a$**	GalNAc$_3$-1a	A_d	153
678381	**GalNAc$_3$-3$_a$-$_o$**$\mathbf{A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}$ $A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	GalNAc$_3$-3a	A_d	154
678382	**GalNAc$_3$-7$_a$-$_o$**$\mathbf{A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}$ $A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	GalNAc$_3$-7a	A_d	154
678383	**GalNAc$_3$-10$_a$-$_o$**$\mathbf{A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}$ $A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	GalNAc$_3$-10a	A_d	154
678384	**GalNAc$_3$-13$_a$-$_o$**$\mathbf{A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}$ $A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	GalNAc$_3$-13a	A_d	154

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9, GalNAc$_3$-3$_a$ was shown in Example 39, GalNAc$_3$-7$_a$ was shown in Example 48, GalNAc$_3$-10$_a$ was shown in Example 46, and GalNAc$_3$-13$_a$ was shown in Example 62.

Treatment

[0502] Six week old, male C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were each injected subcutaneously once per week at a dosage shown below, for a total of three doses, with an oligonucleotide listed in Table 72 or with PBS. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration. A1AT liver mRNA levels were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. A1AT plasma protein levels were determined using the Mouse Alpha 1-Antitrypsin ELISA (catalog # 41-A1AMS-E01, Alpco, Salem, NH). The results below are presented as the average percent of A1AT liver mRNA and plasma protein levels for each treatment group, normalized to the PBS control.

[0503] As illustrated in Table 73, treatment with antisense oligonucleotides lowered A1AT liver mRNA and A1AT plasma protein levels in a dose-dependent manner. The oligonucleotides comprising a GalNAc conjugate were significantly more potent than the parent (ISIS 476366).

Table 73

A1AT liver mRNA and plasma protein levels					
ISIS No.	Dosage (mg/kg)	A1AT liver mRNA (% PBS)	A1AT plasma protein (% PBS)	$GalNAc_3$ Cluster	CM
PBS	n/a	100	100	n/a	n/a
476366	5	86	78	n/a	n/a
	15	73	61		
	45	30	38		
656326	0.6	99	90	$GalNAc_3$-1a	A_d
	2	61	70		
	6	15	30		
	18	6	10		
678381	0.6	105	90	$GalNAc_3$-3a	A_d
	2	53	60		
	6	16	20		
	18	7	13		
678382	0.6	90	79	$GalNAc_3$-7a	A_d
	2	49	57		
	6	21	27		
	18	8	11		
678383	0.6	94	84	$GalNAc_3$-10a	A_d
	2	44	53		
	6	13	24		
	18	6	10		
678384	0.6	106	91	$GalNAc_3$-13a	A_d
	2	65	59		
	6	26	31		
	18	11	15		

[0504] Liver transaminase and BUN levels in plasma were measured at time of sacrifice using standard protocols. Body weights and organ weights were also measured. The results are shown in Table 74 below. Body weight is

shown as % relative to baseline. Organ weights are shown as % of body weight relative to the PBS control group.

Table 74

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	Body weight (% baseline)	Liver weight (Rel % BW)	Kidney weight (Rel % BW)	Spleen weight (Rel % BW)
PBS	n/a	25	51	37	119	100	100	100
476366	5	34	68	35	116	91	98	106
	15	37	74	30	122	92	101	128
	45	30	47	31	118	99	108	123
656326	0.6	29	57	40	123	100	103	119
	2	36	75	39	114	98	111	106
	6	32	67	39	125	99	97	122
	18	46	77	36	116	102	109	101
678381	0.6	26	57	32	117	93	109	110
	2	26	52	33	121	96	106	125
	6	40	78	32	124	92	106	126
	18	31	54	28	118	94	103	120
678382	0.6	26	42	35	114	100	103	103
	2	25	50	31	117	91	104	117
	6	30	79	29	117	89	102	107
	18	65	112	31	120	89	104	113
678383	0.6	30	67	38	121	91	100	123
	2	33	53	33	118	98	102	121
	6	32	63	32	117	97	105	105
	18	36	68	31	118	99	103	108
678384	0.6	36	63	31	118	98	103	98
	2	32	61	32	119	93	102	114
	6	34	69	34	122	100	100	96
	18	28	54	30	117	98	101	104

Example 81: Duration of action *in vivo* of oligonucleotides targeting A1AT comprising a $GalNAc_3$ cluster

The oligonucleotides listed in Table 72 were tested in a single dose study for duration of action in mice.

Treatment

[0505] Six week old, male C57BL/6 mice were each injected subcutaneously once with an oligonucleotide listed in Table 72 or with PBS. Each treatment group consisted of 4 animals. Blood was drawn the day before dosing to determine baseline and at 5, 12, 19, and 25 days following the dose. Plasma A1AT protein levels were measured via ELISA (see Example 80). The results below are presented as the average percent of plasma A1AT protein levels for each treatment group, normalized to baseline levels. The results show that the oligonucleotides comprising a GalNAc conjugate were more potent and had longer duration of action than the parent lacking a GalNAc conjugate (ISIS 476366). Furthermore, the oligonucleotides comprising a 5'-GalNAc conjugate (ISIS 678381, 678382, 678383, and 678384) were generally even more potent with even longer duration of action than the oligonucleotide comprising a 3'-GalNAc conjugate (ISIS 656326).

Table 75

Plasma A1AT protein levels in mice					
ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	A1AT (% baseline)	$GalNAc_3$ Cluster	CM
PBS	n/a	5	93	n/a	n/a
		12	93		
		19	90		
		25	97		
476366	100	5	38	n/a	n/a
		12	46		
		19	62		
		25	77		
656326	18	5	33	$GalNAc_3$-1a	A_d
		12	36		
		19	51		
		25	72		
678381	18	5	21	$GalNAc_3$-3a	A_d
		12	21		
		19	35		
		25	48		
678382	18	5	21	$GalNAc_3$-7a	A_d
		12	21		
		19	39		
		25	60		
678383	18	5	24	$GalNAc_3$-10a	A_d
		12	21		
		19	45		
		25	73		
678384	18	5	29	$GalNAc_3$-13a	A_d
		12	34		
		19	57		
		25	76		

Example 82: Antisense inhibition *in vitro* by oligonucleotides targeting SRB-1 comprising a $GalNAc_3$ conjugate

[0506] Primary mouse liver hepatocytes were seeded in 96 well plates at 15,000 cells/well 2 hours prior to treatment. The oligonucleotides listed in Table 76 were added at 2, 10, 50, or 250 nM in Williams E medium and cells were incubated overnight at 37 °C in 5% CO_2. Cells were lysed 16 hours following oligonucleotide addition, and total RNA was purified using RNease 3000 BioRobot (Qiagen). SRB-1 mRNA levels were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. IC_{50} values were determined using Prism 4 software (GraphPad). The results show that oligonucleotides comprising a variety of different GalNAc conjugate groups and a variety of different cleavable

moieties are significantly more potent in an *in vitro* free uptake experiment than the parent oligonucleotides lacking a GalNAc conjugate group (ISIS 353382 and 666841).

Table 76

Inhibition of SRB-1 expression *in vitro*						
ISIS No.	Sequence (5' to 3')	Linkages	GalNAc cluster	CM	IC_{50} (nM)	SEQ ID No.
353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	n/a	n/a	250	143
655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do}\text{-}GalNAc_3\text{-}1_a}$	PS	$GalNAc_3\text{-}1_a$	A_d	40	144
661161	$\mathbf{GalNAc_3\text{-}3_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}3_a$	A_d	40	145
661162	$\mathbf{GalNAc_3\text{-}3_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	PO/PS	$GalNAc_3\text{-}3_a$	A_d	8	145
664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do}\text{-}GalNAc_3\text{-}9_a}$	PS	$GalNAc_3\text{-}9_a$	A_d	20	144
665001	$\mathbf{GalNAc_3\text{-}8_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}8_a$	A_d	70	145
666224	$\mathbf{GalNAc_3\text{-}5_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}5_a$	A_d	80	145
666841	$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	PO/PS	n/a	n/a	>250	143
666881	$\mathbf{GalNAc_3\text{-}10_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}10_a$	A_d	30	145
666904	$\mathbf{GalNAc_3\text{-}3_a\text{-}_o\text{-}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}3_a$	PO	9	143
666924	$\mathbf{GalNAc_3\text{-}3_a\text{-}_o\text{-}T_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}3_a$	T_d	15	148
666961	$\mathbf{GalNAc_3\text{-}6_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}6_a$	A_d	150	145
666981	$\mathbf{GalNAc_3\text{-}7_a\text{-}_o\text{-}A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3\text{-}7_a$	A_d	20	145

Inhibition of SRB-1 expression *in vitro*						
ISIS No.	Sequence (5' to 3')	Linkages	GalNAc cluster	CM	IC_{50} (nM)	SEQ ID No.
670061	**$GalNAc_3$-13_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3$-13_a	A_d	30	145
670699	**$GalNAc_3$-3_a-$_o$,T_{d_o}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	PO/PS	$GalNAc_3$-3_a	T_d	15	148
670700	**$GalNAc_3$-3_a-$_o$,A_{e_o}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T$	PO/PS	$GalNAc_3$-3_a	A_e	30	145
670701	**$GalNAc_3$-3_a-$_o$,T_{e_o}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	PO/PS	$GalNAc_3$-3_a	T_e	25	148
671144	**$GalNAc_3$-12_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3$-12_a	A_d	40	145
671165	**$GalNAc_3$-13_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T$	PO/PS	$GalNAc_3$-13_a	A_d	8	145
671261	**$GalNAc_3$-14_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3$-14_a	A_d	>250	145
671262	**$GalNAc_3$-15_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3$-15_a	A_d	>250	145
673501	**$GalNAc_3$-7_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	PO/PS	$GalNAc_3$-7_a	A_d	30	145
673502	**$GalNAc_3$-10_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	PO/PS	$GalNAc_3$-10_a	A_d	8	145
675441	**$GalNAc_3$-17_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3$-17_a	A_d	30	145
675442	**$GalNAc_3$-18_a-$_o$,A_{d_o}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	$GalNAc_3$-18_a	A_d	20	145
677841	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}$ $^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{d_o}$-$GalNAc_3$-$19_a$**	PS	$GalNAc_3$-19_a	A_d	40	144

