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(54) Title: CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE

(57) Abstract: Provided herein are oligomeric compounds with conjugate groups. In certain embodiments, the oligomeric compounds are conjugated to *N*-Acetylgalactosamine.

CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE

SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled CORE0115WOSEQ_ST25.txt, created on May 1, 2014, which is 692 Kb in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

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 silencing 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.

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. For another example, an antisense oligonucleotide targeting ApoB, KYNAMRO™, has been approved by the U.S. Food and Drug Administration (FDA) as an adjunct treatment to lipid-lowering

medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), ApoB, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

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.

SUMMARY OF THE INVENTION

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.

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.

In certain embodiments of the present invention, 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.

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).

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.

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.

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).

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).

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.

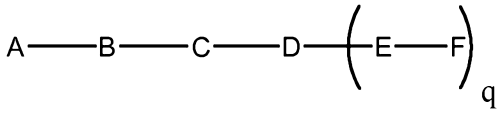
In certain embodiments, conjugation allows one to alter antisense compounds in ways that have less attractive consequences in the absence of conjugation. For example, in certain embodiments, replacing one or more phosphorothioate linkages of a fully phosphorothioate antisense compound with phosphodiester 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.

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.

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.

In certain embodiments, the present disclosure provides conjugated antisense compounds represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

D is the branching group

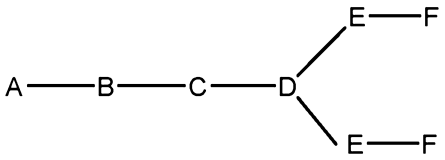
each E is a tether;

each F is a ligand; and

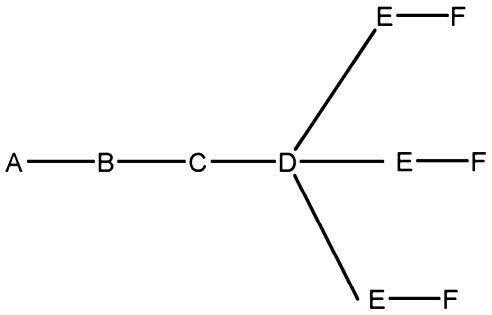
q is an integer between 1 and 5.

In the above diagram and in similar diagrams herein, the branching group "D" branches as many times as is necessary to accommodate the number of (E-F) groups as indicated by "q". Thus, where q = 1, the formula is:

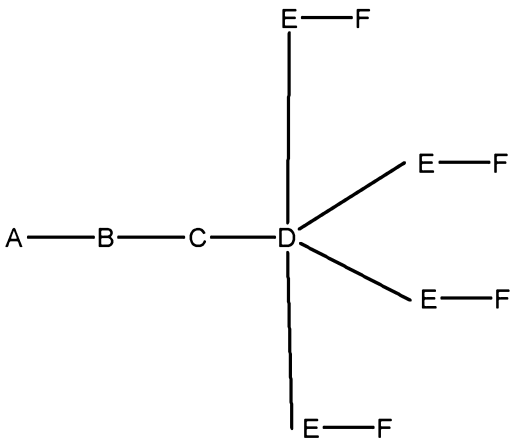
where q = 2, the formula is:



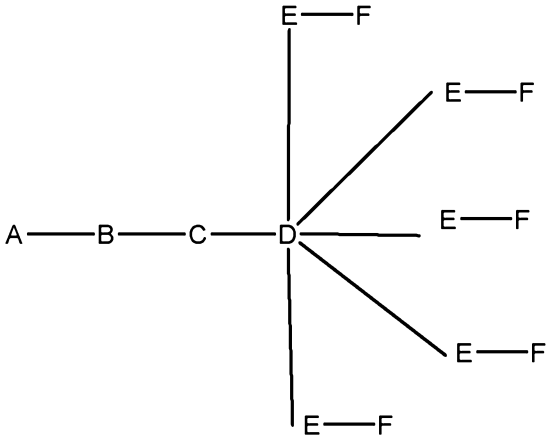
where q = 3, the formula is:



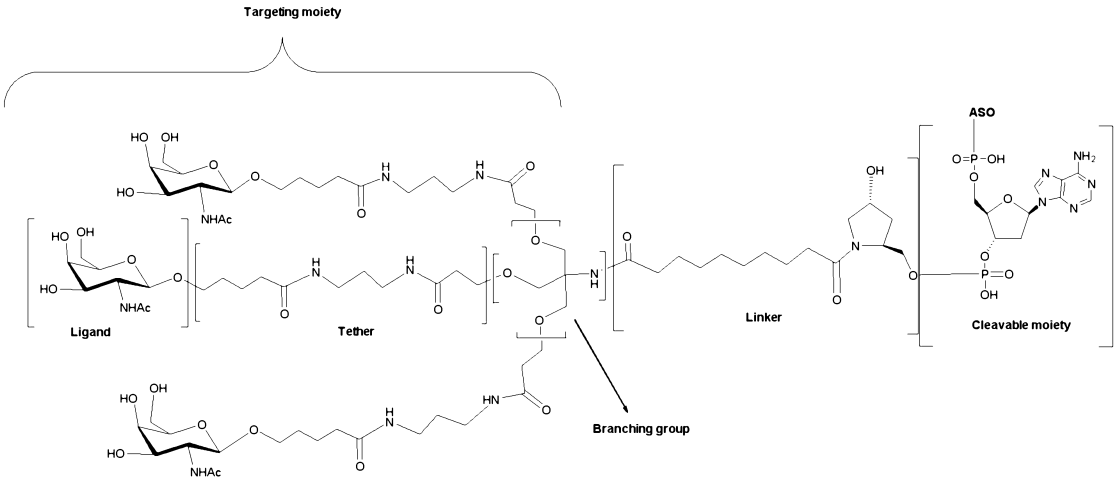
where q = 4, the formula is:



where q = 5, the formula is:



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



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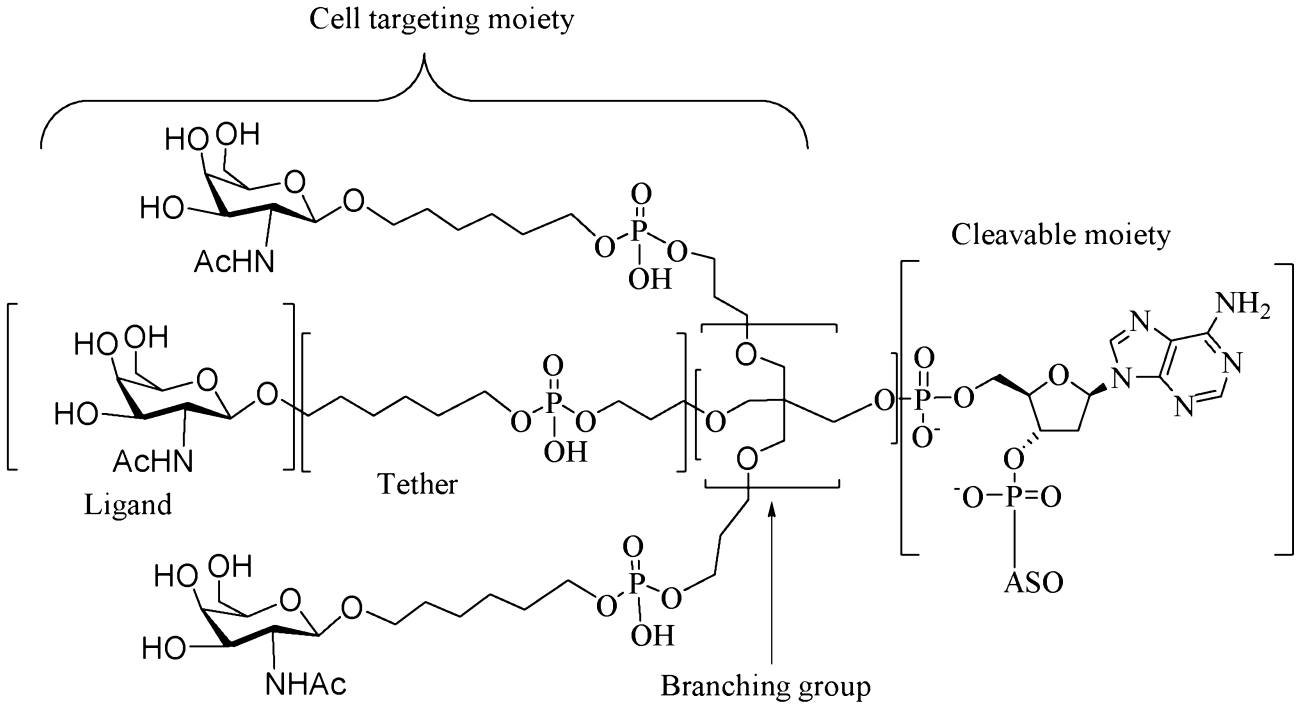
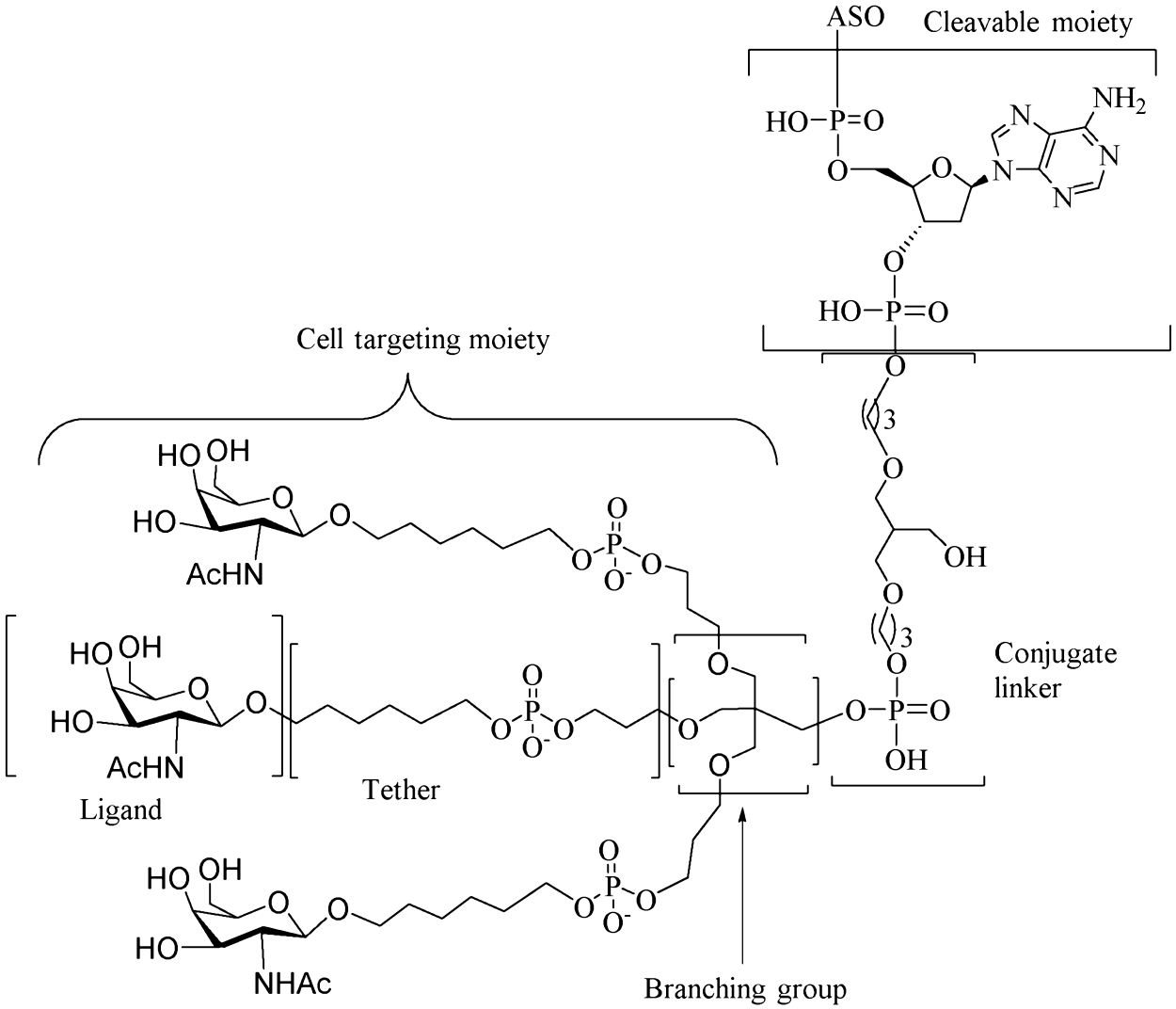
In certain embodiments, conjugated antisense compounds are provided having the structure:



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



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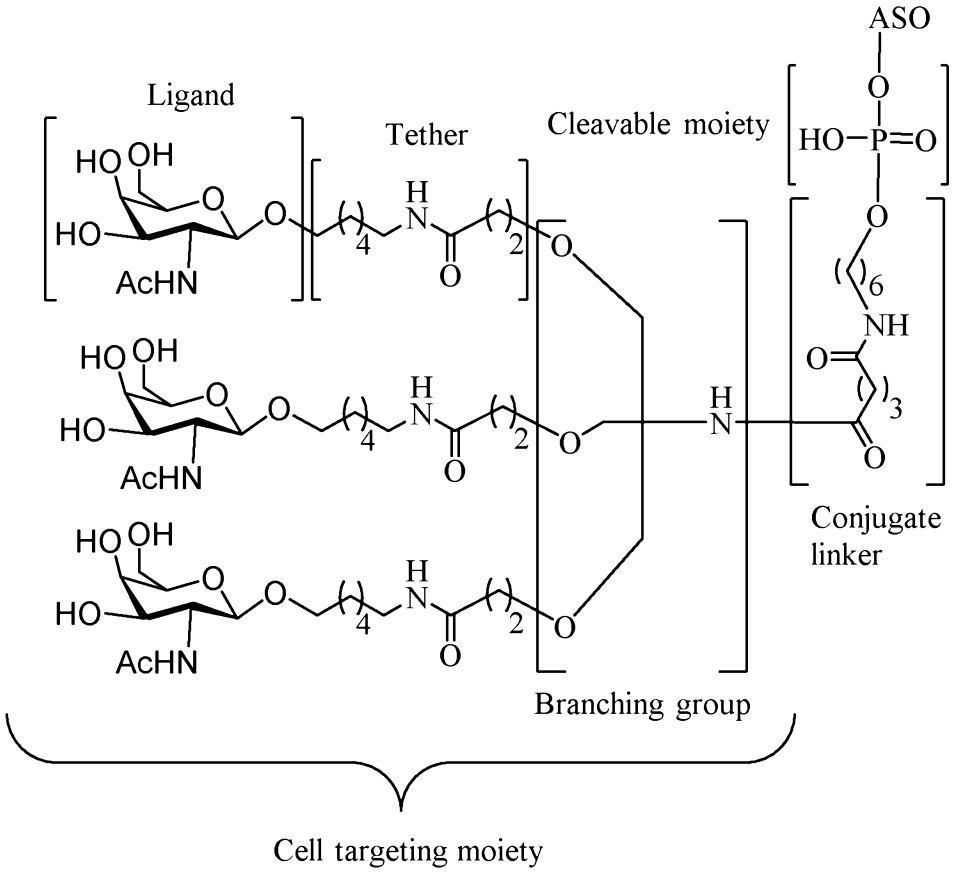
In certain embodiments, conjugated antisense compounds are provided having the structure:



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

Embodiment 1. A conjugated antisense compound comprising: an antisense oligonucleotide comprising 12-30 linked nucleosides and a conjugate group, wherein the conjugate group comprises: a cleavable moiety; a conjugate linker; and a cell- targeting moiety.

Embodiment 2. The conjugated antisense compound of embodiment 1, wherein:
the cleavable moiety is covalently bound to the antisense oligonucleotide;
the conjugate linker is covalently bound to the cleavable moiety; and
the cell-targeting moiety is covalently bound to the conjugate linker.

Embodiment 3. The conjugated antisense compound of embodiment 1 or 2, wherein the cell-targeting moiety comprises a branching group.

Embodiment 4. The conjugated antisense compound of embodiment 3, wherein the branching group is covalently attached to the conjugate linker.

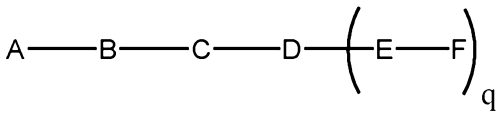
Embodiment 5. The conjugated antisense compound of any of embodiments 1-4, wherein the cell-targeting moiety comprises at least one tether.

Embodiment 6. The conjugated antisense compound of embodiment 5, wherein the at least one tether is covalently attached to the branching group.

Embodiment 7. The conjugated antisense compound of any of embodiments 1-6, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 8. The conjugated antisense compound of embodiment 7, wherein each of the at least one ligands is covalently attached to a tether.

Embodiment 9. The conjugated antisense compound of embodiment 1-8, wherein the compound has a structure represented by formula I below:



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.

Embodiment 10. The conjugated antisense compound of any of embodiments 1-9, wherein the cleavable moiety comprises 1-4 linked cleavable moiety nucleosides, wherein the linkage between the antisense oligonucleotide and the first cleavable moiety nucleoside is a phosphodiester internucleoside linkage.

Embodiment 11. The conjugated antisense compound of embodiment 10, wherein each internucleoside linkage between each of the linked cleavable moiety nucleosides is a phosphodiester internucleoside linkage.

Embodiment 12. The conjugated antisense compound of embodiment 10 or 11, wherein the cleavable moiety comprises 1-3 linked cleavable moiety nucleosides.

Embodiment 13. The conjugated antisense compound of embodiment 10 or 11, wherein the cleavable moiety comprises 1-2 linked cleavable moiety nucleosides.

Embodiment 14. The conjugated antisense compound of embodiment 10, wherein the cleavable moiety comprises one cleavable moiety nucleoside.

Embodiment 15. The conjugated antisense compound of any of embodiments 1-14, wherein the cleavable moiety is a cleavable moiety nucleoside selected from the group consisting of a purine, a substituted purine, a pyrimidine, or a substituted pyrimidine.

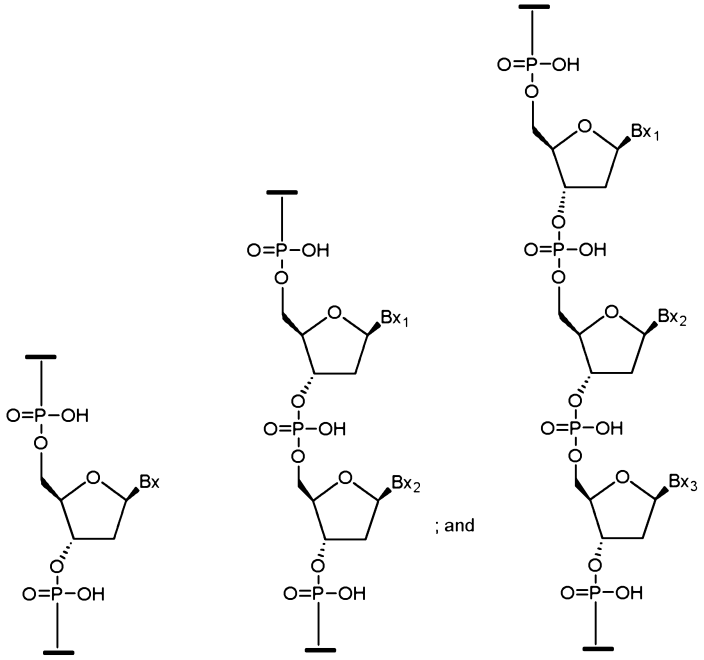
Embodiment 16. The conjugated antisense compound of any of embodiments 1-14, wherein the cleavable moiety is a cleavable moiety nucleoside selected from cytidine, uridine, adenosine, thymidine, and guanosine.

Embodiment 17. The conjugated antisense compound of any of embodiments 1-14, wherein the cleavable moiety is a cleavable moiety deoxynucleoside selected from deoxyadenosine, deoxyguanosine, deoxyinosine, thymidine, deoxyuridine, and deoxycytidine.

Embodiment 18. The conjugated antisense compound of any of embodiments 1-17, wherein the cleavable moiety comprises deoxyadenosine.

Embodiment 19. The conjugated antisense compound of any of embodiments 1-18, wherein the cleavable moiety is deoxyadenosine.

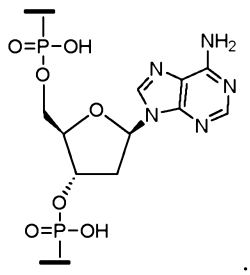
Embodiment 20. The conjugated antisense compound of any of embodiments 1-19, wherein the cleavable moiety has a structure selected from among:



wherein each of Bx, Bx_1, Bx_2, and Bx_3 is independently a heterocyclic base moiety.

Embodiment 21. The conjugated antisense compound of embodiment 20, wherein the heterocyclic base moiety is selected from among: uracil, thymine, cytosine, 5-methylcytosine, adenine or guanine.

Embodiment 22. The conjugated antisense compound of any of embodiments 1-19, wherein the cleavable moiety has the structure:



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Embodiment 23. The conjugated antisense compound of any of embodiments 1-22, wherein the conjugate linker comprises a pyrrolidine.

Embodiment 24. The conjugated antisense compound of any of embodiments 1-23, wherein the conjugate linker comprises PEG.

Embodiment 25. The conjugated antisense compound of any of embodiments 1-24, wherein the conjugate linker comprises an amide.

Embodiment 26. The conjugated antisense compound of any of embodiments 1-25, wherein the conjugate linker comprises a polyamide.

Embodiment 27. The conjugated antisense compound of any of embodiments 1-26, wherein the conjugate linker comprises an amine.

Embodiment 28. The conjugated antisense compound of any of embodiments 1-27, wherein the conjugate linker comprises one or more disulfide bonds.

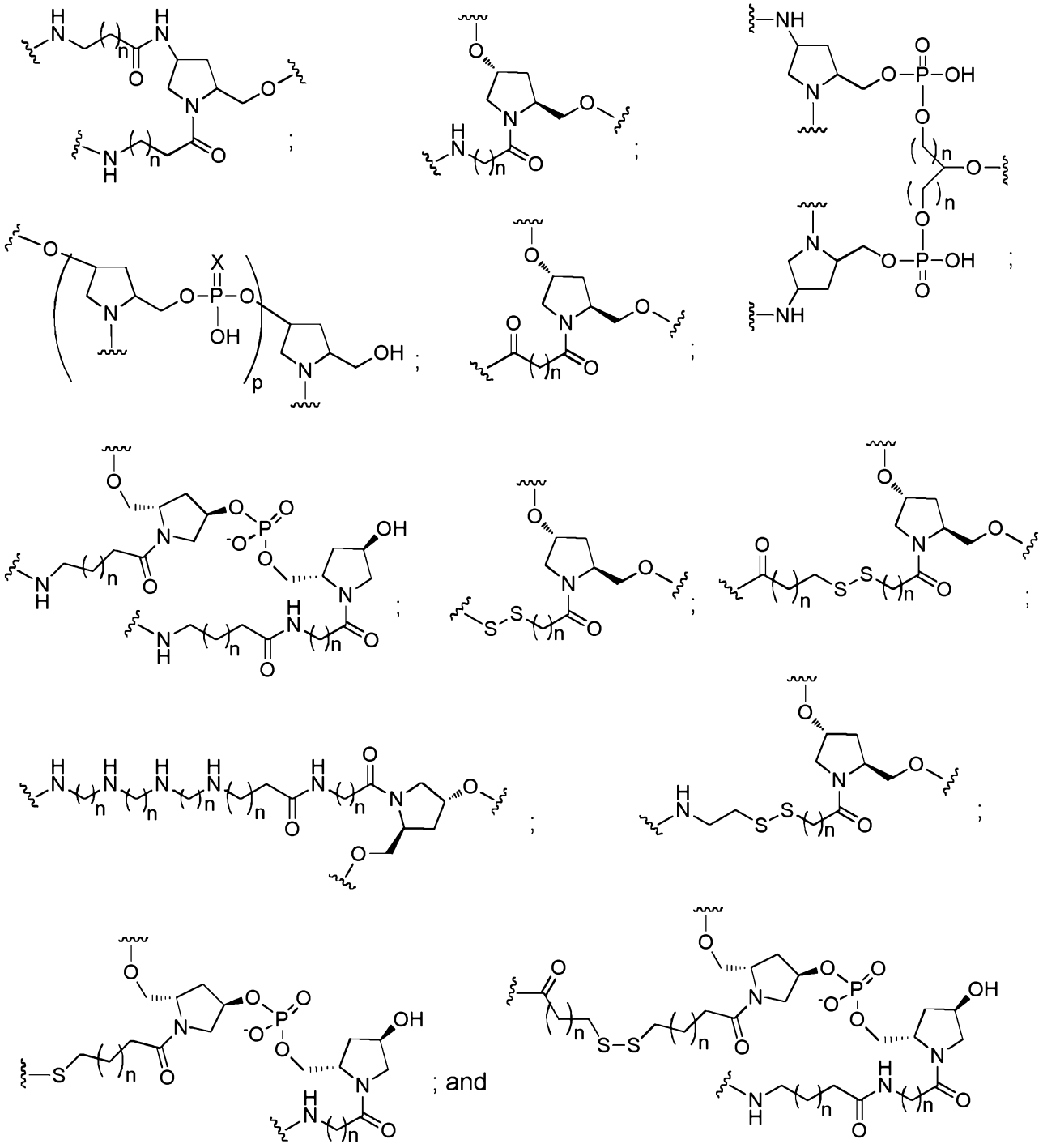
Embodiment 29. The conjugated antisense compound of any of embodiments 1-28, wherein the conjugate linker comprises a protein binding moiety.

Embodiment 30. The conjugated antisense compound of embodiment 29, wherein the protein binding moiety comprises a lipid.

Embodiment 31. The conjugated antisense compound of embodiment 30, wherein the protein binding moiety is selected from among: cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), a vitamin (e.g., folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (e.g., monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid.

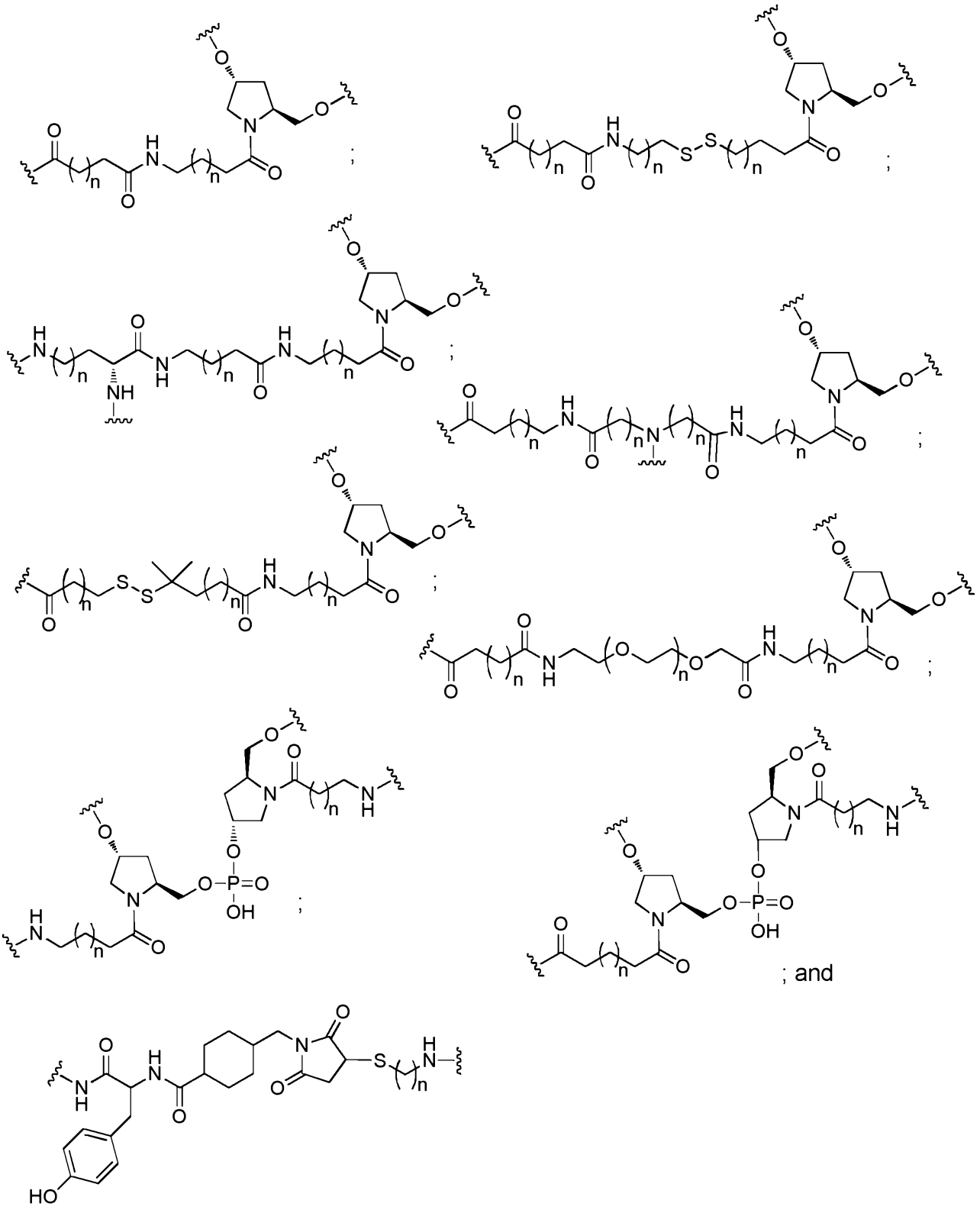
Embodiment 32. The conjugated antisense compound of any of embodiments 1-31 wherein the protein binding moiety is a C16 to C22 long chain saturated or unsaturated fatty acid, cholesterol, cholic acid, vitamin E, adamantane or 1-pentafluoropropyl.

Embodiment 33. The conjugated antisense compound of any of embodiments 1-32 wherein the conjugate linker has a structure selected from among:



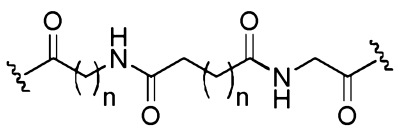
wherein n is from 1 to 20; and p is from 1 to 6. In such embodiments having more than one n, each n is selected independently.

Embodiment 34. The conjugated antisense compound of any of embodiments 1-33 wherein the conjugate linker has a structure selected from among:



wherein n is from 1 to 20.

Embodiment 35. The conjugated antisense compound of any of embodiments 1-33 wherein the conjugate linker has a structure selected from among: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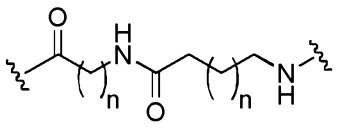
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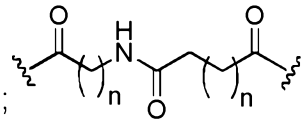
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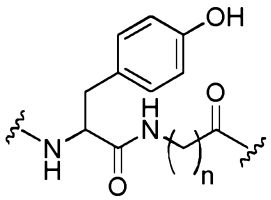
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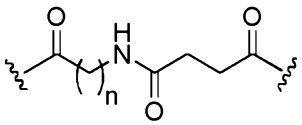
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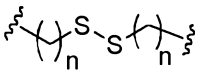
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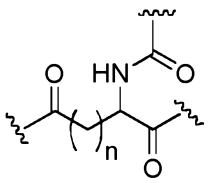
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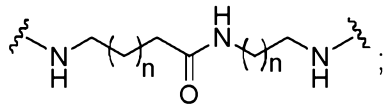
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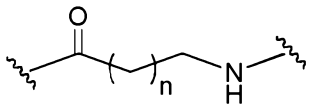
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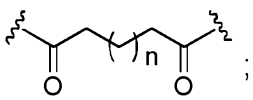
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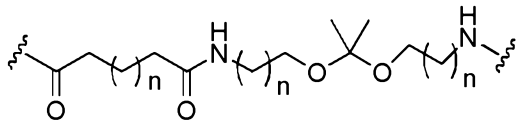
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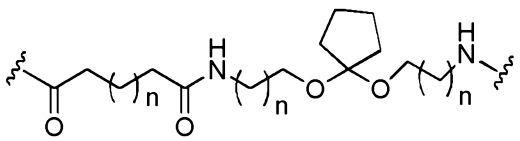
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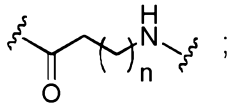
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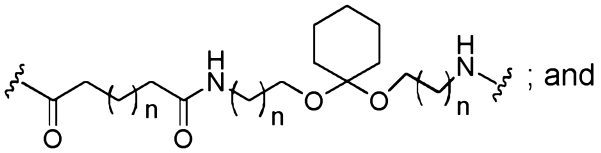
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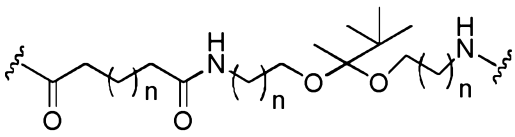
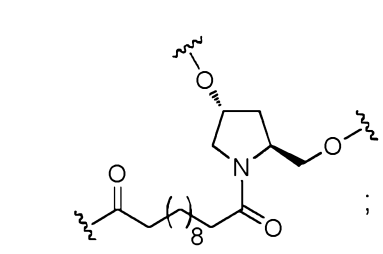


wherein n is from 1 to 20.

Embodiment 36. The conjugated antisense compound of any of embodiments 1-33 wherein the conjugate linker has a structure selected from among: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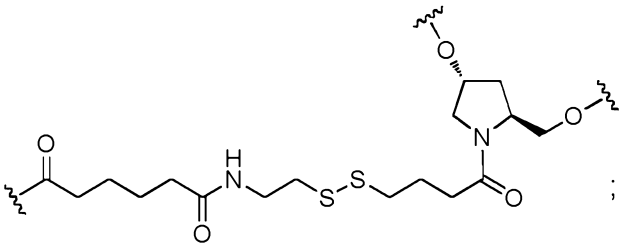
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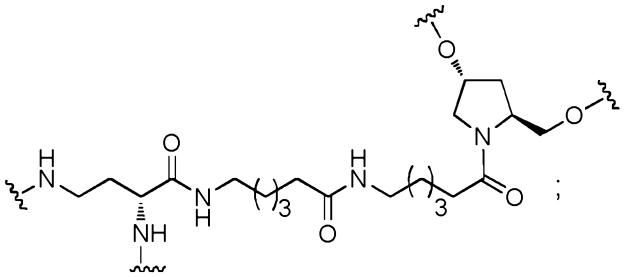
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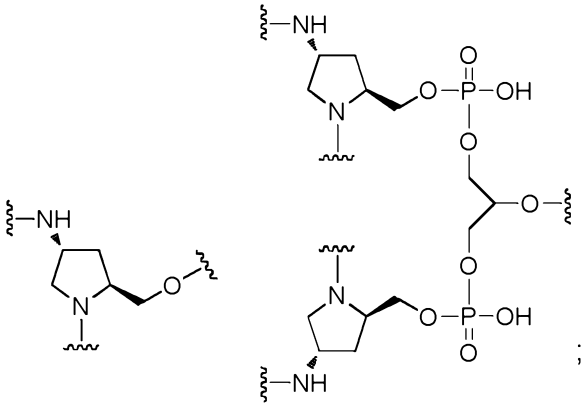
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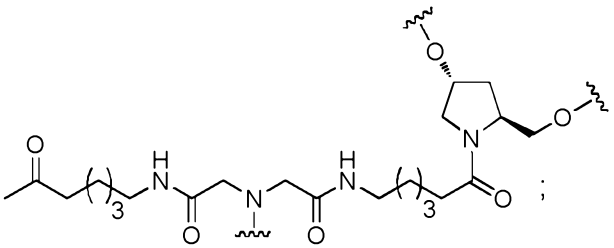
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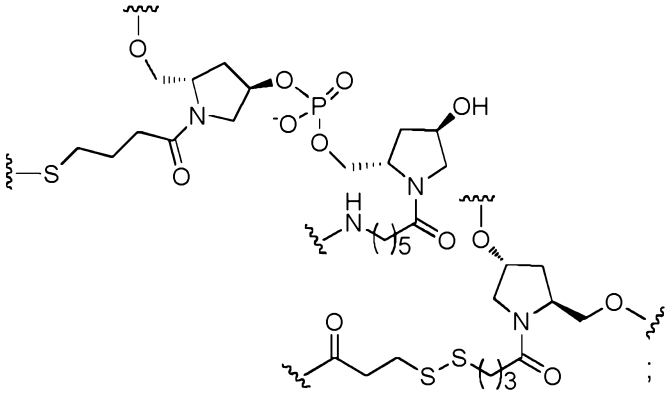
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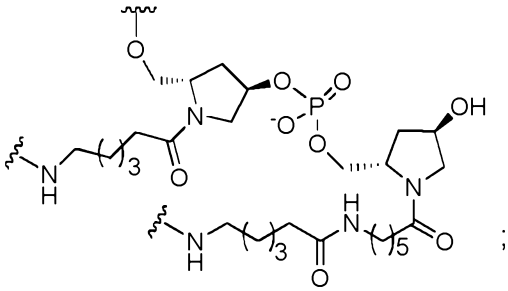
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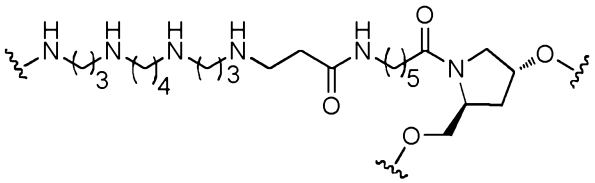
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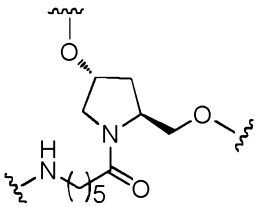
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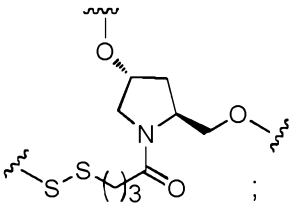
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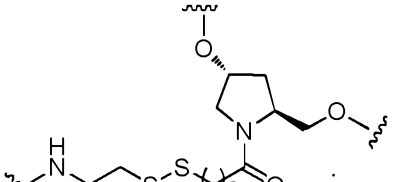
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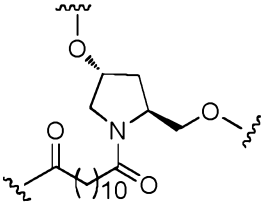
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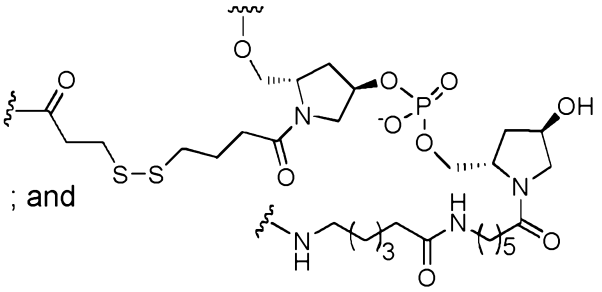
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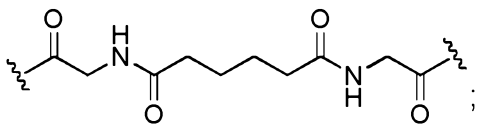
Embodiment 37. The conjugated antisense compound of any of embodiments 1-33 wherein the conjugate linker has a structure selected from among: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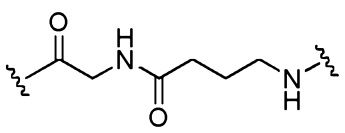
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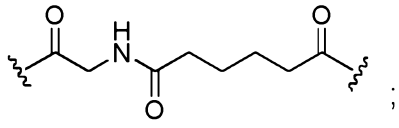
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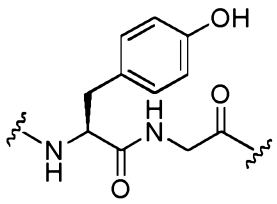
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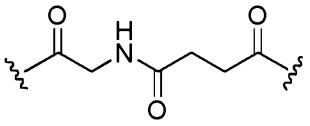
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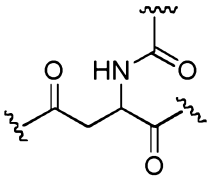
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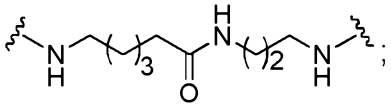
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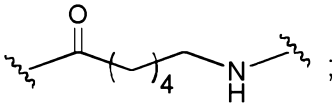
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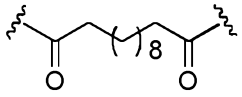
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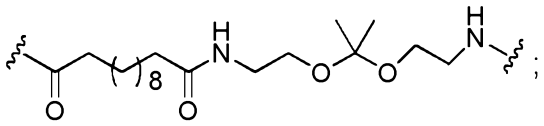
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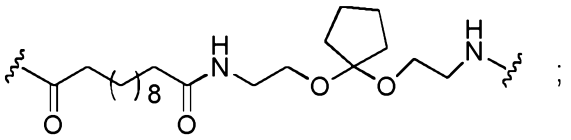
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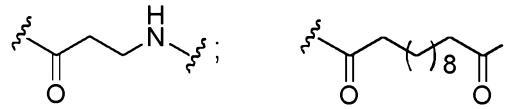
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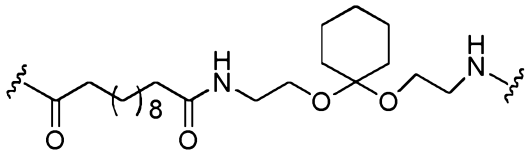
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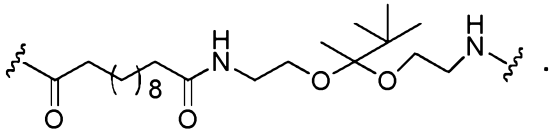
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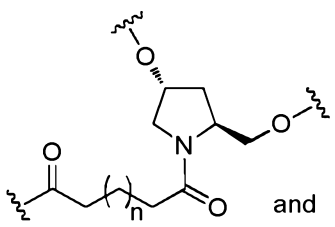
Embodiment 38. The conjugated antisense compound of any of embodiments 1-33 wherein the conjugate linker has a structure selected from among: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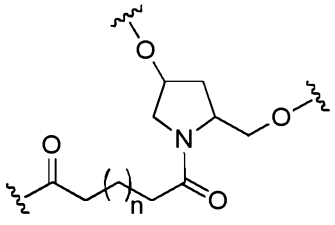
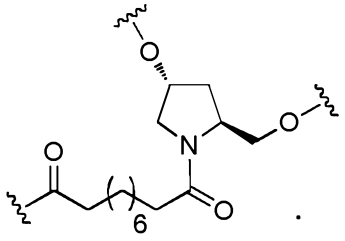


wherein n is from 1 to 20.