Inhibition of SRB-1 expression *in vitro*						
ISIS No.	Sequence (5' to 3')	Linkages	GalNAc cluster	CM	IC_{50} (nM)	SEQ ID No.
677842	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}$ $^{m}C_{ds}T_{ds}T_{cs}{}^{m}C_{cs}{}^{m}C_{cs}T_{cs}T_{co}\mathbf{A_{do'}}$-**GalNAc$_3-20_a$**	PS	GalNAc$_3$-20$_a$	A_d	30	144
677843	**GalNAc$_3$-23$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	GalNAc$_3$-23$_a$	A_d	40	145

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9, GalNAc$_3$-3$_a$ was shown in Example 39, GalNAc$_3$-5$_a$ was shown in Example 49, GalNAc$_3$-6$_a$ was shown in Example 51, GalNAc$_3$-7$_a$ was shown in Example 48, GalNAc$_3$-8$_a$ was shown in Example 47, GalNAc$_3$-9$_a$ was shown in Example 52, GalNAc$_3$-10$_a$ was shown in Example 46, GalNAc$_3$-12$_a$ was shown in Example 61, GalNAc$_3$-13a was shown in Example 62, GalNAc$_3$-14$_a$ was shown in Example 63, GalNAc$_3$-15$_a$ was shown in Example 64, GalNAc$_3$-17$_a$ was shown in Example 68, GalNAc$_3$-18$_a$ was shown in Example 69, GalNAc$_3$-19$_a$ was shown in Example 70, GalNAc$_3$-20$_a$ was shown in Example 71, and GalNAc$_3$-23$_a$ was shown in Example 76.

Example 83: Antisense inhibition *in vivo* by oligonucleotides targeting Factor XI comprising a GalNAc$_3$ cluster

[0507] The oligonucleotides listed in Table 77 below were tested in a study for dose-dependent inhibition of Factor XI in mice.

Table 77

Modified oligonucleotides targeting Factor XI				
ISIS No.	Sequence (5' to 3')	GalNAc cluster	CM	SEQ ID No.
404071	$T_{os}G_{cs}G_{cs}T_{cs}A_{cs}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{cs}G_{es}$ $A_{es}G_{es}G_{e}$	n/a	n/a	146
656173	$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}$ $A_{es}G_{es}G_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-1_a$**	GalNAc$_3$-1$_a$	A_d	147
663086	**GalNAc$_3$-3$_{a\text{-}o'}$A$_{do}$**$T_{cs}G_{co}G_{co}T_{co}A_{co}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	GalNAc$_3$-3$_a$	A_d	155
678347	**GalNAc$_3$-7$_{a\text{-}o'}$A$_{do}$**$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{ds}{}^{m}C_{ds}A_{co}G_{co}A_{cs}G_{cs}G_{c}$	GalNAc$_3$-7 $_a$	A_d	155
678348	**GalNAc$_3$-10$_{a\text{-}o'}$A$_{do}$**$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	GalNAc$_3$-10$_a$	A_d	155
678349	**GalNAc$_3$-13$_{a\text{-}o'}$A$_{do}$**$T_{cs}G_{co}G_{co}T_{co}A_{co}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{co}G_{co}A_{cs}G_{cs}G_{c}$	GalNAc$_3$-13$_a$	A_d	155

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9, GalNAc$_3$-3$_a$ was shown in Example 39, GalNAc$_3$-7$_a$ was shown in Example 48, GalNAc$_3$-10$_a$ was shown in Example 46, and GalNAc$_3$-13$_a$ was shown in Example

62.

Treatment

[0508] Six to eight week old mice were each injected subcutaneously once per week at a dosage shown below, for a total of three doses, with an oligonucleotide listed below or with PBS. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final dose. Factor XI liver mRNA levels were measured using real-time PCR and normalized to cyclophilin according to standard protocols. Liver transaminases, BUN, and bilirubin were also measured. The results below are presented as the average percent for each treatment group, normalized to the PBS control.

[0509] As illustrated in Table 78, treatment with antisense oligonucleotides lowered Factor XI liver mRNA in a dose-dependent manner. The results show that the oligonucleotides comprising a GalNAc conjugate were more potent than the parent lacking a GalNAc conjugate (ISIS 404071). Furthermore, the oligonucleotides comprising a 5'-GalNAc conjugate (ISIS 663086, 678347, 678348, and 678349) were even more potent than the oligonucleotide comprising a 3'-GalNAc conjugate (ISIS 656173).

Table 78

Factor XI liver mRNA, liver transaminase, BUN, and bilirubin levels

ISIS No.	Dosage (mg/kg)	Factor XI mRNA (% PBS)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	Bilirubin (mg/dL)	$GalNAc_3$ Cluster	SEQ ID No.
PBS	n/a	100	63	70	21	0.18	n/a	n/a
404071	3	65	41	58	21	0.15	n/a	146
	10	33	49	53	23	0.15		
	30	17	43	57	22	0.14		
656173	0.7	43	90	89	21	0.16	$GalNAc_3$-1a	147
	2	9	36	58	26	0.17		
	6	3	50	63	25	0.15		
663086	0.7	33	91	169	25	0.16	$GalNAc_3$-3a	155
	2	7	38	55	21	0.16		
	6	1	34	40	23	0.14		
678347	0.7	35	28	49	20	0.14	$GalNAc_3$-7a	155
	2	10	180	149	21	0.18		
	6	1	44	76	19	0.15		
678348	0.7	39	43	54	21	0.16	$GalNAc_3$-10a	155
	2	5	38	55	22	0.17		
	6	2	25	38	20	0.14		
678349	0.7	34	39	46	20	0.16	$GalNAc_3$-13a	155
	2	8	43	63	21	0.14		
	6	2	28	41	20	0.14		

Example 84: Duration of action *in vivo* of oligonucleotides targeting Factor XI comprising a $GalNAc_3$ Conjugate

[0510] The oligonucleotides listed in Table 77 were tested in a single dose study for duration of action in mice.

Treatment

[0511] Six to eight week old mice were each injected subcutaneously once with an oligonucleotide listed in Table 77 or with PBS. Each treatment group consisted of 4 animals. Blood was drawn by tail bleeds the day before dosing to determine baseline and at 3, 10, and 17 days following the dose. Plasma Factor XI protein levels were measured by ELISA using Factor XI capture and biotinylated detection antibodies from R & D Systems, Minneapolis, MN (catalog # AF2460 and # BAF2460, respectively) and the OptEIA Reagent Set B (Catalog # 550534, BD Biosciences, San Jose, CA). The results below are presented as the average percent of plasma Factor XI protein levels for each treatment group, normalized to baseline levels. The results show that the oligonucleotides comprising a GalNAc conjugate were more potent with longer duration of action than the parent lacking a GalNAc conjugate (ISIS 404071). Furthermore, the oligonucleotides comprising a 5'-GalNAc conjugate (ISIS 663086, 678347, 678348, and 678349) were even more potent with an even longer duration of action than the oligonucleotide comprising a 3'-GalNAc conjugate (ISIS 656173).

Table 79

Plasma Factor XI protein levels in mice						
ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	Factor XI (% baseline)	$GalNAc_3$ Cluster	CM	SEQ ID No.
PBS	n/a	3	123	n/a	n/a	n/a
		10	56			
		17	100			
404071	30	3	11	n/a	n/a	146
		10	47			
		17	52			
656173	6	3	1	$GalNAc_3$-1a	A_d	147
		10	3			
		17	21			
663086	6	3	1	$GalNAc_3$-3a	A_d	155
		10	2			
		17	9			
678347	6	3	1	$GalNAc_3$-7a	A_d	155
		10	1			
		17	8			
678348	6	3	1	$GalNAc_3$-10a	A_d	155
		10	1			
		17	6			
678349	6	3	1	$GalNAc_3$-13a	A_d	155
		10	1			
		17	5			

Example 89: Antisense inhibition *in vivo* by oligonucleotides targeting Apolipoprotein A (Apo(a)) comprising a $GalNAc_3$ conjugate

[0512] The oligonucleotides listed in Table 92 below were tested in a study for dose-dependent inhibition of Apo(a)

in transgenic mice.

Table 92

Modified ASOs targeting Apo(a)				
ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
494372	$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}$ $T_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	n/a	n/a	58
681257	**$GalNAc_3$-7_a-$_o$**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7a	PO	58

The structure of $GalNAc_3$-7_a was shown in Example 48.

Treatment

[0513] Eight week old, female C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were each injected subcutaneously once per week at a dosage shown below, for a total of six doses, with an oligonucleotide listed in Table 92 or with PBS. Each treatment group consisted of 3-4 animals. Tail bleeds were performed the day before the first dose and weekly following each dose to determine plasma Apo(a) protein levels. The mice were sacrificed two days following the final administration. Apo(a) liver mRNA levels were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. Apo(a) plasma protein levels were determined using ELISA, and liver transaminase levels were determined. The mRNA and plasma protein results in Table 93 are presented as the treatment group average percent relative to the PBS treated group. Plasma protein levels were further normalized to the baseline (BL) value for the PBS group. Average absolute transaminase levels and body weights (% relative to baseline averages) are reported in Table 94.

[0514] As illustrated in Table 93, treatment with the oligonucleotides lowered Apo(a) liver mRNA and plasma protein levels in a dose-dependent manner. Furthermore, the oligonucleotide comprising the GalNAc conjugate was significantly more potent with a longer duration of action than the parent oligonucleotide lacking a GalNAc conjugate. As illustrated in Table 94, transaminase levels and body weights were unaffected by the oligonucleotides, indicating that the oligonucleotides were well tolerated.

Table 93

Apo(a) liver mRNA and plasma protein levels									
ISIS No.	Dosage (mg/kg)	Apo(a) mRNA (% PBS)	Apo(a) plasma protein (% PBS)						
			BL	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
PBS	n/a	100	100	120	119	113	88	121	97
494372	3	80	84	89	91	98	87	87	79
	10	30	87	72	76	71	57	59	46
	30	5	92	54	28	10	7	9	7
681257	0.3	75	79	76	89	98	71	94	78
	1	19	79	88	66	60	54	32	24
	3	2	82	52	17	7	4	6	5
	10	2	79	17	6	3	2	4	5

Table 94

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Body weight (% baseline)
PBS	n/a	37	54	103
494372	3	28	68	106
	10	22	55	102
	30	19	48	103
681257	0.3	30	80	104
	1	26	47	105
	3	29	62	102
	10	21	52	107

Example 93: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising mixed wings and a 5'-GalNAc$_3$ conjugate

[0515] The oligonucleotides listed in Table 100 were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Table 100

Modified ASOs targeting SRB-1				
ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No.
449093	$T_{ks}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}\ A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	n/a	n/a	165
699806	**GalNAc$_3$-3$_a$-$_o$**,$T_{ks}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	GalNAc$_3$-3a	PO	165
699807	**GalNAc$_3$-7$_a$-$_o$**,$T_{ks}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	GalNAc$_3$-7a	PO	165
699809	**GalNAc$_3$-7$_a$-$_o$**, $T_{ks}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}\ A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{e}$	GalNAc$_3$-7a	PO	165
699811	**GalNAc$_3$-7$_a$-$_o$**,$T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	GalNAc$_3$-7a	PO	165
699813	**GalNAc$_3$-7$_a$-$_o$**,$T_{ks}T_{ds}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ds}{}^{m}C_{k}$	GalNAc$_3$-7a	PO	165
699815	**GalNAc$_3$-7$_a$-$_o$**,$T_{es}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}\ A_{ds}T_{ds}\ G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{e}$	GalNAc$_3$-7a	PO	165

The structure of GalNAc$_3$-3$_a$ was shown previously in Example 39, and the structure of GalNAc$_3$-7a was shown previously in Example 48. Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "k" indicates 6'-*(S)*-CH$_3$ bicyclic nucleoside (cEt); "s" indicates phosphorothioate internucleoside linkages (PS); "o" indicates phosphodiester internucleoside linkages (PO). Supersript "m" indicates

5-methylcytosines.

Treatment

[0516] Six to eight week old C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with an oligonucleotide listed in Table 100 or with saline. Each treatment group consisted of **4** animals. The mice were sacrificed 72 hours following the final administration. Liver SRB-1 mRNA levels were measured using real-time PCR. SRB-1 mRNA levels were normalized to cyclophilin mRNA levels according to standard protocols. The results are presented as the average percent of SRB-1 mRNA levels for each treatment group relative to the saline control group. As illustrated in Table 101, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner, and the gapmer oligonucleotides comprising a GalNAc conjugate and having wings that were either full cEt or mixed sugar modifications were significantly more potent than the parent oligonucleotide lacking a conjugate and comprising full cEt modified wings.

[0517] Body weights, liver transaminases, total bilirubin, and BUN were also measured, and the average values for each treatment group are shown in Table 101. Body weight is shown as the average percent body weight relative to the baseline body weight (% BL) measured just prior to the oligonucleotide dose.

Table 101

SRB-1 mRNA, ALT, AST, BUN, and total bilirubin levels and body weights

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% PBS)	ALT (U/L)	AST (U/L)	Bil	BUN	Body weight (% BL)
PBS	n/a	100	31	84	0.15	28	102
449093	1	111	18	48	0.17	31	104
	3	94	20	43	0.15	26	103
	10	36	19	50	0.12	29	104
699806	0.1	114	23	58	0.13	26	107
	0.3	59	21	45	0.12	27	108
	1	25	30	61	0.12	30	104
699807	0.1	121	19	41	0.14	25	100
	0.3	73	23	56	0.13	26	105
	1	24	22	69	0.14	25	102
699809	0.1	125	23	57	0.14	26	104
	0.3	70	20	49	0.10	25	105
	1	33	34	62	0.17	25	107
699811	0.1	123	48	77	0.14	24	106
	0.3	94	20	45	0.13	25	101
	1	66	57	104	0.14	24	107
699813	0.1	95	20	58	0.13	28	104
	0.3	98	22	61	0.17	28	105
	1	49	19	47	0.11	27	106
699815	0.1	93	30	79	0.17	25	105
	0.3	64	30	61	0.12	26	105
	1	24	18	41	0.14	25	106

Example 95: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising bicyclic

nucleosides and a 5'-GalNAc$_3$ conjugate

[0518] The oligonucleotides listed in Table 104 were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Table 104

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No
440762	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	n/a	n/a	137
666905	**GalNAc$_3$-3$_{a}$-o'**$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	GalNAc$_3$-3$_a$	PO	137
699782	**GalNAc$_3$-7$_{a}$-o'**$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	GalNAc$_3$-7$_a$	PO	137
699783	**GalNAC$_3$-3$_{a}$-o'**$T_{ls}{}^{m}C_{ls}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ls}{}^{m}C_{l}$	GalNAc$_3$-3$_a$	PO	137
653621	$T_{ls}{}^{m}C_{ls}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ls}{}^{m}C_{lo}$**A$_{do}$'-GalNAc$_3-1_a$**	GalNAc$_3$-1$_a$	A$_d$	138
439879	$T_{gs}{}^{m}C_{gs}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{d}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{gs}{}^{m}C_{g}$	n/a	n/a	137
699789	**GalNA$_{C3}$-3$_{a}$-o'**$T_{gs}{}^{m}C_{gs}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{d}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{gs}{}^{m}C_{g}$	GalNAc$_3$-3$_a$	PO	137

[0519] Subscript "g" indicates a fluoro-HNA nucleoside, subscript "1" indicates a locked nucleoside comprising a 2'-O-CH_2-**4'** bridge. See the Example 7**4** table legend for other abbreviations. The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9, the structure of GalNAc$_3$-3$_a$ was shown previously in Example 39, and the structure of GalNAc$_3$-7a was shown previously in Example **48**.

Treatment

[0520] The study was completed using the protocol described in Example 93. Results are shown in Table 105 below and show that oligonucleotides comprising a GalNAc conjugate and various bicyclic nucleoside modifications were significantly more potent than the parent oligonucleotide lacking a conjugate and comprising bicyclic nucleoside modifications. Furthermore, the oligonucleotide comprising a GalNAc conjugate and fluoro-HNA modifications was significantly more potent than the parent lacking a conjugate and comprising fluoro-HNA modifications. The results of the body weights, liver transaminases, total bilirubin, and BUN measurements indicated that the compounds were all well tolerated.

Table 105

SRB-1 mRNA, ALT, AST, BUN and total bilirubin levels and body weights

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% PBS)
PBS	n/a	100
440762	1	104
	3	65
	10	35
666905	0.1	105
	0.3	56
	1	18

SRB-1 mRNA, ALT, AST, BUN and total bilirubin levels and body weights		
ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% PBS)
699782	0.1	93
	0.3	63
	1	15
699783	0.1	105
	0.3	53
	1	12
653621	0.1	109
	0.3	82
	1	27
439879	1	96
	3	77
	10	37
699789	0.1	82
	0.3	69
	1	26

Example 96: Plasma protein binding of antisense oligonucleotides comprising a $GalNAc_3$ conjugate group

[0521] Oligonucleotides listed in Table 70 targeting ApoC-III and oligonucleotides in Table 106 targeting Apo(a) were tested in an ultra-filtration assay in order to assess plasma protein binding.

Table 106

Modified oligonucleotides targeting Apo(a)				
ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No
494372	$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{es}G_{es}T_{es}$ $T_{es}{}^{m}C_{e}$	n/a	n/a	58
693401	$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}$ $T_{es}{}^{m}C_{e}$	n/a	n/a	58
681251	**$GalNAc_3$-7_a-$_o$**$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}$ $T_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7_a	PO	58
681257	**$GalNAc_3$-7_a-$_o$**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}$ $T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7_a	PO	58

See the Example 74 for table legend. The structure of $GalNAc_3$-7a was shown previously in Example 48.

[0522] Ultrafree-MC ultrafiltration units (30,000 NMWL, low-binding regenerated cellulose membrane, Millipore, Bedford, MA) were pre-conditioned with 300 µL of 0.5% Tween 80 and centrifuged at 2000 g for 10 minutes, then with 300µL of a 300 µg/mL solution of a control oligonucleotide in H_2O and centrifuged at 2000 g for 16 minutes. In order to assess non-specific binding to the filters of each test oligonucleotide from Tables 70 and 106 to be used in

the studies, 300 µL of a 250 ng/mL solution of oligonucleotide in H_2O at pH 7.4 was placed in the pre-conditioned filters and centrifuged at 2000 g for 16 minutes. The unfiltered and filtered samples were analyzed by an ELISA assay to determine the oligonucleotide concentrations. Three replicates were used to obtain an average concentration for each sample. The average concentration of the filtered sample relative to the unfiltered sample is used to determine the percent of oligonucleotide that is recovered through the filter in the absence of plasma (% recovery).

[0523] Frozen whole plasma samples collected in K3-EDTA from normal, drug-free human volunteers, cynomolgus monkeys, and CD-1 mice, were purchased from Bioreclamation LLC (Westbury, NY). The test oligonucleotides were added to 1.2 mL aliquots of plasma at two concentrations (5 and 150 µg/mL). An aliquot (300 µL) of each spiked plasma sample was placed in a pre-conditioned filter unit and incubated at 37°C for 30 minutes, immediately followed by centrifugation at 2000 g for 16 minutes. Aliquots of filtered and unfiltered spiked plasma samples were analyzed by an ELISA to determine the oligonucleotide concentration in each sample. Three replicates per concentration were used to determine the average percentage of bound and unbound oligonucleotide in each sample. The average concentration of the filtered sample relative to the concentration of the unfiltered sample is used to determine the percent of oligonucleotide in the plasma that is not bound to plasma proteins (% unbound). The final unbound oligonucleotide values are corrected for non-specific binding by dividing the % unbound by the % recovery for each oligonucleotide. The final % bound oligonucleotide values are determined by subtracting the final % unbound values from 100. The results are shown in Table 107 for the two concentrations of oligonucleotide tested (5 and 150 µg/mL) in each species of plasma. The results show that GalNAc conjugate groups do not have a significant impact on plasma protein binding. Furthermore, oligonucleotides with full PS internucleoside linkages and mixed PO/PS linkages both bind plasma proteins, and those with full PS linkages bind plasma proteins to a somewhat greater extent than those with mixed PO/PS linkages.