Embodiment 39. The conjugated antisense compound of any of embodiments 1-33 wherein the conjugate linker has the structure:



Embodiment 40. The conjugated antisense compound of any of embodiments 1-39, wherein the cell-targeting moiety comprises a carbohydrate.

Embodiment 41. The conjugated antisense compound of any of embodiments 1-40, wherein the cell-targeting moiety comprises a carbohydrate cluster.

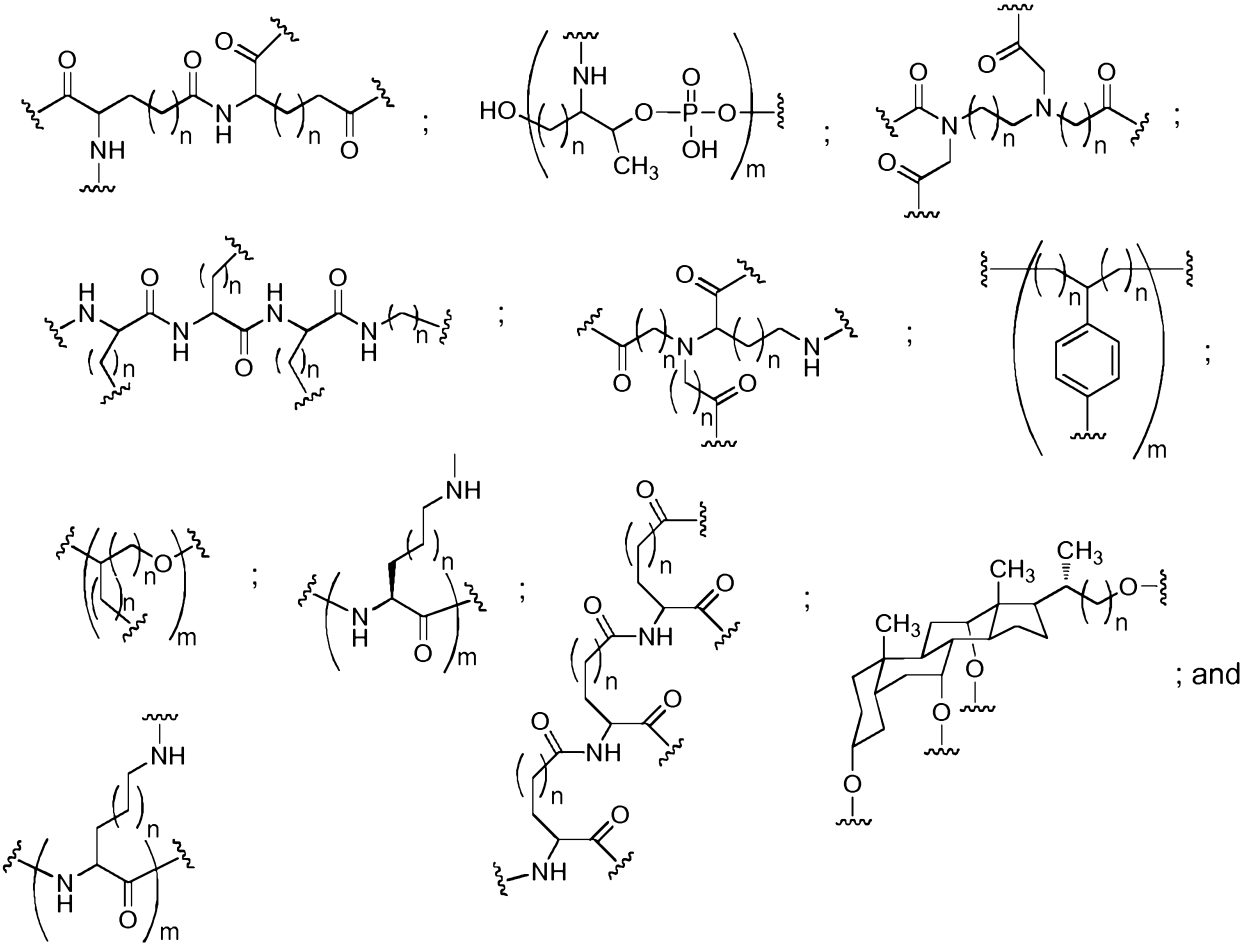
Embodiment 42. The conjugated antisense compound of any of embodiments 1-41, wherein the cell-targeting moiety comprises a cell surface receptor ligand.

Embodiment 43. The conjugated antisense compound of any of embodiments 1-42, wherein the targeting moiety comprises at least one *N*-Acetylgalactosamine (GalNAc).

Embodiment 44. The conjugated antisense compound of any of embodiments 1-43, wherein the targeting moiety comprises a branching group.

Embodiment 45. The conjugated antisense compound of embodiment 44, wherein the branching group comprises an ether.

Embodiment 46. The conjugated antisense compound of embodiment 44 or 45, wherein the branching group has the following structure:

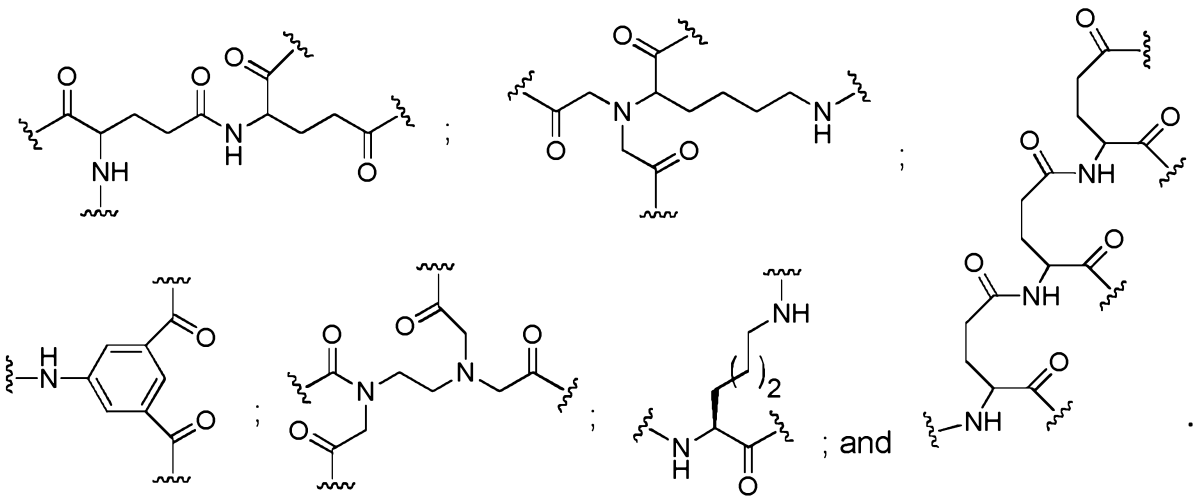


; and

wherein each n is, independently, from 1 to 20; and

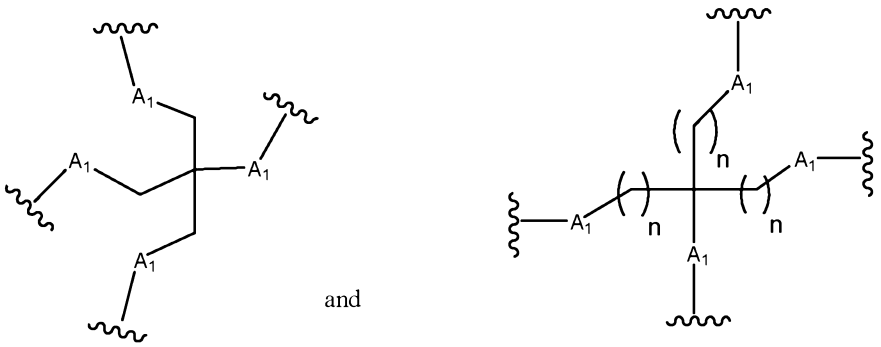
m is from 2 to 6.

Embodiment 47. The conjugated antisense compound of embodiment 44 or 45, wherein the branching group has the following structure:



; ; ; ; ; and .

Embodiment 48. The conjugated antisense compound of embodiment 44 or 45, wherein the branching group has the following structure:

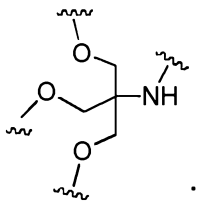


and

wherein each A_1 is independently, O, S, C=O or NH; and

each n is, independently, from 1 to 20.

Embodiment 49. The conjugated antisense compound of embodiment 44 or 45, wherein the branching group has the following structure:



.

Embodiment 50. The conjugated antisense compound of any embodiments 1-49, wherein the cell-targeting moiety comprises a tether.

Embodiment 51. The conjugated antisense compound of any embodiments 1-49, wherein the cell-targeting moiety comprises two tethers.

Embodiment 52. The conjugated antisense compound of any embodiments 1-49, wherein the cell-targeting moiety comprises three tethers.

Embodiment 53. The conjugated antisense compound of any embodiments 1-49, wherein the cell-targeting moiety comprises four or more tethers.

Embodiment 54. The conjugated antisense compound of any of embodiments 1-53, wherein at least one tether comprises PEG.

Embodiment 55. The conjugated antisense compound of any of embodiments 1-54, wherein at least one tether comprises an amide.

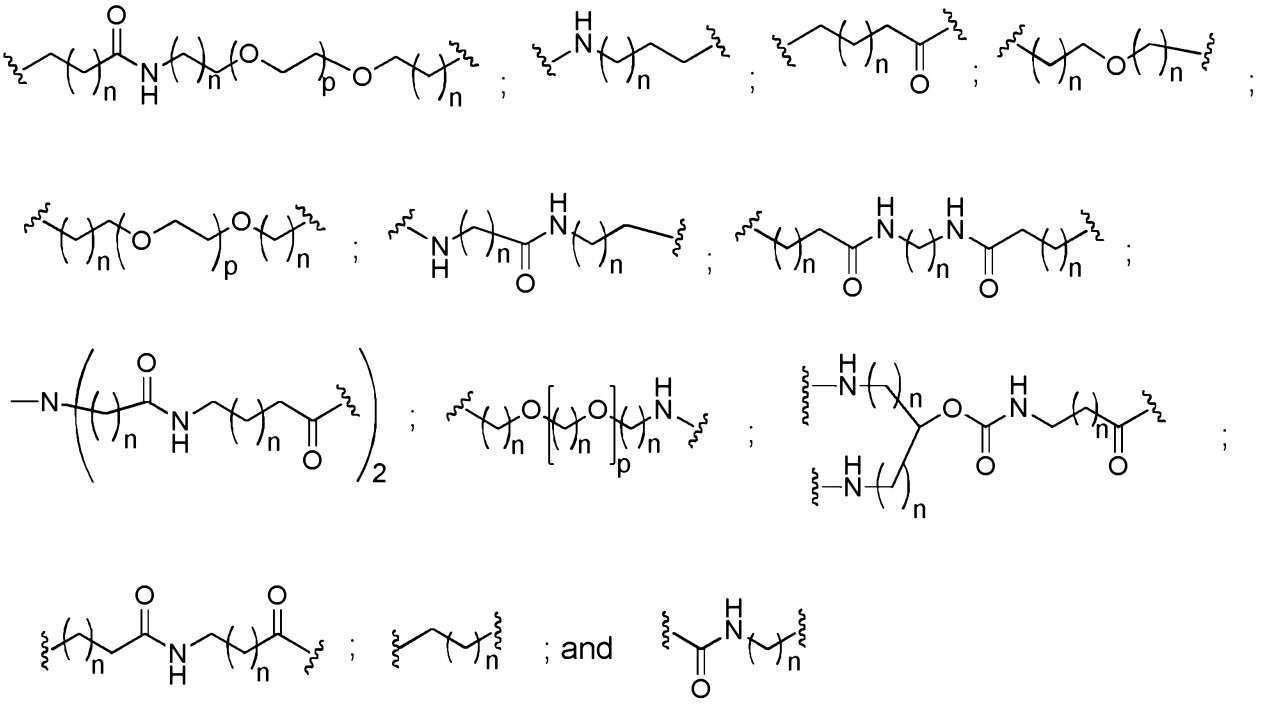
Embodiment 56. The conjugated antisense compound of any of embodiments 1-55, wherein at least one tether comprises a polyamide.

Embodiment 57. The conjugated antisense compound of any of embodiments 1-56, wherein at least one tether comprises an amine.

Embodiment 58. The conjugated antisense compound of any of embodiments 1-57, wherein at least two tethers are different from one another.

Embodiment 59. The conjugated antisense compound of any of embodiments 1-57, wherein all of the tethers are the same as one another.

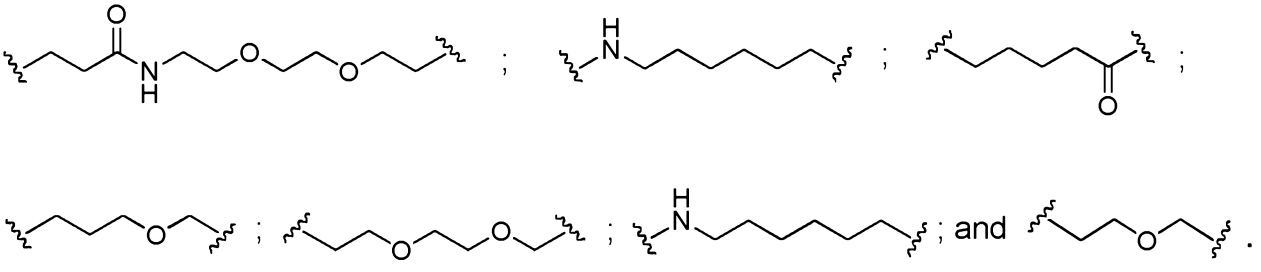
Embodiment 60. The conjugated antisense compound of any of embodiments 1-59, wherein each tether is selected from among:



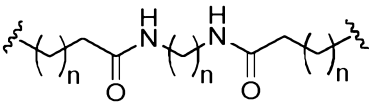
wherein each n is, independently, from 1 to 20; and

each p is from 1 to about 6.

Embodiment 61. The conjugated antisense compound of any of embodiments 1-60, wherein each tether is selected from among:

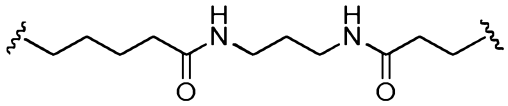


Embodiment 62. The conjugated antisense compound of any of embodiments 1-61, wherein each tether has the following structure:



wherein each n is, independently, from 1 to 20.

Embodiment 63. The conjugated antisense compound of any of embodiments 1-61, wherein each tether has the following structure:



Embodiment 64. The conjugated antisense compound of any of embodiments 1-63, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 65. The conjugated antisense compound of embodiment 64, wherein the cell-targeting moiety comprises one ligand.

Embodiment 66. The conjugated antisense compound of embodiment 64, wherein the targeting moiety comprises two ligands.

Embodiment 67. The conjugated antisense compound of embodiment 64, wherein the targeting moiety comprises three ligands.

Embodiment 68. The conjugated antisense compound of any of embodiments 64-67, wherein a ligand is covalently attached to each tether.

Embodiment 69. The conjugated antisense compound of any of embodiments 1 to 68, wherein at least one ligand is *N*-Acetylgalactosamine (GalNAc).

Embodiment 70. The conjugated antisense compound of any of embodiments 1 to 69, wherein each ligand is N-Acetylgalactosamine (GalNAc).

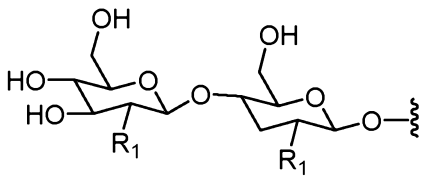
Embodiment 71. The conjugated antisense compound of any of embodiments 1-70, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-

D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

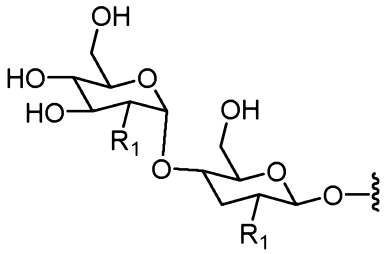
Embodiment 72. The conjugated antisense compound of any of embodiments 1-71, wherein the ligand is galactose.

Embodiment 73. The conjugated antisense compound of any of embodiments 1-71, wherein the ligand is mannose-6-phosphate.

Embodiment 74. The conjugated antisense compound of any of embodiments 1-71, wherein each ligand is selected from among:

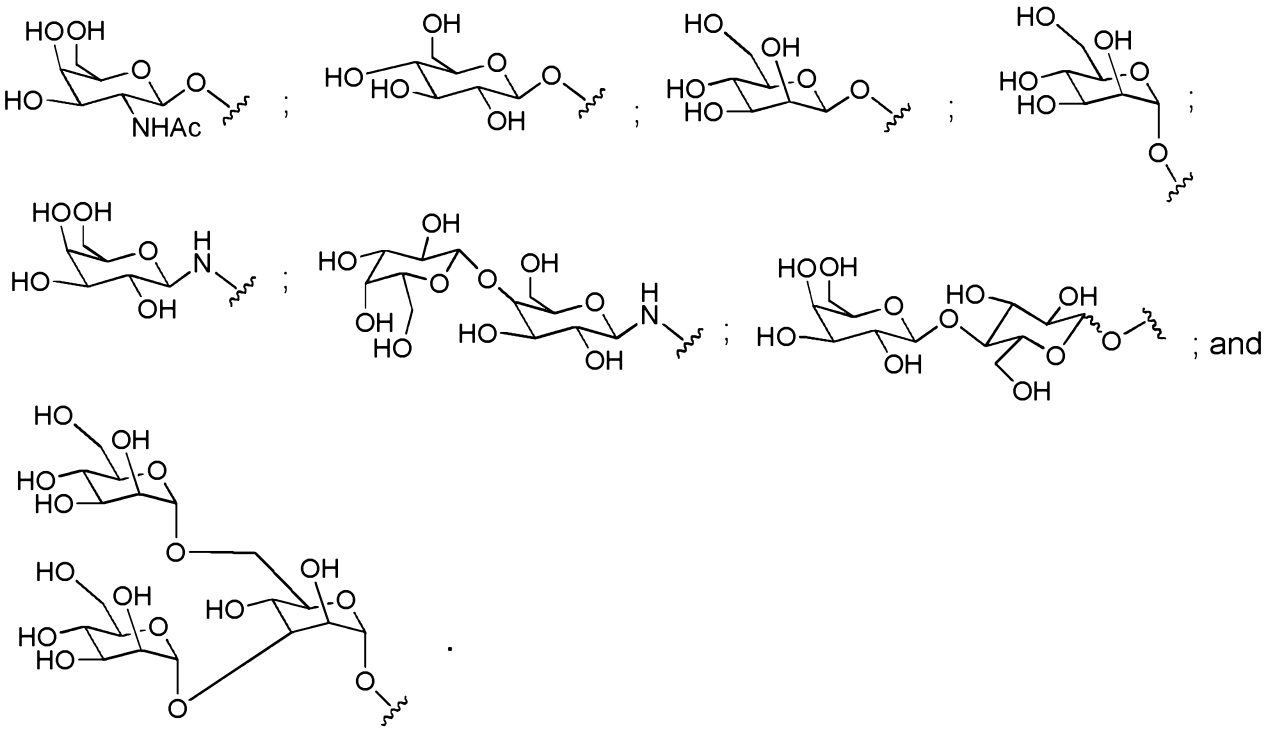


and

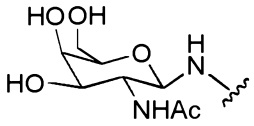


wherein each R_1 is selected from OH and NHCOOH.

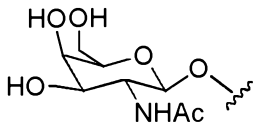
Embodiment 75. The conjugated antisense compound of any of embodiments 1-71, wherein each ligand is selected from among:



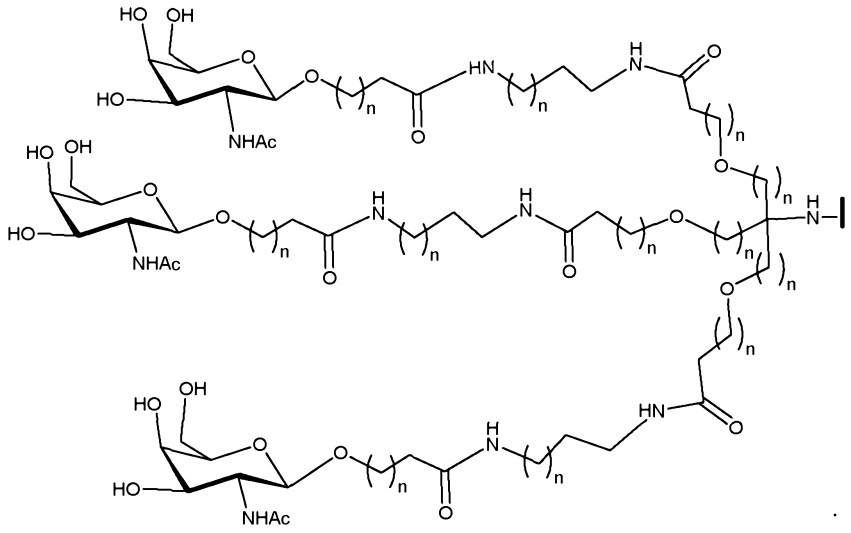
Embodiment 76. The conjugated antisense compound of any of embodiments 1-71, wherein each ligand has the following structure:



Embodiment 77. The conjugated antisense compound of any of embodiments 1-71, wherein each ligand has the following structure:

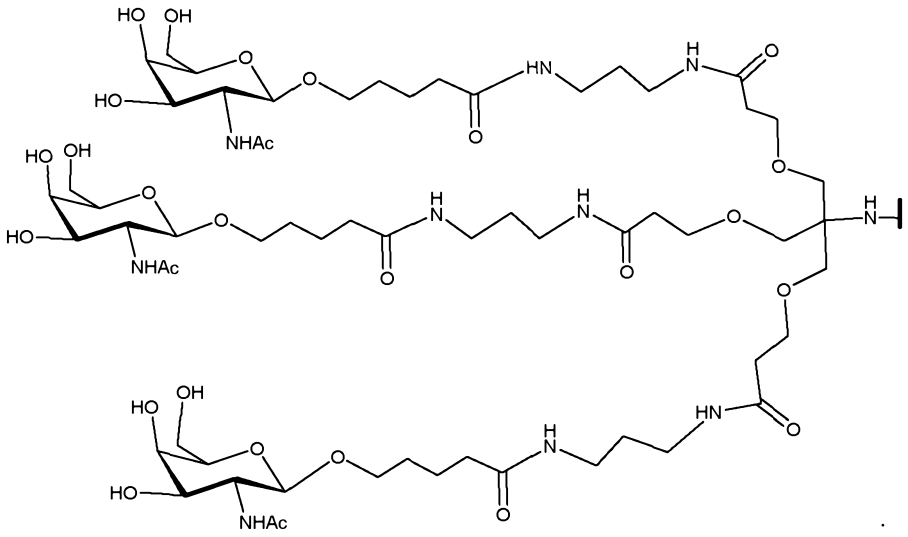


Embodiment 78. The conjugated antisense compound of any of embodiments 1-77, wherein the cell-targeting group has the following structure:

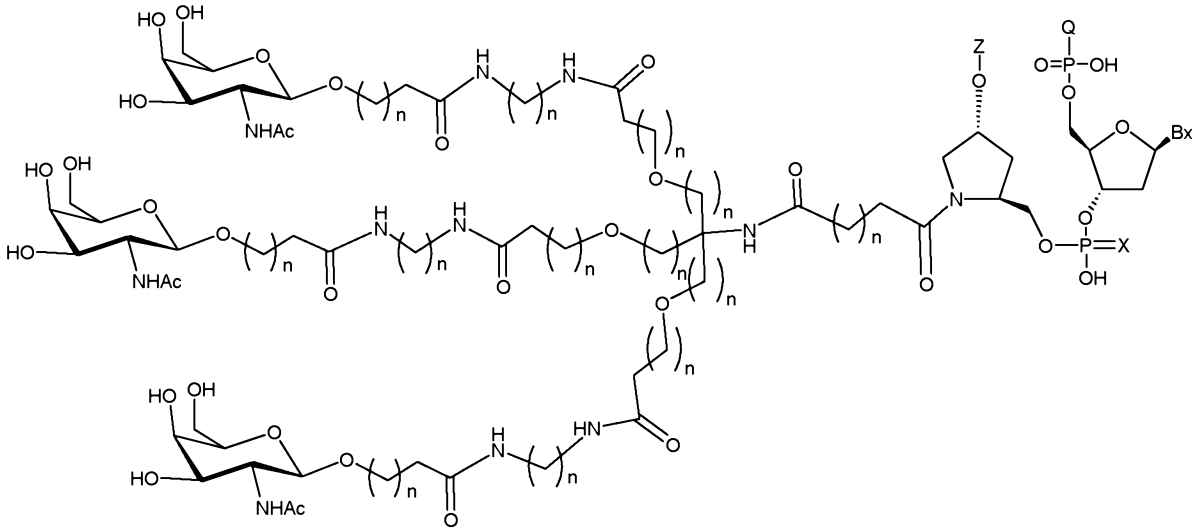


wherein each n is, independently, from 1 to 20.

Embodiment 79. The conjugated antisense compound of any of embodiments 1-77, wherein the cell-targeting group has the following structure:



Embodiment 80. The conjugated antisense compound of any of embodiments 1-79, wherein the conjugate has the following structure:



wherein each n is, independently, from 1 to 20;

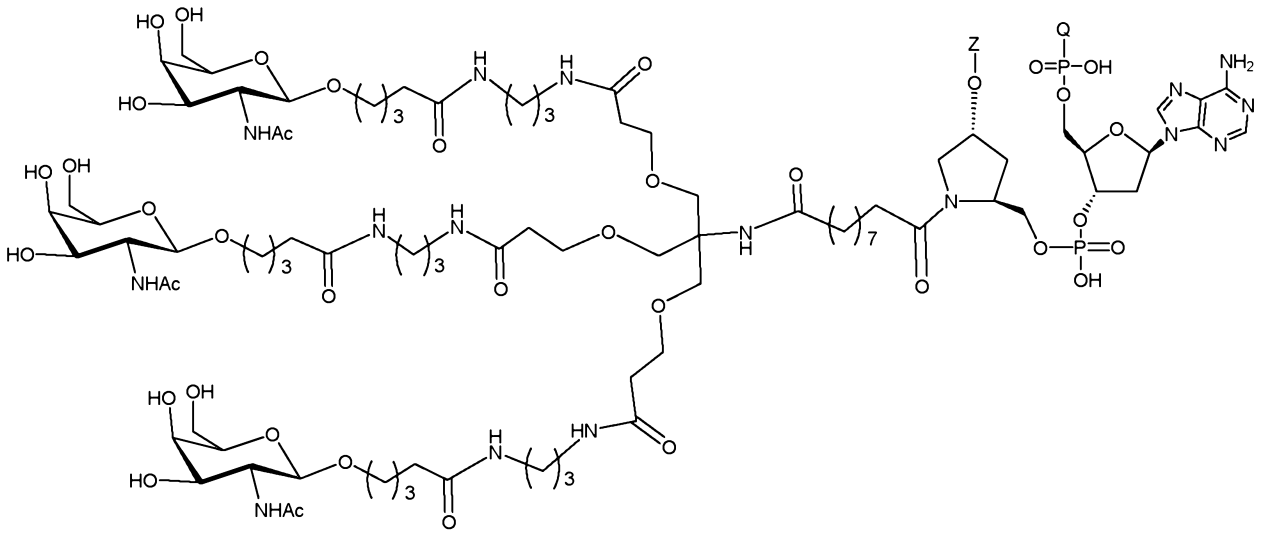
Z is H or a linked solid support;

Q is said antisense compound;

X is O or S; and

Bx is a heterocyclic base moiety.

Embodiment 81. The conjugated antisense compound of any of embodiments 1-79, wherein the conjugate has the following structure:



wherein Z is H or a linked solid support;

Q is said antisense compound.

Embodiment 82. The conjugated antisense compound of any of embodiments 1-81, wherein the conjugate group is attached to the 2'-position of a nucleoside of the antisense oligonucleotide.

Embodiment 83. The conjugated antisense compound of any of embodiments 1-81, wherein the conjugate group is attached to the 3'-position of a nucleoside of the antisense oligonucleotide.

Embodiment 84. The conjugated antisense compound of any of embodiments 1-81, wherein the conjugate group is attached to the 5'-position of a nucleoside of the antisense oligonucleotide.

Embodiment 85. The conjugated antisense compound of any of embodiments 1-82, wherein the conjugate group is attached to the 5'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 86. The conjugated antisense compound of any of embodiments 1-84, wherein the conjugate group is attached to the 3'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 87. The conjugated antisense compound of any of embodiments 1-84, wherein the conjugate group is attached to an internal nucleoside of the antisense oligonucleotide.

Embodiment 88. The conjugated antisense compound of any of embodiments 1-87, wherein the conjugate group increases uptake of the conjugated antisense compound into a hepatocyte relative to an unconjugated antisense compound.

Embodiment 89. The conjugated antisense compound of any of embodiments 1-88, wherein the conjugate group increases the uptake of the conjugated antisense compound into a liver cell relative to an unconjugated antisense compound.

Embodiment 90. The conjugated antisense compound of any of embodiments 1-89, wherein the conjugate group increases accumulation of the conjugated antisense compound in the liver relative to an unconjugated antisense compound.

Embodiment 91. The conjugated antisense compound of any of embodiments 1-90, wherein the conjugate group decreases accumulation of the conjugated antisense compound in the kidneys relative to an unconjugated antisense compound.

Embodiment 92. The conjugated antisense compound of any of embodiments 1-91, wherein the antisense oligonucleotide is an RNase H based antisense compound.

Embodiment 93. The conjugated antisense compound of any of embodiments 1-92, wherein the antisense oligonucleotide comprises at least one modified nucleoside.

Embodiment 94. The conjugated antisense compound of any of embodiments 1-93, wherein each nucleoside of the antisense oligonucleotide is a modified nucleoside.

Embodiment 95. The conjugated antisense compound of any of embodiments 1-94, wherein the antisense oligonucleotide is single-stranded.

Embodiment 96. The conjugated antisense compound of embodiment 93-95, wherein at least one modified nucleoside comprises a modified sugar moiety.

Embodiment 97. The conjugated antisense compound of embodiment 96, wherein the antisense oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 98. The conjugated antisense compound of embodiment 97, wherein the 5'-region consists of 2 linked 5'-region nucleosides.

Embodiment 99. The conjugated antisense compound of embodiment 97, wherein the 5'-region consists of 3 linked 5'-region nucleosides.

Embodiment 100. The conjugated antisense compound of embodiment 97, wherein the 5'-region consists of 4 linked 5'-region nucleosides.

Embodiment 101. The conjugated antisense compound of embodiment 97, wherein the 5'-region consists of 5 linked 5'-region nucleosides.

Embodiment 102. The conjugated antisense compound of any of embodiments 97-101, wherein the 3'-region consists of 2 linked 3'-region nucleosides.

Embodiment 103. The conjugated antisense compound of any of embodiments 97-101, wherein the 3'-region consists of 3 linked 3'-region nucleosides.

Embodiment 104. The conjugated antisense compound of any of embodiments 97-91, wherein the 3'-region consists of 4 linked 3'-region nucleosides.

Embodiment 105. The conjugated antisense compound of any of embodiments 97-101, wherein the 3'-region consists of 5 linked 3'-region nucleosides.

Embodiment 106. The conjugated antisense compound of any of embodiments 97-105, wherein the central region consists of 5 linked central region nucleosides.

Embodiment 107. The conjugated antisense compound of any of embodiments 97-105, wherein the central region consists of 6 linked central region nucleosides.

Embodiment 108. The conjugated antisense compound of any of embodiments 97-105, wherein the central region consists of 7 linked central region nucleosides.

Embodiment 109. The conjugated antisense compound of any of embodiments 97-105, wherein the central region consists of 8 linked central region nucleosides.

Embodiment 110. The conjugated antisense compound of any of embodiments 97-105, wherein the central region consists of 9 linked central region nucleosides.

Embodiment 111. The conjugated antisense compound of any of embodiments 97-105, wherein the central region consists of 10 linked central region nucleosides.

Embodiment 112. The conjugated antisense compound of any of embodiments 1-111, wherein the antisense oligonucleotide consists of 14 to 26 linked nucleosides.

Embodiment 113. The conjugated antisense compound of any of embodiments 1-111, wherein the antisense oligonucleotide consists of 15 to 25 linked nucleosides.

Embodiment 114. The conjugated antisense compound of any of embodiments 1-111, wherein the antisense oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 115. The conjugated antisense compound of any of embodiments 1-114, wherein each modified nucleoside independently comprises a 2'-substituted sugar moiety or a bicyclic sugar moiety.

Embodiment 116. The conjugated antisense compound of embodiment 115, wherein the at least one modified nucleoside comprises a 2'-substituted sugar moiety.

Embodiment 117. The conjugated antisense compound of embodiment 116, wherein each modified nucleoside comprising a 2'-substituted sugar moiety comprises a 2' substituent independently selected from among: halogen, optionally substituted allyl, optionally substituted amino, azido, optionally substituted SH, CN, OCN, CF_3, OCF_3, O, S, or N(Rm)-alkyl; O, S, or N(Rm)-alkenyl; O, S or N(Rm)-alkynyl; optionally substituted O-alkylenyl-O-alkyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted O-alkaryl, optionally substituted O-aralkyl, $O(CH_2)_2SCH_3$, $O-(CH_2)_2-O-N(Rm)(Rn)$ or O-CH2-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl;

wherein each optionally substituted group is optionally substituted with a substituent group independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

Embodiment 118. The conjugated antisense compound of embodiment 116, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, $OCH_2-CH=CH_2$, $O(CH_2)_2-OCH_3$, $O(CH_2)_2-SCH_3$, $O(CH_2)_2-OCF_3$, $O(CH_2)_3-N(R_1)(R_2)$, $O(CH_2)_2-ON(R_1)(R_2)$, $O(CH_2)_2-O(CH_2)_2-N(R_1)(R_2)$, $OCH_2C(=O)-N(R_1)(R_2)$,

$OCH_2C(=O)$-$N(R_3)$-$(CH_2)_2$-$N(R_1)(R_2)$, and $O(CH_2)_2$-$N(R_3)$-$C(=NR_4)[N(R_1)(R_2)]$; wherein R_1, R_2, R_3 and R_4 are each, independently, H or C_1-C_6 alkyl.

Embodiment 119. The conjugated antisense compound of embodiment 116, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$.

Embodiment 120. The conjugated antisense compound of embodiment 116, wherein the at least one 2'-modified nucleoside comprises a 2'-MOE sugar moiety.

Embodiment 121. The conjugated antisense compound of embodiment 116, wherein the at least one 2'-modified nucleoside comprises a 2'-OMe sugar moiety.

Embodiment 122. The conjugated antisense compound of embodiment 116, wherein the at least one 2'-modified nucleoside comprises a 2'-F sugar moiety.

Embodiment 123. The conjugated antisense compound of any of embodiments 1-122, wherein the antisense oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 124. The conjugated antisense compound of embodiment 123, wherein the modified nucleoside comprises an F-HNA sugar moiety.

Embodiment 125. The conjugated antisense compound of embodiment 123, wherein the modified nucleoside comprises an HNA sugar moiety.

Embodiment 126. The conjugated antisense compound of any of embodiments 1-125 wherein the antisense oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 127. The conjugated antisense compound of embodiment 126, wherein the bicyclic sugar moiety is a cEt sugar moiety.

Embodiment 128. The conjugated antisense compound of embodiment 126, wherein bicyclic sugar moiety is an LNA sugar moiety.

Embodiment 129. The conjugated antisense compound of any of embodiments 1-128, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 130. The conjugated antisense compound of embodiment 129, wherein each internucleoside linkage of the antisense oligonucleotide is a modified internucleoside linkage.

Embodiment 131. The conjugated antisense compound of embodiment 129, wherein the antisense oligonucleotide comprises at least one modified linkage and at least one unmodified phosphodiester internucleoside linkage.

Embodiment 132. The conjugated antisense compound of any of embodiments 129-131 wherein at least one modified internucleoside linkage is a phosphosphorothioate internucleoside linkage.

Embodiment 133. The conjugated antisense compound of any of embodiments 129-122, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 134. The conjugated antisense compound of any of embodiments 129-133, wherein the antisense oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 135. The conjugated antisense compound of any of embodiments 129-133, wherein the antisense oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 136. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 137. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 138. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 139. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 140. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 8 phosphodiester internucleoside linkages.

Embodiment 141. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 9 phosphodiester internucleoside linkages.

Embodiment 142. The conjugated antisense compound of any of embodiments 129-132, wherein the antisense oligonucleotide comprises at least 10 phosphodiester internucleoside linkages.

Embodiment 143. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 16 phosphorothioate internucleoside linkages.

Embodiment 144. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 15 phosphorothioate internucleoside linkages.

Embodiment 145. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 14 phosphorothioate internucleoside linkages.

Embodiment 146. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 13 phosphorothioate internucleoside linkages.

Embodiment 147. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 12 phosphorothioate internucleoside linkages.

Embodiment 148. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 11 phosphorothioate internucleoside linkages.

Embodiment 149. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 10 phosphorothioate internucleoside linkages.

Embodiment 150. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 9 phosphorothioate internucleoside linkages.

Embodiment 151. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 8 phosphorothioate internucleoside linkages.

Embodiment 152. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 7 phosphorothioate internucleoside linkages.

Embodiment 153. The conjugated antisense compound of any of embodiments 129-142, wherein the antisense oligonucleotide comprises fewer than 6 phosphorothioate internucleoside linkages.

Embodiment 154. The conjugated antisense compound of any of embodiments 129-153, wherein each terminal internucleoside linkage of the antisense oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 155. The conjugated antisense compound of any of embodiments 129-154, wherein each internucleoside linkage linking two deoxynucleosides of the antisense oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 156. The conjugated antisense compound of any of embodiments 129-155, wherein each non-terminal internucleoside linkage linking two modified nucleosides of the antisense oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 157. The conjugated antisense compound of any of embodiments 129-156, wherein each non-terminal internucleoside linkage of the antisense oligonucleotide that is 3' of a modified nucleoside is a phosphodiester internucleoside linkage.

Embodiment 158. The conjugated antisense compound of any of embodiments 129-157, wherein each internucleoside linkage of the antisense oligonucleotide that is 3' of a deoxynucleoside is a phosphorothioate internucleoside linkage.

Embodiment 159. The conjugated antisense compound of any of embodiments 1-158 wherein the antisense oligonucleotides has a chemical motif selected from among:

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$; and
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each s is a phosphorothioate internucleoside linkage, and each y is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage, provided that at least one y is a phosphodiester internucleotide linkage.

Embodiment 160. The conjugated antisense compound of any of embodiments 1-158 wherein the antisense oligonucleotides has a chemical motif selected from among:

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$; and
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each o is a phosphodiester internucleoside linkage, and each s is a phosphorothioate internucleoside linkage.

Embodiment 161. The conjugated antisense compound of embodiment 159 or 160, wherein each M is independently selected from among: a 2'-MOE nucleoside and a bicyclic nucleoside.

Embodiment 162. The conjugated antisense compound of embodiment 161, wherein each M is independently selected from among a 2'-MOE nucleoside, a cEt nucleoside, and an LNA nucleoside.

Embodiment 163. The conjugated antisense compound of embodiment 159 or 160, wherein each M is a 2'-MOE nucleoside.

Embodiment 164. The conjugated antisense compound of embodiment 159 or 160, wherein each M is a cEt nucleoside.

Embodiment 165. The conjugated antisense compound of embodiments 159 or 160, wherein each M is an LNA nucleoside.

Embodiment 166. The conjugated antisense compound of any of embodiments 1-165, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 8 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 167. The conjugated antisense compound of any of embodiments 1-165, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 10 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 168. The conjugated antisense compound of any of embodiments 1-165, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 12 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 169. The conjugated antisense compound of any of embodiments 1-165, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 14 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 170. The conjugated antisense compound of any of embodiments 1-165, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 16 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 171. The conjugated antisense compound of any of embodiments 1-165, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 18 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 172. The conjugated antisense compound of any of embodiments 1-171, wherein the antisense oligonucleotide is at least 90% complementary to a target nucleic acid.

Embodiment 173. The conjugated antisense compound of any of embodiments 1-171, wherein the antisense oligonucleotide is at least 95% complementary to a target nucleic acid.