Table 107

Percent of modified oligonucleotide bound to plasma proteins						
ISIS No.	Human plasma		Monkey plasma		Mouse plasma	
	5 µg/mL	150 µg/mL	5 µg/mL	150 µg/mL	5 µg/mL	150 µg/mL
304801	99.2	98.0	99.8	99.5	98.1	97.2
663083	97.8	90.9	99.3	99.3	96.5	93.0
674450	96.2	97.0	98.6	94.4	94.6	89.3
494372	94.1	89.3	98.9	97.5	97.2	93.6
693401	93.6	89.9	96.7	92.0	94.6	90.2
681251	95.4	93.9	99.1	98.2	97.8	96.1
681257	93.4	90.5	97.6	93.7	95.6	92.7

Example 98: Evaluation of pro-inflammatory effects of oligonucleotides comprising a GalNAc conjugate in hPMBC assay

[0524] The oligonucleotides listed in Table 109 and were tested for pro-inflammatory effects in an hPMBC assay as described in Examples 23 and 24. (See Tables 30, 83, 95, and 108 for descriptions of the oligonucleotides.) ISIS 353512 is a high responder used as a positive control, and the other oligonucleotides are described in Tables 83, 95, and 108. The results shown in Table 109 were obtained using blood from one volunteer donor. The results show that the oligonucleotides comprising mixed PO/PS internucleoside linkages produced significantly lower pro-inflammatory responses compared to the same oligonucleotides having full PS linkages. Furthermore, the GalNAc conjugate group did not have a significant effect in this assay.

Table 109

ISIS No.	E_{max}/EC_{50}	$GalNAc_3$ cluster	Linkages	CM
353512	3630	n/a	PS	n/a
420915	802	n/a	PS	n/a
682881	1311	$GalNAc_3$-10	PS	A_d
682888	0.26	$GalNAc_3$-10	PO/PS	A_d
684057	1.03	$GalNAc_3$-19	PO/PS	A_d

Example 99: Binding affinities of oligonucleotides comprising a GalNAc conjugate for the asialoglycoprotein receptor

[0525] The binding affinities of the oligonucleotides listed in Table 110 (see Table 76 for descriptions of the oligonucleotides) for the asialoglycoprotein receptor were tested in a competitive receptor binding assay. The competitor ligand, α1-acid glycoprotein (AGP), was incubated in 50 mM sodium acetate buffer (pH 5) with 1 U neuraminidase-agarose for 16 hours at 37°C, and > 90% desialylation was confirmed by either sialic acid assay or size exclusion chromatography (SEC). Iodine monochloride was used to iodinate the AGP according to the procedure by Atsma et al. (*see* J Lipid Res. 1991 Jan; 32(1):173-81.) In this method, desialylated α1-acid glycoprotein (de-AGP) was added to 10 mM iodine chloride, $Na^{125}I$, and 1 M glycine in 0.25 M NaOH. After incubation for 10 minutes at room temperature, ^{125}I -labeled de-AGP was separated from free ^{125}I by concentrating the mixture twice utilizing a 3 KDMWCO spin column. The protein was tested for labeling efficiency and purity on a HPLC system equipped with an Agilent SEC-3 column (7.8x300mm) and a β-RAM counter. Competition experiments utilizing ^{125}I -labeled de-AGP and various GalNAc-cluster containing ASOs were performed as follows. Human HepG2 cells (10^6 cells/ml) were plated on 6-well plates in 2 ml of appropriate growth media. MEM media supplemented with 10% fetal bovine serum (FBS), 2 mM L-Glutamine and 10mM HEPES was used. Cells were incubated 16-20 hours @ 37°C with 5% and 10% CO_2 respectively. Cells were washed with media without FBS prior to the experiment. Cells were incubated for 30 min @37°C with 1ml competition mix containing appropriate growth media with 2% FBS, 10^{-8} M ^{125}I -labeled de-AGP and GalNAc-cluster containing ASOs at concentrations ranging from 10^{-11} to 10^{-5} M. Non-specific binding was determined in the presence of 10^{-2} M GalNAc sugar. Cells were washed twice with media without FBS to remove unbound ^{125}I -labeled de-AGP and competitor GalNAc ASO. Cells were lysed using Qiagen's RLT buffer containing 1% β-mercaptoethanol. Lysates were transferred to round bottom assay tubes after a brief 10 min freeze/thaw cycle and assayed on a γ-counter. Non-specific binding was subtracted before dividing ^{125}I protein counts by the value of the lowest GalNAc-ASO concentration counts. The inhibition curves were fitted according to a single site competition binding equation using a nonlinear regression algorithm to calculate the binding affinities (K_D's).

[0526] The results in Table 110 were obtained from experiments performed on five different days. Results for oligonucleotides marked with superscript "a" are the average of experiments run on two different days. The results show that the oligonucleotides comprising a GalNAc conjugate group on the 5'-end bound the asialoglycoprotein receptor on human HepG2 cells with 1.5 to 16-fold greater affinity than the oligonucleotides comprising a GalNAc conjugate group on the 3'-end.

Table 110

Asialoglycoprotein receptor binding assay results			
ISIS No.	GalNAc conjugate	Oligonucleotide end to which GalNAc conjugate is attached	K_D (nM)
661161[a]	$GalNAc_3$-3	5'	3.7
666881[a]	$GalNAc_3$-10	5'	7.6

Asialoglycoprotein receptor binding assay results			
ISIS No.	GalNAc conjugate	Oligonucleotide end to which GalNAc conjugate is attached	K_D (nM)
666981	$GalNAc_3$-7	5'	6.0
670061	$GalNAc_3$-13	5'	7.4
655861[a]	$GalNAc_3$-1	3'	11.6
677841[a]	$GalNAc_3$-19	3'	60.8

Example 100: Antisense inhibition *in vivo* by oligonucleotides comprising a GalNAc conjugate group targeting Apo(a) *in vivo*

[0527] The oligonucleotides listed in Table 111a below were tested in a single dose study for duration of action in mice.

Table 111a

Modified ASOs targeting APO(a)				
ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
681251	**$GalNAc_3$-7_{a-o}**$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7a	PO	58
681257	**$GalNAc_3$-7_{a-o}**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7a	PO	58

The structure of $GalNAc_3$-7_a was shown in Example 48.

Treatment

[0528] Female transgenic mice that express human Apo(a) were each injected subcutaneously once per week, for a total of 6 doses, with an oligonucleotide and dosage listed in Table 111b or with PBS. Each treatment group consisted of 3 animals. Blood was drawn the day before dosing to determine baseline levels of Apo(a) protein in plasma and at 72 hours, 1 week, and 2 weeks following the first dose. Additional blood draws will occur at 3 weeks, 4 weeks, 5 weeks, and 6 weeks following the first dose. Plasma Apo(a) protein levels were measured using an ELISA. The results in Table 111b are presented as the average percent of plasma Apo(a) protein levels for each treatment group, normalized to baseline levels (% BL), The results show that the oligonucleotides comprising a GalNAc conjugate group exhibited potent reduction in Apo(a) expression. This potent effect was observed for the oligonucleotide that comprises full PS internucleoside linkages and the oligonucleotide that comprises mixed PO and PS linkages.

Table 111b

Apo(a) plasma protein levels				
ISIS No.	Dosage (mg/kg)	Apo(a) at 72 hours (% BL)	Apo(a) at 1 week (% BL)	Apo(a) at 3 weeks (% BL)
PBS	n/a	116	104	107
681251	0.3	97	108	93
	1.0	85	77	57
	3.0	54	49	11

Apo(a) plasma protein levels				
ISIS No.	Dosage (mg/kg)	Apo(a) at 72 hours (% BL)	Apo(a) at 1 week (% BL)	Apo(a) at 3 weeks (% BL)
	10.0	23	15	4
681257	0.3	114	138	104
	1.0	91	98	54
	3.0	69	40	6
	10.0	30	21	4

Example 101: Antisense inhibition by oligonucleotides comprising a GalNAc cluster linked via a stable moiety

[0529] The oligonucleotides listed in Table 112 were tested for inhibition of mouse APOC-III expression *in vivo.* C57B1/6 mice were each injected subcutaneously once with an oligonucleotide listed in Table 112 or with PBS. Each treatment group consisted of 4 animals. Each mouse treated with ISIS 440670 received a dose of 2, 6, 20, or 60 mg/kg. Each mouse treated with ISIS 680772 or 696847 received 0.6, 2, 6, or 20 mg/kg. The GalNAc conjugate group of ISIS 696847 is linked via a stable moiety, a phosphorothioate linkage instead of a readily cleavable phosphodiester containing linkage. The animals were sacrificed 72 hours after the dose. Liver APOC-III mRNA levels were measured using real-time PCR. APOC-III mRNA levels were normalized to cyclophilin mRNA levels according to standard protocols. The results are presented in Table 112 as the average percent of APOC-III mRNA levels for each treatment group relative to the saline control group. The results show that the oligonucleotides comprising a GalNAc conjugate group were significantly more potent than the oligonucleotide lacking a conjugate group. Furthermore, the oligonucleotide comprising a GalNAc conjugate group linked to the oligonucleotide via a cleavable moiety (ISIS 680772) was even more potent than the oligonucleotide comprising a GalNAc conjugate group linked to the oligonucleotide via a stable moiety (ISIS 696847).

Table 112

Modified oligonucleotides targeting mouse APOC-III					
ISIS No.	Sequences (5' to 3')	CM	Dosage (mg/kg)	APOC-III mRNA (% PBS)	SEQ ID No.
440670	$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}$ $G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	n/a	2	92	162
			6	86	
			20	59	
			60	37	
680772	$\mathbf{GalNAc_3\text{-}7_{a\text{-}o}}$,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}$ $T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	PO	0.6	79	162
			2	58	
			6	31	
			20	13	
696847	$\mathbf{GalNAc_3\text{-}7_{a\text{-}s}}$,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}$ $T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	n/a (PS)	0.6	83	162
			2	73	
			6	40	
			20	28	

The structure of $GalNAc_3\text{-}7_a$ was shown in Example 48.

Example 108: Antisense inhibition *in vivo* by oligonucleotides comprising a GalNAc conjugate group targeting Apo(a) *in vivo*

[0530] The oligonucleotides listed in Table 118 below were tested in a single dose study in mice.

Table 118

Modified ASOs targeting APO(a)				
ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
494372	$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}$ $T_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	n/a	n/a	58
681251	**$GalNAc_3$-7_{a-o}**$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7a	PO	58
681255	**$GalNAc_3$-3_{a-o}**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-3a	PO	58
681256	**$GalNAc_3$-10_{a-o}**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-10a	PO	58
681257	**$GalNAc_3$-7_{a-o}**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-7a	PO	58
681258	**$GalNAc_3$-13_{a-o}**$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}$ $T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e}$	$GalNAc_3$-13a	PO	58
681260	$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}$ $T_{es}T_{es}{}^{m}C_{eo}$**A_{do}-$GalNAc_3$-19**	$GalNAc_3$-19a	A_d	167

The structure of $GalNAc_3$-7_a was shown in Example **48**.

Treatment

[0531] Male transgenic mice that express human Apo(a) were each injected subcutaneously once with an oligonucleotide and dosage listed in Table 119 or with PBS. Each treatment group consisted of **4** animals. Blood was drawn the day before dosing to determine baseline levels of Apo(a) protein in plasma and at 1 week following the first dose. Additional blood draws will occur weekly for approximately 8 weeks. Plasma Apo(a) protein levels were measured using an ELISA. The results in Table 119 are presented as the average percent of plasma Apo(a) protein levels for each treatment group, normalized to baseline levels (% BL), The results show that the antisense oligonucleotides reduced Apo(a) protein expression. Furthermore, the oligonucleotides comprising a GalNAc conjugate group exhibited even more potent reduction in Apo(a) expression than the oligonucleotide that does not comprise a conjugate group.

Table 119

Apo(a) plasma protein levels		
ISIS No.	Dosage (mg/kg)	Apo(a) at 1 week (% BL)
PBS	n/a	143
494372	50	58
681251	10	15

Apo(a) plasma protein levels		
ISIS No.	Dosage (mg/kg)	Apo(a) at 1 week (% BL)
681255	10	14
681256	10	17
681257	10	24
681258	10	22
681260	10	26

SEQUENCE LISTING

[0532]

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US5877022A [0010]
- WO2005000201A [0010] [0403]
- WO20030143397A [0010]
- WO20131774688A [0010] [0215] [0215]
- US20040242516A [0010] [0215] [0215]
- US8138328B [0010]
- US8673632B [0010] [0215] [0215]
- US7259150B [0010] [0215] [0215]
- US8106022B [0021] [0026] [0374] [0375]
- US7262177B [0026] [0374] [0375] [0375]
- WO2008101157A [0279] [0295]
- US7399845B [0284] [0287]
- WO2009006478A [0284] [0287] [0447]
- WO2008150729A [0284] [0287]
- US20040171570A [0284] [0287]
- US7427672B [0284]
- WO2008154401A [0284] [0287]
- US7053207B [0287]
- US6268490B [0287]
- US6770748B [0287]
- US6794499B [0287]
- US7034133B [0287]

- US6525191B [0287]
- US6670461B [0287]
- WO2004106356A [0287]
- WO199414226A [0287]
- WO2005021570A [0287]
- WO2007134181A [0287] [0289] [0295]
- US20070287831A [0287]
- US20080039618A [0287]
- US129154 [0287]
- US60989574B [0287]
- US610269958 [0287]
- US610269988 [0287]
- US61056564B [0287]
- US61086231B [0287]
- US61097787B [0287]
- US61099844B [0287]
- US20050130923A [0290] [0295]
- US5698685A [0291]
- US5166315A [0291]
- US5185444A [0291]
- US5034506A [0291]
- US3687808A [0298] [0299]
- US4845205A [0299]
- US5130302A [0299]
- US5134066A [0299]
- US5175273A [0299]
- US5367066A [0299]
- US5432272A [0299]
- US5457187A [0299]
- US5459255A [0299]
- US5484908A [0299]
- US5502177A [0299]
- US5525711A [0299]
- US5552540A [0299]
- US5587469A [0299]
- US5594121A [0299]
- US5596091A [0299]
- US5614617A [0299]
- US5645985A [0299]
- US5681941A [0299]
- US5750692A [0299]
- US5763588A [0299]
- US5830653A [0299]
- US6005096A [0299]
- US5994517A [0374] [0375]
- US6300319B [0374] [0375]
- US6660720B [0374] [0375]
- US6906182B [0374] [0375]
- US7491805B [0374] [0375] [0375]
- US7723509B [0374] [0375]
- US20060148740A [0374] [0375]
- US20110123520A [0374] [0375]
- WO2013033230A [0374] [0375]

- WO2012037254A [0374] [0375] [0388]
- WO1998013381A [0375]
- WO2011038356A [0375]
- WO1997046098A [0375]
- WO2008098788A [0375]
- WO2004101619A [0375]
- WO2011120053A [0375]
- WO2011100131A [0375]
- WO2011163121A [0375]
- WO2012177947A [0375]
- WO2013075035A [0375]
- WO2012083185A [0375]
- WO2012083046A [0375]
- WO2009082607A [0375]
- WO2009134487A [0375]
- WO2010144740A [0375]
- WO2010148013A [0375]
- WO1997020563A [0375]
- WO2010088537A [0375]
- WO2002043771A [0375]
- WO2010129709A [0375]
- WO2012068187A [0375]
- WO2009126933A [0375]
- WO2004024757A [0375]
- WO2010054406A [0375]
- WO2012089352A [0375]
- WO2012089602A [0375]
- WO2013166121A [0375]
- WO2013165816A [0375]
- US4751219A [0375]
- US8552163B [0375]
- US6908903B [0375]
- US7582744B [0375]
- US8137695B [0375]
- US6383812B [0375]
- US6525031B [0375]
- US8541548B [0375]
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- US8313772B [0375]
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- US8435491B [0375]
- US8404862B [0375]
- US7851615B [0375]
- US20110097264A [0375]
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- US20130004427A [0375]
- US20050164235A [0375]
- US20080281044A [0375]
- US20100240730A [0375]

- US20030119724A [0375]
- US20060183886A [0375]
- US20080206869A [0375]
- US20110269814A [0375]
- US20090286973A [0375]
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- US20120136042A [0375]
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- US20090203135A [0375]
- US20120035115A [0375]
- US20120095075A [0375]
- US20120101146A [0375]
- US20120128760A [0375]
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- US20120230938A [0375]
- US20130109817A [0375]
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- US20130236968A [0375]
- US20030077829A [0375]
- US20080108801A [0375]
- US20090203132A [0375]
- US20100331390A [0403]
- WO2011115818A [0447]
- WO2010077578A [0447]
- WO2010036698A [0447]
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- WO2007090071A [0447]
- US7569686B [0447]
- WO61818442A [0532]
- WO61823626A [0532]
- WO61843887A [0532]
- WO61871673A [0532]
- WO61880790A [0532]
- WO61976991A [0532]
- WO61986867A [0532]

Non-patent literature cited in the description

- **KRAFT et al.**Eur J Hum Genet, 1996, vol. 4, 274-87 [0006]
- **SCHULTZ et al.**PLoS One, 2010, vol. 5, e14328- [0007]
- **BERGMARK et al.**J Lipid Res, 2008, vol. 49, 2230-2239 [0008]
- **TSIMIKAS et al.**Circulation, 2009, vol. 119, 131711-1719 [0008]
- **KOSCHINSKYMARCOVINA**Curr Opin Lipidol, 2004, vol. 15, 167-174 [0009]
- **RIFAI et al.**Clin Chem, 2004, vol. 50, 1364-71 [0009]
- **ERQOU et al.**JAMA, 2009, vol. 302, 412-23 [0009]
- **KAMSTRUP et al.**Circulation, 2008, vol. 117, 176-84 [0009]
- **CLARKE et al.**NEJM, 2009, vol. 361, 2518-2528 [0009]
- **SOLFRIZZI et al.**J Neurol Neurosurg Psychiatry, 2002, vol. 72, 732-736 [0009]