Embodiment 174. The conjugated antisense compound of any of embodiments 1-171, wherein the antisense oligonucleotide is 100% complementary to a target nucleic acid.

Embodiment 175. The conjugated antisense compound of any of embodiments 166-174, wherein the target nucleic acid is a pre-mRNA.

Embodiment 176. The conjugated antisense compound of any of embodiments 166-174, wherein the target nucleic acid is an mRNA.

Embodiment 177. The conjugated antisense compound of any of embodiments 166-176, wherein the target nucleic acid is expressed in the liver.

Embodiment 178. The conjugated antisense compound of embodiment 177, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 179. The conjugated antisense compound of embodiment 177 or 178, wherein the target nucleic encodes a protein selected from among: Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI, Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, and Transthyretin.

Embodiment 180. The conjugated antisense compound of embodiment 166-179 wherein the target nucleic acid is a viral nucleic acid.

Embodiment 181. The conjugated antisense compound of embodiment 180, wherein the viral nucleic acid expressed in the liver.

Embodiment 182. The conjugated antisense compound of embodiment 181, wherein the target nucleic acid is a Hepatitis B viral nucleic acid.

Embodiment 183. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NOs.: 17, 18, 19, 20, 21, 22, 23, or 24.

Embodiment 184. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NO.: 25, 26, 27, 28, 29, or 30.

Embodiment 185. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 31.

Embodiment 186. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 32.

Embodiment 187. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 33.

Embodiment 188. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 34.

Embodiment 189. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 35, 36, 37, 38, 39, 40, 41, 42, or 43.

Embodiment 190. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 44, 45, 46, 47, or 48.

Embodiment 191. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 192. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 60, 61, 62, 63, 64, 65, 66, or 67.

Embodiment 193. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NO.: 69, 70, 71, or 72.

Embodiment 194. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 73.

Embodiment 195. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 74, 75, 76, 77, 78, 79, 80, or 81.

Embodiment 196. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 68.

Embodiment 197. The conjugated antisense compound of any of embodiments 1-179, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 82-103.

Embodiment 198. A method of reducing the amount or activity of a target nucleic acid in a cell, comprising contacting a cell with the conjugated antisense compound of any of embodiments 1-197.

Embodiment 199. The method of embodiment 198, wherein the cell is a liver cell.

Embodiment 200. The method of embodiment 199, wherein the cell is a hepatocyte.

Embodiment 201. The method of any of embodiments 198-200 wherein the cell is in vitro.

Embodiment 202. The method of any of embodiments 198-200 wherein the cell is in an animal.

Embodiment 203. The method of embodiment 202 wherein the animal is a mouse.

Embodiment 204. The method of embodiment 202 wherein the animal is a human.

Embodiment 205. A pharmaceutical composition comprising an conjugated antisense compound according to any of embodiments 1-197 and a pharmaceutically acceptable carrier or diluent.

Embodiment 206. The pharmaceutical composition of embodiment 205 wherein the pharmaceutically acceptable carrier or diluent is selected from among sterile water and sterile saline.

Embodiment 207. A method of treating a disease or condition in an animal comprising administering the pharmaceutical composition of embodiment 205 or 206 to the animal and thereby treating the disease or condition in the animal.

Embodiment 208. The method of embodiment 207 wherein the animal is a mouse.

Embodiment 209. The method of embodiment 207 wherein the animal is a human.

Embodiment 210. The method of any of embodiments 207-209, wherein the disease or condition is a liver disease or condition.

Embodiment 211. The method of any of embodiments 207-210 wherein the administration is parenteral.

Embodiment 212. The method embodiment 211 wherein the administration is by subcutaneous injection.

Embodiment 213. The method of embodiment 211 wherein the administration is by intravenous injection.

Embodiment 214. The method of embodiment 211 wherein the administration is by intramuscular injection.

Embodiment 215. The method of any of embodiments 207-214 wherein the conjugated antisense compound is provided at a dose of 1-10 mg/kg.

Embodiment 216. The method of any of embodiments 207-214 wherein the conjugated antisense compound is provided at a dose of less than 1 mg/kg.

Embodiment 217. The method of any of embodiments 207-216 wherein the conjugated antisense compound is provided at a dose of greater than 10 mg/kg.

Embodiment 218. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided for a dosing period of at least 2 months.

Embodiment 219. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided for a dosing period of at least 4 months.

Embodiment 220. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided for a dosing period of at least 6 months.

Embodiment 221. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of about one dose every week.

Embodiment 222. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of about one dose every two weeks.

Embodiment 223. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of about one dose every three weeks.

Embodiment 224. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every four weeks.

Embodiment 225. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every five weeks.

Embodiment 226. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every six weeks.

Embodiment 227. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every seven weeks.

Embodiment 228. The method of any of embodiments 207-217 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every eight weeks.

Embodiment 229. A conjugated antisense compound comprising: an antisense oligonucleotide comprising 12-30 linked nucleosides, and a conjugate group, wherein the conjugate group comprises at least one cell-targeting moiety.

Embodiment 230. The conjugated antisense compound of embodiment 229, wherein the conjugate group comprises 2 cell-targeting moieties.

Embodiment 231. The conjugated antisense compound of embodiment 229, wherein the conjugate group comprises 3 cell-targeting moieties.

Embodiment 232. The conjugated antisense compound of embodiment 229, wherein the conjugate group comprises 4 cell-targeting moieties.

Embodiment 233. The conjugated antisense compound of any of embodiments 229-232, wherein each cell-targeting moiety comprises a cleavable bond.

Embodiment 234. The conjugated antisense compound of any of embodiments 229-233, wherein each cell-targeting moiety comprises a tether and a ligand.

Embodiment 235. The conjugated antisense compound of embodiment 234, wherein the ligand is a cell surface receptor ligand.

Embodiment 236. The conjugated antisense compound of embodiment 235, wherein at least one tether comprises a cleavable bond.

Embodiment 237. The conjugated antisense compound of embodiment 235, wherein each tether comprises a cleavable bond.

Embodiment 238. The conjugated antisense compound of any of embodiments 229-237, wherein the conjugate group comprises a conjugate linker.

Embodiment 239. The conjugated antisense compound of embodiment 238, wherein the conjugate linker comprises one or more cleavable bonds.

Embodiment 240. The conjugated antisense compound of any of embodiments 229-239, wherein the conjugate group comprises a branching group.

Embodiment 241. The conjugated antisense compound of embodiment 240, wherein the branching group comprises one or more cleavable bonds.

Embodiment 242. The conjugated antisense compound of any of embodiments 229-241, wherein the conjugate group comprises a cleavable moiety.

Embodiment 243. The conjugated antisense compound of embodiment 242, wherein the cleavable moiety comprises one or more cleavable bonds.

Embodiment 244. The conjugated antisense compound of any of embodiments 229-243, wherein the conjugate group comprises at least one cleavable bond.

Embodiment 245. The conjugated antisense compound of any of embodiments 229-243, wherein the conjugate group comprises at least two cleavable bonds.

Embodiment 246. The conjugated antisense compound of any of embodiments 229-243, wherein the conjugate group comprises at least 3 cleavable bonds.

Embodiment 247. The conjugated antisense compound of any of embodiments 229-243, wherein the conjugate group comprises at least 4 cleavable bonds.

Embodiment 248. The conjugated antisense compound of any of embodiments 229-243, wherein the conjugate group comprises at least 5 cleavable bonds.

Embodiment 249. The conjugated antisense compound of any of embodiments 229-248, comprising a cleavable bond selected from among an amide, a polyamide, an ester, an ether, a phosphodiester, a phosphate ester, a carbamate, a di-sulfide, or a peptide.

Embodiment 250. The conjugated antisense compound of embodiment 249, wherein the peptide is a di-peptide.

Embodiment 251. The conjugated antisense compound of embodiment 249, wherein the peptide is a tri-peptide.

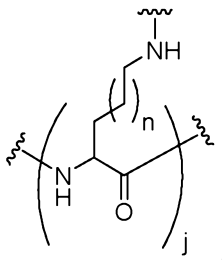
Embodiment 252. The conjugated antisense compound of embodiment 249, wherein the peptide is lysine.

Embodiment 253. The conjugated antisense compound of embodiment 249, wherein the peptide is a lysine derivative.

Embodiment 254. The conjugated antisense compound of any of embodiments 250-251, wherein one or more peptides are lysine.

Embodiment 255. The conjugated antisense compound of any of embodiments 250-251, wherein two or more peptides are lysine.

Embodiment 256. The conjugated antisense compound of any of embodiments 229 to 255 wherein the conjugate group comprises: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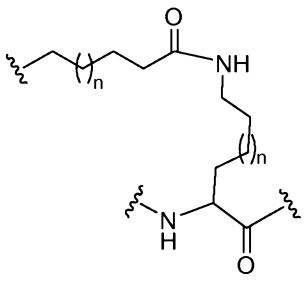
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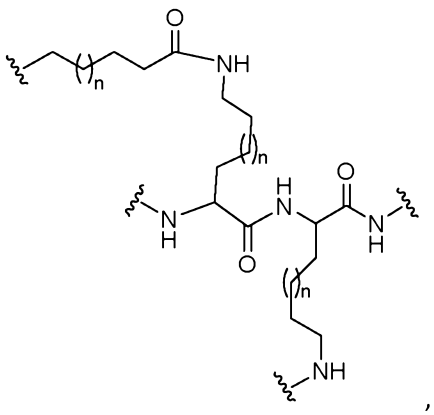
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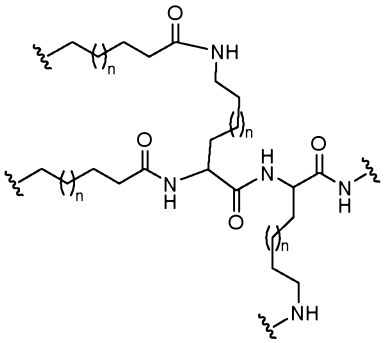
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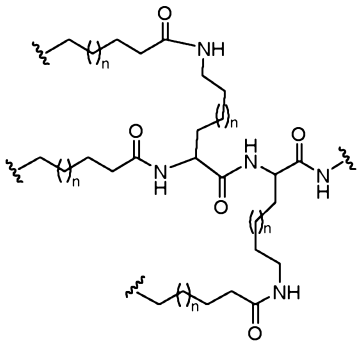
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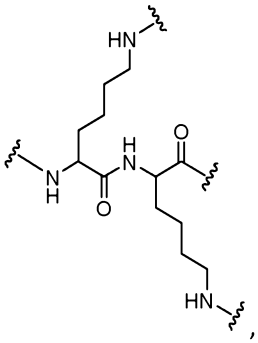
wherein each j is an integer from 1 to 3; and

wherein each n is an integer from 1 to 20.

Embodiment 257. The conjugated antisense compound of any of embodiments 229 to 255 wherein the conjugate group comprises: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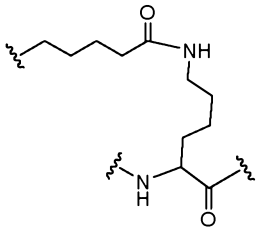
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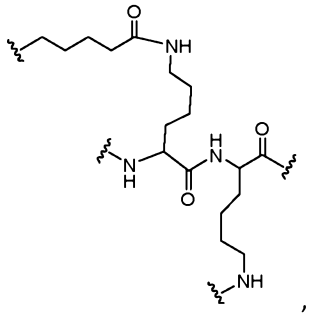
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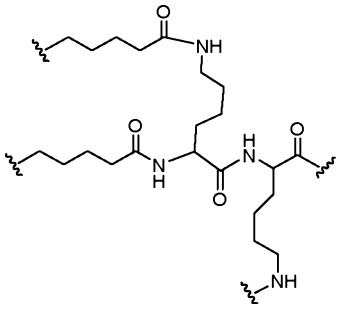
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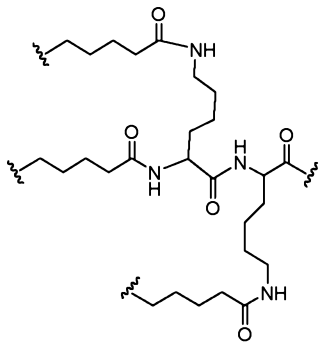
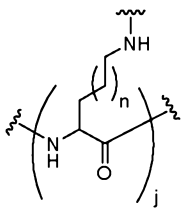

, or .

Embodiment 258. The conjugated antisense compound of any of embodiments 229 to 257 wherein the branching group comprises: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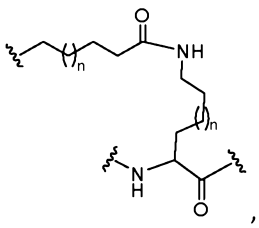
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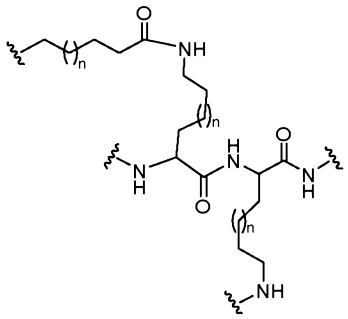
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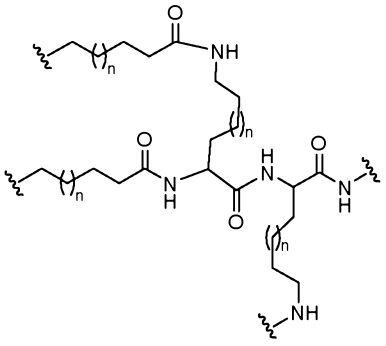
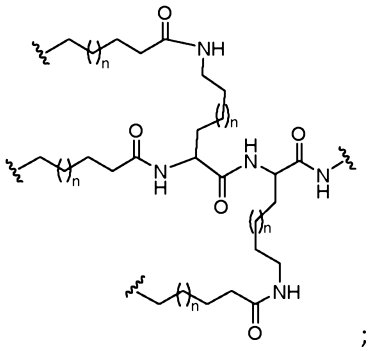

, or

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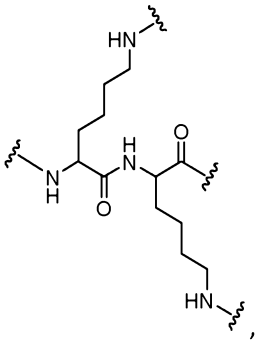
wherein each j is an integer from 1 to 3; and

wherein each n is an integer from 1 to 20.

Embodiment 259. The conjugated antisense compound of any of embodiments 229 to 257 wherein the branching group comprises: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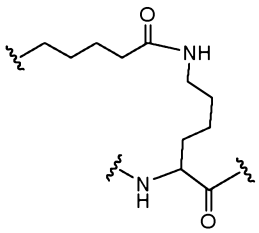
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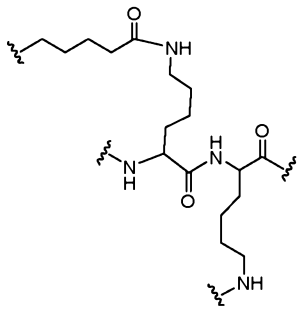
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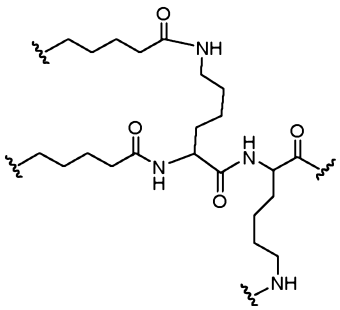
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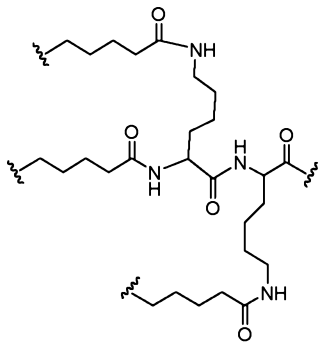
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Embodiment 260. The conjugated antisense compound of any of embodiments 229-259, wherein the cell-targeting moiety comprises a carbohydrate.

Embodiment 261. The conjugated antisense compound of any of embodiments 229-259, wherein the cell-targeting moiety comprises a carbohydrate cluster.

Embodiment 262. The conjugated antisense compound of any of embodiments 229-259, wherein the cell-targeting moiety comprises a cell surface receptor ligand.

Embodiment 263. The conjugated antisense compound of any of embodiments 229-259, wherein the cell-targeting moiety comprises at least one *N*-Acetylgalactosamine (GalNAc).

Embodiment 264. The conjugated antisense compound of any of embodiments 229-263, wherein:
the cleavable moiety is covalently bound to the antisense oligonucleotide;
the conjugate linker is covalently bound to the cleavable moiety; and
the cell-targeting moiety is covalently bound to the conjugate linker.

Embodiment 265. The conjugated antisense compound of any of embodiments 229-264, wherein the cell-targeting moiety comprises a branching group.

Embodiment 266. The conjugated antisense compound of embodiment 265, wherein the branching group is covalently attached to the conjugate linker.

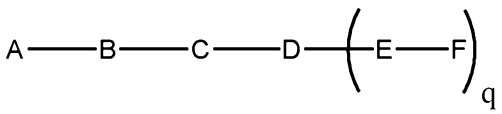
Embodiment 267. The conjugated antisense compound of any of embodiments 229-266, wherein the cell-targeting moiety comprises at least one tether.

Embodiment 268. The conjugated antisense compound any of embodiments 229-267, wherein the at least one tether is covalently attached to the branching group.

Embodiment 269. The conjugated antisense compound of any of embodiments 229-267, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 270. The conjugated antisense compound of embodiment 269, wherein each of the at least one ligand is covalently attached to a tether.

Embodiment 271. The conjugated antisense compound of any of embodiments 229-270, wherein the compound has a structure represented by formula I below:



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.

Embodiment 272. The conjugated antisense compound any of embodiments 229-271, wherein the cleavable moiety comprises 1-4 linked cleavable moiety nucleosides, wherein the linkage between the antisense oligonucleotide and the first cleavable moiety nucleoside is a phosphodiester internucleoside linkage.

Embodiment 273. The conjugated antisense compound of embodiment 272, wherein each internucleoside linkage between each of the linked cleavable moiety nucleosides is a phosphodiester internucleoside linkage.

Embodiment 274. The conjugated antisense compound of embodiment 271 or 272, wherein the cleavable moiety comprises 1-3 linked cleavable moiety nucleosides.

Embodiment 275. The conjugated antisense compound of embodiment 271 or 272, wherein the cleavable moiety comprises 1-2 linked cleavable moiety nucleosides.

Embodiment 276. The conjugated antisense compound of embodiment 271, wherein the cleavable moiety comprises one cleavable moiety nucleoside.

Embodiment 277. The conjugated antisense compound of any of embodiments 229 to 276, wherein the cleavable moiety is a cleavable moiety nucleoside selected from the group consisting of a purine, a substituted purine, a pyrimidine, or a substituted pyrimidine.

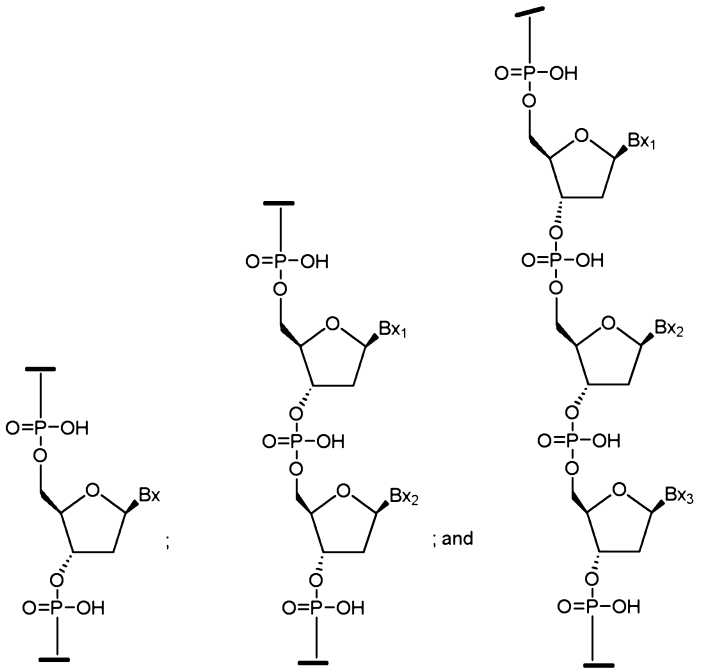
Embodiment 278. The conjugated antisense compound of any of embodiments 229 to 276, wherein the cleavable moiety is a cleavable moiety nucleoside selected from cytidine, uridine, adenosine, thymidine, and guanosine.

Embodiment 279. The conjugated antisense compound of any of embodiments 229 to 276, wherein the cleavable moiety is a cleavable moiety deoxynucleoside selected from deoxyadenosine, deoxyguanosine, deoxyinosine, thymidine, deoxyuridine, and deoxycytidine.

Embodiment 280. The conjugated antisense compound of any of embodiments 229 to 280, wherein the cleavable moiety comprises deoxyadenosine.

Embodiment 281. The conjugated antisense compound of any of embodiments 229 to 280, wherein the cleavable moiety is deoxyadenosine.

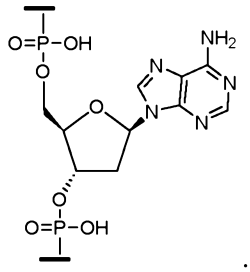
Embodiment 282. The conjugated antisense compound of any of embodiments 229 to 276, wherein the cleavable moiety has a structure selected from among:



wherein each of Bx, Bx_1, Bx_2, and Bx_3 is independently a heterocyclic base moiety.

Embodiment 283. The conjugated antisense compound of embodiment 282, wherein the heterocyclic base moiety is selected from among: uracil, thymine, cytosine, 5-methylcytosine, adenine or guanine.

Embodiment 284. The conjugated antisense compound of any of embodiments 229 to 276, wherein the cleavable moiety has the structure:



Embodiment 285. The conjugated antisense compound of any of embodiments 229 to 285, wherein the conjugate linker comprises a pyrrolidine.

Embodiment 286. The conjugated antisense compound of any of embodiments 229 to 286, wherein the conjugate linker comprises PEG.

Embodiment 287. The conjugated antisense compound of any of embodiments 229 to 287, wherein the conjugate linker comprises an amide.

Embodiment 288. The conjugated antisense compound of any of embodiments 229 to 288, wherein the conjugate linker comprises a polyamide.

Embodiment 289. The conjugated antisense compound of any of embodiments 229 to 289, wherein the conjugate linker comprises an amine.

Embodiment 290. The conjugated antisense compound of any of embodiments 229 to 290, wherein the conjugate linker comprises one or more disulfide bonds.

Embodiment 291. The conjugated antisense compound of any of embodiments 229 to 291, wherein the conjugate linker comprises a protein binding moiety.

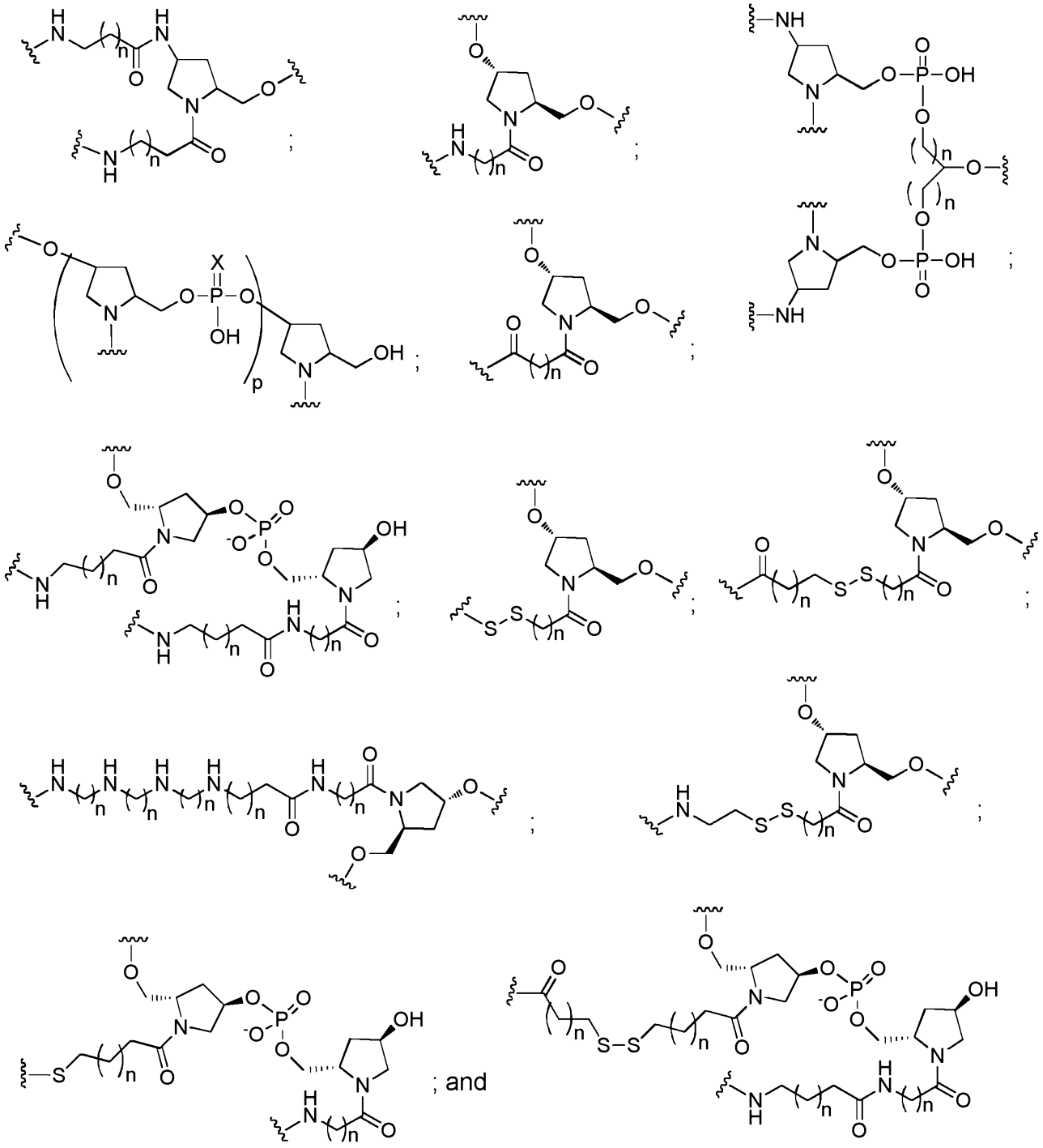
Embodiment 292. The conjugated antisense compound of embodiment 292, wherein the protein binding moiety comprises a lipid.

Embodiment 293. The conjugated antisense compound of embodiment 293, wherein the protein binding moiety is selected from among: cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,

O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), a vitamin (e.g., folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (e.g., monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, e.g., sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid.

Embodiment 294. The conjugated antisense compound of any of embodiments 229 to 293 wherein the protein binding moiety is a C16 to C22 long chain saturated or unsaturated fatty acid, cholesterol, cholic acid, vitamin E, adamantane or 1-pentafluoropropyl.

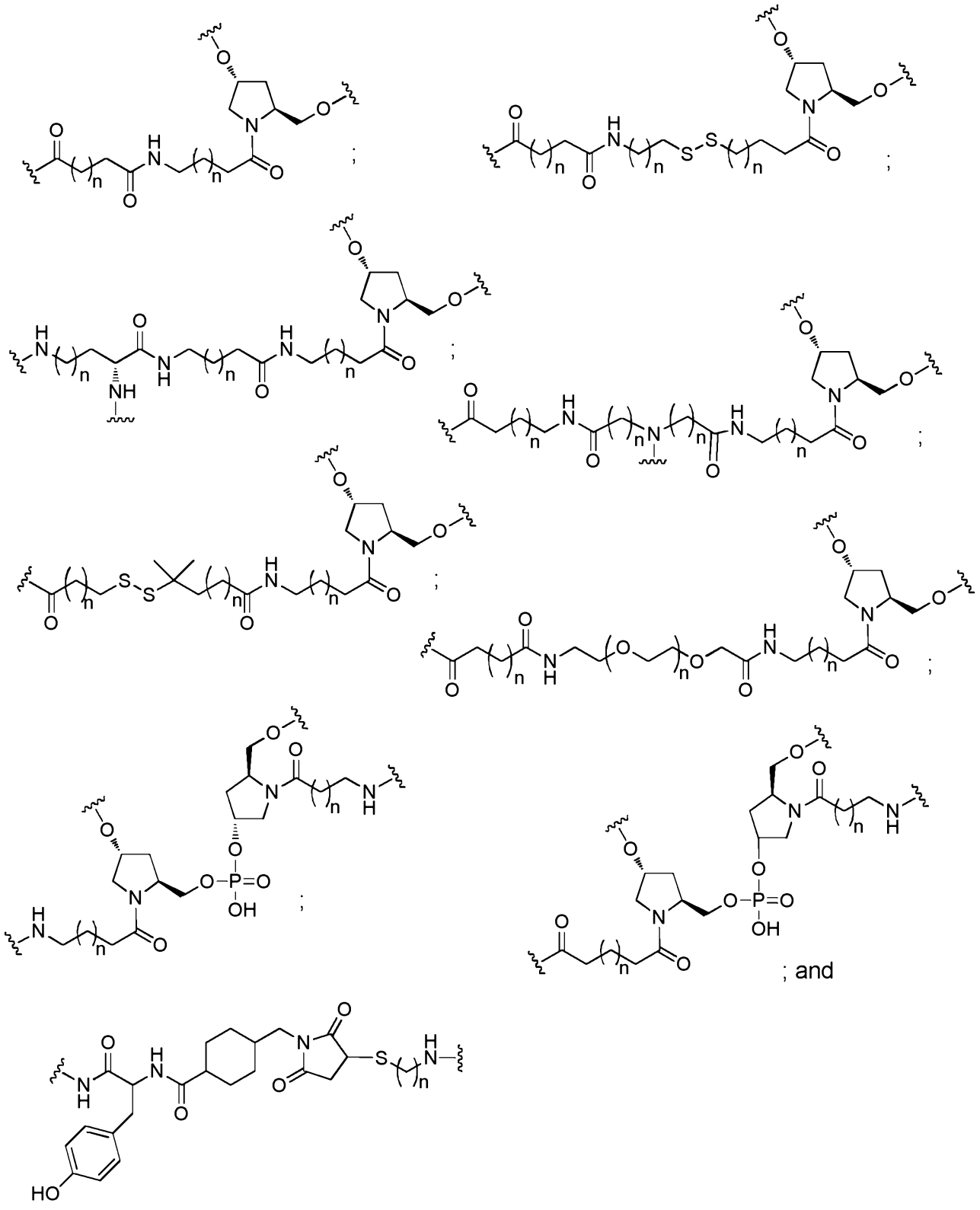
Embodiment 295. The conjugated antisense compound of any of embodiments 229 to 294 wherein the conjugate linker has a structure selected from among:



; and

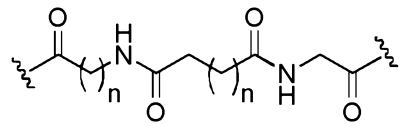
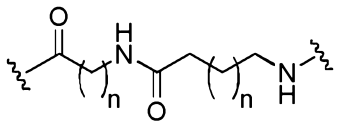
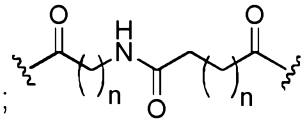
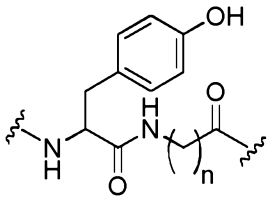
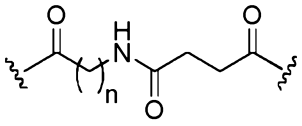
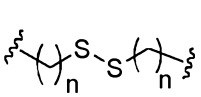
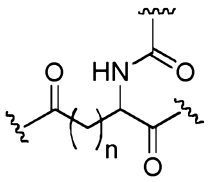
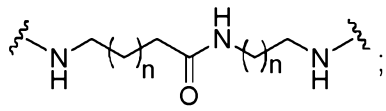
wherein each n is, independently from 1 to 20; and p is from 1 to 6.

Embodiment 296. The conjugated antisense compound of any of embodiments 229 to 295 wherein the conjugate linker has a structure selected from among:



wherein each n is, independently, from 1 to 20.

Embodiment 297. The conjugated antisense compound of any of embodiments 229 to 295 wherein the conjugate linker has a structure selected from among:


;

;

;

;

;

;

;

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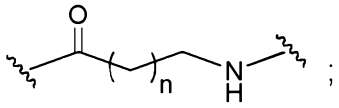
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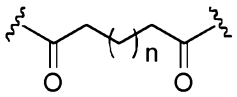
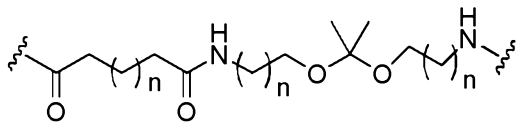
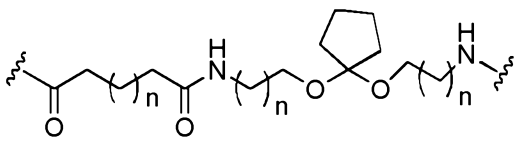

;

;

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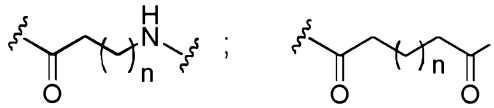
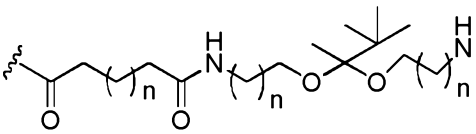

;

;

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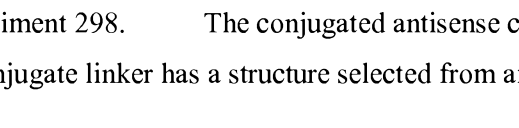
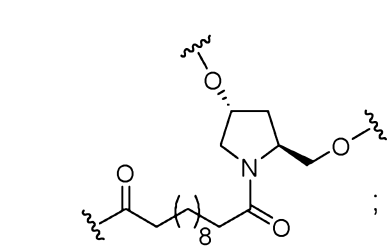

; and

;

wherein each n is, independently, from 1 to 20.

Embodiment 298. The conjugated antisense compound of any of embodiments 229 to 295 wherein the conjugate linker has a structure selected from among: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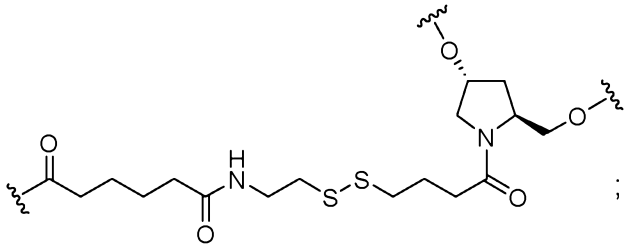
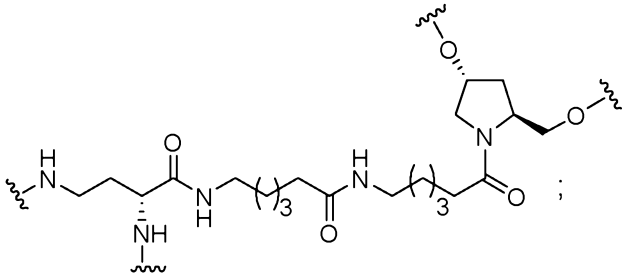
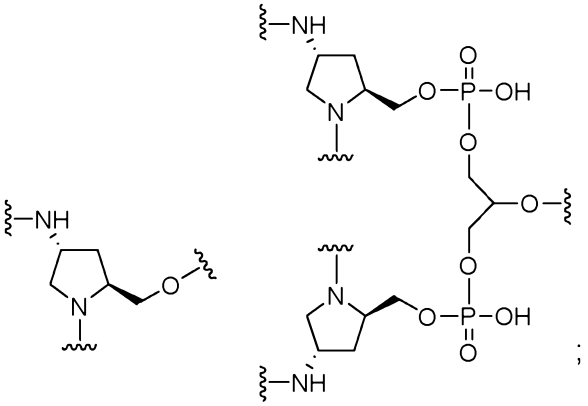

;


;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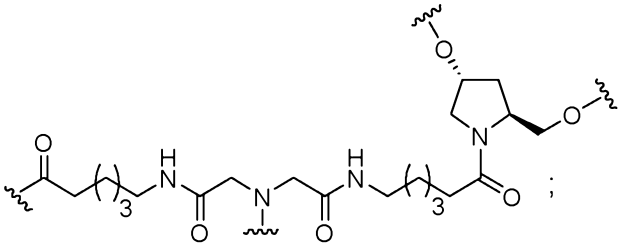
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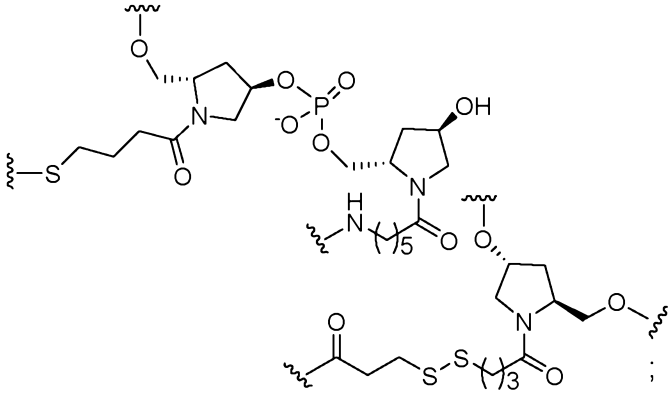
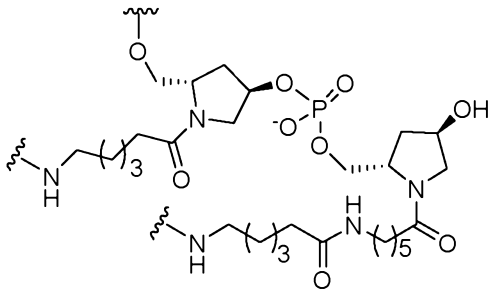

;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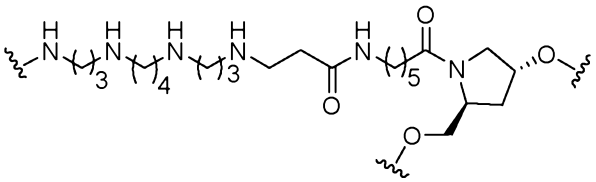
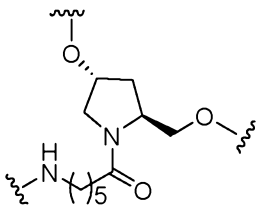

;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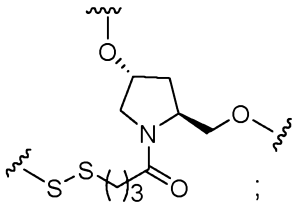
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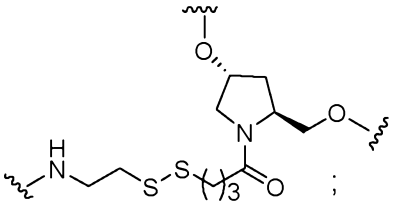
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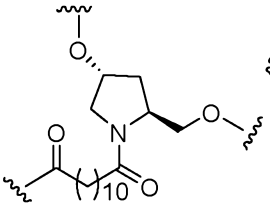
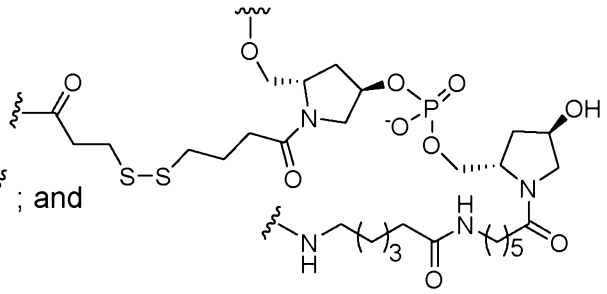
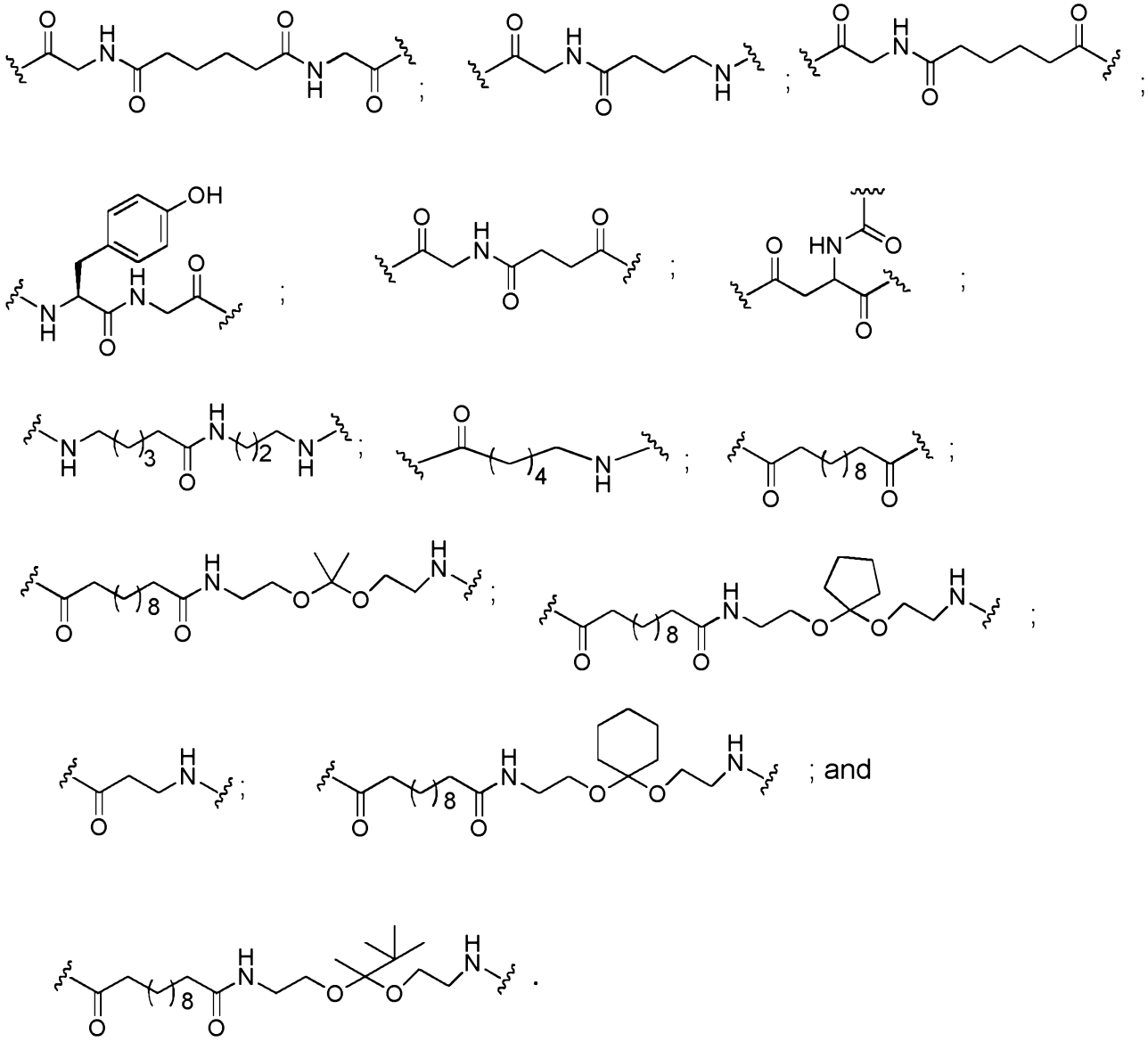
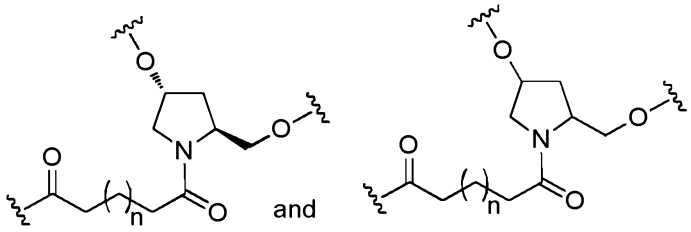

; and


.