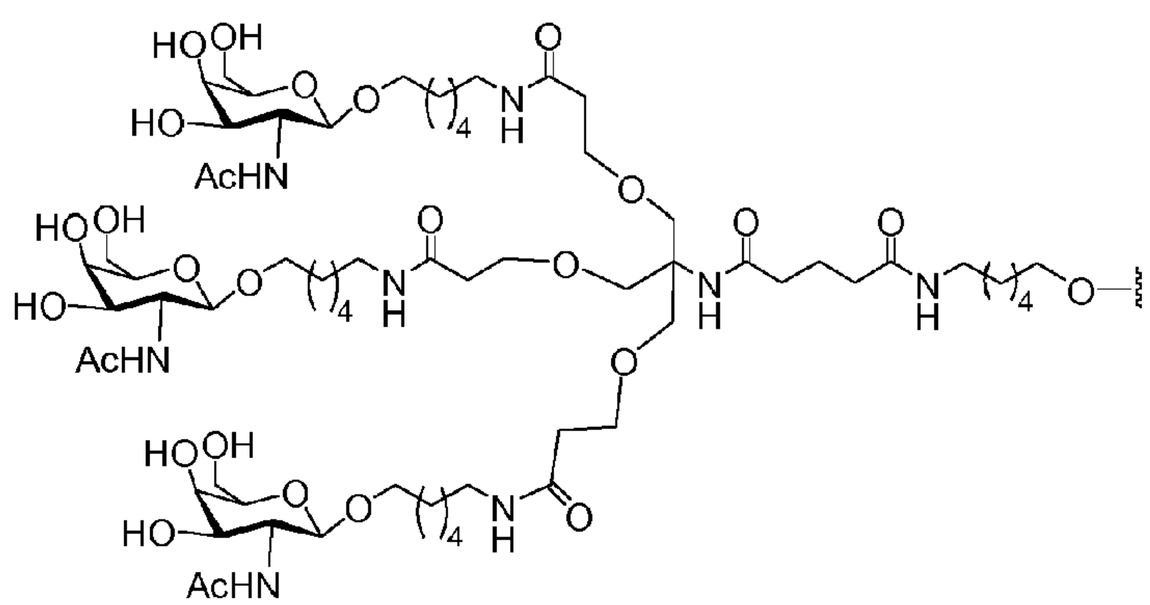
- **MERKI et al.**J Am Coll Cardiol, 2011, vol. 57, 1611-1621 [0010]
- **PARK et al.**PNAS, 2005, vol. 102, 4717125-17129 [0021]
- **KHOREV et al.**Bioorganic and Medicinal Chemistry, 2008, vol. 16, 95216-5231 [0021]
- Carbohydrate Modifications in Antisense ResearchAmerican Chemical Society19940000 [0041]
- Remington's Pharmaceutical SciencesMack Publishing Co.20050000 [0041]
- Antisense Drug Technology, Principles, Strategies, and ApplicationsCRC Press [0041]
- **SAMBROOK et al.**Molecular Cloning, A laboratory ManualCold Spring Harbor Laboratory Press19890000 [0041]
- ACS Symposium Series 58040-65 [0077]
- **MAIER et al.**Synthesis of Antisense Oligonucleotides Conjugated to a Multivalent Carbohydrate Cluster for Cellular TargetingBioconjugate Chemistry, 2003, vol. 14, 18-29 [0088]
- **RENSEN et al.**Design and Synthesis of Novel N-Acetylgalactosamine-Terminated Glycolipids for Targeting of Lipoproteins to the Hepatic Asiaglycoprotein ReceptorJ. Med. Chem., 2004, vol. 47, 5798-5808 [0088]
- **T. W. GREENEP. G. M. WUTS**Protective Groups in Organic ChemistryJohn Wiley & Sons, Inc [0092]
- Arch. Int. Med., 1988, vol. 148, 36-39 [0170]
- **FREDRICKSONLEE**Circulation, 1965, vol. 31, 321-327 [0171]
- **FREDRICKSON et al.**New Eng J Med, 1967, vol. 276, 134-42 [0171]
- **YUAN et al.**CMAJ, 2007, vol. 176, 1113-1120 [0172]
- JAMA, 2001, vol. 285, 2486-2497 [0191]
- **STAHLWERMUTH**Handbook of Pharmaceutical Salts: Properties, Selection and UseWiley-VCH20020000 [0197]
- **CHATTOPADHYAYA et al.**J. Org. Chem., 2009, vol. 74, 118-134 [0284]
- **SINGH et al.**Chem. Commun., 1998, vol. 4, 455-456 [0287]
- **KOSHKIN et al.**Tetrahedron, 1998, vol. 54, 3607-3630 [0287]
- **WAHLESTEDT et al.**Proc. Natl. Acad. Sci. U. S. A., 2000, vol. 97, 5633-5638 [0287]
- **KUMAR et al.**Bioorg. Med. Chem. Lett., 1998, vol. 8, 2219-2222 [0287]
- **SINGH et al.**J. Org. Chem., 1998, vol. 63, 10035-10039 [0287]
- **SRIVASTAVA et al.**J. Am. Chem. Soc., 2007, vol. 129, 268362-8379 [0287]
- **ELAYADI et al.**Curr. Opinion Invens. Drugs, 2001, vol. 2, 558-561 [0287]
- **BRAASCH et al.**Chem. Biol., 2001, vol. 8, 1-7 [0287]
- **ORUM et al.**Curr. Opinion Mol. Ther., 2001, vol. 3, 239-243 [0287]
- **FRIEDEN et al.**Nucleic Acids Research, 2003, vol. 21, 6365-6372 [0288]
- **FREIER et al.**Nucleic Acids Research, 1997, vol. 25, 224429-4443 [0290]
- **ALBAEK et al.**J. Org. Chem., 2006, vol. 71, 7731-7740 [0290]
- **BRAASCH et al.**Biochemistry, 2002, vol. 41, 4503-4510 [0291]
- **LEUMANN, CJ.**Bioorg. & Med. Chem., 2002, vol. 10, 841-854 [0292]
- **LEUMANN, J. C**Bioorganic & Medicinal Chemistry, 2002, vol. 10, 841-854 [0294]
- **SRIVASTAVA et al.**J. Am. Chem. Soc., 2007, vol. 129, 268362-8379 [0295]
- The Concise Encyclopedia Of Polymer Science And EngineeringJohn Wiley & Sons19900000858-859 [0298]
- **ENGLISCH et al.**Angewandte Chemie, 1991, vol. 30, 613- [0298]
- **SANGHVI, Y.S.**Antisense Research and ApplicationsCRC Press19930000273-288 [0298]
- Carbohydrate Modifications in Antisense ResearchACS Symposium Series 58040-65 [0302]
- **BIESSEN et al.**The Cholesterol Derivative of a Triantennary Galactoside with High Affinity for the Hepatic Asialoglycoprotein Receptor: a Potent Cholesterol Lowering AgentJ. Med. Chem., 1995, vol. 38, 1846-1852 [0374]
- **BIESSEN et al.**Synthesis of Cluster Galactosides with High Affinity for the Hepatic Asialoglycoprotein ReceptorJ. Med. Chem., 1995, vol. 38, 1538-1546 [0374]
- **LEE et al.**New and more efficient multivalent glyco-ligands for asialoglycoprotein receptor of mammalian hepatocytesBioorganic & Medicinal Chemistry, 2011, vol. 19, 2494-2500 [0374]
- **RENSEN et al.**Determination of the Upper Size Limit for Uptake and Processing of Ligands by the Asialoglycoprotein Receptor on Hepatocytes in Vitro and in VivoJ. Biol. Chem., 2001, vol. 276, 4037577-37584 [0374]
- **RENSEN et al.**Design and Synthesis of Novel N-Acetylgalactosamine-Terminated Glycolipids for Targeting of

Lipoproteins to the Hepatic Asialoglycoprotein ReceptorJ. Med. Chem., 2004, vol. 47, 5798-5808 [0374]
- **SLIEDREGT et al.**Design and Synthesis of Novel Amphiphilic Dendritic Galactosides for Selective Targeting of Liposomes to the Hepatic Asialoglycoprotein ReceptorJ. Med. Chem., 1999, vol. 42, 609-618 [0374]
- **VALENTIJN et al.**Solid-phase synthesis of lysine-based cluster galactosides with high affinity for the Asialoglycoprotein ReceptorTetrahedron, 1997, vol. 53, 2759-770 [0374]
- **LEE**Carbohydr Res, 1978, vol. 67, 509-514 [0375]
- **CONNOLLY et al.**J Biol Chem, 1982, vol. 257, 939-945 [0375]
- **PAVIA et al.**Int J Pep Protein Res, 1983, vol. 22, 539-548 [0375]
- **LEE et al.**Biochem, 1984, vol. 23, 4255-4261 [0375]
- **LEE et al.**Glycoconjugate J, 1987, vol. 4, 317-328 [0375]
- **TOYOKUNI et al.**Tetrahedron Lett, 1990, vol. 31, 2673-2676 [0375]
- **BIESSEN et al.**J Med Chem, 1995, vol. 38, 1538-1546 [0375]
- **VALENTIJN et al.**Tetrahedron, 1997, vol. 53, 759-770 [0375]
- **KIM et al.**Tetrahedron Lett, 1997, vol. 38, 3487-3490 [0375]
- **LEE et al.**Bioconjug Chem, 1997, vol. 8, 762-765 [0375]
- **KATO et al.**Glycobiol, 2001, vol. 11, 821-829 [0375]
- **RENSEN et al.**J Biol Chem, 2001, vol. 276, 37577-37584 [0375]
- **LEE et al.**Methods Enzymol, 2003, vol. 362, 38-43 [0375]
- **WESTERLIND et al.**Glycoconj J, 2004, vol. 21, 227-241 [0375]
- **LEE et al.**Bioorg Med Chem Lett, 2006, vol. 16, 195132-5135 [0375]
- **MAIERHOFER et al.**Bioorg Med Chem, 2007, vol. 15, 7661-7676 [0375]
- **KHOREV et al.**Bioorg Med Chem, 2008, vol. 16, 5216-5231 [0375]
- **LEE et al.**Bioorg Med Chem, 2011, vol. 19, 2494-2500 [0375]
- **KORNILOVA et al.**Analyt Biochem, 2012, vol. 425, 43-46 [0375]
- **PUJOL et al.**Angew Chemie Int Ed Engl, 2012, vol. 51, 7445-7448 [0375]
- **BIESSEN et al.**J Med Chem, 1995, vol. 38, 1846-1852 [0375]
- **SLIEDREGT et al.**J Med Chem, 1999, vol. 42, 609-618 [0375]
- **RENSEN et al.**J Med Chem, 2004, vol. 47, 5798-5808 [0375]
- **RENSEN et al.**Arterioscler Thromb Vasc Biol, 2006, vol. 26, 169-175 [0375]
- **VAN ROSSENBERG et al.**Gene Ther, 2004, vol. 11, 457-464 [0375]
- **SATO et al.**J Am Chem Soc, 2004, vol. 126, 14013-14022 [0375]
- **LEE et al.**J Org Chem, 2012, vol. 77, 7564-7571 [0375]
- **BIESSEN et al.**FASEB J, 2000, vol. 14, 1784-1792 [0375]
- **RAJUR et al.**Bioconjug Chem, 1997, vol. 8, 935-940 [0375]
- **DUFF et al.**Methods Enzymol, 2000, vol. 313, 297-321 [0375]
- **MAIER et al.**Bioconjug Chem, 2003, vol. 14, 18-29 [0375]
- **JAYAPRAKASH et al.**Org Lett, 2010, vol. 12, 5410-5413 [0375]
- **MANOHARAN**Antisense Nucleic Acid Drug Dev, 2002, vol. 12, 103-128 [0375]
- **MERWIN et al.**Bioconjug Chem, 1994, vol. 5, 612-620 [0375]
- **TOMIYA et al.**Bioorg Med Chem, 2013, vol. 21, 5275-5281 [0375]
- **GEARY, R. S.E. WANCEWICZ et al.**Effect of Dose and Plasma Concentration on Liver Uptake and Pharmacologic Activity of a 2'-Methoxyethyl Modified Chimeric Antisense Oligonucleotide Targeting PTENBiochem. Pharmacol., 2009, vol. 78, 3284-91 [0378]
- **KOLLER, E.T. M. VINCENT et al.**Mechanisms of single-stranded phosphorothioate modified antisense oligonucleotide accumulation in hepatocytesNucleic Acids Res., 2011, vol. 39, 114795-807 [0378]
- **GEARY, R.**Pharmacokinetic Properties of 2'-O-(2-Methoxyethyl)-Modified Oligonucleotide Analogs in RatsJournal of Pharmacology and Experimental Therapeutics, vol. 296, 3890-897 [0381]
- Pharmacological Properties of 2'-O-Methoxyethyl Modified OligonucleotidesAntisense a Drug Technology20080000 [0381]
- J Lab Clin Med., 1996, vol. 128, 3329-38 [0382]
- Toxicologic PropertiesAntisense a Drug Technology20080000342-351 [0382] [0383]
- **LIPPI et al.**Clinica Chimica Acta, 2011, vol. 412, 797-801 [0427]
- **SETH et al.**Bioorg. Med. Chem., 2011, vol. 21, 41122-1125 [0447]