Embodiment 299. The conjugated antisense compound of any of embodiments 229 to 295 wherein the conjugate linker has a structure selected from among:

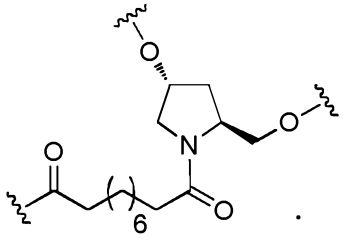


Embodiment 300. The conjugated antisense compound of any of embodiments 229 to 295 wherein the conjugate linker has a structure selected from among:



wherein n is from 1 to 20.

Embodiment 301. The conjugated antisense compound of any of embodiments 229 to 295 wherein the conjugate linker has the structure:



Embodiment 302. The conjugated antisense compound of any of embodiments 229 to 301, wherein the cell-targeting moiety comprises a carbohydrate.

Embodiment 303. The conjugated antisense compound of any of embodiments 229 to 302, wherein the cell-targeting moiety comprises a carbohydrate cluster.

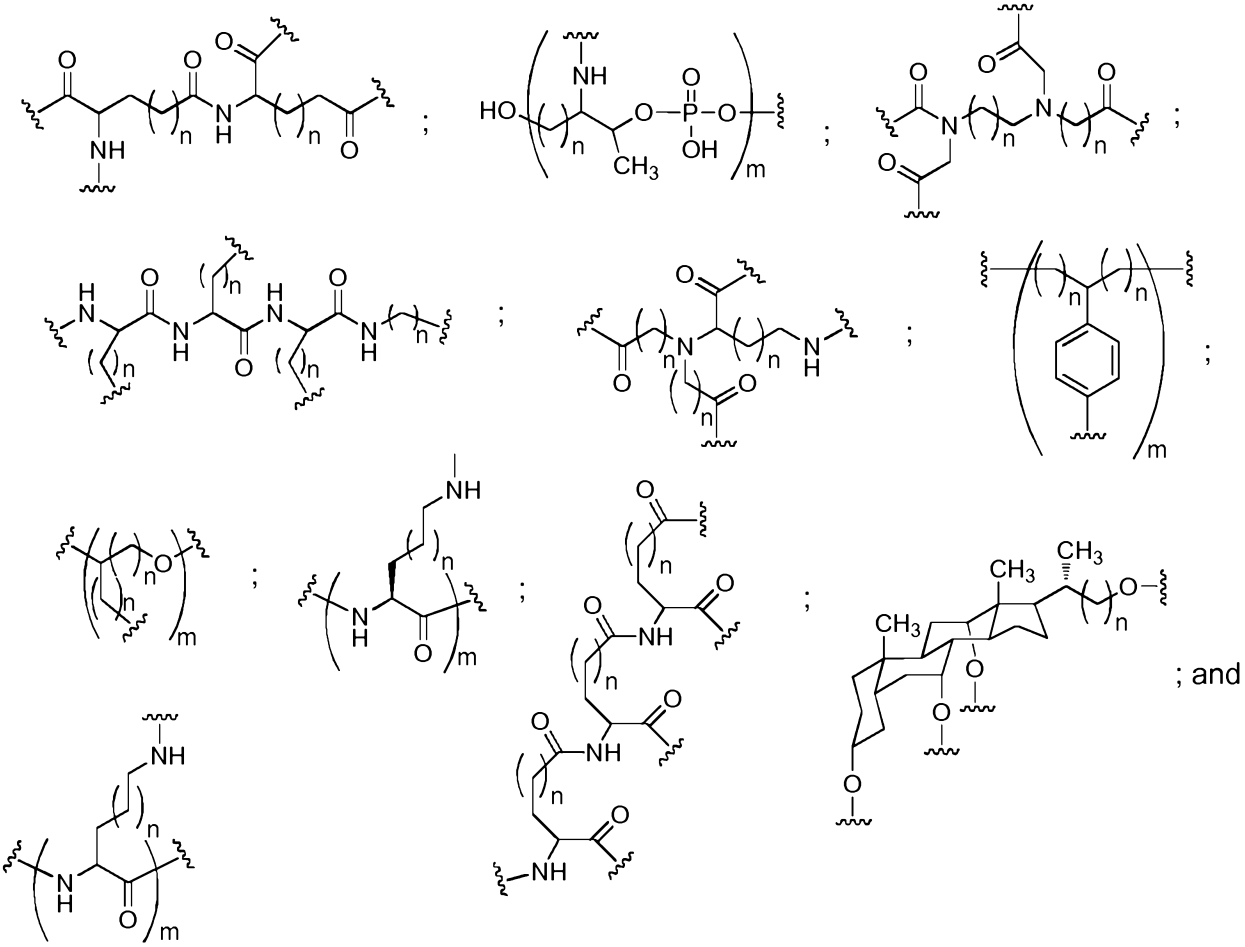
Embodiment 304. The conjugated antisense compound of any of embodiments 229 to 303, wherein the cell-targeting moiety comprises a cell surface receptor ligand.

Embodiment 305. The conjugated antisense compound of any of embodiments 229 to 304, wherein the targeting moiety comprises at least one *N*-Acetylgalactosamine (GalNAc).

Embodiment 306. The conjugated antisense compound of any of embodiments 229 to 305, wherein the targeting moiety comprises a branching group.

Embodiment 307. The conjugated antisense compound of embodiment 306, wherein the branching group comprises an ether.

Embodiment 308. The conjugated antisense compound of embodiment 306 or 307, wherein the branching group has the following structure:

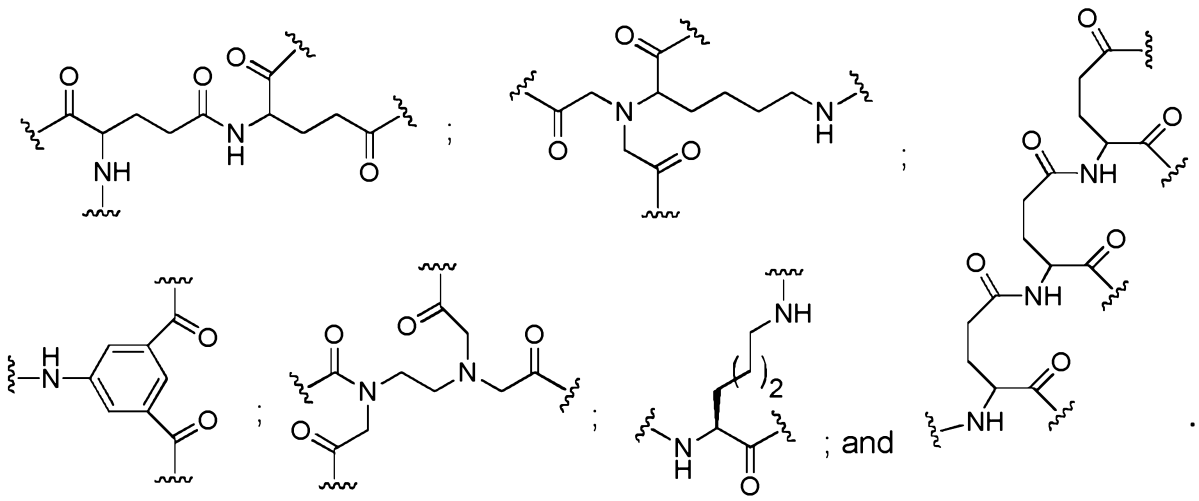


; and

wherein each n is, independently, from 1 to 20; and

m is from 2 to 6.

Embodiment 309. The conjugated antisense compound of embodiment 306 or 307, wherein the branching group has the following structure:



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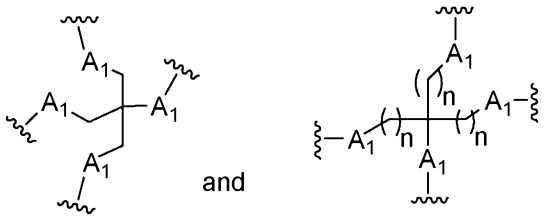
Embodiment 310. The conjugated antisense compound of embodiment 306 or 307, wherein the branching group has the following structure:



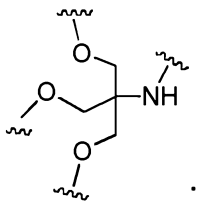
10

wherein each A_1 is independently, O, S, C=O or NH; and

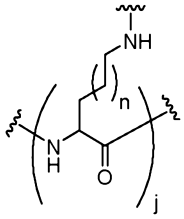
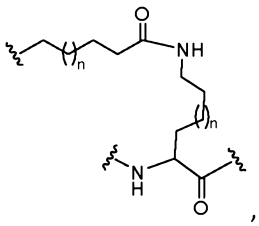
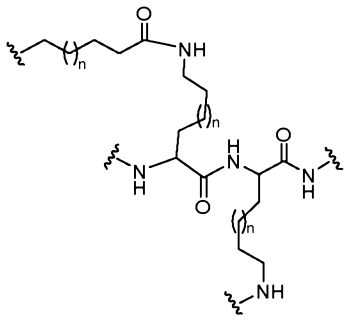
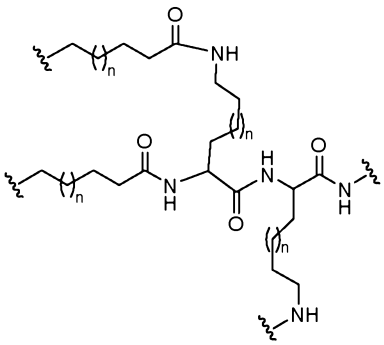
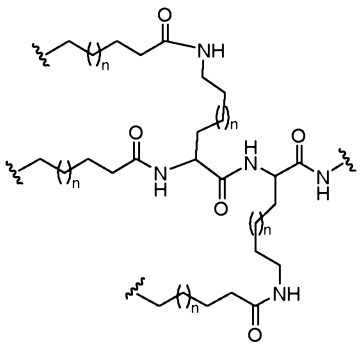
each n is, independently, from 1 to 20.

Embodiment 311. The conjugated antisense compound of embodiment 306 or 307, wherein the

15 branching group has the following structure:



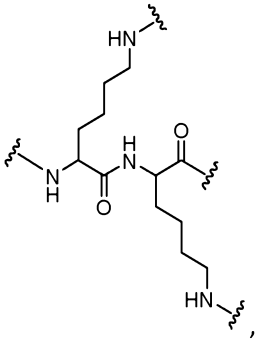
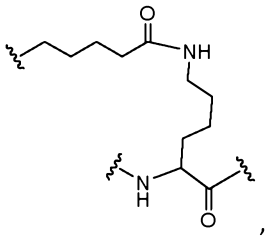
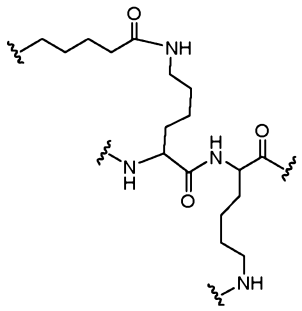
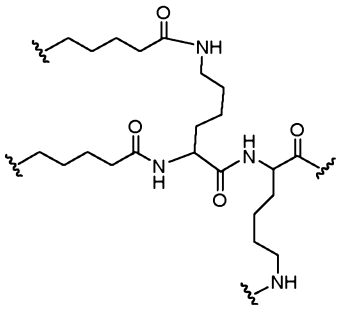
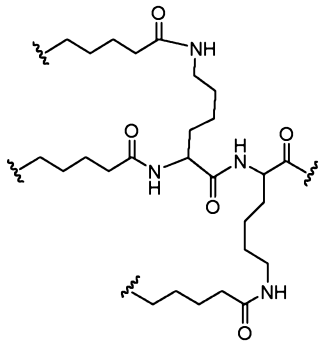
Embodiment 312. The conjugated antisense compound of any of embodiments 306 or 307 wherein the branching group comprises:


j ,

,

,

, or

;

wherein each j is an integer from 1 to 3; and

wherein each n is an integer from 1 to 20.

Embodiment 313. The conjugated antisense compound of any of embodiments 306 or 307 wherein the branching group comprises:

Embodiment 314. The conjugated antisense compound of any embodiments 229-313, wherein the cell-targeting moiety comprises a tether.

Embodiment 315. The conjugated antisense compound of any embodiments 229-313, wherein the cell-targeting moiety comprises two tethers.

Embodiment 316. The conjugated antisense compound of any embodiments 229-313, wherein the cell-targeting moiety comprises three tethers.

Embodiment 317. The conjugated antisense compound of any embodiments 229-313, wherein the cell-targeting moiety comprises four or more tethers.

Embodiment 318. The conjugated antisense compound of any of embodiments 229-317, wherein at least one tether comprises PEG.

Embodiment 319. The conjugated antisense compound of any of embodiments 229-318, wherein at least one tether comprises an amide.

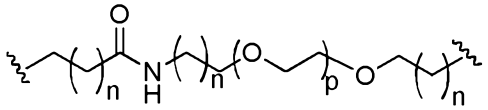
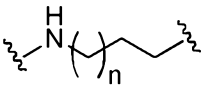
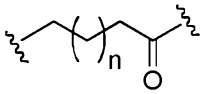
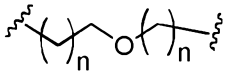
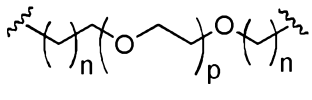
Embodiment 320. The conjugated antisense compound of any of embodiments 229-319, wherein at least one tether comprises a polyamide.

Embodiment 321. The conjugated antisense compound of any of embodiments 229-320, wherein at least one tether comprises an amine.

Embodiment 322. The conjugated antisense compound of any of embodiments 229-321, wherein at least two tethers are different from one another.

Embodiment 323. The conjugated antisense compound of any of embodiments 229-321, wherein all of the tethers are the same as one another.

Embodiment 324. The conjugated antisense compound of any of embodiments 229-323, wherein each tether is selected from among:


;

;

;

;

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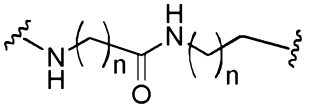
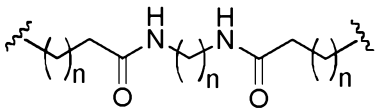
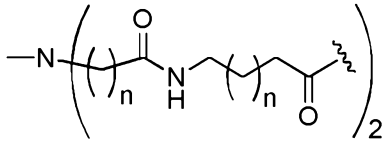
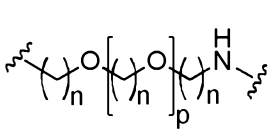
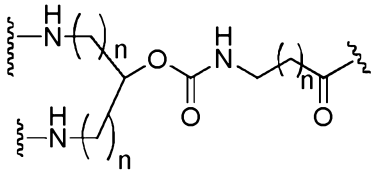
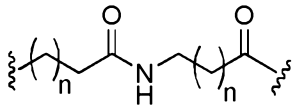
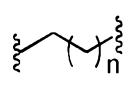
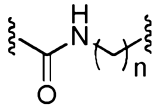
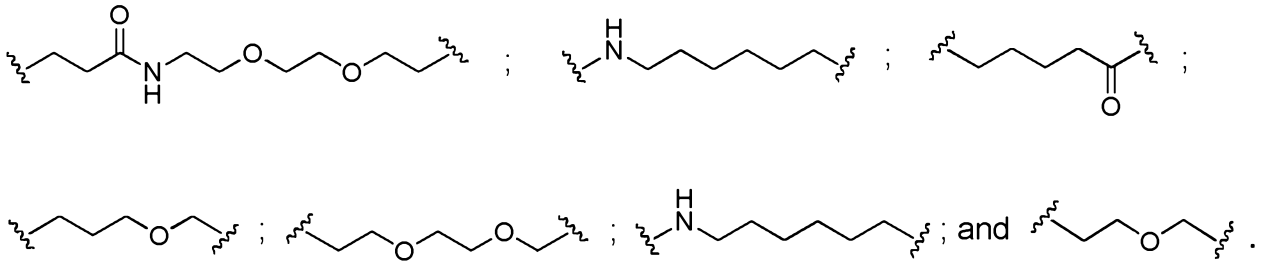
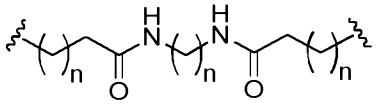

;

;

;

;

;

;

; and


wherein each n is, independently, from 1 to 20; and
each p is from 1 to about 6.

Embodiment 325. The conjugated antisense compound of any of embodiments 229-324, wherein each tether is selected from among:

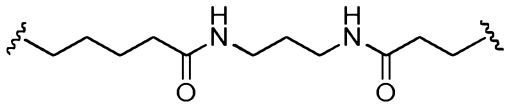


Embodiment 326. The conjugated antisense compound of any of embodiments 229-324, wherein each tether has the following structure:



wherein each n is, independently, from 1 to 20.

Embodiment 327. The conjugated antisense compound of any of embodiments 229-324, wherein each tether has the following structure:



Embodiment 328. The conjugated antisense compound of any of embodiments 229-328, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 329. The conjugated antisense compound of embodiment 328, wherein the cell-targeting moiety comprises one ligand.

Embodiment 330. The conjugated antisense compound of embodiment 328, wherein the targeting moiety comprises two ligands.

Embodiment 331. The conjugated antisense compound of embodiment 328, wherein the targeting moiety comprises three ligands.

Embodiment 332. The conjugated antisense compound of any of embodiments 328-331, wherein a ligand is covalently attached to each tether.

Embodiment 333. The conjugated antisense compound of any of embodiments 229-332, wherein at least one ligand is *N*-Acetylgalactosamine (GalNAc).

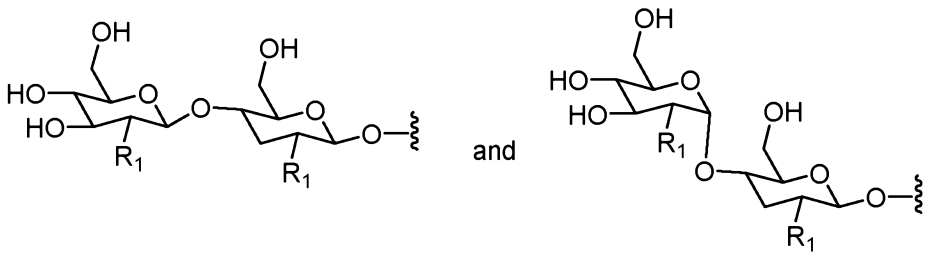
Embodiment 334. The conjugated antisense compound of any of embodiments 229-332, wherein each ligand is N-Acetylgalactosamine (GalNAc).

Embodiment 335. The conjugated antisense compound of any of embodiments 229-332, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

Embodiment 336. The conjugated antisense compound of any of embodiments 229-332, wherein the ligand is galactose.

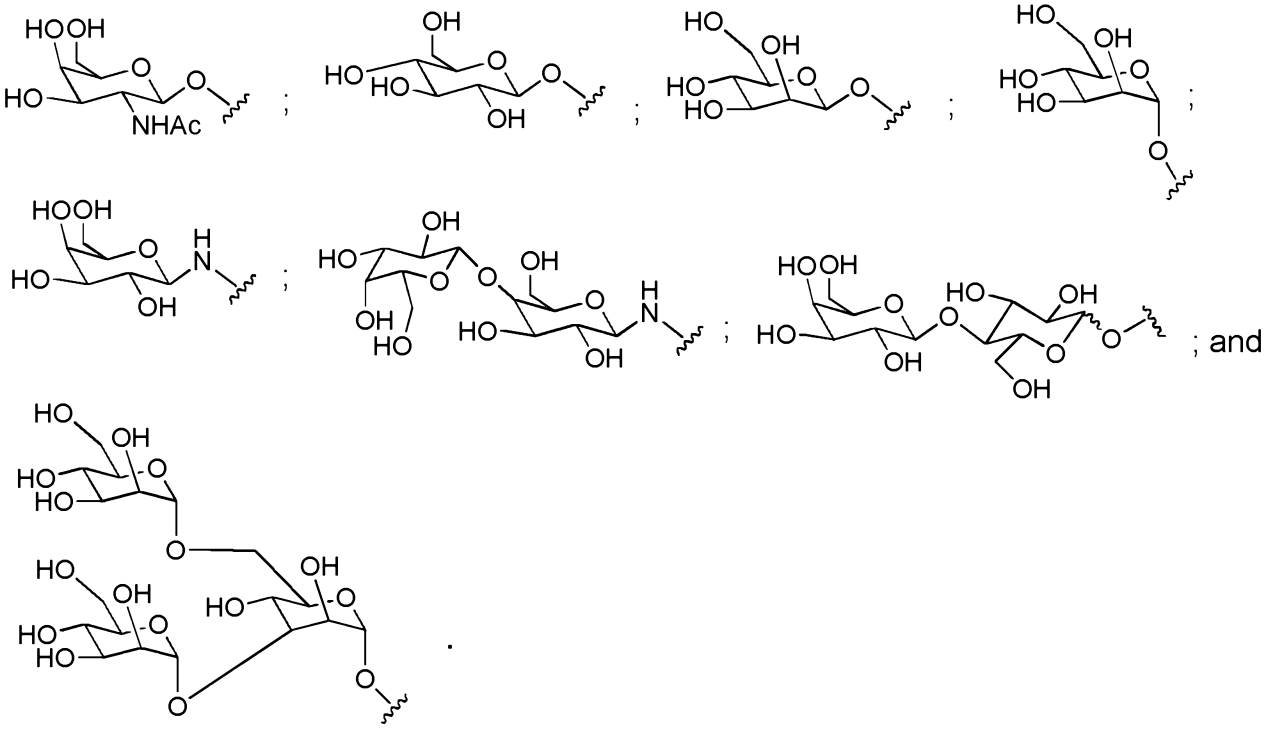
Embodiment 337. The conjugated antisense compound of any of embodiments 229-332, wherein the ligand is mannose-6-phosphate.

Embodiment 338. The conjugated antisense compound of any of embodiments 229-332, wherein each ligand is selected from among:

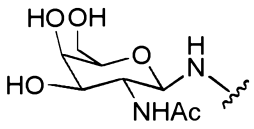


wherein each R_1 is selected from OH and NHCOOH.

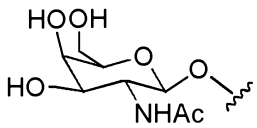
Embodiment 339. The conjugated antisense compound of any of embodiments 229-332, wherein each ligand is selected from among:



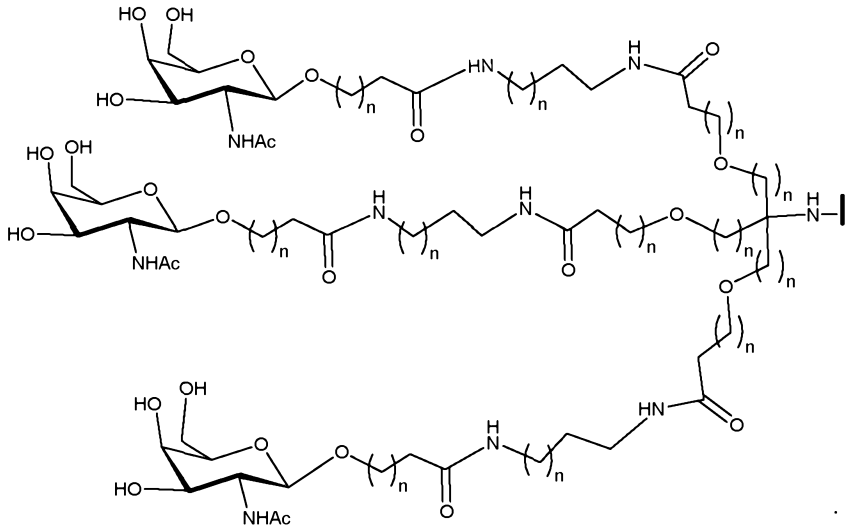
Embodiment 340. The conjugated antisense compound of any of embodiments 229-332, wherein each ligand has the following structure:



Embodiment 341. The conjugated antisense compound of any of embodiments 229-332, wherein each ligand has the following structure:

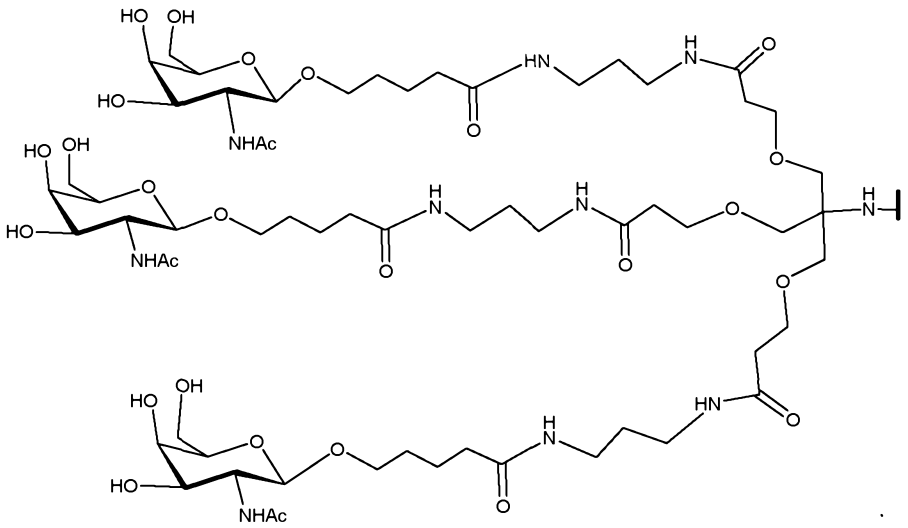


Embodiment 342. The conjugated antisense compound of any of embodiments 229-332, wherein the cell-targeting group has the following structure:

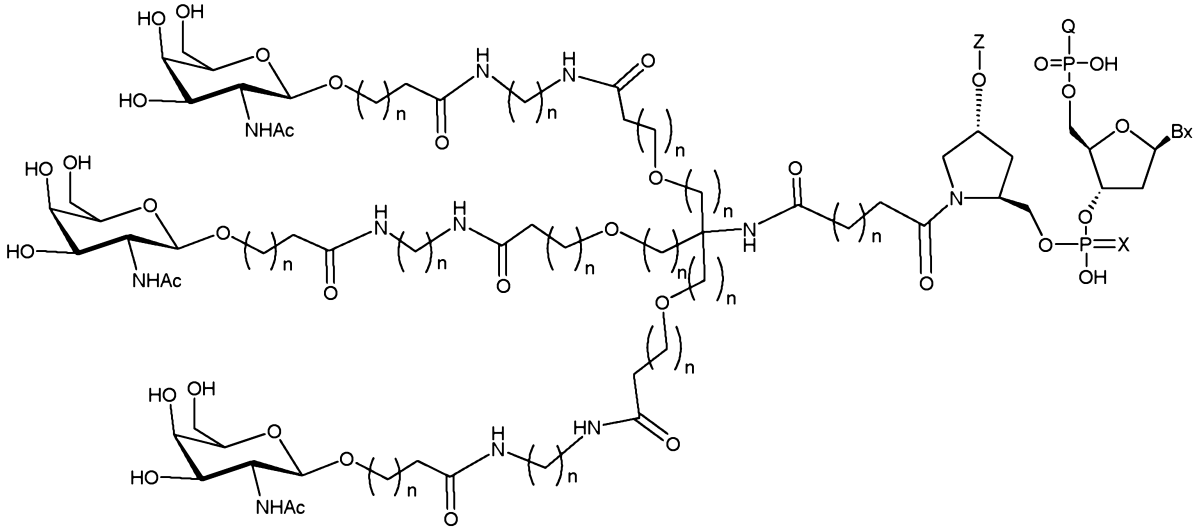


wherein each n is, independently, from 1 to 20.

Embodiment 343. The conjugated antisense compound of any of embodiments 229-336, wherein the cell-targeting group has the following structure:



Embodiment 344. The conjugated antisense compound of any of embodiments 229-336, wherein the conjugate has the following structure:



wherein each n is, independently, from 1 to 20;

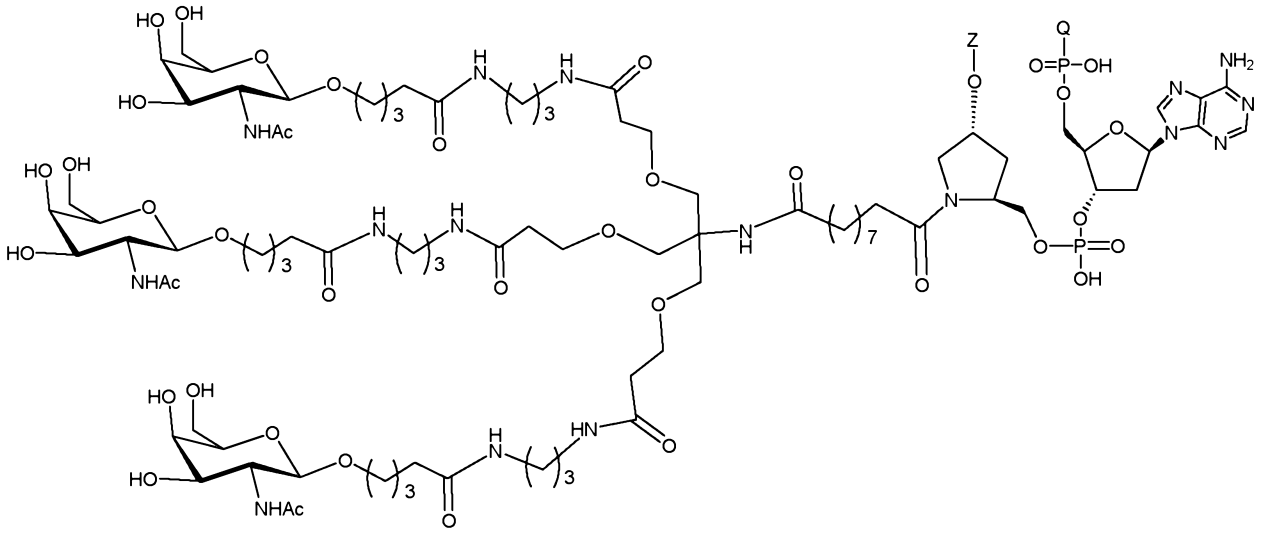
Z is H or a linked solid support;

Q is said antisense compound;

X is O or S; and

Bx is a heterocyclic base moiety.

Embodiment 345. The conjugated antisense compound of any of embodiments 229-336, wherein the conjugate has the following structure:



wherein Z is H or a linked solid support; and

Q is said antisense compound.

Embodiment 346. The conjugated antisense compound of any of embodiments 229-345, wherein the conjugate group is attached to the 2'-position of a nucleoside of the antisense oligonucleotide.

Embodiment 347. The conjugated antisense compound of any of embodiments 229-345, wherein the conjugate group is attached to the 3'-position of a nucleoside of the antisense oligonucleotide.

Embodiment 348. The conjugated antisense compound of any of embodiments 229-345, wherein the conjugate group is attached to the 5'-position of a nucleoside of the antisense oligonucleotide.

Embodiment 349. The conjugated antisense compound of any of embodiments 229-345, wherein the conjugate group is attached to the 5'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 350. The conjugated antisense compound of any of embodiments 229-350, wherein the conjugate group is attached to the 3'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 351. The conjugated antisense compound of any of embodiments 229-350, wherein the conjugate group is attached to an internal nucleoside of the antisense oligonucleotide.

Embodiment 352. The conjugated antisense compound of any of embodiments 229-351, wherein the conjugate group increases uptake of the conjugated antisense compound into a hepatocyte relative to an unconjugated antisense compound.

Embodiment 353. The conjugated antisense compound of any of embodiments 229-352, wherein the conjugate group increases the uptake of the conjugated antisense compound into a liver cell relative to an unconjugated antisense compound.

Embodiment 354. The conjugated antisense compound of any of embodiments 229-353, wherein the conjugate group increases accumulation of the conjugated antisense compound in the liver relative to an unconjugated antisense compound.

Embodiment 355. The conjugated antisense compound of any of embodiments 229-354, wherein the conjugate group decreases accumulation of the conjugated antisense compound in the kidneys relative to an unconjugated antisense compound.

Embodiment 356. The conjugated antisense compound of any of embodiments 229-355, wherein the antisense oligonucleotide is an RNase H based antisense compound.

Embodiment 357. The conjugated antisense compound of any of embodiments 229-356, wherein the antisense oligonucleotide comprises at least one modified nucleoside.

Embodiment 358. The conjugated antisense compound of any of embodiments 229-357, wherein each nucleoside of the antisense oligonucleotide is a modified nucleoside.

Embodiment 359. The conjugated antisense compound of any of embodiments 229-358, wherein the antisense oligonucleotide is single-stranded.

Embodiment 360. The conjugated antisense compound of embodiment 357-359, wherein at least one modified nucleoside comprises a modified sugar moiety.

Embodiment 361. The conjugated antisense compound of embodiment 359, wherein the antisense oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 362. The conjugated antisense compound of embodiment 361, wherein the 5'-region consists of 2 linked 5'-region nucleosides.

Embodiment 363. The conjugated antisense compound of embodiment 361, wherein the 5'-region consists of 3 linked 5'-region nucleosides.

Embodiment 364. The conjugated antisense compound of embodiment 361, wherein the 5'-region consists of 4 linked 5'-region nucleosides.

Embodiment 365. The conjugated antisense compound of embodiment 361, wherein the 5'-region consists of 5 linked 5'-region nucleosides.

Embodiment 366. The conjugated antisense compound of any of embodiments 361-365, wherein the 3'-region consists of 2 linked 3'-region nucleosides.

Embodiment 367. The conjugated antisense compound of any of embodiments 361-365, wherein the 3'-region consists of 3 linked 3'-region nucleosides.

Embodiment 368. The conjugated antisense compound of any of embodiments 361-365, wherein the 3'-region consists of 4 linked 3'-region nucleosides.

Embodiment 369. The conjugated antisense compound of any of embodiments 361-365, wherein the 3'-region consists of 5 linked 3'-region nucleosides.

Embodiment 370. The conjugated antisense compound of any of embodiments 361-369, wherein the central region consists of 5 linked central region nucleosides.

Embodiment 371. The conjugated antisense compound of any of embodiments 361-369, wherein the central region consists of 6 linked central region nucleosides.

Embodiment 372. The conjugated antisense compound of any of embodiments 361-369, wherein the central region consists of 7 linked central region nucleosides.

Embodiment 373. The conjugated antisense compound of any of embodiments 361-369, wherein the central region consists of 8 linked central region nucleosides.

Embodiment 374. The conjugated antisense compound of any of embodiments 361-369, wherein the central region consists of 9 linked central region nucleosides.

Embodiment 375. The conjugated antisense compound of any of embodiments 361-369, wherein the central region consists of 10 linked central region nucleosides.

Embodiment 376. The conjugated antisense compound of any of embodiments 229-376, wherein the antisense oligonucleotide consists of 14 to 26 linked nucleosides.

Embodiment 377. The conjugated antisense compound of any of embodiments 229-376, wherein the antisense oligonucleotide consists of 15 to 25 linked nucleosides.

Embodiment 378. The conjugated antisense compound of any of embodiments 229-376, wherein the antisense oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 379. The conjugated antisense compound of any of embodiments 229-378, wherein each modified nucleoside independently comprises a 2'-substituted sugar moiety or a bicyclic sugar moiety.

Embodiment 380. The conjugated antisense compound of embodiment 379, wherein the at least one modified nucleoside comprises a 2'-substituted sugar moiety.

Embodiment 381. The conjugated antisense compound of embodiment 380, wherein each modified nucleoside comprising a 2'-substituted sugar moiety comprises a 2' substituent independently selected from among: halogen, optionally substituted allyl, optionally substituted amino, azido, optionally substituted SH, CN, OCN, CF3, OCF3, O, S, or N(Rm)-alkyl; O, S, or N(Rm)-alkenyl; O, S or N(Rm)-alkynyl; optionally substituted O-alkylenyl-O-alkyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted O-alkaryl, optionally substituted O-aralkyl, O(CH2)2SCH3, O-(CH2)2-O-N(Rm)(Rn) or O-CH2-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl;

wherein each optionally substituted group is optionally substituted with a substituent group independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

Embodiment 382. The conjugated antisense compound of embodiment 380, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-SCH_3, $O(CH_2)_2$-OCF_3, $O(CH_2)_3$-$N(R_1)(R_2)$, $O(CH_2)_2$-$ON(R_1)(R_2)$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_3)$-$(CH_2)_2$-$N(R_1)(R_2)$, and $O(CH_2)_2$-$N(R_3)$-$C(=NR_4)[N(R_1)(R_2)]$; wherein R_1, R_2, R_3 and R_4 are each, independently, H or C_1-C_6 alkyl.

Embodiment 383. The conjugated antisense compound of embodiment 380, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-N(H)CH_3, $OCH_2C(=O)$-N(H)-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-N(H)-C(=NH)NH_2.

Embodiment 384. The conjugated antisense compound of embodiment 380, wherein the at least one 2'-modified nucleoside comprises a 2'-MOE sugar moiety.

Embodiment 385. The conjugated antisense compound of embodiment 380, wherein the at least one 2'-modified nucleoside comprises a 2'-OMe sugar moiety.

Embodiment 386. The conjugated antisense compound of embodiment 380, wherein the at least one 2'-modified nucleoside comprises a 2'-F sugar moiety.

Embodiment 387. The conjugated antisense compound of any of embodiments 229-386, wherein the antisense oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 388. The conjugated antisense compound of embodiment 387, wherein the modified nucleoside comprises an F-HNA sugar moiety.

Embodiment 389. The conjugated antisense compound of embodiment 387, wherein the modified nucleoside comprises an HNA sugar moiety.

Embodiment 390. The conjugated antisense compound of any of embodiments 229-389 wherein the antisense oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 391. The conjugated antisense compound of embodiment 390, wherein the bicyclic sugar moiety is a cEt sugar moiety.

Embodiment 392. The conjugated antisense compound of embodiment 390, wherein bicyclic sugar moiety is an LNA sugar moiety.

Embodiment 393. The conjugated antisense compound of any of embodiments 1-392, wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 394. The conjugated antisense compound of embodiment 393, wherein each internucleoside linkage of the antisense oligonucleotide is a modified internucleoside linkage.

Embodiment 395. The conjugated antisense compound of embodiment 394, wherein the antisense oligonucleotide comprises at least one modified linkage and at least one unmodified phosphodiester internucleoside linkage.

Embodiment 396. The conjugated antisense compound of any of embodiments 393-395 wherein at least one modified internucleoside linkage is a phosphosphorothioate internucleoside linkage.

Embodiment 397. The conjugated antisense compound of any of embodiments 393-396, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 398. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 399. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 400. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 401. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 402. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 403. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 404. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 8 phosphodiester internucleoside linkages.

Embodiment 405. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 9 phosphodiester internucleoside linkages.

Embodiment 406. The conjugated antisense compound of any of embodiments 393-396, wherein the antisense oligonucleotide comprises at least 10 phosphodiester internucleoside linkages.

Embodiment 407. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 16 phosphorothioate internucleoside linkages.

Embodiment 408. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 15 phosphorothioate internucleoside linkages.

Embodiment 409. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 14 phosphorothioate internucleoside linkages.

Embodiment 410. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 13 phosphorothioate internucleoside linkages.

Embodiment 411. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 12 phosphorothioate internucleoside linkages.