- J. Org. Chem., 2010, vol. 75, 51569-1581 [0447]
- Nucleic Acids Symposium Series, 2008, vol. 52, 1553-554 [0447]
- **WEBER et al.**J. Med. Chem, 1991, vol. 34, 2692- [0449]
- **RENSEN et al.**J. Med. Chem., 2004, vol. 47, 5798-5808 [0453]
- J. Med. Chem., 2004, vol. 47, 5798-5808 [0473]
- Analytical Biochemistry, 1995, vol. 229, 54-60 [0483]
- J Lipid Res, 1991, vol. 32, 1173-81 [0525]

Patentkrav

1. Forbindelse, der omfatter et modificeret oligonukleotid og en konjugatgruppe, hvor det modificerede oligonukleotid består af 20 koblede nukleosider og har en nukleobasesekvens, der omfatter 20 sammenhængende nukleobaser, der er komplementære til en del med tilsvarende længde af nukleobaserne 3901 til 3920 af SEQ ID NO: 1, hvor nukleobasesekvensen af det modificerede oligonukleotid er mindst 100 % komplementær til SEQ ID NO: 1; og hvor konjugatgruppen omfatter:



.

2. Forbindelse ifølge krav 1, hvor:

(i) det modificerede oligonukleotid omfatter mindst ét modificeret sukker, eventuelt hvor: (a) mindst ét modificeret sukker er et bicyklisk sukker, eventuelt et begrænset ethyl eller et sukker, der omfatter en 4'-$(CH_2)_n$-O-2'-bro, hvor n er 1 eller 2, eller (b) mindst ét modificeret sukker omfatter et 2'-O-methoxyethyl eller er et 3'-fluor-HNA,

(ii) mindst ét nukleosid omfatter en modificeret nukleobase, eventuelt hvor den modificerede nukleobase er en 5-methylcytosin, og/eller

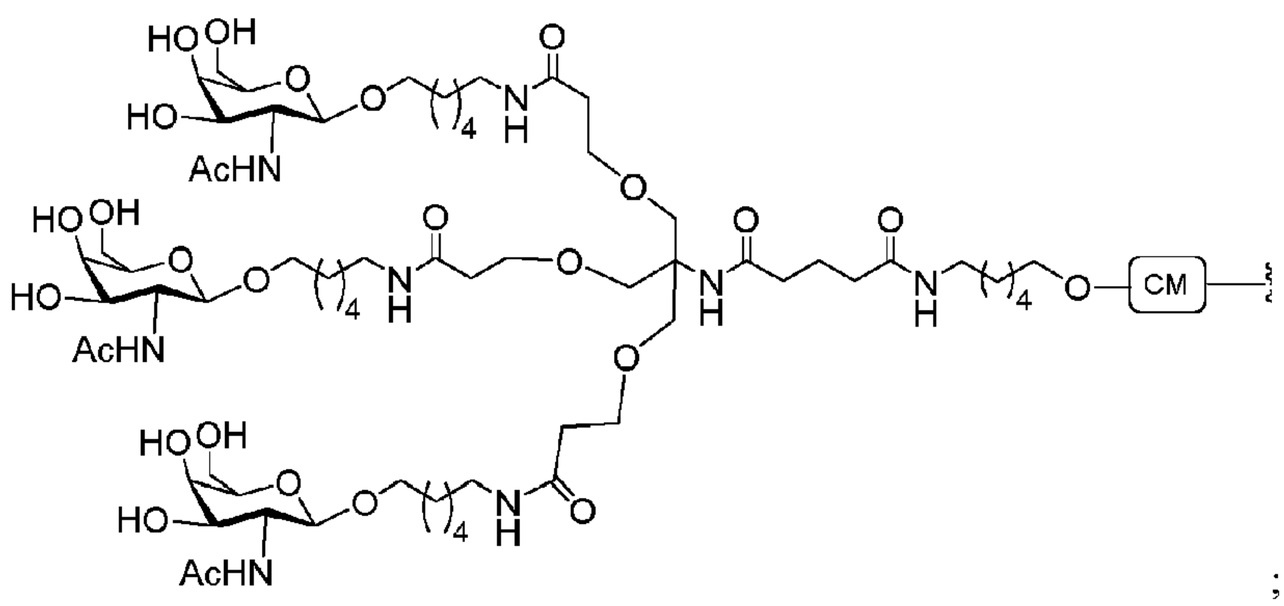
(iii) hver internukleosidkobling i det modificerede oligonukleotid er valgt blandt en phosphodiester-internukleosidkobling og en phosphorothioat-internukleosidkobling, eventuelt hvor det modificerede oligonukleotid omfatter: (a) mindst 5 phosphodiester-internukleosidkoblinger eller (b) mindst 2 phosphorothioat-internukleosidkoblinger.

3. Forbindelse ifølge krav 1 eller krav 2, hvor det modificerede oligonukleotid er enkeltstrenget.

4. Forbindelse ifølge et hvilket som helst af kravene 1-3, hvor konjugatgruppen er koblet til det modificerede oligonukleotid i 5'-enden af det modificerede oligonukleotid.

5. Forbindelse ifølge et hvilket som helst af kravene 1-3, hvor konjugatgruppen er koblet til det modificerede oligonukleotid i 3'-enden af det modificerede oligonukleotid.

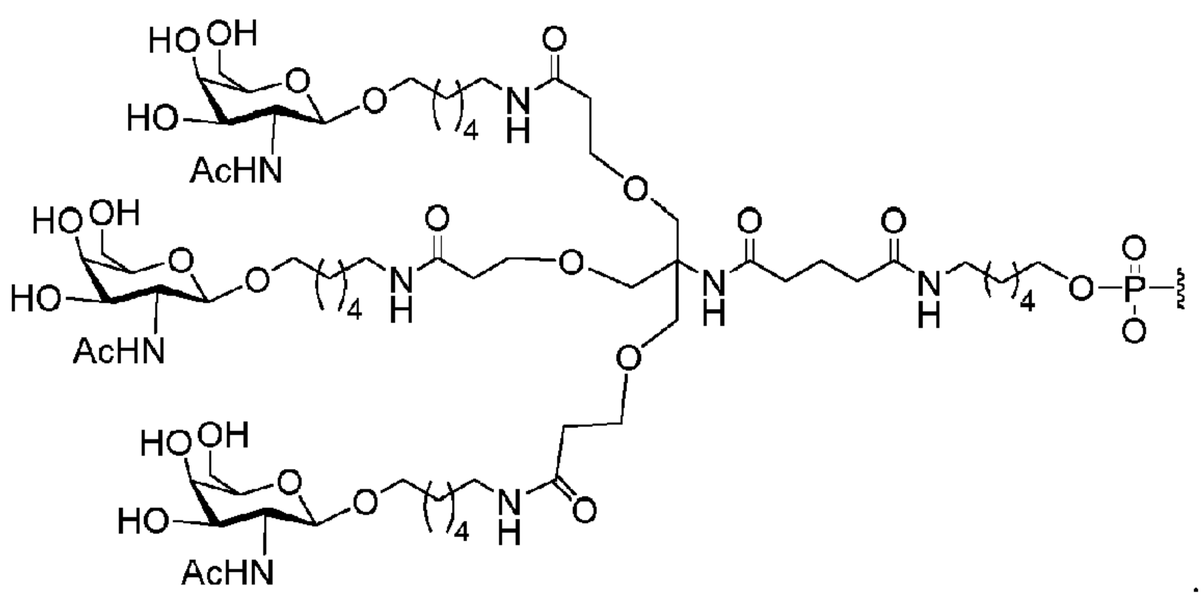
6. Forbindelse ifølge et hvilket som helst af kravene 1-5, hvor konjugatgruppen omfatter:



;

hvor den spaltbare del (CM) er en binding eller gruppe, der kan spaltes under fysiologiske betingelser.