Embodiment 412. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 11 phosphorothioate internucleoside linkages.

Embodiment 413. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 10 phosphorothioate internucleoside linkages.

Embodiment 414. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 9 phosphorothioate internucleoside linkages.

Embodiment 415. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 8 phosphorothioate internucleoside linkages.

Embodiment 416. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 7 phosphorothioate internucleoside linkages.

Embodiment 417. The conjugated antisense compound of any of embodiments 393-396 or 398-406, wherein the antisense oligonucleotide comprises fewer than 6 phosphorothioate internucleoside linkages.

Embodiment 418. The conjugated antisense compound of any of embodiments 393-418, wherein each terminal internucleoside linkage of the antisense oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 419. The conjugated antisense compound of any of embodiments 393-396 or 398-418, wherein each internucleoside linkage linking two deoxynucleosides of the antisense oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 420. The conjugated antisense compound of any of embodiments 393-396 or 398-419, wherein each non-terminal internucleoside linkage linking two modified nucleosides of the antisense oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 421. The conjugated antisense compound of any of embodiments 393-396 or 398-420, wherein each non-terminal internucleoside linkage of the antisense oligonucleotide that is 3' of a modified nucleoside is a phosphodiester internucleoside linkage.

Embodiment 422. The conjugated antisense compound of any of embodiments 393-396 or 398-418, wherein each internucleoside linkage of the antisense oligonucleotide that is 3' of a deoxynucleoside is a phosphorothioate internucleoside linkage.

Embodiment 423. The conjugated antisense compound of any of embodiments 229-422 wherein the antisense oligonucleotides has a chemical motif selected from among:

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$; and

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each s is a phosphorothioate internucleoside linkage, and each y is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage, provided that at least one y is a phosphodiester internucleotide linkage.

Embodiment 424. The conjugated antisense compound of any of embodiments 229-422 wherein the antisense oligonucleotides has a chemical motif selected from among:

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$; and

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each o is a phosphodiester internucleoside linkage, and each s is a phosphorothioate internucleoside linkage.

Embodiment 425. The conjugated antisense compound of embodiment 423 or 424, wherein each M is independently selected from among: a 2'-MOE nucleoside and a bicyclic nucleoside.

Embodiment 426. The conjugated antisense compound of embodiment 425, wherein each M is independently selected from among a 2'-MOE nucleoside, a cEt nucleoside, and an LNA nucleoside.

Embodiment 427. The conjugated antisense compound of embodiment 425 or 426, wherein each M is a 2'-MOE nucleoside.

Embodiment 428. The conjugated antisense compound of embodiment 425 or 426, wherein each M is a cEt nucleoside.

Embodiment 429. The conjugated antisense compound of embodiments 425 or 426, wherein each M is an LNA nucleoside.

Embodiment 430. The conjugated antisense compound of any of embodiments 229-429, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 8 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 431. The conjugated antisense compound of any of embodiments 229-429, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 10 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 432. The conjugated antisense compound of any of embodiments 229-429, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 12 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 433. The conjugated antisense compound of any of embodiments 229-429, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 14 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 434. The conjugated antisense compound of any of embodiments 229-429, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 16 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 435. The conjugated antisense compound of any of embodiments 229-429, wherein the antisense oligonucleotide has a nucleobase sequence comprising an at least 18 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 436. The conjugated antisense compound of any of embodiments 229-435, wherein the antisense oligonucleotide is at least 90% complementary to a target nucleic acid.

Embodiment 437. The conjugated antisense compound of any of embodiments 229-435, wherein the antisense oligonucleotide is at least 95% complementary to a target nucleic acid.

Embodiment 438. The conjugated antisense compound of any of embodiments 229-435, wherein the antisense oligonucleotide is 100% complementary to a target nucleic acid.

Embodiment 439. The conjugated antisense compound of any of embodiments 430-438, wherein the target nucleic acid is a pre-mRNA.

Embodiment 440. The conjugated antisense compound of any of embodiments 430-438, wherein the target nucleic acid is an mRNA.

Embodiment 441. The conjugated antisense compound of any of embodiments 430-440, wherein the target nucleic acid is expressed in the liver.

Embodiment 442. The conjugated antisense compound of embodiment 441, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 443. The conjugated antisense compound of embodiment 441 or 442, wherein the target nucleic encodes a protein selected from among: Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI,

Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, and Transthyretin.

Embodiment 444. The conjugated antisense compound of embodiment 430-440 wherein the target nucleic acid is a viral nucleic acid.

Embodiment 445. The conjugated antisense compound of embodiment 444, wherein the viral nucleic acid expressed in the liver.

Embodiment 446. The conjugated antisense compound of embodiment 445, wherein the target nucleic acid is a Hepatitis B viral nucleic acid.

Embodiment 447. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NOs.: 17, 18, 19, 20, 21, 22, 23, or 24.

Embodiment 448. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NO.: 25, 26, 27, 28, 29, or 30.

Embodiment 449. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 31.

Embodiment 450. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 32.

Embodiment 451. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 33.

Embodiment 452. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 34.

Embodiment 453. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 35, 36, 37, 38, 39, 40, 41, 42, or 43.

Embodiment 454. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 44, 45, 46, 47, or 48.

Embodiment 455. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 456. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 60, 61, 62, 63, 64, 65, 66, or 67.

Embodiment 457. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NO.: 69, 70, 71, or 72.

Embodiment 458. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 73.

Embodiment 459. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 74, 75, 76, 77, 78, 79, 80, or 81.

Embodiment 460. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 68.

Embodiment 461. The conjugated antisense compound of any of embodiments 229-443, wherein the antisense oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 82-103.

Embodiment 462. A method of reducing the amount or activity of a target nucleic acid in a cell, comprising contacting a cell with the conjugated antisense compound of any of embodiments 229-461.

Embodiment 463. The method of embodiment 462, wherein the cell is a liver cell.

Embodiment 464. The method of embodiment 462, wherein the cell is a hepatocyte.

Embodiment 465. The method of any of embodiments 462-464 wherein the cell is in vitro.

Embodiment 466. The method of any of embodiments 462-464 wherein the cell is in an animal.

Embodiment 467. The method of embodiment 466 wherein the animal is a mouse.

Embodiment 468. The method of embodiment 466 wherein the animal is a human.

Embodiment 469. A pharmaceutical composition comprising an conjugated antisense compound according to any of embodiments 229-469 and a pharmaceutically acceptable carrier or diluent.

Embodiment 470. The pharmaceutical composition of embodiment 469 wherein the pharmaceutically acceptable carrier or diluent is selected from among sterile water and sterile saline.

Embodiment 471. A method of treating a disease or condition in an animal comprising administering the pharmaceutical composition of embodiment 469 or 470 to the animal and thereby treating the disease or condition in the animal.

Embodiment 472. The method of embodiment 471 wherein the animal is a mouse.

Embodiment 473. The method of embodiment 471 wherein the animal is a human.

Embodiment 474. The method of any of embodiments 471-473, wherein the disease or condition is a liver disease or condition.

Embodiment 475. The method of any of embodiments 471-474 wherein the administration is parenteral.

Embodiment 476. The method embodiment 475 wherein the administration is by subcutaneous injection.

Embodiment 477. The method of embodiment 475 wherein the administration is by intravenous injection.

Embodiment 478. The method of embodiment 475 wherein the administration is by intramuscular injection.

Embodiment 479. The method of any of embodiments 471-478 wherein the conjugated antisense compound is provided at a dose of 1-10 mg/kg.

Embodiment 480. The method of any of embodiments 471-478 wherein the conjugated antisense compound is provided at a dose of less than 1 mg/kg.

Embodiment 481. The method of any of embodiments 471-480 wherein the conjugated antisense compound is provided at a dose of greater than 10 mg/kg.

Embodiment 482. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided for a dosing period of at least 2 months.

Embodiment 483. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided for a dosing period of at least 4 months.

Embodiment 484. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided for a dosing period of at least 6 months.

Embodiment 485. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of about one dose every week.

Embodiment 486. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of about one dose every two weeks.

Embodiment 487. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of about one dose every three weeks.

Embodiment 488. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every four weeks.

Embodiment 489. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every five weeks.

Embodiment 490. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every six weeks.

Embodiment 491. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every seven weeks.

Embodiment 492. The method of any of embodiments 471-481 wherein the conjugated antisense compound is provided at a dosing frequency of one dose every eight weeks.

Embodiment 493. A conjugate compound comprising at least one phosphorus linking group or neutral linking group and one or more ligands.

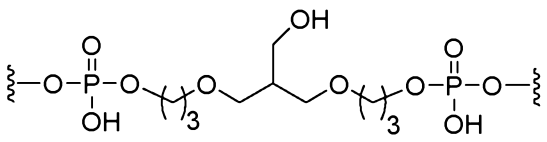
Embodiment 494. The conjugate compound of embodiment 493 comprising two or more ligands.

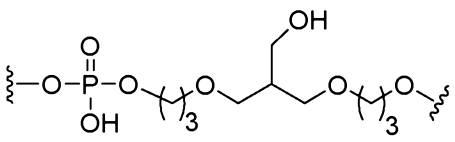
Embodiment 495. The conjugate compound of embodiment 493 comprising three ligands.

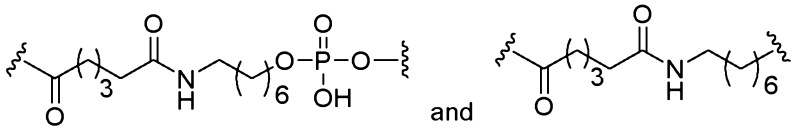
Embodiment 496. The conjugate compound of any of embodiments 493 to 495, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

Embodiment 497. The conjugate compound of any of embodiments 493 to 495, wherein the ligand is N-acetyl galactoseamine.

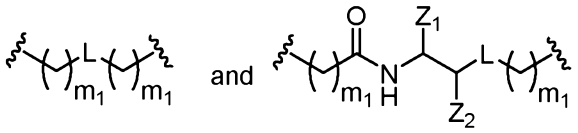
Embodiment 498. The conjugate compound of any of embodiments 493 to 497, wherein conjugate group comprises a structure selected from among:







Embodiment 499. The conjugate compound of any of embodiments 493 to 498, wherein the conjugate compound has a tether having a structure selected from among:



wherein L is either a phosphorus linking group or a neutral linking group;

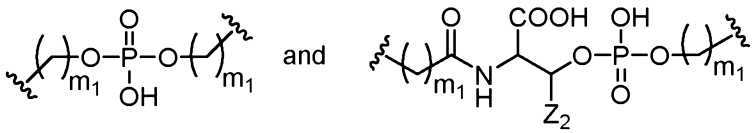
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 500. The conjugate compound of embodiment 499, wherein the tether has a structure selected from among:



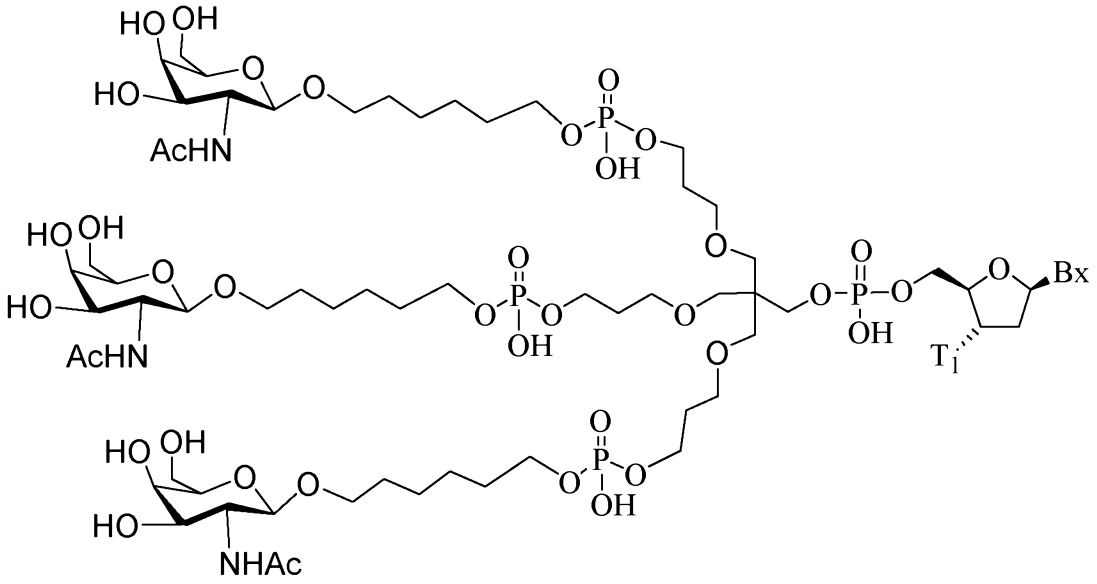
wherein Z_2 is H or CH_3; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 501. The conjugate compound of any of embodiments 493 to 500, wherein the conjugate compound is covalently attached to an oligonucleotide.

Embodiment 502. An oligomeric compound comprising an oligonucleotide at least one conjugate group, wherein the at least one conjugate group is a conjugate compound of any of embodiments 493 to 500.

Embodiment 503. A compound having the formula (I):



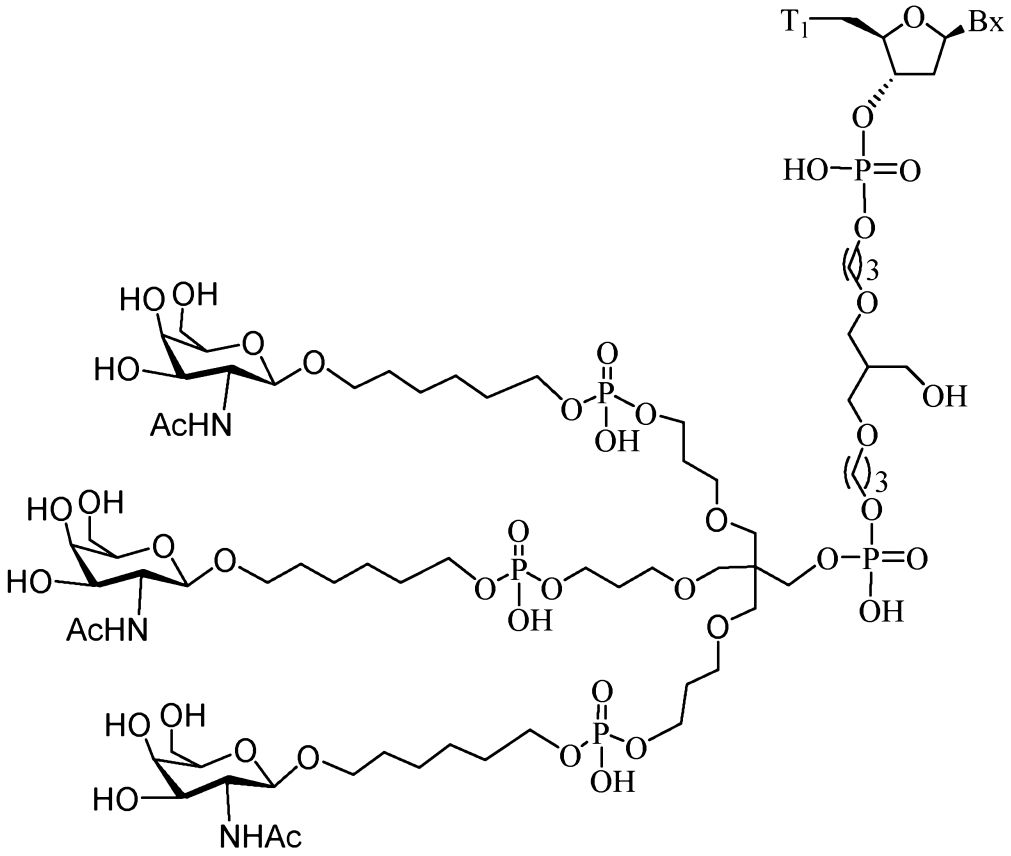
(I)

wherein:

Bx is a heterocyclic base moiety; and

T_1 is a hydroxyl, hydrogen, a hydroxyl protecting group, phosphorus moiety, or a reactive phosphorus group.

Embodiment 504. A compound having the formula (II):



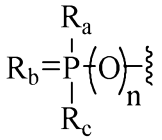
(II)

wherein:

Bx is a heterocyclic base moiety; and

T_1 is a hydroxyl, hydrogen, a hydroxyl protecting group, phosphorus moiety, or a reactive phosphorus group.

Embodiment 505. The compound of any of embodiment 503 or 504, wherein said phosphorus moiety has the formula:



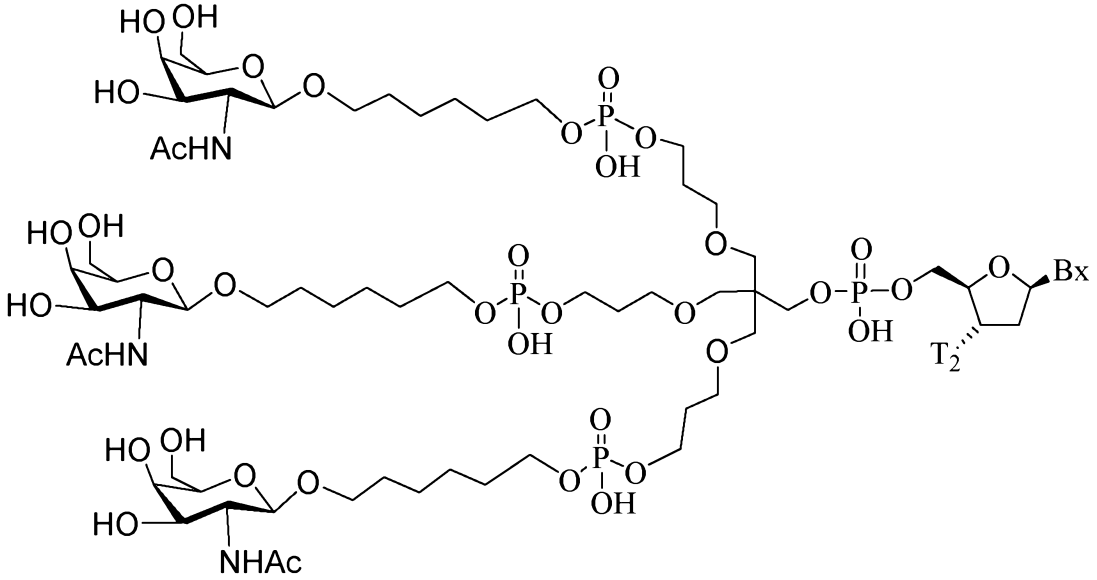
wherein:

n is 0 or 1;

R_a and R_c are each, independently, 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

R_b is O or S.

Embodiment 506. An oligomeric compound comprising an oligonucleotide and at least one conjugate group, wherein the at least one conjugate group is a conjugate compound of formula (III):



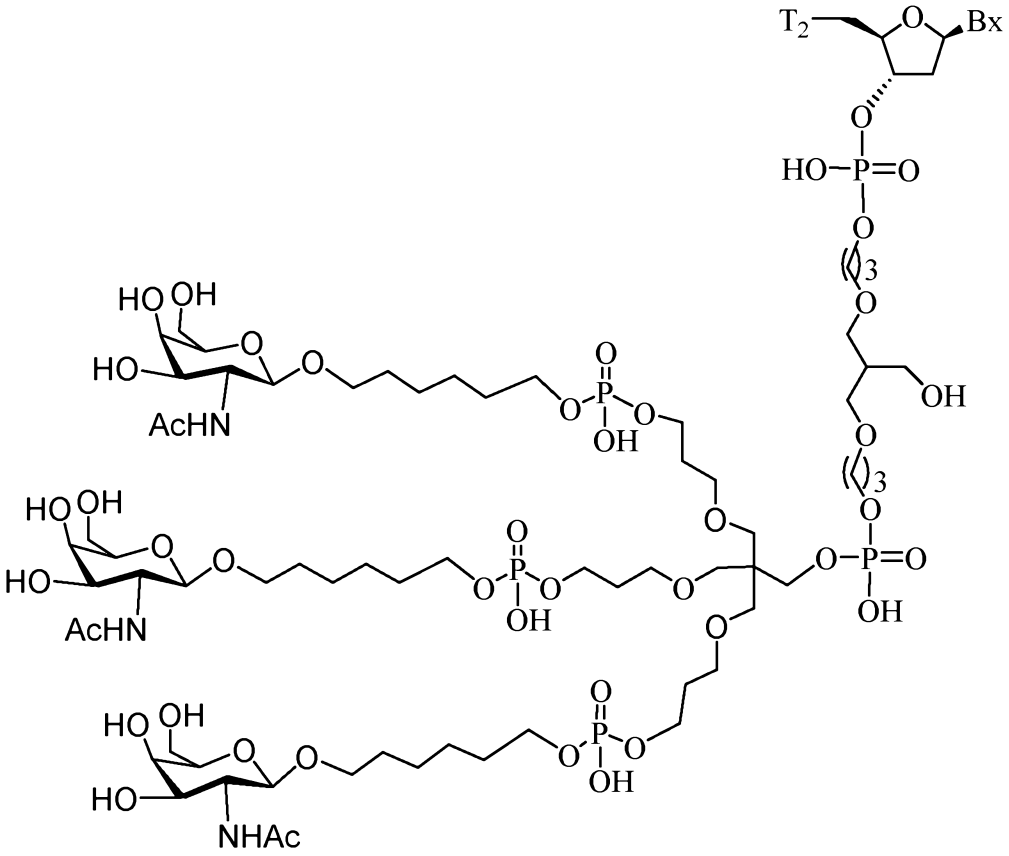
(III)

wherein:

Bx is a heterocyclic base moiety; and

T_2 is an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound.

Embodiment 507. An oligomeric compound comprising an oligonucleotide and at least one conjugate group, wherein the at least one conjugate group is a conjugate compound of formula (IV):



(IV)

wherein:

Bx is a heterocyclic base moiety; and

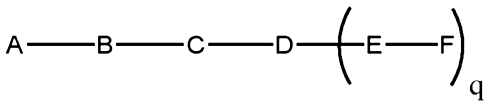
T_2 is an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound.

Embodiment 508. The compound or oligomeric compound of any of embodiments 503 to 507, wherein the heterocyclic base moiety is a pyrimidine, substituted pyrimidine, purine or substituted purine.

Embodiment 509. The compound or oligomeric compound of any of embodiments 503 to 507, wherein Bx is uracil, thymine, cytosine, 5-methyl cytosine, adenine, or guanine.

Embodiment 510. The compound or oligomeric compound of any of embodiments 503 to 507, wherein Bx is adenine.

Embodiment 511. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

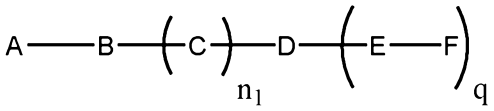
D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 512. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein:

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

D is the branching group

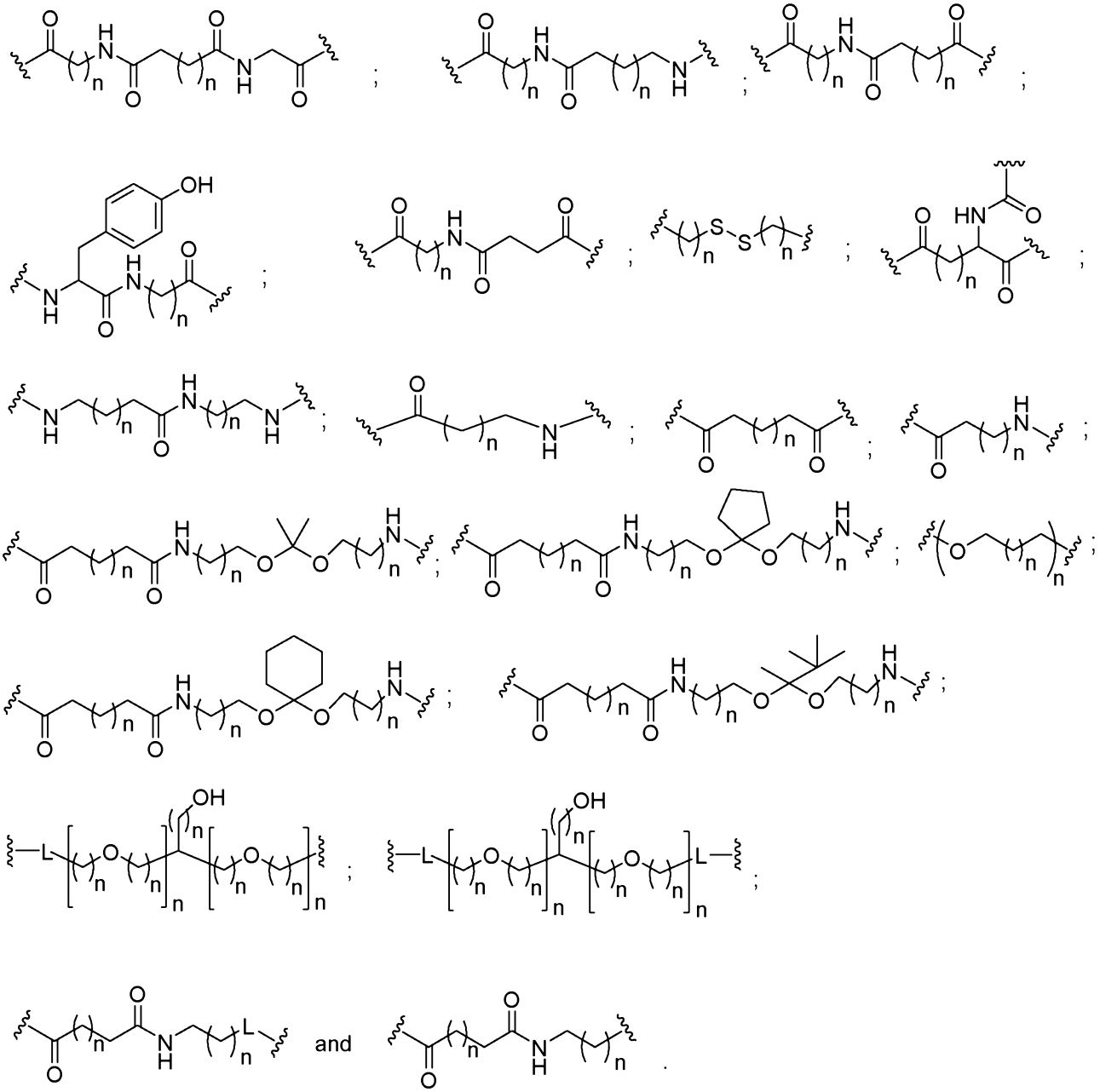
each E is a tether;

each F is a ligand;

n_1 is 0 or 1; and

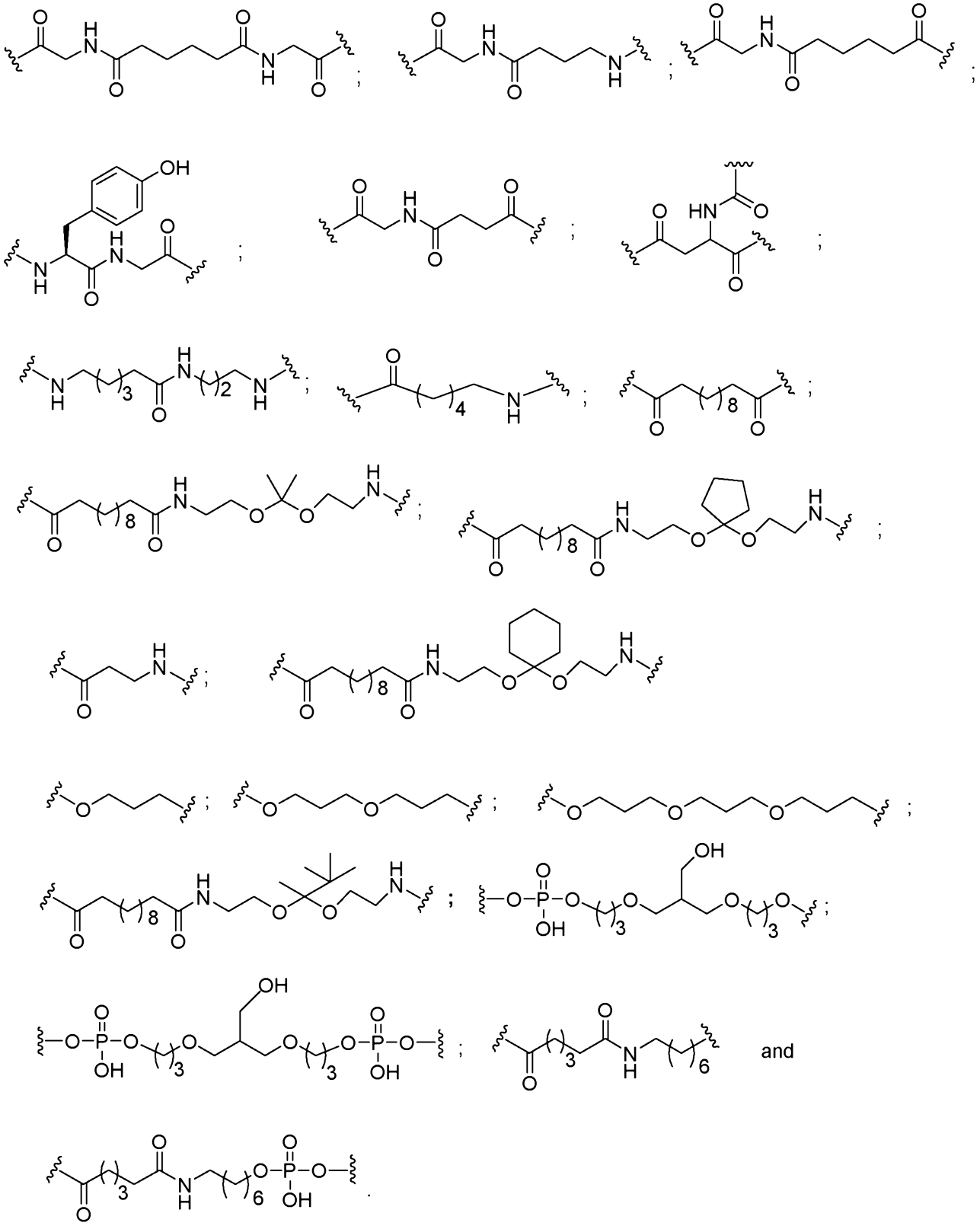
q is an integer between 1 and 5.

Embodiment 513. The conjugated antisense compound of embodiment 511 or 512, wherein the conjugate linker has a structure selected from among:



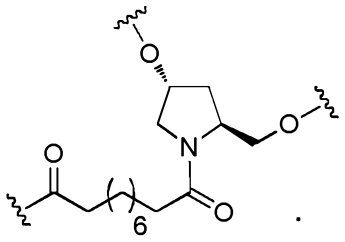
wherein each L is, independently, a phosphorus linking group or a neutral linking group; and each n is, independently, from 1 to 20.

Embodiment 514. The conjugated antisense compound of embodiment 511 or 512, wherein the conjugate linker has a structure selected from among:

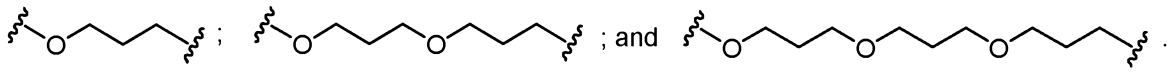


and

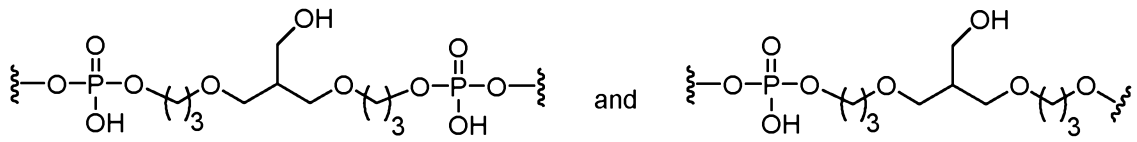
Embodiment 515. The conjugated antisense compound of embodiment 511 or 512, wherein the conjugate linker has the structure:



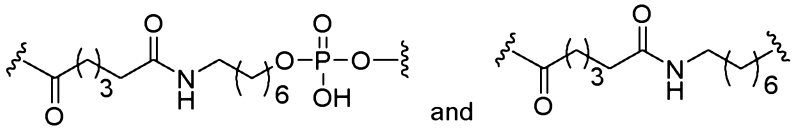
Embodiment 516. The conjugated antisense compound of embodiment 511 or 512, wherein the conjugate linker has one of the structures selected from:



Embodiment 517. The conjugated antisense compound of embodiment 511 or 512, wherein the conjugate linker has one of the structures selected from:



Embodiment 518. The conjugated antisense compound of embodiment 511 or 512, wherein the conjugate linker has one of the structures selected from:



Embodiment 519. The conjugated antisense compound of any of embodiments 511 or 518, wherein the conjugate linker comprises a pyrrolidine.

Embodiment 520. The conjugated antisense compound of any of embodiments 511 or 519, wherein the conjugate linker does not comprise a pyrrolidine.

Embodiment 521. The conjugated antisense compound of any of embodiments 511 or 520, wherein the conjugate linker comprises PEG.

Embodiment 522. The conjugated antisense compound of any of embodiments 511 or 521, wherein the conjugate linker comprises an amide.

Embodiment 523. The conjugated antisense compound of any of embodiments 511 or 522, wherein the conjugate linker does not comprise an amide.

Embodiment 524. The conjugated antisense compound of any of embodiments 511 or 523, wherein the conjugate linker comprises a polyamide.

Embodiment 525. The conjugated antisense compound of any of embodiments 511 or 524, wherein the conjugate linker comprises an amine.

Embodiment 526. The conjugated antisense compound of any of embodiments 511 or 525, wherein the conjugate linker comprises one or more disulfide bonds.

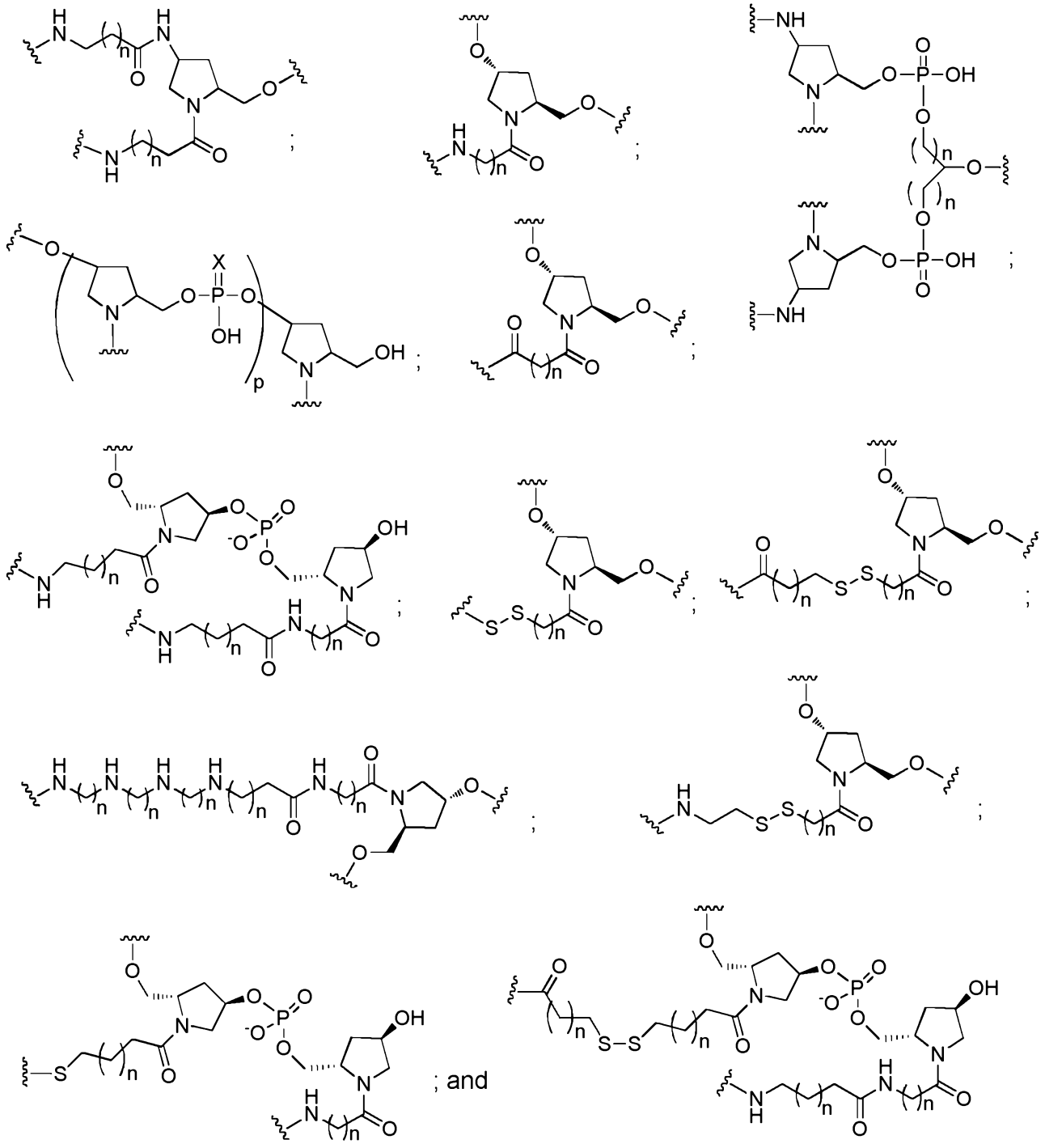
Embodiment 527. The conjugated antisense compound of any of embodiments 511 or 526, wherein the conjugate linker comprises a protein binding moiety.

Embodiment 528. The conjugated antisense compound of embodiment 527, wherein the protein binding moiety comprises a lipid.

Embodiment 529. The conjugated antisense compound of embodiment 528, wherein the protein binding moiety is selected from among: cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), a vitamin (e.g., folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (e.g., monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, e.g., sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid.

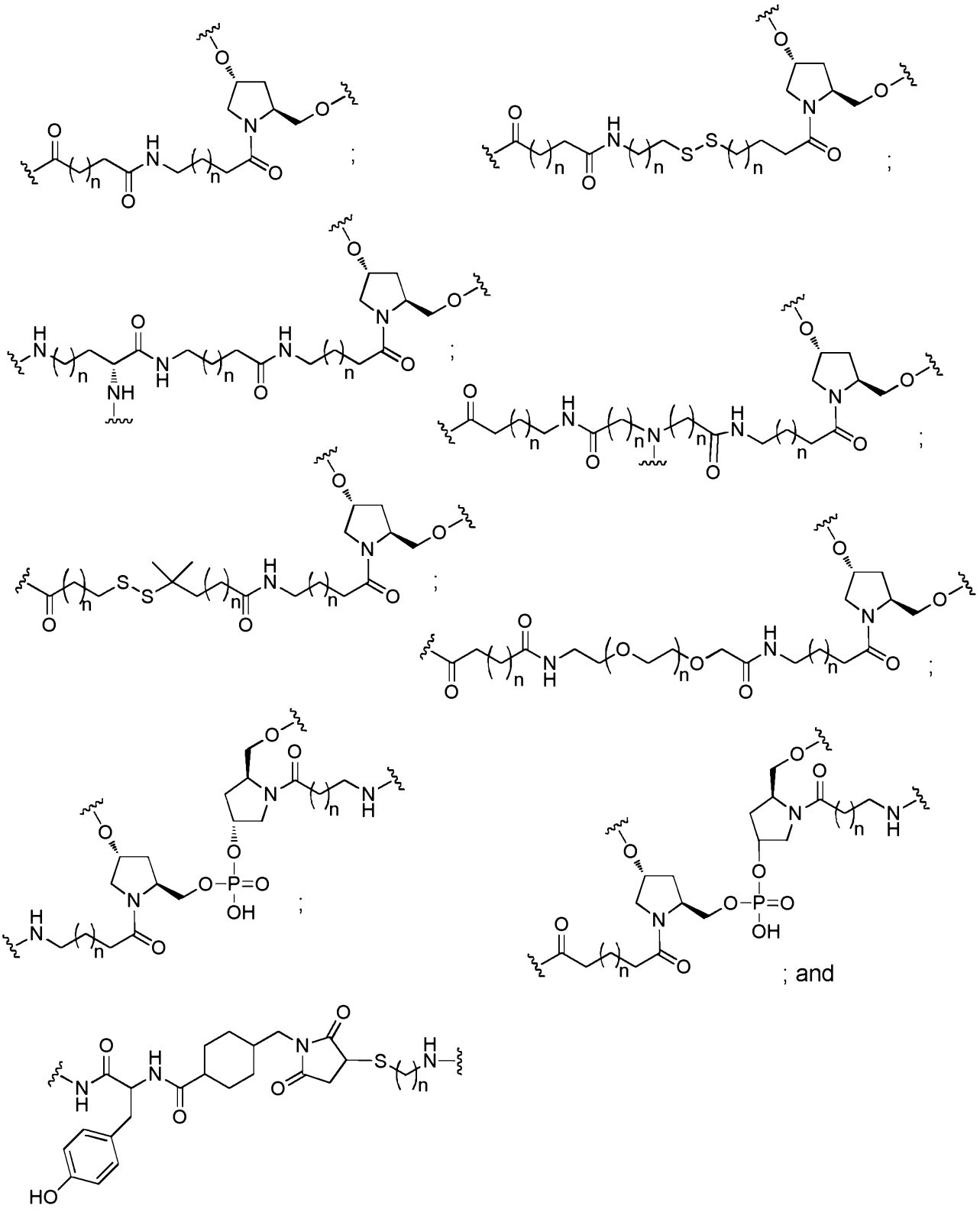
Embodiment 530. The conjugated antisense compound of any of embodiments 527 to 529 wherein the protein binding moiety is a C16 to C22 long chain saturated or unsaturated fatty acid, cholesterol, cholic acid, vitamin E, adamantane or 1-pentafluoropropyl.

Embodiment 531. The conjugated antisense compound of any of embodiments 511 to 512 wherein the conjugate linker has a structure selected from among:



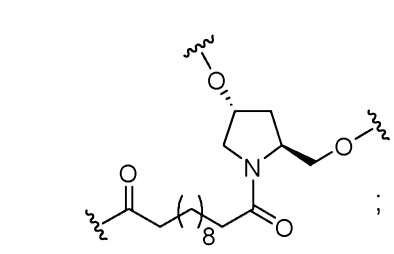
wherein each n is, independently, is from 1 to 20; and p is from 1 to 6.

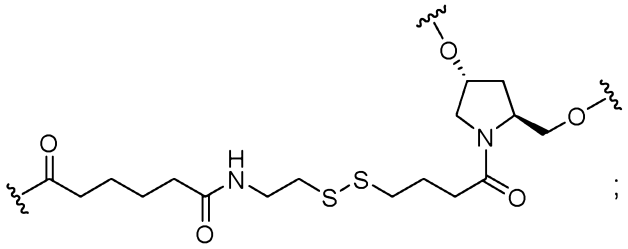
Embodiment 532. The conjugated antisense compound of any of embodiments 511 to 512 wherein the conjugate linker has a structure selected from among:

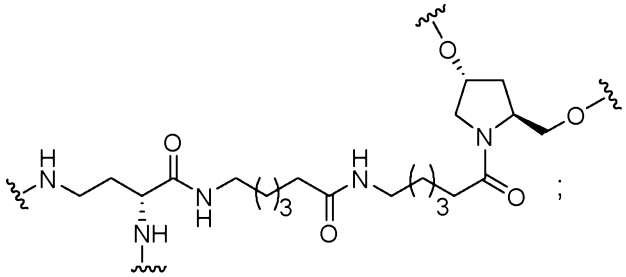


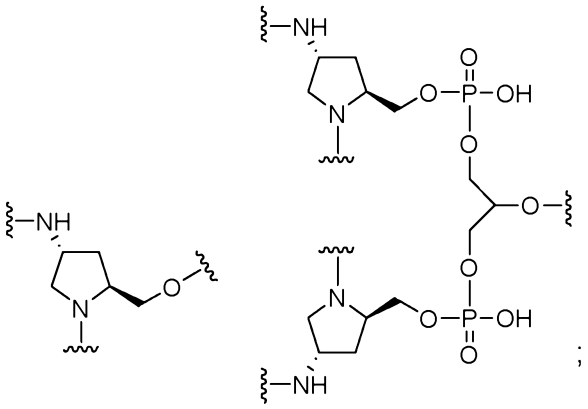
wherein each n is, independently, from 1 to 20.

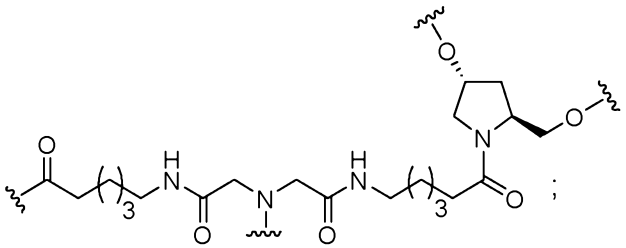
Embodiment 533. The conjugated antisense compound of any of embodiments 511 to 512 wherein the conjugate linker has a structure selected from among:

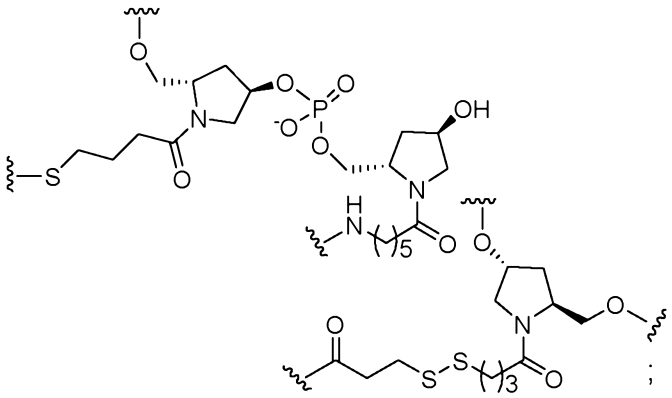

;

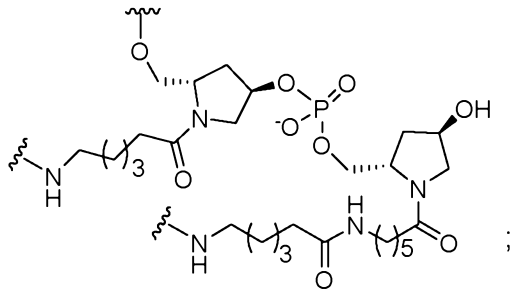

;

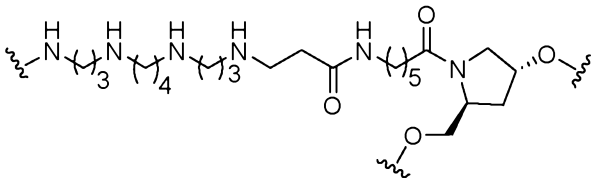

;

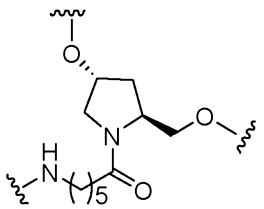

;

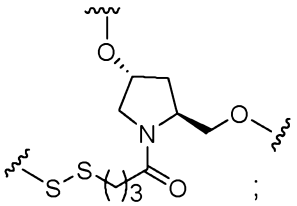

;

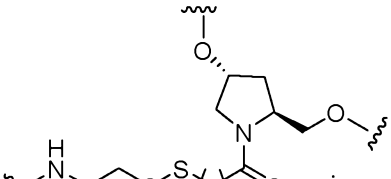

;

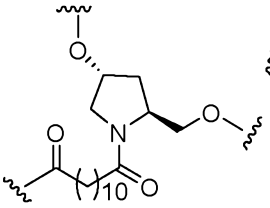

;

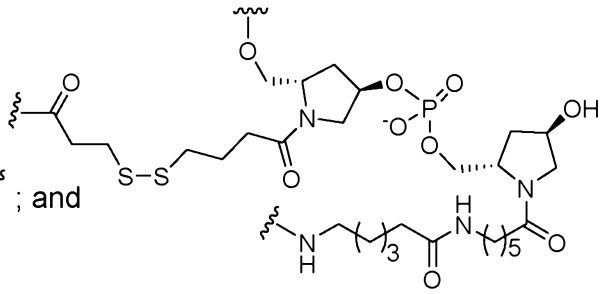

;


;

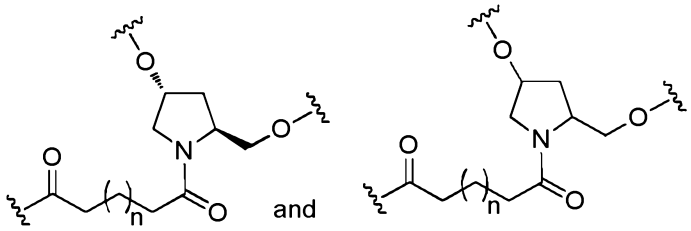

;


;


; and

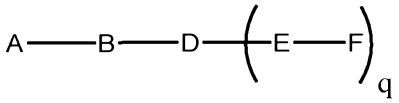

.

Embodiment 534. The conjugated antisense compound of any of embodiments 511 to 512 wherein the conjugate linker has a structure selected from among:



wherein n is from 1 to 20.

Embodiment 535. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety;

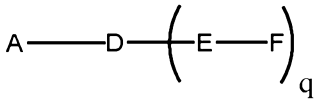
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 536. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

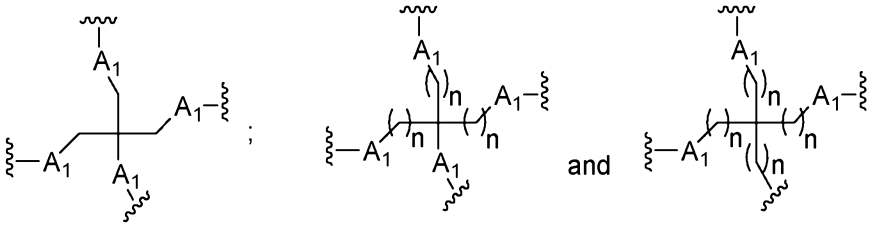
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

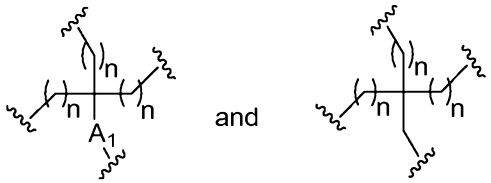
Embodiment 537. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has one of the following structures:



wherein each A_1 is independently, O, S, C=O or NH; and

each n is, independently, from 1 to 20.

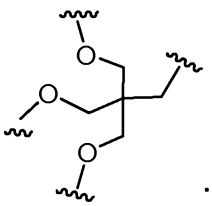
Embodiment 538. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has one of the following structures:



wherein each A_1 is independently, O, S, C=O or NH; and

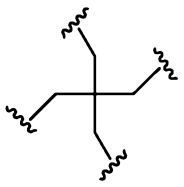
each n is, independently, from 1 to 20.

Embodiment 539. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has the following structure:



.

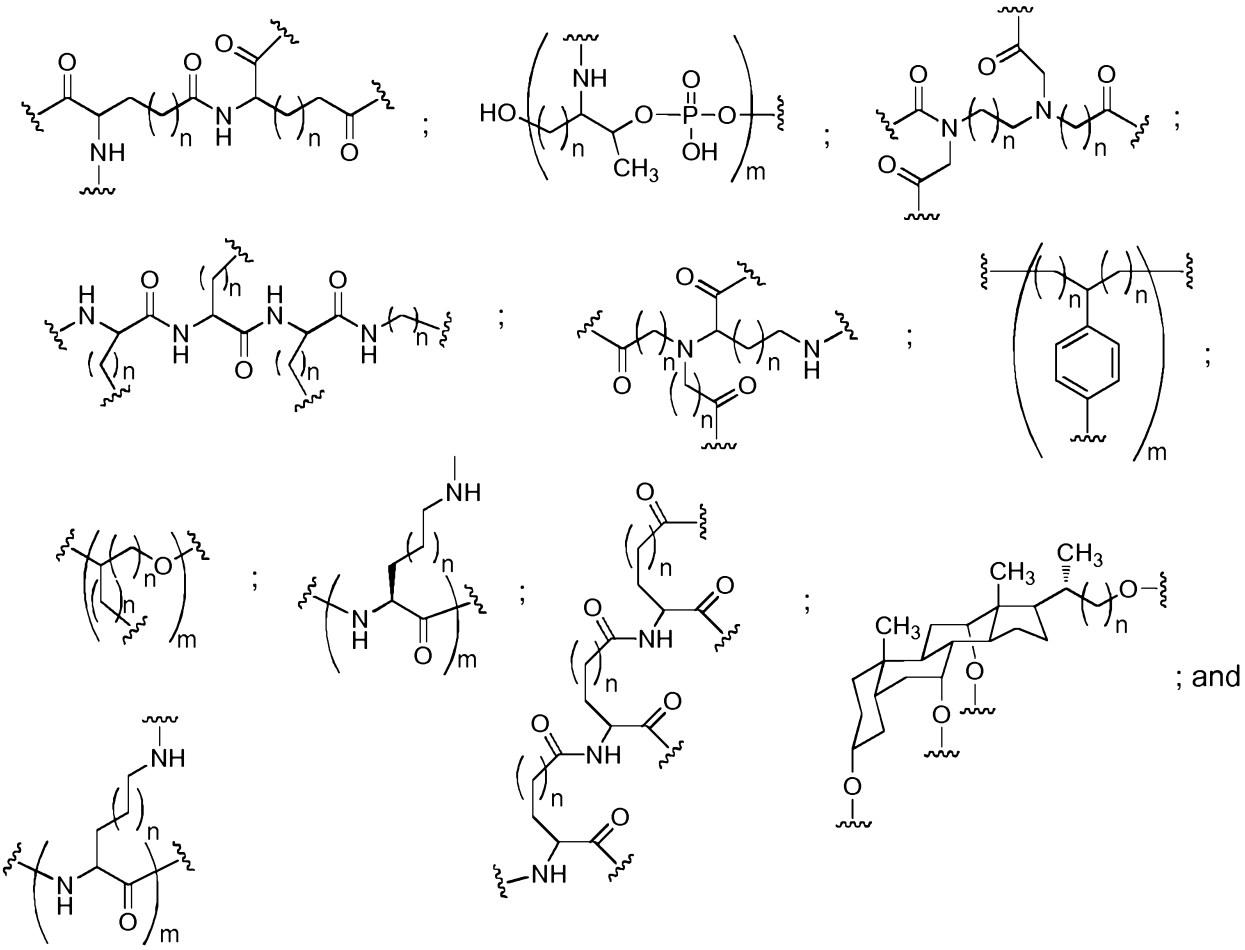
Embodiment 540. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has the following structure:



.

Embodiment 541. The conjugated antisense compound of any of embodiments 511 to 536, wherein the branching group comprises an ether.

Embodiment 542. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has the following structure:

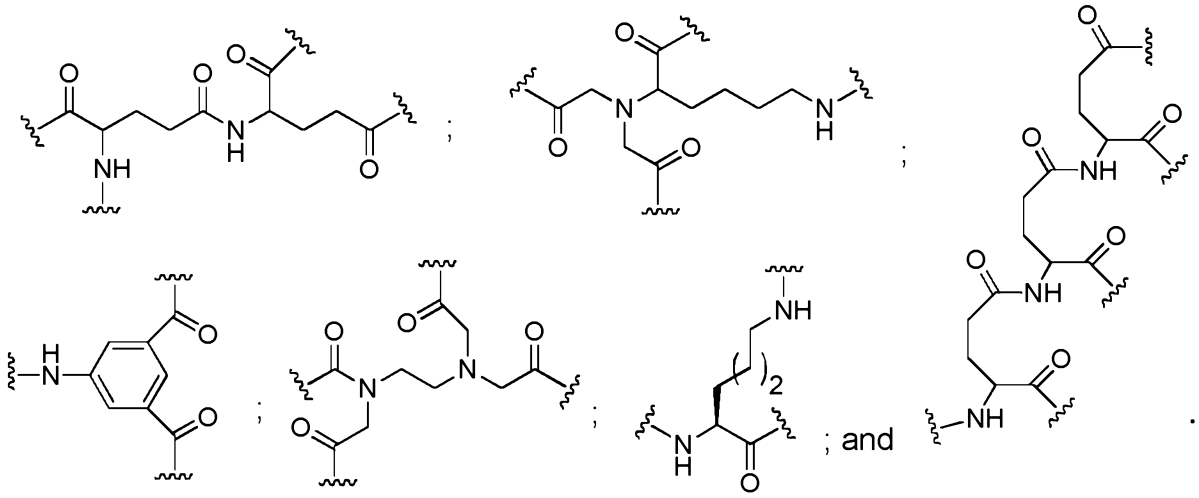


; and

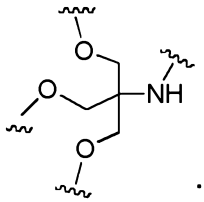
each n is, independently, from 1 to 20; and

m is from 2 to 6.

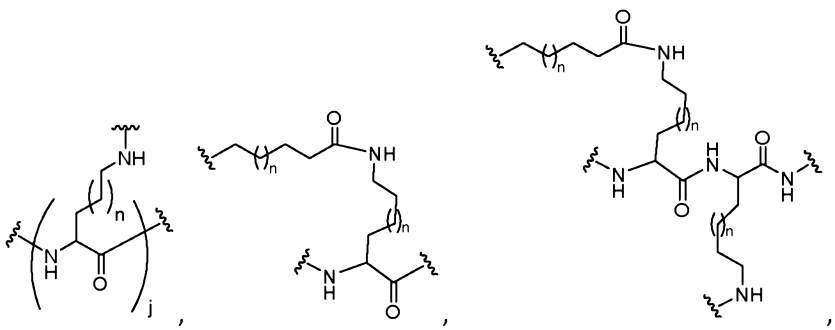
Embodiment 543. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has the following structure:

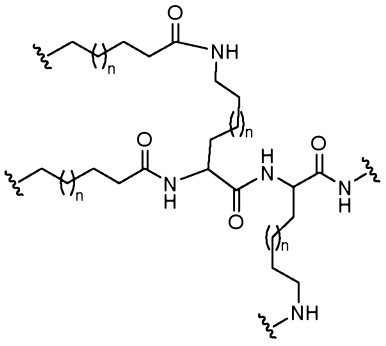
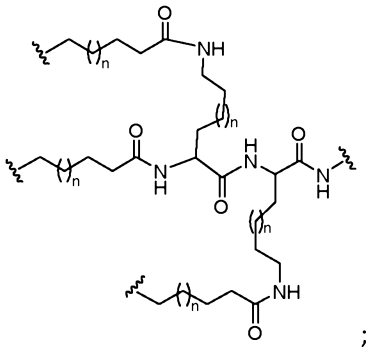


Embodiment 544. The conjugated antisense compound of embodiment 511 to 536, wherein the branching group has the following structure:



Embodiment 545. The conjugated antisense compound of any of embodiments 511 to 536, wherein the branching group comprises:

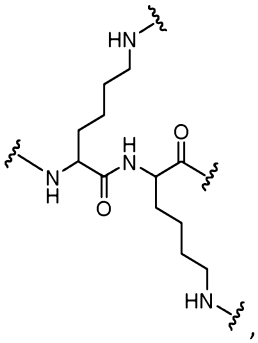
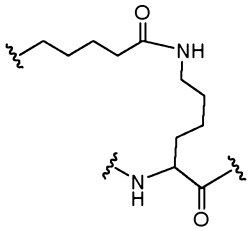
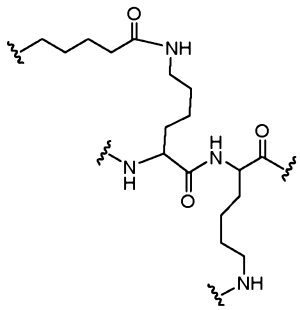
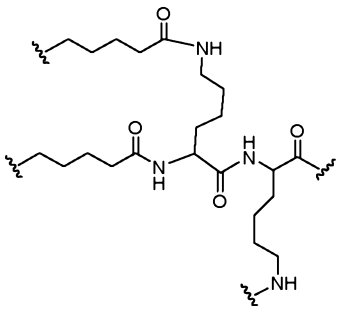
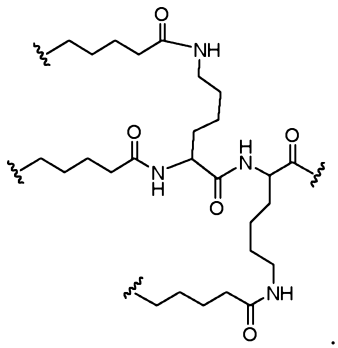



, or

;

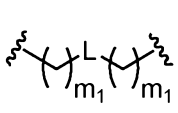
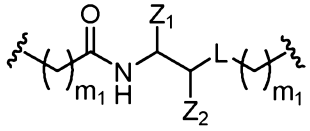
wherein each j is an integer from 1 to 3; and

wherein each n is an integer from 1 to 20.

Embodiment 546. The conjugated antisense compound of any of embodiments 511 to 536 wherein the branching group comprises:


,

,

,

, or

.

Embodiment 547. The conjugated antisense compound of embodiment 511 to 546, wherein each tether is selected from among:


and


wherein L is selected from a phosphorus linking group and a neutral linking group;

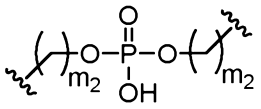
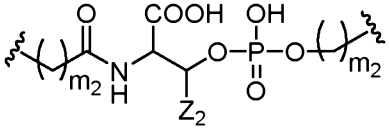
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 548. The conjugated antisense compound of embodiment 511 to 546, wherein each tether is selected from among:


and


wherein Z_2 is H or CH_3; and

each m_2 is, independently, from 0 to 20 wherein at least one m_2 is greater than 0 for each tether.

Embodiment 549. The conjugated antisense compound of any of embodiments 511 to 546, wherein at least one tether comprises PEG.

Embodiment 550. The conjugated antisense compound of any of embodiments 511 to 546, wherein at least one tether comprises an amide.

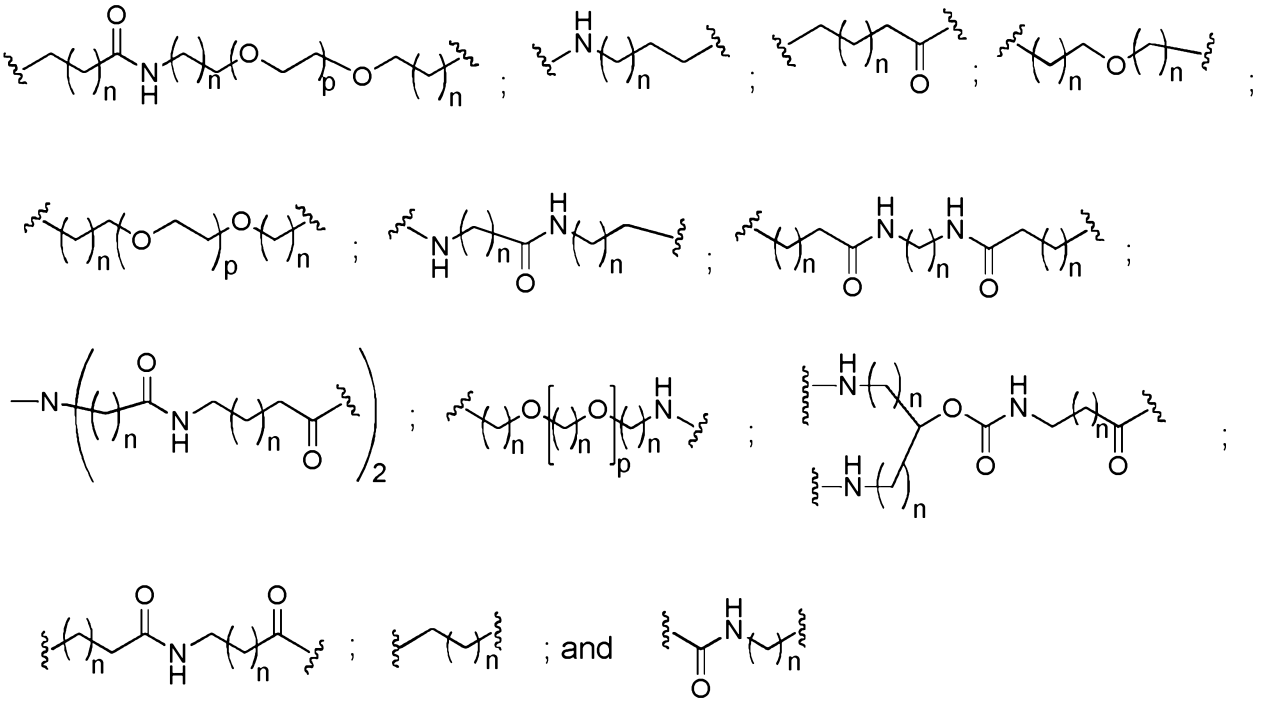
Embodiment 551. The conjugated antisense compound of any of embodiments 511 to 546, wherein at least one tether comprises a polyamide.

Embodiment 552. The conjugated antisense compound of any of embodiments 511 to 546, wherein at least one tether comprises an amine.

Embodiment 553. The conjugated antisense compound of any of embodiments 511 to 546, wherein at least two tethers are different from one another.

Embodiment 554. The conjugated antisense compound of any of embodiments 511 to 546, wherein all of the tethers are the same as one another.

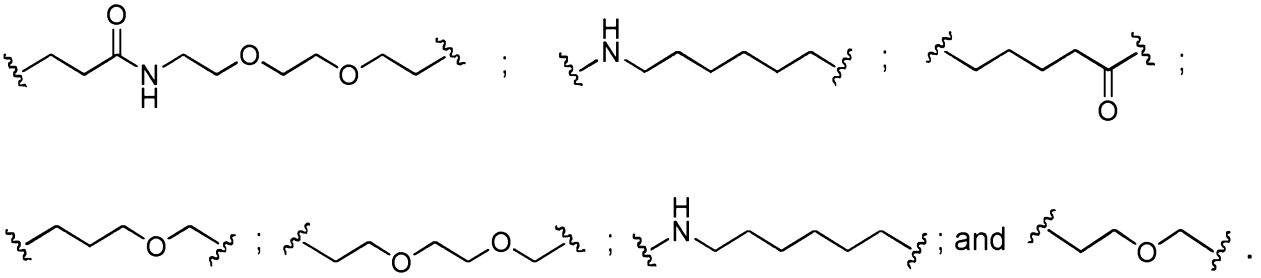
Embodiment 555. The conjugated antisense compound of any of embodiments 511 to 546, wherein each tether is selected from among:



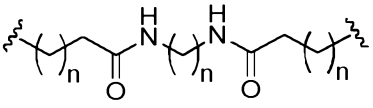
wherein each n is, independently, from 1 to 20; and

each p is from 1 to about 6.

Embodiment 556. The conjugated antisense compound of any of embodiments 511 to 546, wherein each tether is selected from among:

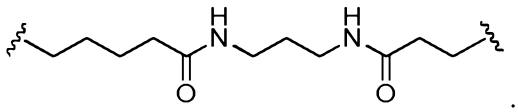


Embodiment 557. The conjugated antisense compound of any of embodiments 511 to 546, wherein each tether has the following structure:

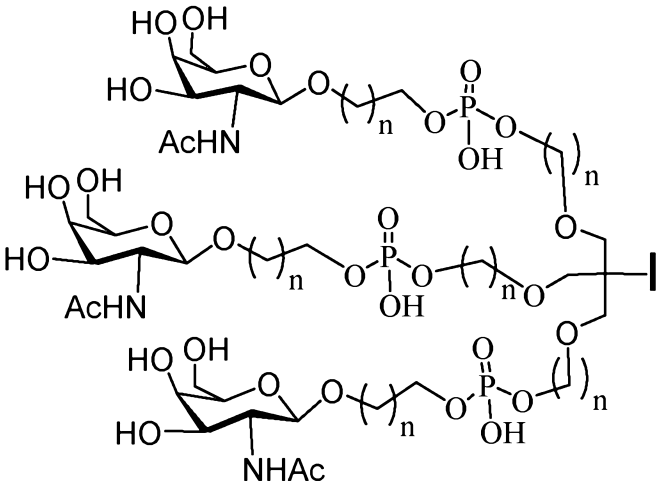


wherein each n is, independently, from 1 to 20.

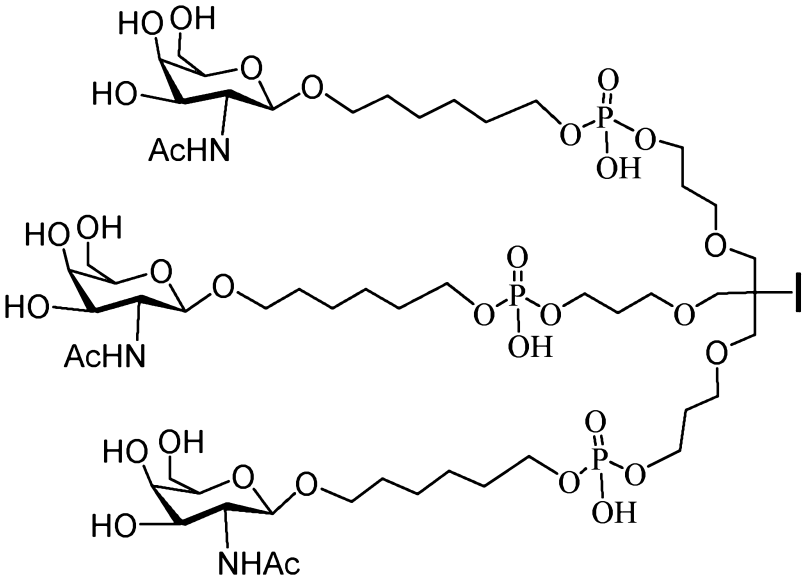
Embodiment 558. The conjugated antisense compound of any of embodiments 511 to 546, wherein each tether has the following structure:



Embodiment 559. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 558, wherein the cell-targeting moiety has the following structure:



Embodiment 560. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 558, wherein the cell-targeting moiety has the following structure:



Embodiment 561. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 558, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 562. The conjugated antisense compound of embodiment 493 to 502 or 511 to 558, wherein the cell-targeting moiety comprises one ligand.

Embodiment 563. The conjugated antisense compound of embodiment 493 to 502 or 511 to 558, wherein the targeting moiety comprises two ligands.

Embodiment 564. The conjugated antisense compound of embodiment 493 to 502 or 511 to 558, wherein the targeting moiety comprises three ligands.

Embodiment 565. The conjugated antisense compound of any of embodiments 561 to 564, wherein each ligand is covalently attached to each tether.

Embodiment 566. The conjugated antisense compound of any of embodiments 561 to 564, wherein at least one ligand is *N*-Acetylgalactosamine (GalNAc).

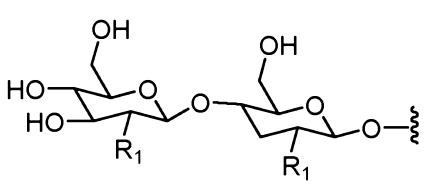
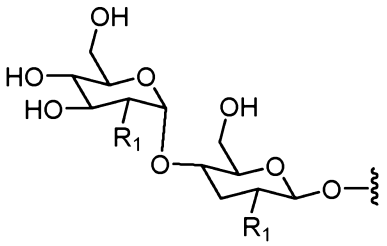
Embodiment 567. The conjugated antisense compound of any of embodiments 561 to 564, wherein each ligand is N-Acetylgalactosamine (GalNAc).

Embodiment 568. The conjugated antisense compound of any of embodiments 561 to 564, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

Embodiment 569. The conjugated antisense compound of any of embodiments 561 to 564, wherein the ligand is galactose.

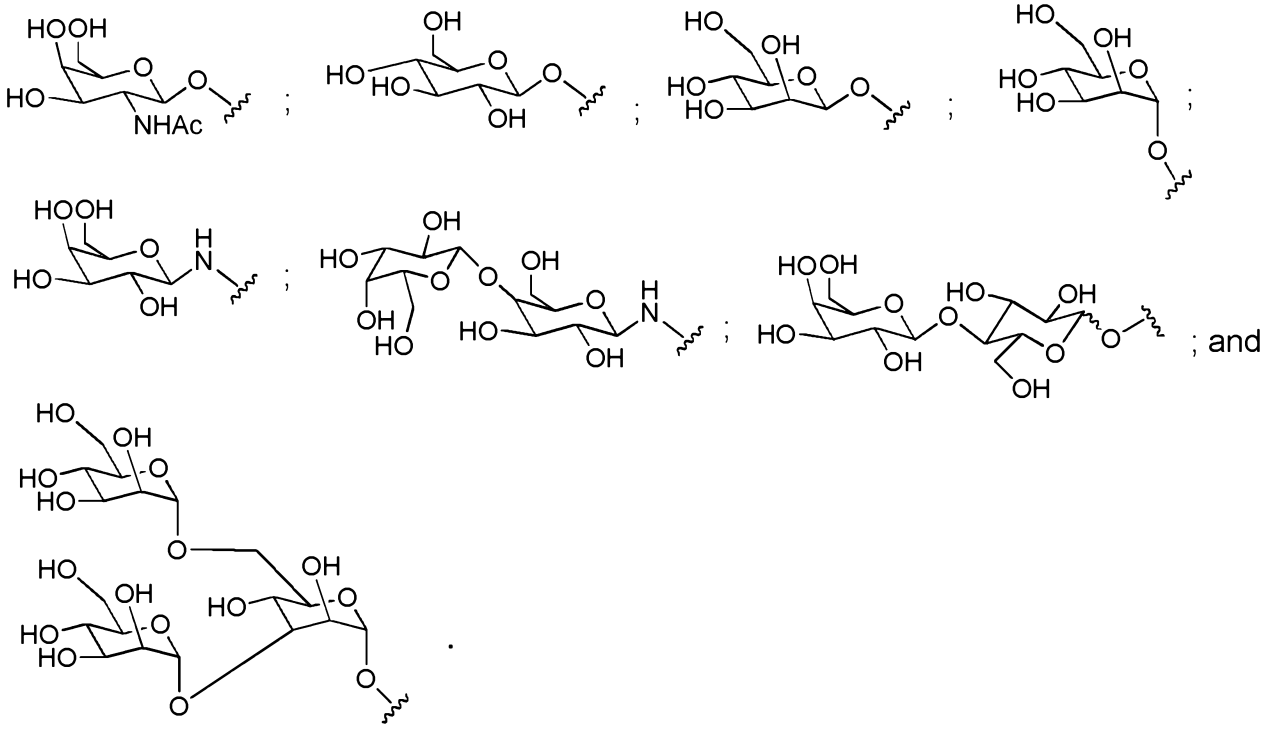
Embodiment 570. The conjugated antisense compound of any of embodiments 561 to 564, wherein the ligand is mannose-6-phosphate.

Embodiment 571. The conjugated antisense compound of any of embodiments 561 to 564, wherein each ligand is selected from among:

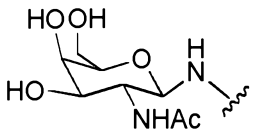

and


wherein each R_1 is selected from OH and NHCOOH.

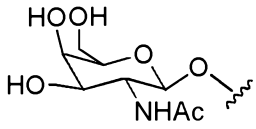
Embodiment 572. The conjugated antisense compound of any of embodiments 561 to 564, wherein each ligand is selected from among:



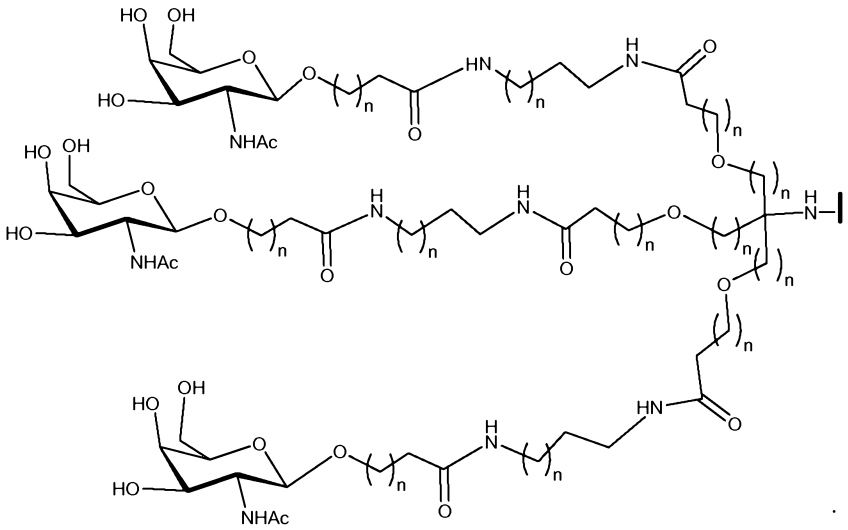
Embodiment 573. The conjugated antisense compound of any of embodiments 561 to 564, wherein each ligand has the following structure:



Embodiment 574. The conjugated antisense compound of any of embodiments 561 to 564, wherein each ligand has the following structure:

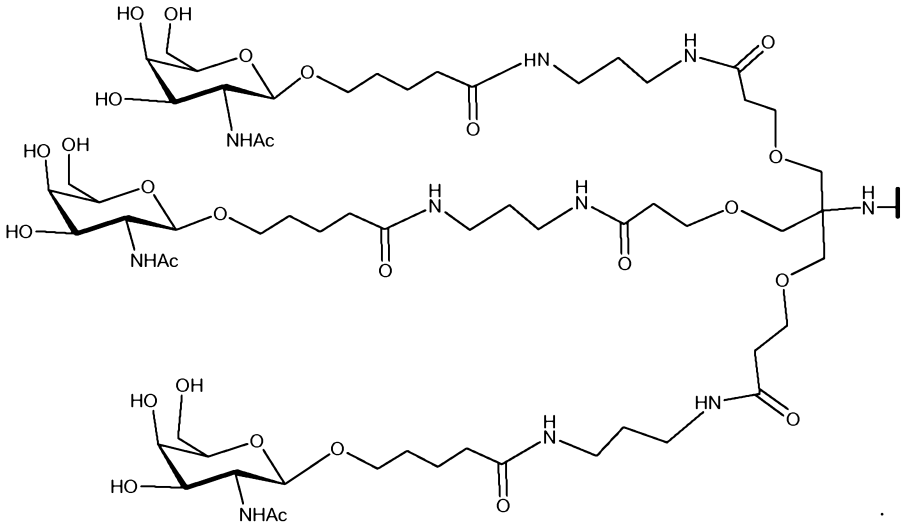


Embodiment 575. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the cell-targeting moiety has the following structure:

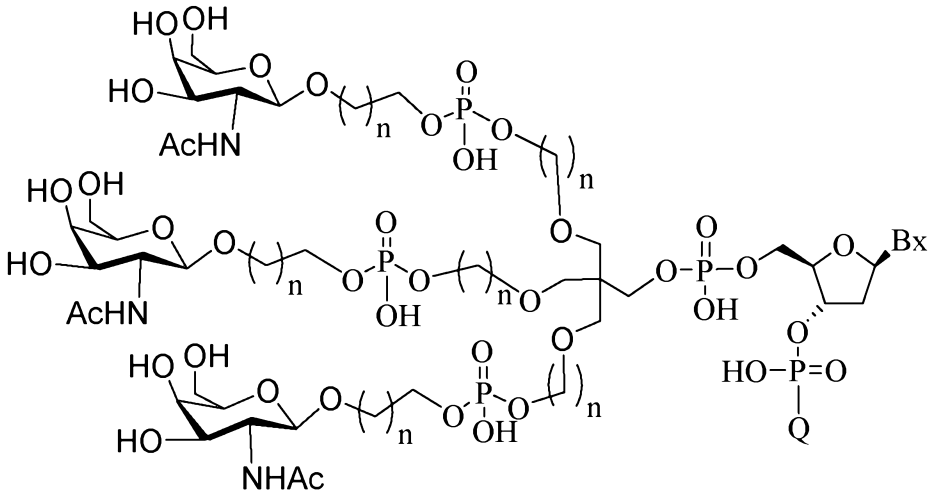


wherein each n is, independently, from 1 to 20.

Embodiment 576. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the cell-targeting moiety has the following structure:



Embodiment 577. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:

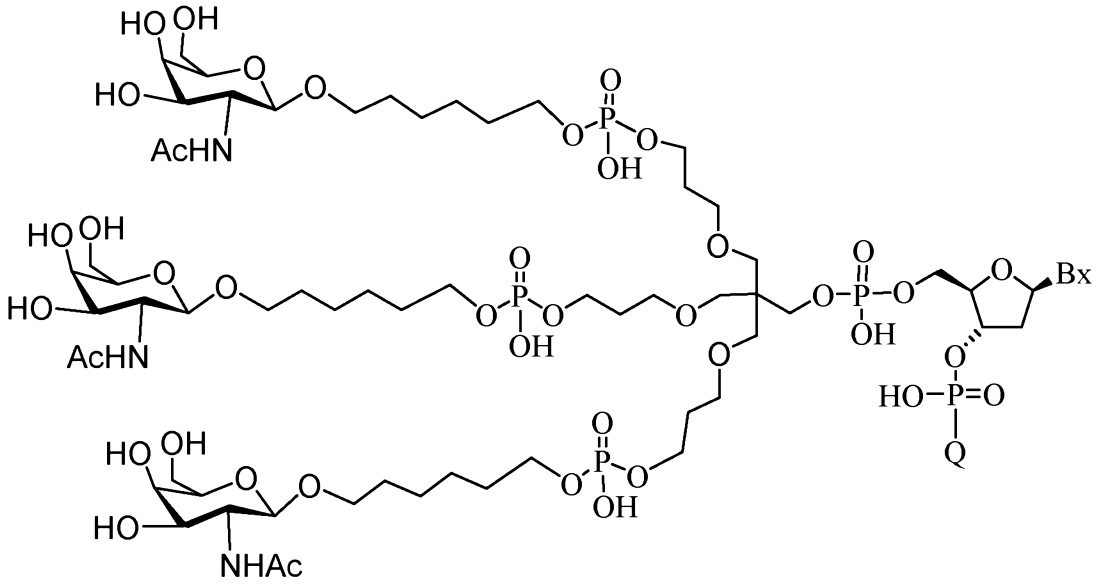


wherein each n is, independently, from 1 to 20;

Q is said antisense compound; and

Bx is a heterocyclic base moiety.