7. Forbindelse ifølge et hvilket som helst af kravene 1-6, hvor konjugatgruppen omfatter:



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8. Forbindelse ifølge krav 1, hvor det modificerede oligonukleotid omfatter:

et gapsegment, der består af koblede deoxynukleosider;

et 5'-vingesegment, der består af koblede nukleosider;

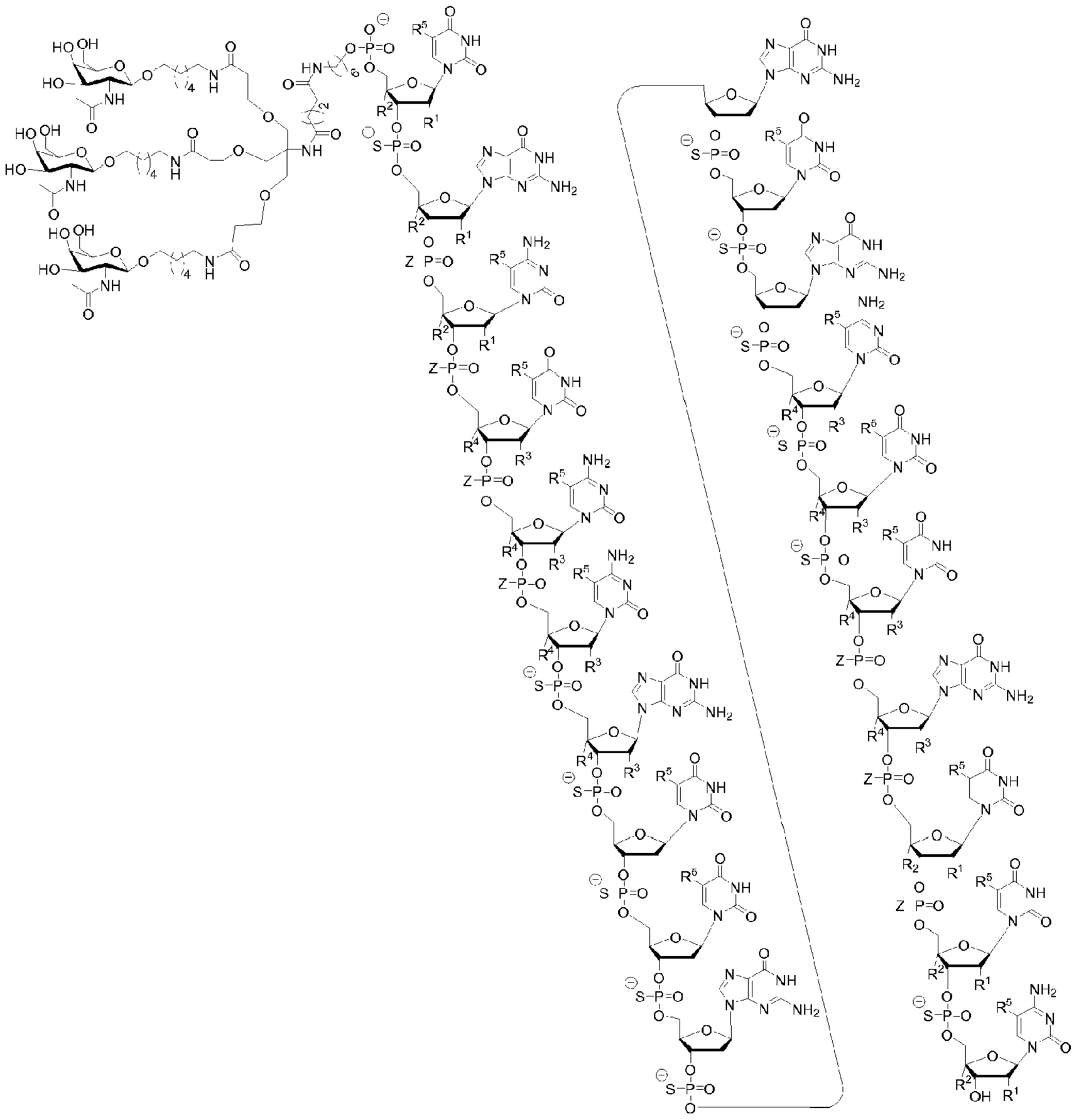
et 3'-vingesegment, der består af koblede nukleosider;

hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, og hvor hvert nukleosid af hvert vingesegment omfatter et modificeret sukker.

9. Forbindelse ifølge krav 1, hvor det modificerede oligonukleotid omfatter:
et gapsegment, der består af 10 koblede deoxynukleosider;
et 5'-vingesegment, der består af 5 koblede nukleosider;
et 3'-vingesegment, der består af 5 koblede nukleosider;
hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, hvor hvert nukleosid af hvert vingesegment omfatter et 2'-O-methoxyethylsukker, og hvor hver cytosinrest er en 5-methylcytosin.

10. Forbindelse ifølge krav 1, hvor det modificerede oligonukleotid består af 20 koblede nukleosider og har nukleobasesekvensen ifølge SEQ ID NO: 58, og hvor det modificerede oligonukleotid omfatter:
et gapsegment, der består af 10 koblede deoxynukleosider;
et 5'-vingesegment, der består af 5 koblede nukleosider;
et 3'-vingesegment, der består af 5 koblede nukleosider;
hvor gapsegmentet er placeret mellem 5'-vingesegmentet og 3'-vingesegmentet, hvor hvert nukleosid af hvert vingesegment omfatter et 2'-O-methoxyethylsukker, hvor mindst én internukleosidkobling er en phosphorothioatkobling, og hvor hver cytosinrest er en 5-methylcytosin.

11. Forbindelse ifølge krav 1 med formlen:



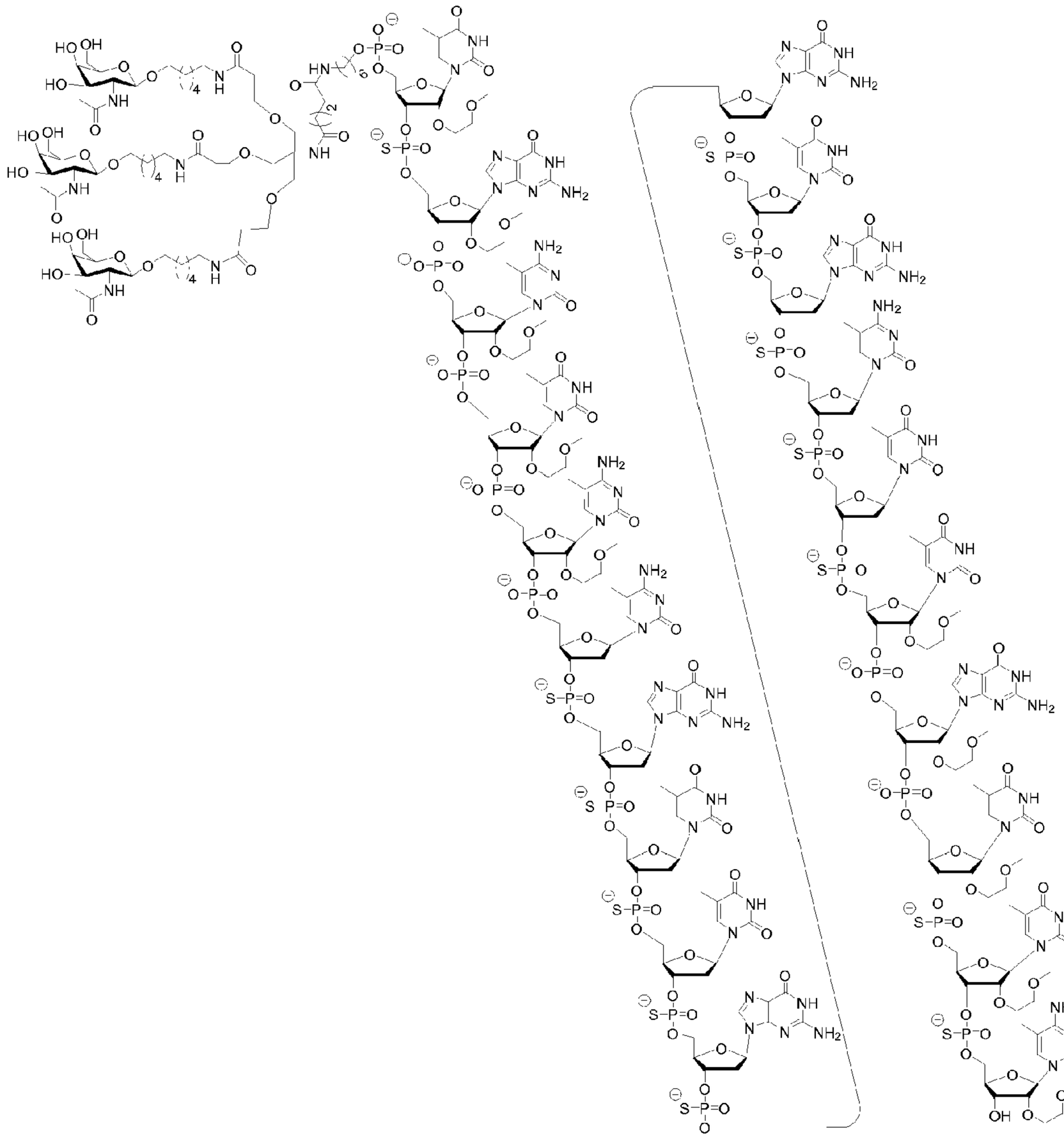
hvor enten R^1 er $-OCH_2CH_2OCH_3$ (MOE), og R^2 er H; eller R^1 og R^2 sammen danner en bro, hvor R^1 er -O-, og R^2 er $-CH_2-$, $-CH(CH_3)-$ eller $-CH_2CH_2-$, og R^1 og R^2 er direkte forbundet, således at den resulterende bro er valgt blandt: $-O-CH_2-$, $-O-CH(CH_3)-$ og $-O-CH_2CH_2-$;

og det for hvert par af R^3 og R^4 på den samme ring og uafhængigt for hver ring gælder at: enten er R^3 valgt blandt H og $-OCH_2CH_2OCH_3$, og R^4 er H; eller R^3 og R^4 sammen danner en bro, hvor R^3 er -O-, og R^4 er $-CH_2-$, $-CH(CH_3)-$ eller $-CH_2CH_2-$, og R^3 og R^4 er direkte forbundet, således at den resulterende bro er valgt blandt: $-O-CH_2-$, $-O-CH(CH_3)-$ og $-O-CH_2CH_2-$;

og R^5 er valgt blandt H og $-CH_3$;

og Z er valgt blandt S^- og O^-.

12. Forbindelse ifølge krav 1 med formlen:



13. Forbindelse ifølge et hvilket som helst af ovennævnte krav, hvor forbindelse er i en saltform, eventuelt hvor forbindelsen er i form af et natriumsalt og/eller kaliumsalt.

14. Farmaceutisk sammensætning, der omfatter en forbindelse ifølge et hvilket som helst af kravene 1-13 og et farmaceutisk acceptabelt fortyndingsmiddel eller bæremateriale.

15. Forbindelse ifølge et hvilket som helst af kravene 1-13 eller sammensætning ifølge krav 14 til anvendelse til behandling, forebyggelse eller forsinkelse af progression af en sygdom, der er forbundet med forhøjet apo(a) og/eller forhøjet Lp(a).

16. Forbindelse eller sammensætning til anvendelse ifølge krav 15, hvor sygdommen er en inflammatorsk, kardiovaskulær eller metabolisk sygdom, forstyrrelse eller tilstand.

17. Forbindelse eller sammensætning til anvendelse ifølge krav 15, hvor sygdommen er aortastenose eller angina.