Embodiment 578. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:

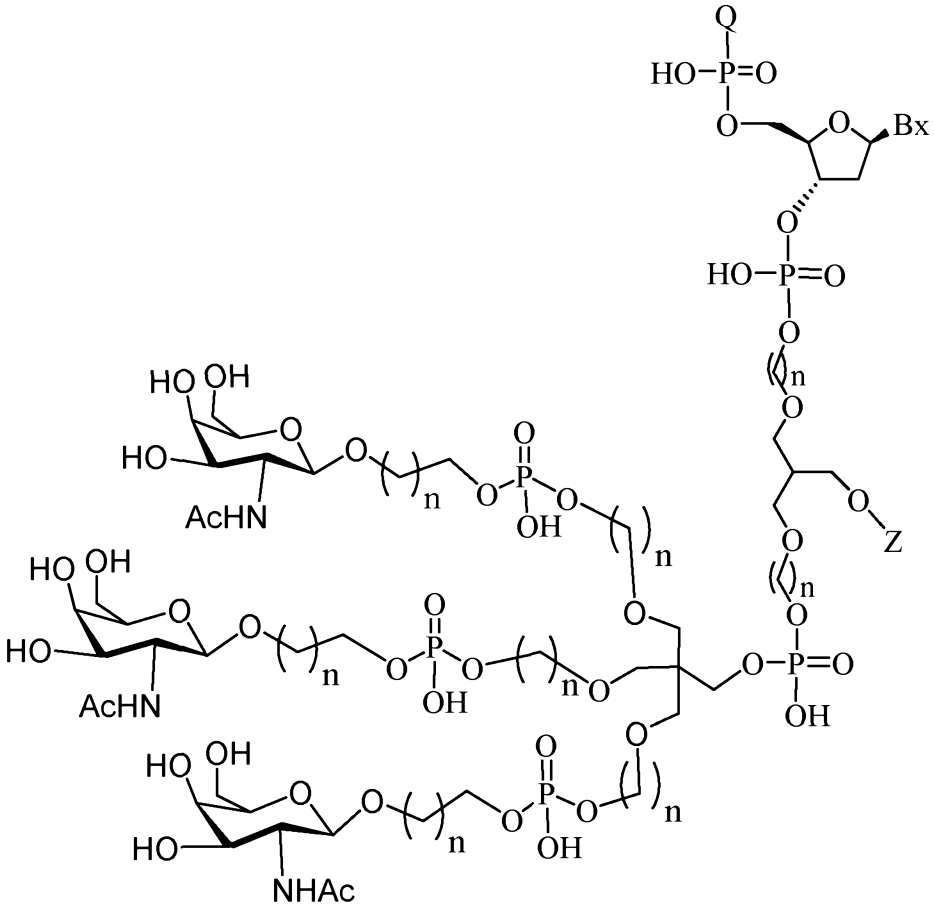


wherein each n is, independently, from 1 to 20;

Q is said antisense compound; and

Bx is a heterocyclic base moiety.

Embodiment 579. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:



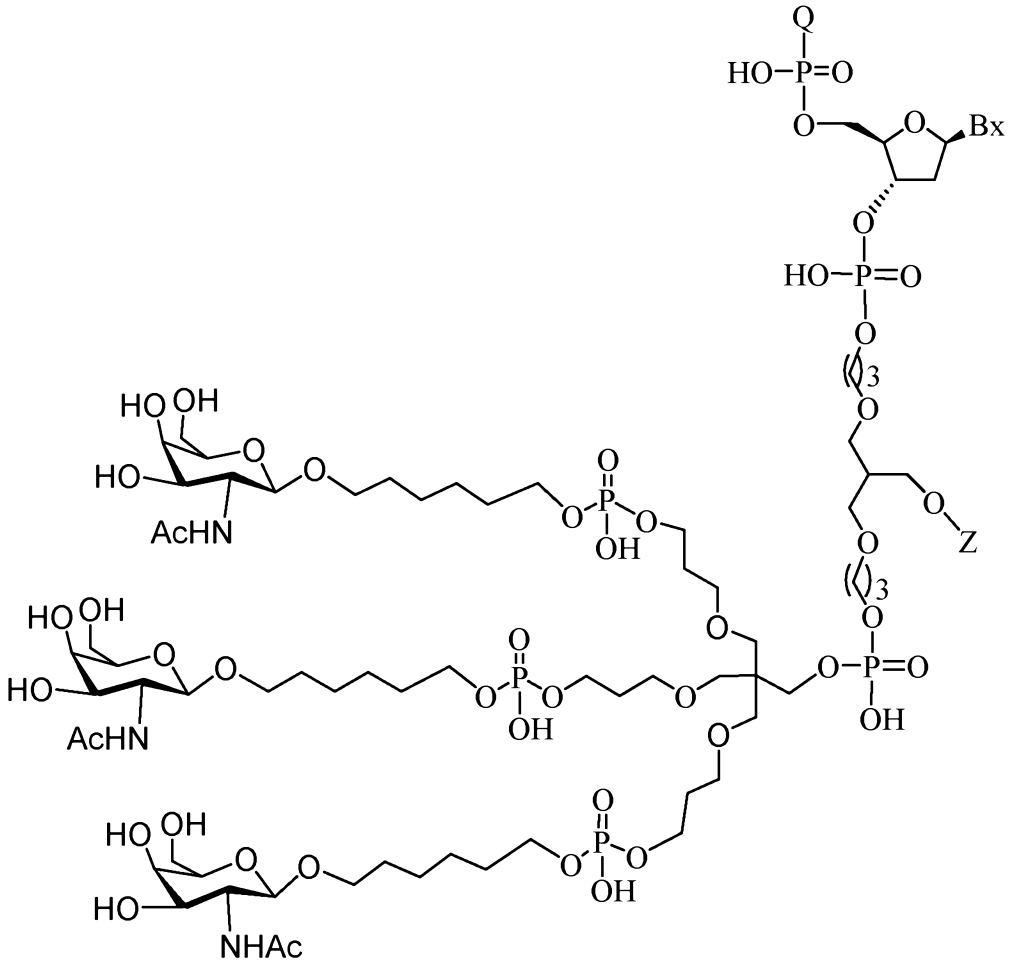
wherein each n is, independently, from 1 to 20;

Q is said antisense compound;

Z is H or a linked solid support; and

Bx is a heterocyclic base moiety.

Embodiment 580. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:



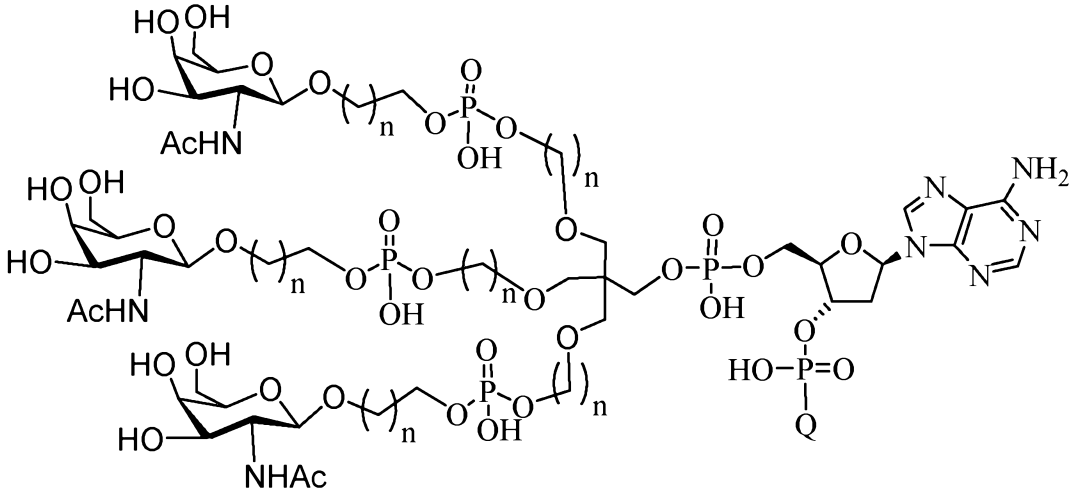
wherein each n is, independently, from 1 to 20;

Q is said antisense compound;

Z is H or a linked solid support; and

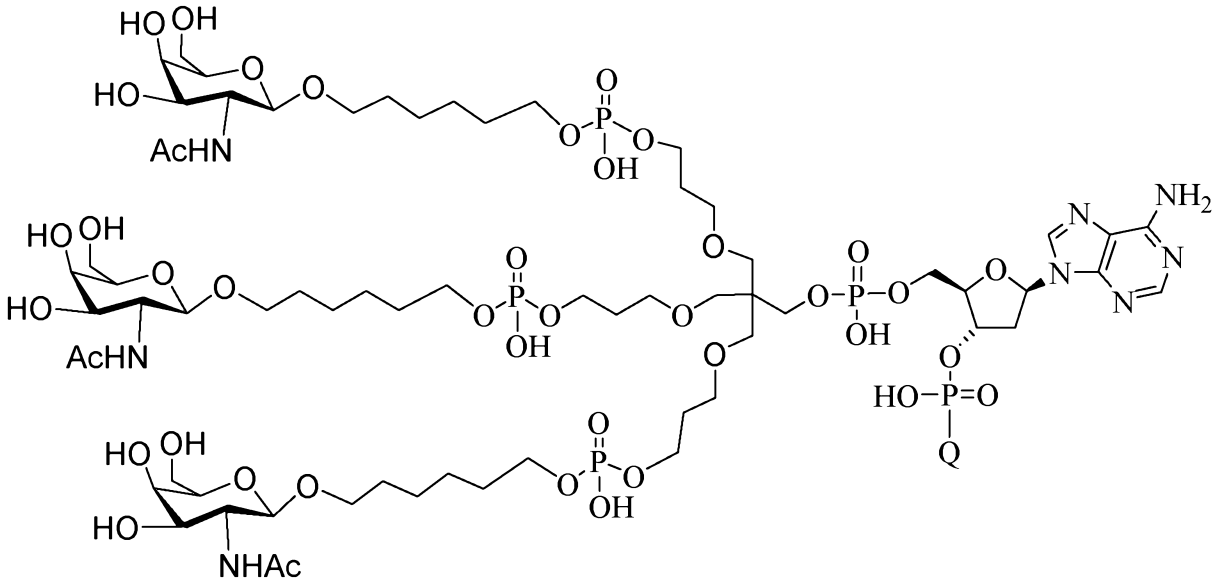
Bx is a heterocyclic base moiety.

Embodiment 581. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:



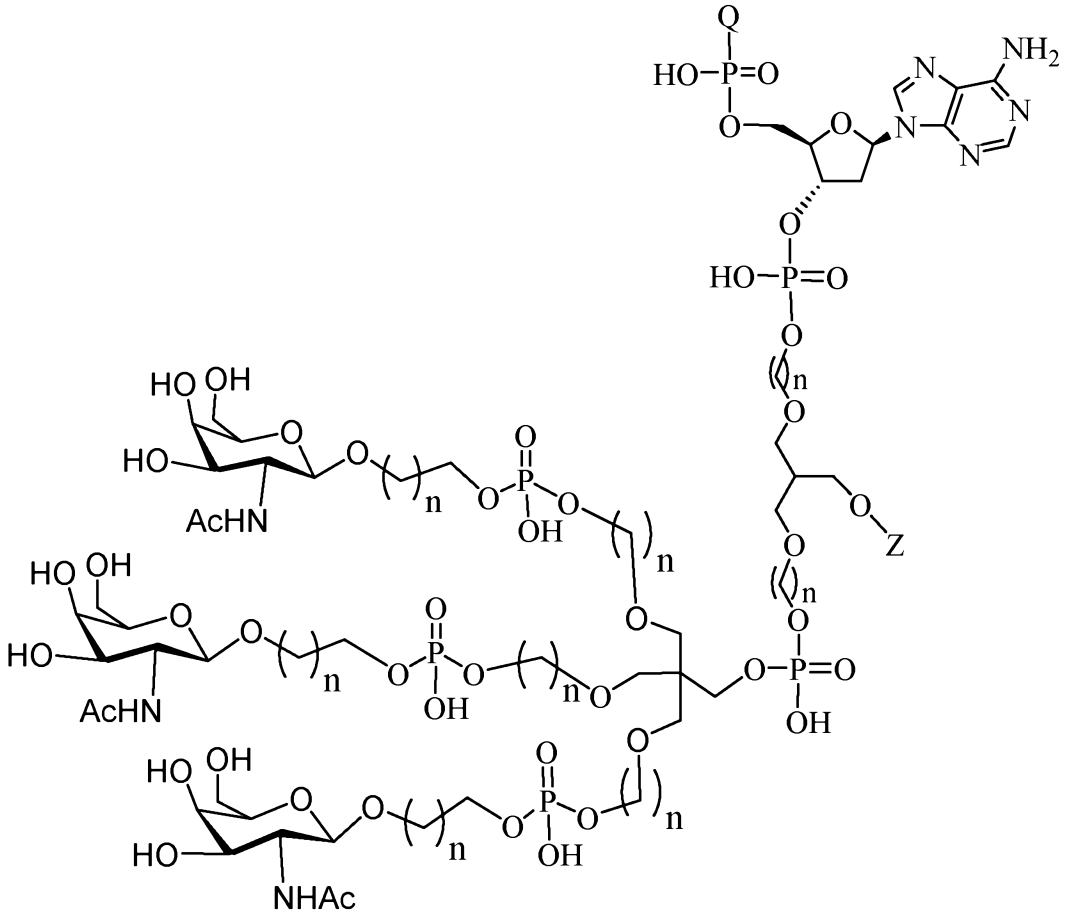
wherein Q is said antisense compound.

Embodiment 582. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:



wherein Q is said antisense compound.

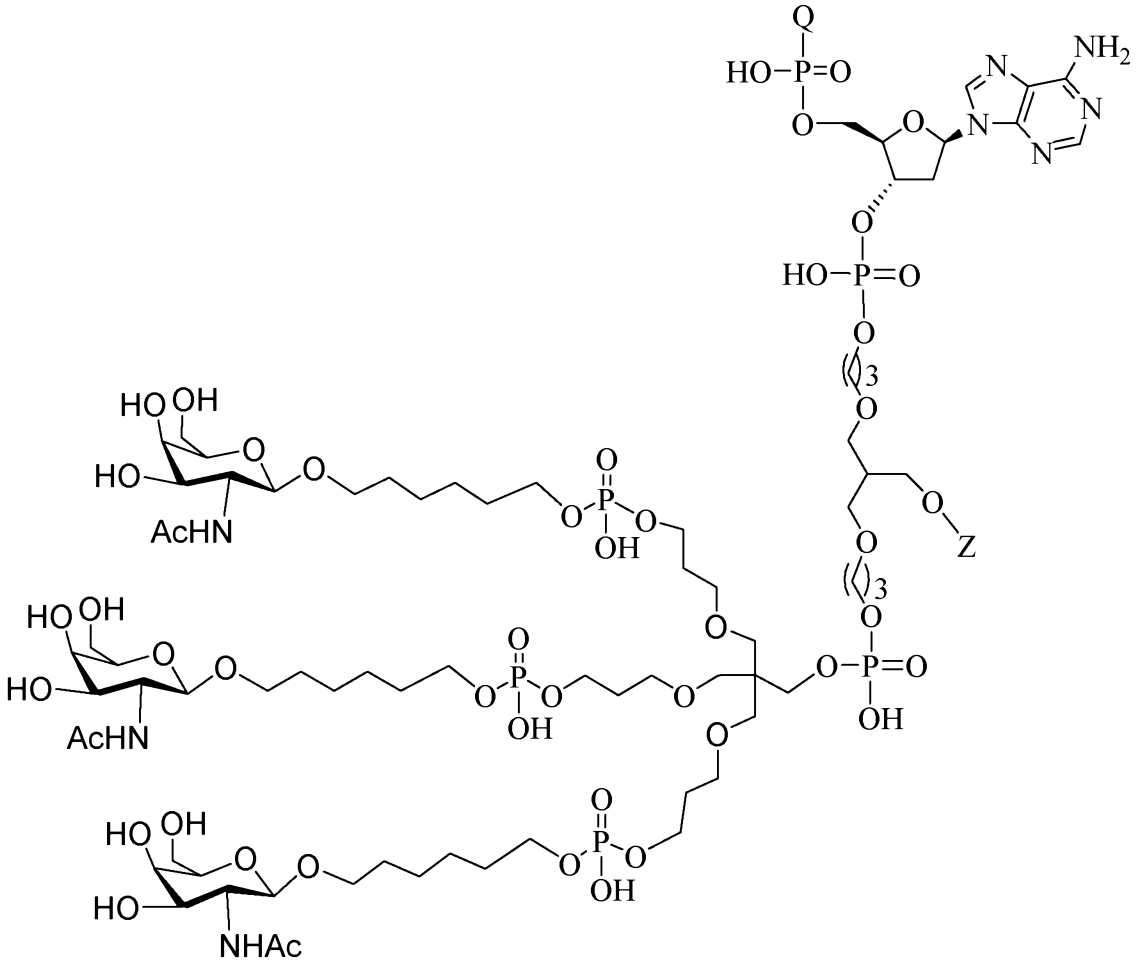
Embodiment 583. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:



wherein Q is said antisense compound; and

Z is H or a linked solid support.

Embodiment 584. The conjugated antisense compound of any of embodiments 493 to 502 or 511 to 574, wherein the conjugate group has the following structure:



wherein Q is said antisense compound; and

Z is H or a linked solid support.

Embodiment 585. A conjugated oligonucleotide comprising an oligonucleotide and a conjugate group, wherein the conjugate group is any conjugate group of any of embodiments 493 to 584.

Embodiment 586. The conjugated oligonucleotide of embodiment 585 wherein the oligonucleotide comprises at least one modified nucleoside.

Embodiment 587. The conjugated oligonucleotide of embodiment 586 wherein the at least one modified nucleoside comprises a modified base.

Embodiment 588. The conjugated oligonucleotide of embodiment 586 or 587 wherein the at least one modified nucleoside comprises a sugar surrogate.

Embodiment 589. The conjugated oligonucleotide of embodiment 588 wherein the sugar surrogate is a tetrahydropyran.

Embodiment 590. The conjugated oligonucleotide of any of embodiment 589 wherein the tetrahydropyran is F-HNA.

Embodiment 591. The conjugated oligonucleotide of any of embodiments 586 to 590 wherein the remainder of the oligonucleotide comprises at least one nucleoside comprising a modified sugar.

Embodiment 592. The conjugated oligonucleotide of embodiment 591 wherein the at least one modified nucleoside comprising a modified sugar is selected from a bicyclic nucleoside and a 2'-modified nucleoside.

Embodiment 593. The conjugated oligonucleotide of embodiment 586 wherein the at least one modified nucleoside is a bicyclic nucleoside.

Embodiment 594. The conjugated oligonucleotide of embodiment 593 wherein the bicyclic nucleoside is a (4'-CH_2-O-2') BNA nucleoside.

Embodiment 595. The conjugated oligonucleotide of embodiment 593 wherein the bicyclic nucleoside is a (4'-$(CH_2)_2$-O-2') BNA nucleoside.

Embodiment 596. The conjugated oligonucleotide of embodiment 593 wherein the bicyclic nucleoside is a (4'-$C(CH_3)$H-O-2') BNA nucleoside.

Embodiment 597. The conjugated oligonucleotide of embodiment 586 wherein the at least one modified nucleoside is a 2'-modifed nucleoside.

Embodiment 598. The conjugated oligonucleotide of embodiment 597 wherein the at least one 2'-modified nucleoside is selected from a 2'-F nucleoside, a 2'-OCH_3 nucleoside, and a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 599. The conjugated oligonucleotide of embodiment 598 wherein the at least one 2'-modified nucleoside is a 2'-F nucleoside.

Embodiment 600. The conjugated oligonucleotide of embodiment 598 wherein the at least one 2'-modified nucleoside is a 2'-OCH_3 nucleoside.

Embodiment 601. The conjugated oligonucleotide of embodiment 598 wherein the at least one 2'-modified nucleoside is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 602. The conjugated oligonucleotide of any of embodiments 585-601 wherein the oligonucleotide comprises at least one unmodified nucleoside.

Embodiment 603. The conjugated oligonucleotide of embodiment 602 wherein the unmodified nucleoside is a ribonucleoside.

Embodiment 604. The conjugated oligonucleotide of embodiment 602 wherein the unmodified nucleoside is a deoxyribonucleoside.

Embodiment 605. The conjugated oligonucleotide of any of embodiments 585 to 604 wherein the oligonucleotide comprises at least two modified nucleosides.

Embodiment 606. The conjugated oligonucleotide of embodiment 605 wherein the at least two modified nucleosides comprise the same modification.

Embodiment 607. The conjugated oligonucleotide of embodiment 605 wherein the at least two modified nucleosides comprise different modifications.

Embodiment 608. The conjugated oligonucleotide of any of embodiments 605 to 607 wherein at least one of the at least two modified nucleosides comprises a sugar surrogate.

Embodiment 609. The conjugated oligonucleotide of any of embodiments 605 to 608 wherein at least one of the at least two modified nucleosides comprises a 2'-modification.

Embodiment 610. The conjugated oligonucleotide of embodiment 609 wherein each of the at least two modified nucleosides is independently selected from 2'-F nucleosides, 2'-OCH_3 nucleosides and 2'-$O(CH_2)_2OCH_3$ nucleosides.

Embodiment 611. The conjugated oligonucleotide of embodiment 610 wherein each of the at least two modified nucleosides is a 2'-F nucleoside.

Embodiment 612. The conjugated oligonucleotide of embodiment 610 wherein each of the at least two modified nucleosides is a 2'-OCH_3 nucleosides.

Embodiment 613. The conjugated oligonucleotide of embodiment 610 wherein each of the at least two modified nucleosides is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 614. The conjugated oligonucleotide of any of embodiments 586 to 613 wherein essentially every nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 615. The conjugated oligonucleotide of any of embodiments 586 to 601 or 606 to 613 wherein every nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 616. The conjugated oligonucleotide of any of embodiments 586 to 615 wherein the oligonucleotide is single-stranded.

Embodiment 617. The conjugated oligonucleotide of any of embodiments 586 to 615 wherein the oligonucleotide is double-stranded.

Embodiment 618. The conjugated oligonucleotide of any of embodiments 586 to 615, wherein the oligonucleotide is an antisense compound.

Embodiment 619. The conjugated oligonucleotide of any of embodiments 586 to 615, wherein the oligonucleotide is a RISC based oligonucleotide.

Embodiment 620. The conjugated oligonucleotide of any of embodiments 586 to 615, wherein the oligonucleotide activates the RISC pathway.

Embodiment 621. The conjugated oligonucleotide of any of embodiments 586 to 615, wherein the oligonucleotide is an RNase H based antisense compound.

Embodiment 622. The conjugated oligonucleotide compound of any of embodiments 586 to 621, wherein the conjugate group is attached to the 5'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 623. The conjugated oligonucleotide compound of any of embodiments 586 to 621, wherein the conjugate group is attached to the 3'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 624. The conjugated oligonucleotide compound of any of embodiments 586 to 621, wherein the conjugate group is attached to an internal nucleoside of the antisense oligonucleotide.

Embodiment 625. The conjugated oligonucleotide compound of any of embodiments 586 to 624, wherein the conjugate group increases uptake of the conjugated oligonucleotide compound into a hepatocyte relative to an unconjugated oligonucleotide compound.

Embodiment 626. The conjugated oligonucleotide compound of any of embodiments 586 to 624, wherein the conjugate group increases the uptake of the conjugated oligonucleotide compound into a liver cell relative to an unconjugated oligonucleotide compound.

Embodiment 627. The conjugated oligonucleotide compound of any of embodiments 586 to 626, wherein the conjugate group increases accumulation of the conjugated oligonucleotide compound in the liver relative to an unconjugated oligonucleotide compound.

Embodiment 628. The conjugated oligonucleotide compound of any of embodiments 586 to 627, wherein the conjugate group decreases accumulation of the conjugated oligonucleotide compound in the kidneys relative to an unconjugated oligonucleotide compound.

Embodiment 629. The conjugated oligonucleotide compound of embodiment 586 to 628, wherein the conjugated oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 630. The conjugated oligonucleotide compound of embodiment 629, wherein the 5'-region consists of 2 linked 5'-region nucleosides.

Embodiment 631. The conjugated oligonucleotide compound of embodiment 629, wherein the 5'-region consists of 3 linked 5'-region nucleosides.

Embodiment 632. The conjugated oligonucleotide compound of embodiment 629, wherein the 5'-region consists of 4 linked 5'-region nucleosides.

Embodiment 633. The conjugated oligonucleotide compound of embodiment 629, wherein the 5'-region consists of 5 linked 5'-region nucleosides.

Embodiment 634. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the 3'-region consists of 2 linked 3'-region nucleosides.

Embodiment 635. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the 3'-region consists of 3 linked 3'-region nucleosides.

Embodiment 636. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the 3'-region consists of 4 linked 3'-region nucleosides.

Embodiment 637. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the 3'-region consists of 5 linked 3'-region nucleosides.

Embodiment 638. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the central region consists of 5 linked central region nucleosides.

Embodiment 639. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the central region consists of 6 linked central region nucleosides.

Embodiment 640. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the central region consists of 7 linked central region nucleosides.

Embodiment 641. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the central region consists of 8 linked central region nucleosides.

Embodiment 642. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the central region consists of 9 linked central region nucleosides.

Embodiment 643. The conjugated oligonucleotide compound of any of embodiments 629-633, wherein the central region consists of 10 linked central region nucleosides.

Embodiment 644. The conjugated oligonucleotide compound of any of embodiments 629-644, wherein the conjugated oligonucleotide consists of 14 to 26 linked nucleosides.

Embodiment 645. The conjugated oligonucleotide compound of any of embodiments 629-644, wherein the conjugated oligonucleotide consists of 15 to 25 linked nucleosides.

Embodiment 646. The conjugated oligonucleotide compound of any of embodiments 629-644, wherein the conjugated oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 647. The conjugated oligonucleotide compound of any of embodiments 629-644, wherein each modified nucleoside independently comprises a 2'-substituted sugar moiety or a bicyclic sugar moiety.

Embodiment 648. The conjugated oligonucleotide compound of embodiment 647, wherein the at least one modified nucleoside comprises a 2'-substituted sugar moiety.

Embodiment 649. The conjugated oligonucleotide compound of embodiment 648, wherein each modified nucleoside comprising a 2'-substituted sugar moiety comprises a 2' substituent independently selected from among: halogen, optionally substituted allyl, optionally substituted amino, azido, optionally substituted SH, CN, OCN, CF_3, OCF_3, O, S, or N(Rm)-alkyl; O, S, or N(Rm)-alkenyl; O, S or N(Rm)-alkynyl; optionally substituted O-alkylenyl-O-alkyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted O-alkaryl, optionally substituted O-aralkyl, $O(CH_2)_2SCH_3$, $O-(CH_2)_2-O-N(Rm)(Rn)$ or $O-CH_2-C(=O)-N(Rm)(Rn)$, where each Rm and Rn is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl;

wherein each optionally substituted group is optionally substituted with a substituent group independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

Embodiment 650. The conjugated oligonucleotide compound of embodiment 648, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, $OCH_2-CH=CH_2$, $O(CH_2)_2-OCH_3$, $O(CH_2)_2-SCH_3$, $O(CH_2)_2-OCF_3$, $O(CH_2)_3-N(R_1)(R_2)$, $O(CH_2)_2-ON(R_1)(R_2)$, $O(CH_2)_2-O(CH_2)_2-N(R_1)(R_2)$, $OCH_2C(=O)-N(R_1)(R_2)$, $OCH_2C(=O)-N(R_3)-(CH_2)_2-N(R_1)(R_2)$, and $O(CH_2)_2-N(R_3)-C(=NR_4)[N(R_1)(R_2)]$; wherein R_1, R_2, R_3 and R_4 are each, independently, H or C_1-C_6 alkyl.

Embodiment 651. The conjugated oligonucleotide compound of embodiment 648, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, $OCH_2-CH=CH_2$, $O(CH_2)_2-OCH_3$ (MOE), $O(CH_2)_2-O(CH_2)_2-N(CH_3)_2$, $OCH_2C(=O)-N(H)CH_3$, $OCH_2C(=O)-N(H)-(CH_2)_2-N(CH_3)_2$, and $OCH_2-N(H)-C(=NH)NH_2$.

Embodiment 652. The conjugated oligonucleotide compound of embodiment 648, wherein the at least one 2'-modified nucleoside comprises a 2'-MOE sugar moiety.

Embodiment 653. The conjugated oligonucleotide compound of embodiment 648, wherein the at least one 2'-modified nucleoside comprises a 2'-OMe sugar moiety.

Embodiment 654. The conjugated oligonucleotide compound of embodiment 648, wherein the at least one 2'-modified nucleoside comprises a 2'-F sugar moiety.

Embodiment 655. The conjugated oligonucleotide compound of any of embodiments 629-644, wherein the conjugated oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 656. The conjugated oligonucleotide compound of embodiment 655, wherein the modified nucleoside comprises an F-HNA sugar moiety.

Embodiment 657. The conjugated oligonucleotide compound of embodiment 655, wherein the modified nucleoside comprises an HNA sugar moiety.

Embodiment 658. The conjugated oligonucleotide compound of any of embodiments 629-657 wherein the conjugated oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 659. The conjugated oligonucleotide compound of embodiment 658, wherein the bicyclic sugar moiety is a cEt sugar moiety.

Embodiment 660. The conjugated oligonucleotide compound of embodiment 658, wherein bicyclic sugar moiety is an LNA sugar moiety.

Embodiment 661. The conjugated oligonucleotide compound of any of embodiments 585 to 660, wherein the conjugated oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 662. The conjugated oligonucleotide compound of embodiment 661, wherein each internucleoside linkage of the conjugated oligonucleotide is a modified internucleoside linkage.

Embodiment 663. The conjugated oligonucleotide compound of embodiment 661, wherein the conjugated oligonucleotide comprises at least one modified linkage and at least one unmodified phosphodiester internucleoside linkage.

Embodiment 664. The conjugated oligonucleotide compound of any of embodiments 661 to 663 wherein at least one modified internucleoside linkage is a phosphosphorothioate internucleoside linkage.

Embodiment 665. The conjugated oligonucleotide compound of any of embodiments 661 to 663, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 666. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 667. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 668. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 669. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 670. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 671. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 672. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 8 phosphodiester internucleoside linkages.

Embodiment 673. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 9 phosphodiester internucleoside linkages.

Embodiment 674. The conjugated oligonucleotide compound of any of embodiments 661 to 662, wherein the conjugated oligonucleotide comprises at least 10 phosphodiester internucleoside linkages.

Embodiment 675. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 16 phosphorothioate internucleoside linkages.

Embodiment 676. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 15 phosphorothioate internucleoside linkages.

Embodiment 677. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 14 phosphorothioate internucleoside linkages.

Embodiment 678. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 13 phosphorothioate internucleoside linkages.

Embodiment 679. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 12 phosphorothioate internucleoside linkages.

Embodiment 680. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 11 phosphorothioate internucleoside linkages.

Embodiment 681. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 10 phosphorothioate internucleoside linkages.

Embodiment 682. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 9 phosphorothioate internucleoside linkages.

Embodiment 683. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 8 phosphorothioate internucleoside linkages.

Embodiment 684. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 7 phosphorothioate internucleoside linkages.

Embodiment 685. The conjugated oligonucleotide compound of any of embodiments 661 or 663 to 674, wherein the conjugated oligonucleotide comprises fewer than 6 phosphorothioate internucleoside linkages.

Embodiment 686. The conjugated oligonucleotide compound of any of embodiments 585 to 685, wherein each terminal internucleoside linkage of the conjugated oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 687. The conjugated oligonucleotide compound of any of embodiments 585 to 662 or 665 to 686, wherein each internucleoside linkage linking two deoxynucleosides of the conjugated oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 688. The conjugated oligonucleotide compound of any of embodiments 585 to 662 or 665 to 687, wherein each non-terminal internucleoside linkage linking two modified nucleosides of the conjugated oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 689. The conjugated oligonucleotide compound of any of embodiments 585 to 662 or 665 to 688, wherein each non-terminal internucleoside linkage of the conjugated oligonucleotide that is 3' of a modified nucleoside is a phosphodiester internucleoside linkage.

Embodiment 690. The conjugated oligonucleotide compound of any of embodiments 585 to 662 or 665 to 689, wherein each internucleoside linkage of the conjugated oligonucleotide that is 3' of a deoxynucleoside is a phosphorothioate internucleoside linkage.

Embodiment 691. The conjugated oligonucleotide compound of any of embodiments 585 to 662 or 665 to 690 wherein the conjugated oligonucleotide has a chemical motif selected from among:

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$
$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$
$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$
$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$; and
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each s is a phosphorothioate internucleoside linkage, and each y is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage, provided that at least one y is a phosphodiester internucleotide linkage.

Embodiment 692. The conjugated oligonucleotide compound of any of embodiments 585 to 662 or 665 to 690 wherein the conjugated oligonucleotides has a chemical motif selected from among:

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$; and
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each o is a phosphodiester internucleoside linkage, and each s is a phosphorothioate internucleoside linkage.

Embodiment 693. The conjugated oligonucleotide compound of embodiment 691 or 692, wherein each M is independently selected from among: a 2'-MOE nucleoside and a bicyclic nucleoside.

Embodiment 694. The conjugated oligonucleotide compound of embodiment 693, wherein each M is independently selected from among a 2'-MOE nucleoside, a cEt nucleoside, and an LNA nucleoside.

Embodiment 695. The conjugated oligonucleotide compound of embodiment 693 or 694, wherein each M is a 2'-MOE nucleoside.

Embodiment 696. The conjugated oligonucleotide compound of embodiment 693 or 694, wherein each M is a cEt nucleoside.

Embodiment 697. The conjugated oligonucleotide compound of embodiments 693 or 694, wherein each M is an LNA nucleoside.

Embodiment 698. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 8 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 699. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 10 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 700. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 12 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 701. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 14 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 702. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 16 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 703. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 18 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 704. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide is at least 90% complementary to a target nucleic acid.

Embodiment 705. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide is at least 95% complementary to a target nucleic acid.

Embodiment 706. The conjugated oligonucleotide compound of any of embodiments 585 to 697, wherein the conjugated oligonucleotide is 100% complementary to a target nucleic acid.

Embodiment 707. The conjugated oligonucleotide compound of any of embodiments 698 to 706, wherein the target nucleic acid is a pre-mRNA.

Embodiment 708. The conjugated oligonucleotide compound of any of embodiments 698 to 706, wherein the target nucleic acid is an mRNA.

Embodiment 709. The conjugated oligonucleotide compound of any of embodiments 698 to 706, wherein the target nucleic acid is a micro RNA.

Embodiment 710. The conjugated oligonucleotide compound of any of embodiments 698 to 709, wherein the target nucleic acid is expressed in the liver.

Embodiment 711. The conjugated oligonucleotide compound of any of embodiments 698 to 709, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 712. The conjugated oligonucleotide compound of any of embodiments 698 to 709, wherein the target nucleic encodes a protein selected from among: Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI,

Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, and Transthyretin.

Embodiment 713. The conjugated oligonucleotide compound of any of embodiments 698 to 709 wherein the target nucleic acid is a viral nucleic acid.

Embodiment 714. The conjugated oligonucleotide compound of embodiment 713, wherein the viral nucleic acid expressed in the liver.

Embodiment 715. The conjugated oligonucleotide compound of embodiment 714, wherein the target nucleic acid is a Hepatitis B viral nucleic acid.

Embodiment 716. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NOs.: 17, 18, 19, 20, 21, 22, 23, or 24.

Embodiment 717. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NO.: 25, 26, 27, 28, 29, or 30.

Embodiment 718. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 31.

Embodiment 719. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 32.

Embodiment 720. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 33.

Embodiment 721. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 34.

Embodiment 722. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 35, 36, 37, 38, 39, 40, 41, 42, or 43.

Embodiment 723. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 44, 45, 46, 47, or 48.

Embodiment 724. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 725. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 60, 61, 62, 63, 64, 65, 66, or 67.

Embodiment 726. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NO.: 69, 70, 71, or 72.

Embodiment 727. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 73.

Embodiment 728. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 74, 75, 76, 77, 78, 79, 80, or 81.

Embodiment 729. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 68.

Embodiment 730. The conjugated oligonucleotide compound of any of embodiments 585 to 708, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 82-103.

Embodiment 731. The conjugated oligonucleotide compound of any of embodiments 585 to 731, wherein the conjugated oligonucleotide is an antisense oligonucleotide.

Embodiment 732. A method of reducing the amount or activity of a target nucleic acid in a cell, comprising contacting a cell with a compound or conjugated antisense compound of any of embodiments 493 to 731.

Embodiment 733. The method of embodiment 732, wherein the cell is a liver cell.

Embodiment 734. The method of embodiment 732, wherein the cell is a hepatocyte.

Embodiment 735. The method of any of embodiments 732 to 734 wherein the cell is in vitro.

Embodiment 736. The method of any of embodiments 732 to 734 wherein the cell is in an animal.

Embodiment 737. The method of embodiment 736 wherein the animal is a mouse.

Embodiment 738. The method of embodiment 736 wherein the animal is a human.

Embodiment 739. A pharmaceutical composition comprising a compound or conjugated oligonucleotide according to any of embodiments 493 to 731 and a pharmaceutically acceptable carrier or diluent.

Embodiment 740. The pharmaceutical composition of embodiment 739 wherein the pharmaceutically acceptable carrier or diluent is selected from among sterile water and sterile saline.

Embodiment 741. A method of treating a disease or condition in an animal comprising administering the pharmaceutical composition of embodiment 739 or 740 to the animal and thereby treating the disease or condition in the animal.

Embodiment 742. The method of embodiment 741 wherein the animal is a mouse.

Embodiment 743. The method of embodiment 741 wherein the animal is a human.

Embodiment 744. The method of any of embodiments 741 to 743, wherein the disease or condition is a liver disease or condition.

Embodiment 745. The method of any of embodiments 741 to 743 wherein the administration is parenteral.

Embodiment 746. The method embodiment 745 wherein the administration is by subcutaneous injection.

Embodiment 747. The method of embodiment 745 wherein the administration is by intravenous injection.

Embodiment 748. The method of embodiment 745 wherein the administration is by intramuscular injection.

Embodiment 749. The method of any of embodiments 741 to 748 wherein the conjugated oligonucleotide is provided at a dose of 1-10 mg/kg.

Embodiment 750. The method of any of embodiments 741 to 748 wherein the conjugated oligonucleotide is provided at a dose of less than 1 mg/kg.

Embodiment 751. The method of any of embodiments 741 to 748 wherein the conjugated oligonucleotide is provided at a dose of greater than 10 mg/kg.

Embodiment 752. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided for a dosing period of at least 2 months.

Embodiment 753. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided for a dosing period of at least 4 months.

Embodiment 754. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided for a dosing period of at least 6 months.

Embodiment 755. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every week.

Embodiment 756. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every two weeks.

Embodiment 757. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every three weeks.

Embodiment 758. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every four weeks.

Embodiment 759. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every five weeks.

Embodiment 760. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every six weeks.

Embodiment 761. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every seven weeks.

Embodiment 762. The method of any of embodiments 741 to 751 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every eight weeks.

Embodiment 763. A conjugated antisense compound comprising: an antisense oligonucleotide comprising 12-30 linked nucleosides, and a conjugate group, wherein the conjugate group comprises at least one cell-targeting moiety.

Embodiment 764. A method of reducing the activity or amount of an Apolipoprotein C-III protein in a cell, comprising contacting a cell with at least one conjugated antisense compound of any of embodiments 493 to 731; and thereby reducing the activity or amount of the Apolipoprotein C-III protein in the cell.

Embodiment 765. A method of decreasing total cholesterol, comprising contacting a cell with at least one compound of any of embodiments 493 to 731; and thereby decreasing total cholesterol.

Embodiment 766. A method of decreasing triglycerides, comprising contacting a cell with at least one compound of any of embodiments 493 to 731; and thereby decreasing triglycerides.

Embodiment 767. A method of lowering LDL, comprising contacting a cell with at least one compound of any of embodiments 493 to 731; and thereby lowering LDL.

Embodiment 768. A method of increasing HDL, comprising contacting a cell with at least one compound of any of embodiments 493 to 731; and thereby increasing HDL.

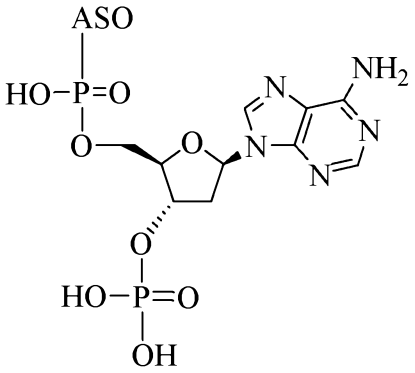
Embodiment 769. The method of any of embodiments 764 to 768, wherein the cell is in vitro.

Embodiment 770. The method of any of embodiments 764 to 768, wherein the cell is in an animal.

Embodiment 771. The method of any of embodiments 764 to 768, wherein the animal is a human.

Embodiment 772. The compound or conjugated oligonucleotide of any of embodiments 1-771 or a prodrug thereof.

Embodiment 773. A prodrug of an antisense compound comprising the structure:



,

wherein ASO represents an antisense oligonucleotide of any of embodiments 1-771.

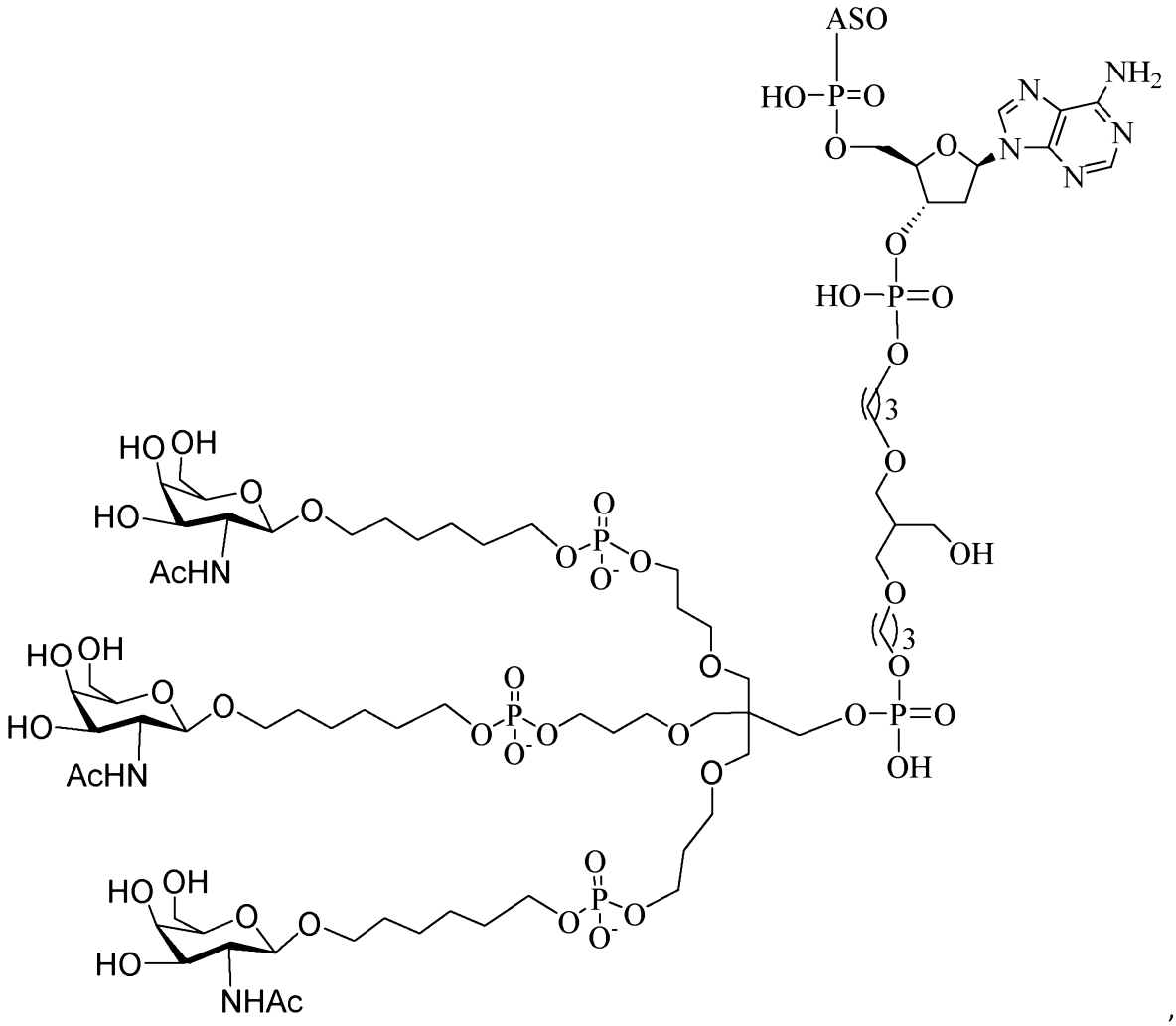
Embodiment 774. A prodrug of an antisense compound comprising the structure, wherein the one or more metabolites of the prodrug has the structure:

,

and wherein ASO represents an antisense oligonucleotide of any of embodiments 1-771.

Embodiment 775. A prodrug of an antisense compound, wherein one or more metabolites of the prodrug comprises an antisense oligonucleotide of any of embodiments 1-771.

Embodiment 776. A prodrug comprising:



wherein ASO represents an antisense oligonucleotide of any of claims 1 to 731.

Embodiment 777. A method of manufacturing an antisense oligonucleotide of any of embodiments 1-771.

Embodiment 778. A method of preparing an antisense oligonucleotide of any of embodiments 1-771.

Embodiment 779. A conjugate compound comprising at least one phosphorus linking group or neutral linking group and one or more ligands.

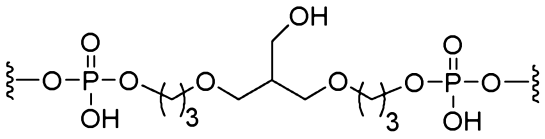
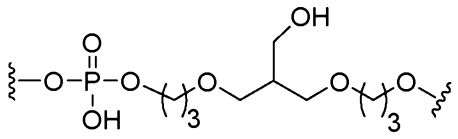
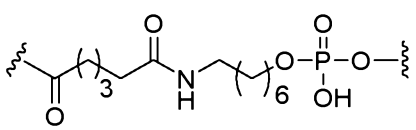
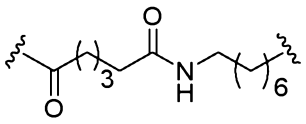
Embodiment 780. The conjugate compound of embodiment 779 comprising two or more ligands.

Embodiment 781. The conjugate compound of embodiment 779 comprising three ligands.

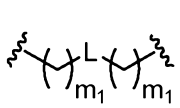
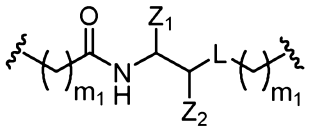
Embodiment 782. The conjugate compound of any of embodiments 779 to 781, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

Embodiment 783. The conjugate compound of any of embodiments 779 to 781, wherein the ligand is N-acetyl galactoseamine.

Embodiment 784. The conjugate compound of any of embodiments 779 to 783, wherein conjugate group comprises a structure selected from among:




and


Embodiment 785. The conjugate compound of any of embodiments 779 to 784, wherein the conjugate compound has a tether having a structure selected from among:


and


wherein L is either a phosphorus linking group or a neutral linking group;

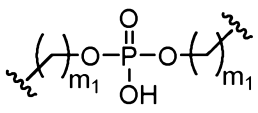
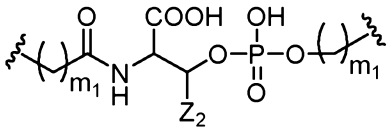
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 786. The conjugate compound of embodiment 785, wherein the tether has a structure selected from among:


and


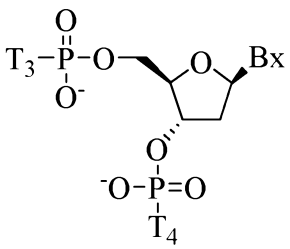
wherein Z_2 is H or CH_3; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 787. The conjugate compound of any of embodiments 779 to 786, wherein the conjugate compound is covalently attached to an oligonucleotide.

Embodiment 788. An oligomeric compound comprising an oligonucleotide and at least one conjugate group, wherein at least one conjugate group is a conjugate compound of any of embodiments 780 to 786.

Embodiment 789. A compound having the formula (V):

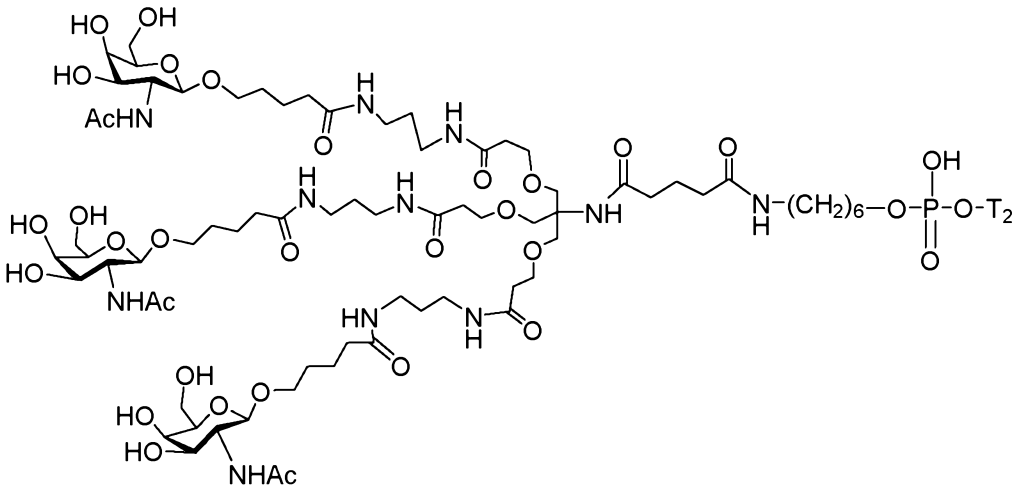


wherein one of T_3 or T_4 is selected from among: GalNAc$_3$-1a, GalNAc$_3$-2a, GalNAc$_3$-3a, GalNAc$_3$-4a, GalNAc$_3$-5a, GalNAc$_3$-6a, GalNAc$_3$-7a, GalNAc$_3$-8a, GalNAc$_3$-9a, GalNAc$_3$-10a, or GalNAc$_3$-11a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; and

wherein Bx is a heterocyclic base moiety.

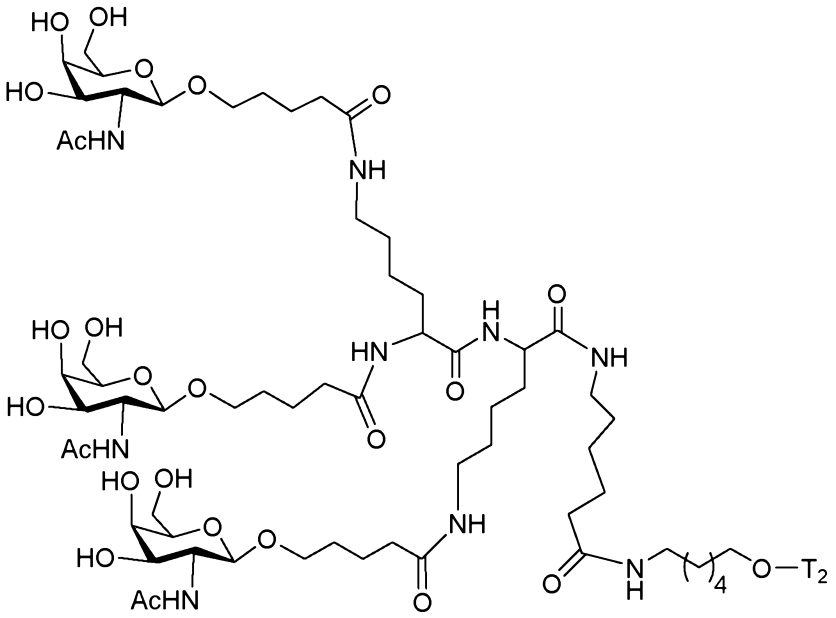
Embodiment 790. A compound having the formula (VIII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

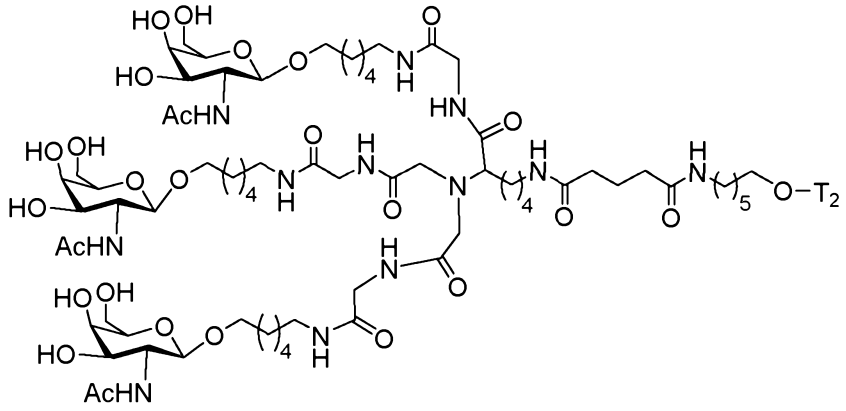
Embodiment 791. A compound having the formula (IX):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

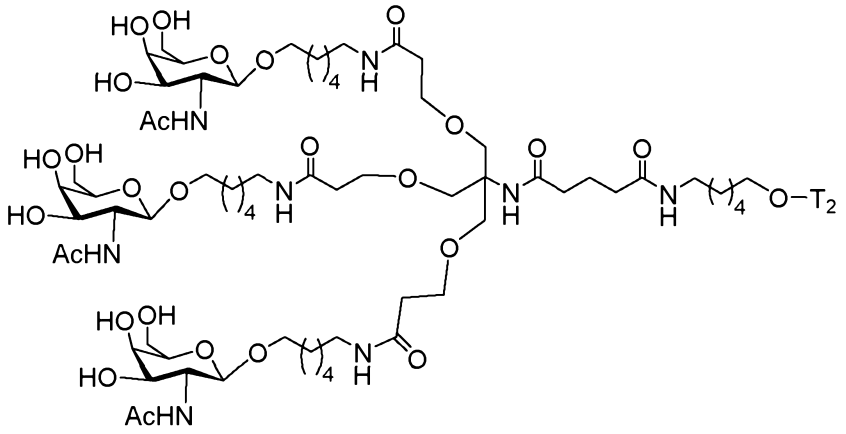
Embodiment 792. A compound having the formula (X):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

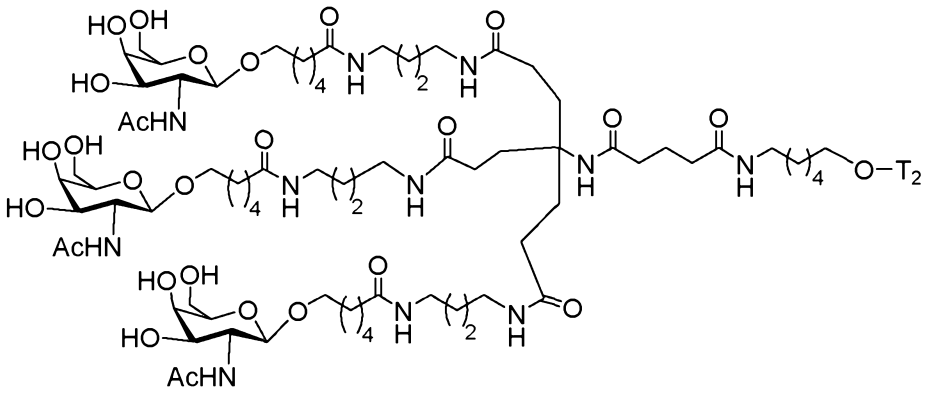
Embodiment 793. A compound having the formula (XI):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

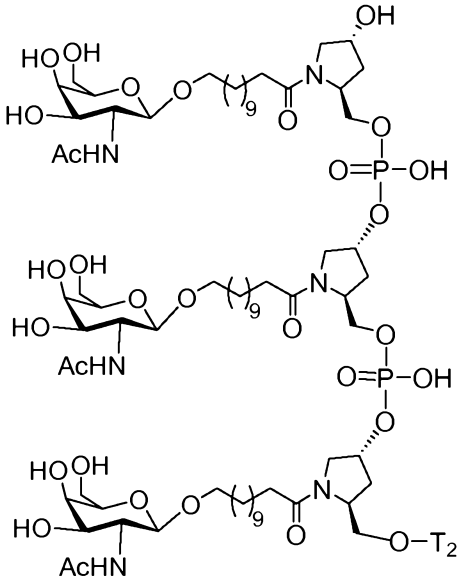
Embodiment 794. A compound having the formula (XII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

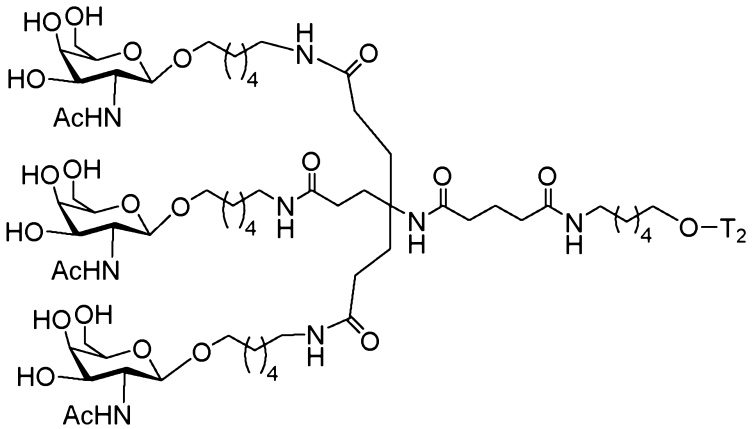
Embodiment 795. A compound having the formula (XIII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

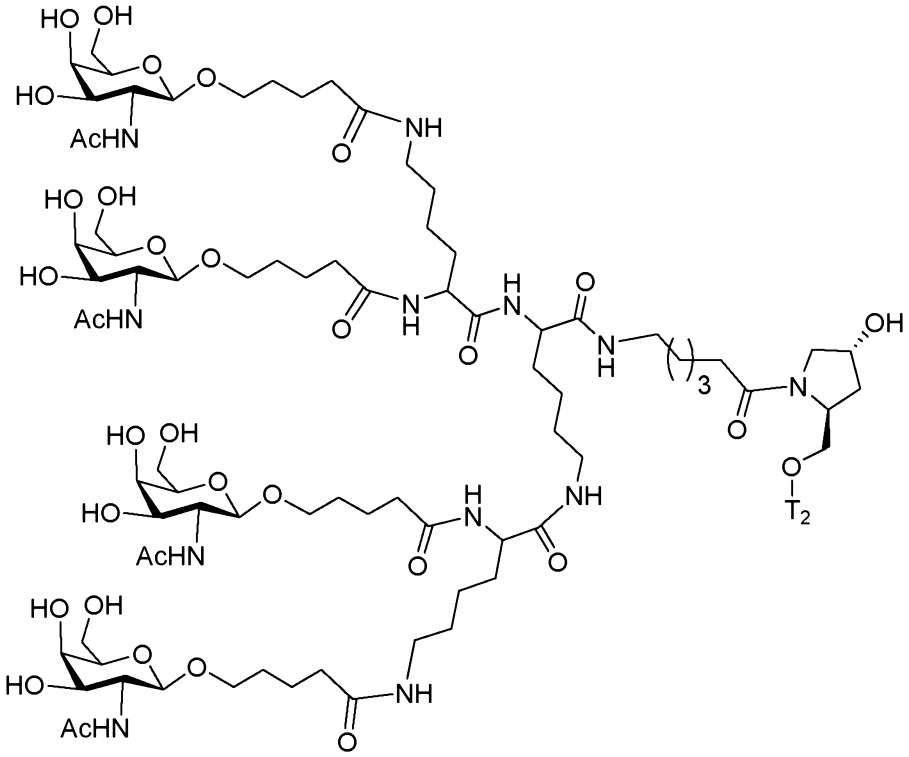
Embodiment 796. A compound having the formula (XIV):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

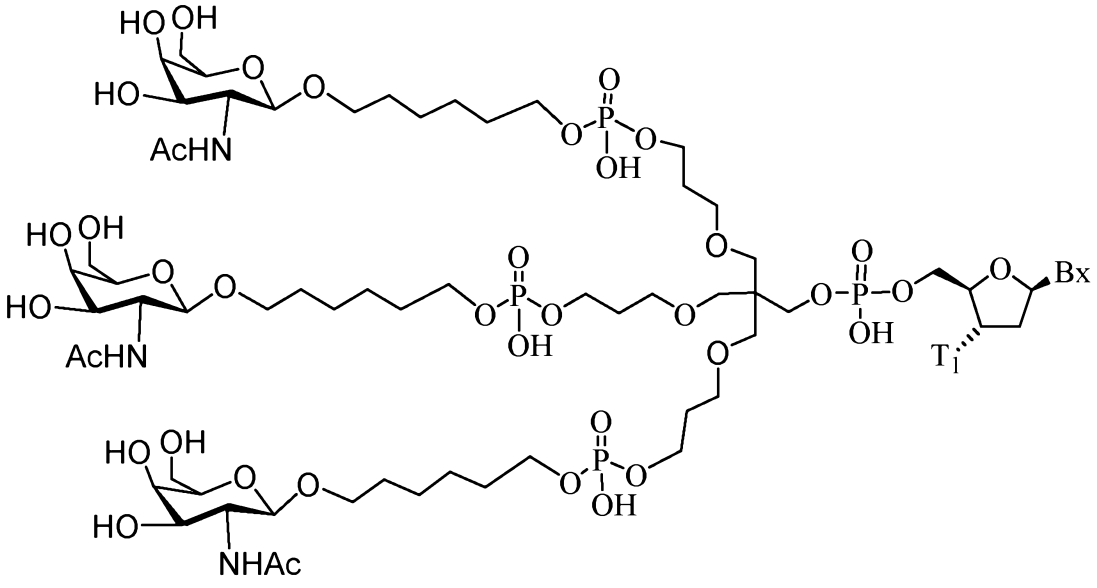
Embodiment 797. A compound having the formula (XV):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 798. A compound having the formula (I):



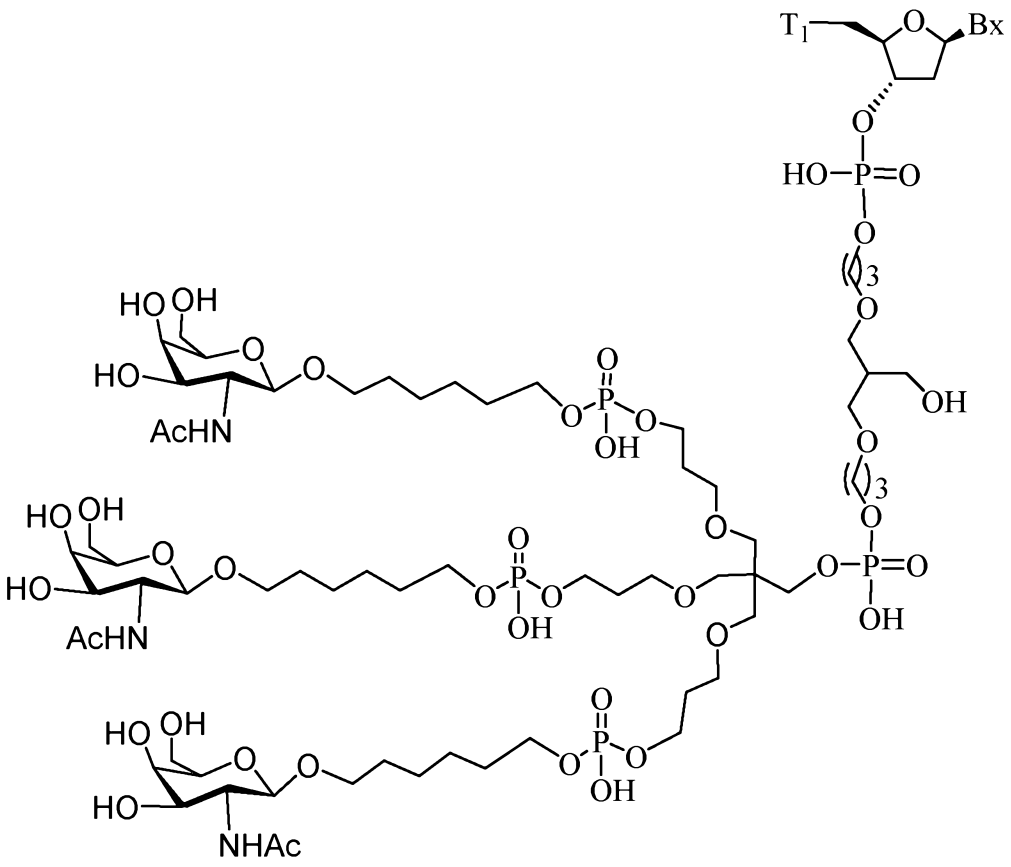
(I)

wherein:

Bx is a heterocyclic base moiety; and

T_1 is a hydroxyl, hydrogen, a hydroxyl protecting group, phosphorus moiety, or a reactive phosphorus group.

Embodiment 799. A compound having the formula (II):



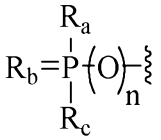
(II)

wherein:

Bx is a heterocyclic base moiety; and

T_1 is a hydroxyl, hydrogen, a hydroxyl protecting group, phosphorus moiety, or a reactive phosphorus group.

Embodiment 800. The compound of any of embodiment 798 or 799, wherein the phosphorus moiety has the formula:



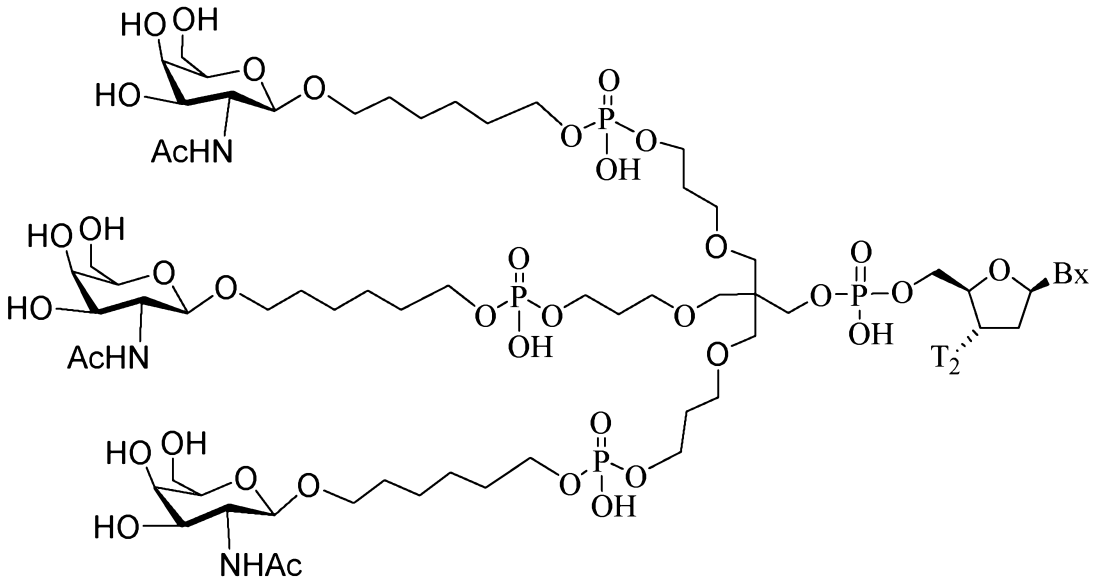
wherein:

n is 0 or 1;

R_a and R_c are each, independently, 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

R_b is O or S.

Embodiment 801. An oligomeric compound comprising an oligonucleotide and at least one conjugate group, wherein the at least one conjugate group is a conjugate compound of formula (III):



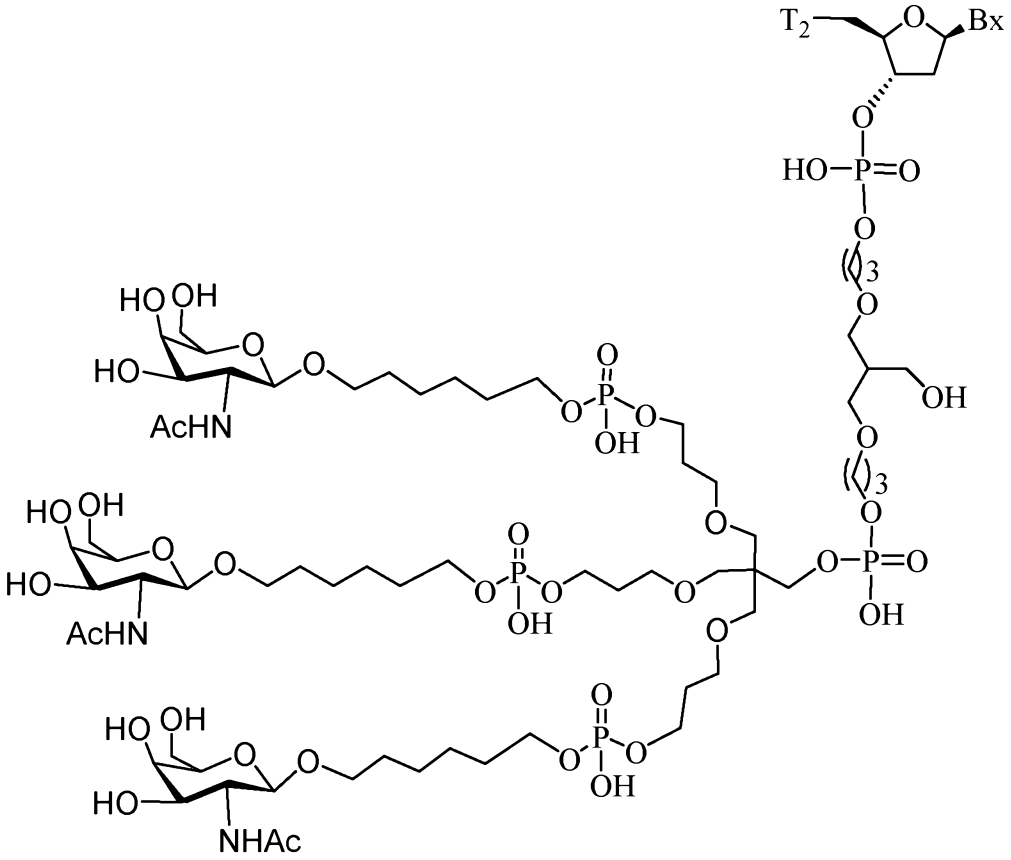
(III)

Wherein;

Bx is a heterocyclic base moiety; and

T_2 is an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound.

Embodiment 802. An oligomeric compound comprising an oligonucleotide and at least one conjugate group, wherein the at least one conjugate group is a conjugate compound of formula (IV):



(IV)

wherein:

Bx is a heterocyclic base moiety; and

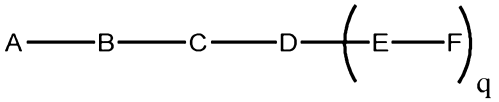
T_2 is an internucleoside linking group attached to a nucleoside, a nucleotide, an oligonucleoside, an oligonucleotide, a monomeric subunit or an oligomeric compound.

Embodiment 803. The compound or oligomeric compound of any of embodiments 798 to 802, wherein the heterocyclic base moiety is a pyrimidine, substituted pyrimidine, purine or substituted purine.

Embodiment 804. The compound or oligomeric compound of any of embodiments 798 to 802, wherein Bx is uracil, thymine, cytosine, 5-methyl cytosine, adenine, or guanine.

Embodiment 805. The compound or oligomeric compound of any of embodiments 798 to 802, wherein Bx is adenine.

Embodiment 806. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



Wherein:

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

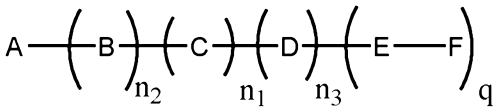
D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 807. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



Wherein:

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

D is the branching group

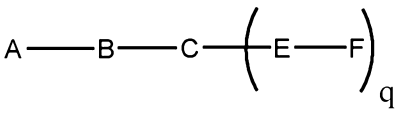
each E is a tether;

each F is a ligand;

n_1 is 0 or 1; and

q is an integer between 1 and 5.

Embodiment 808. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety;

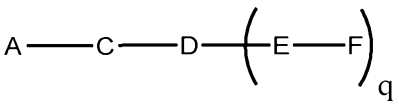
C is the conjugate linker;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 809. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

C is the conjugate linker;

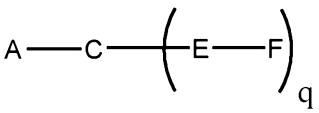
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 810. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

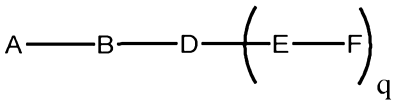
C is the conjugate linker;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 811. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety;

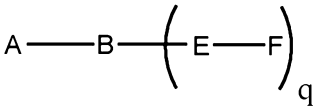
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 812. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

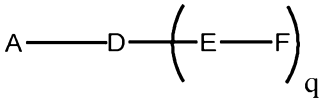
B is the cleavable moiety;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 813. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

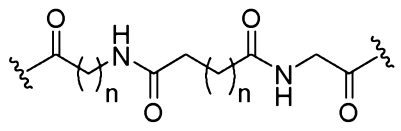
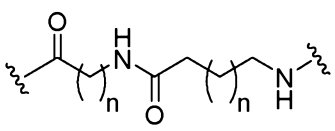
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 814. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has a structure selected from among:


;

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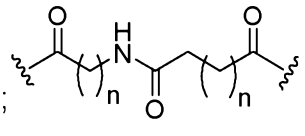
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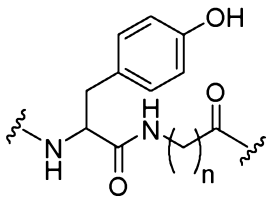
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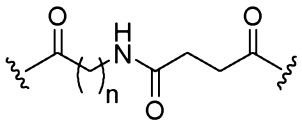
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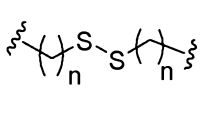
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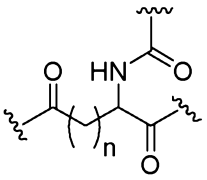
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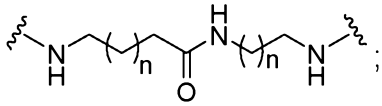
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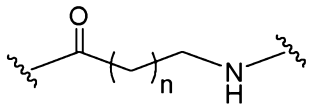
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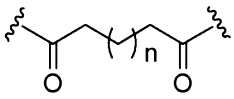
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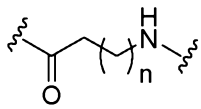
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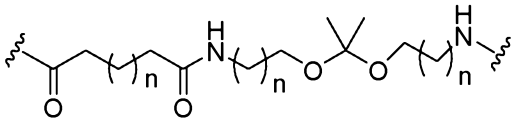
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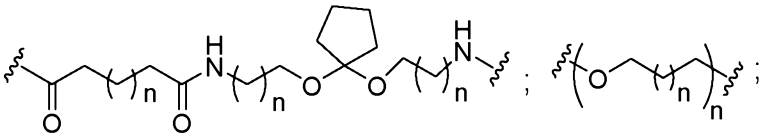
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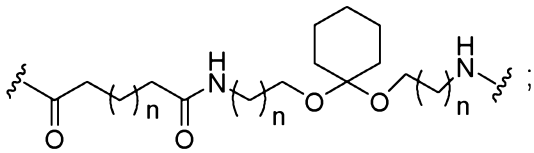
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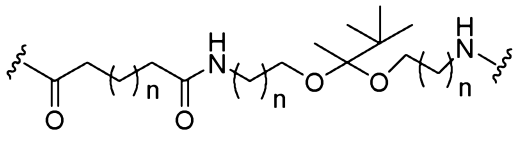
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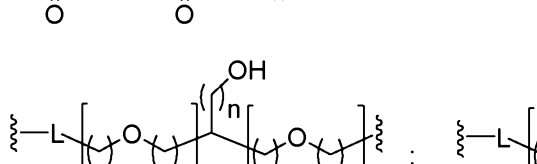
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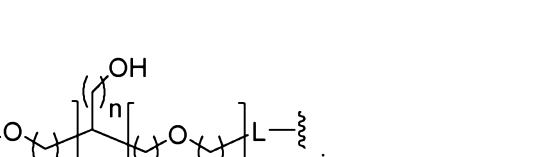
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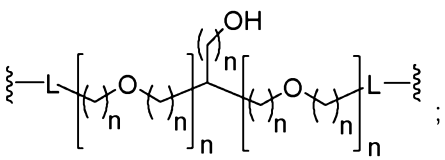
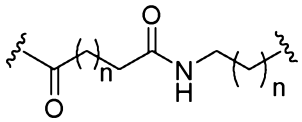
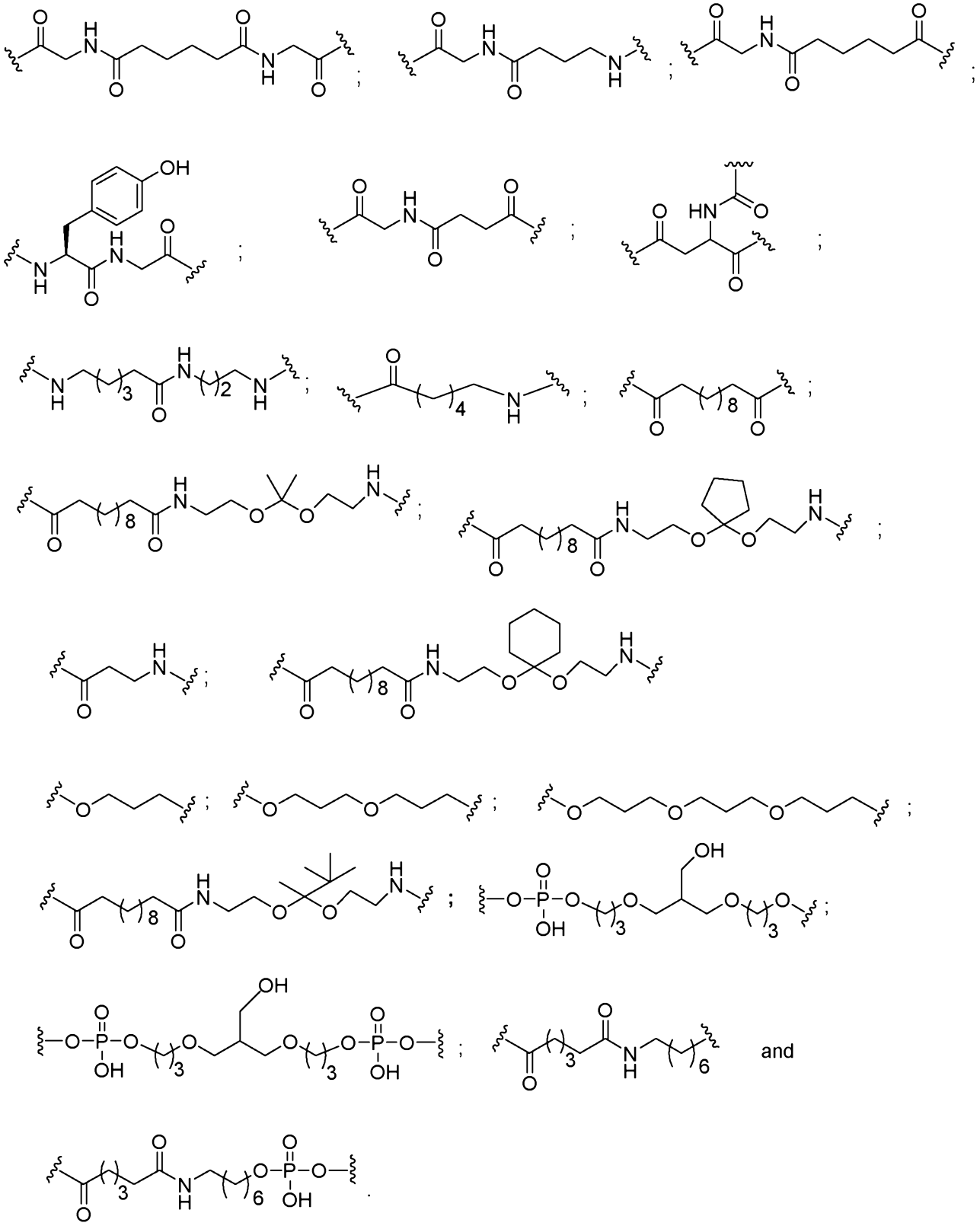
;

and

.

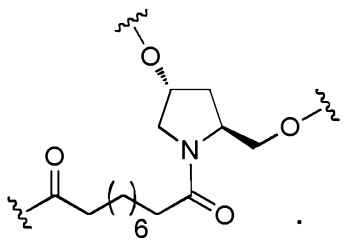
wherein each L is, independently, a phosphorus linking group or a neutral linking group; and each n is, independently, from 1 to 20.

Embodiment 815. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has a structure selected from among:

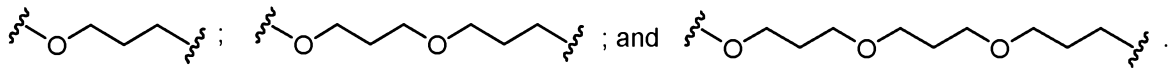


and

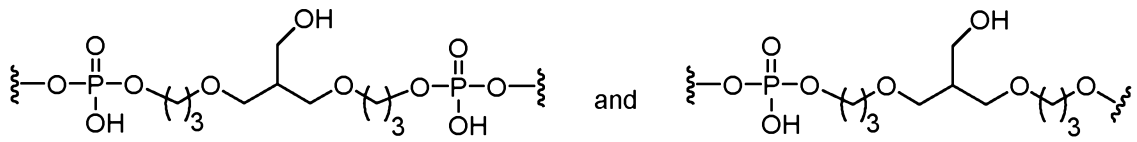
Embodiment 816. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has the structure:



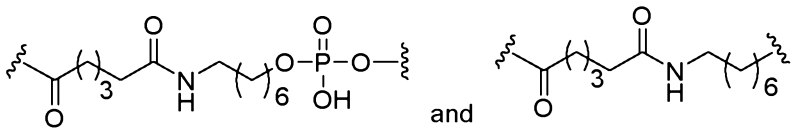
Embodiment 817. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has one of the structures selected from:



Embodiment 818. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has one of the structures selected from:



Embodiment 819. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has one of the structures selected from:



Embodiment 820. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises a pyrrolidine.

Embodiment 821. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker does not comprise a pyrrolidine.

Embodiment 822. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises PEG.

Embodiment 823. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises an amide.

Embodiment 824. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker does not comprise an amide.

Embodiment 825. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises a polyamide.

Embodiment 826. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises an amine.

Embodiment 827. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises one or more disulfide bonds.

Embodiment 828. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker comprises a protein binding moiety.

Embodiment 829. The conjugated antisense compound of embodiment 828, wherein the protein binding moiety comprises a lipid.

Embodiment 830. The conjugated antisense compound of embodiment 829, wherein the protein binding moiety is selected from among: cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), a vitamin (e.g., folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (e.g., monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, e.g., sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid.

Embodiment 831. The conjugated antisense compound of any of embodiments 828 to 830 wherein the protein binding moiety is a C16 to C22 long chain saturated or unsaturated fatty acid, cholesterol, cholic acid, vitamin E, adamantane or 1-pentafluoropropyl.

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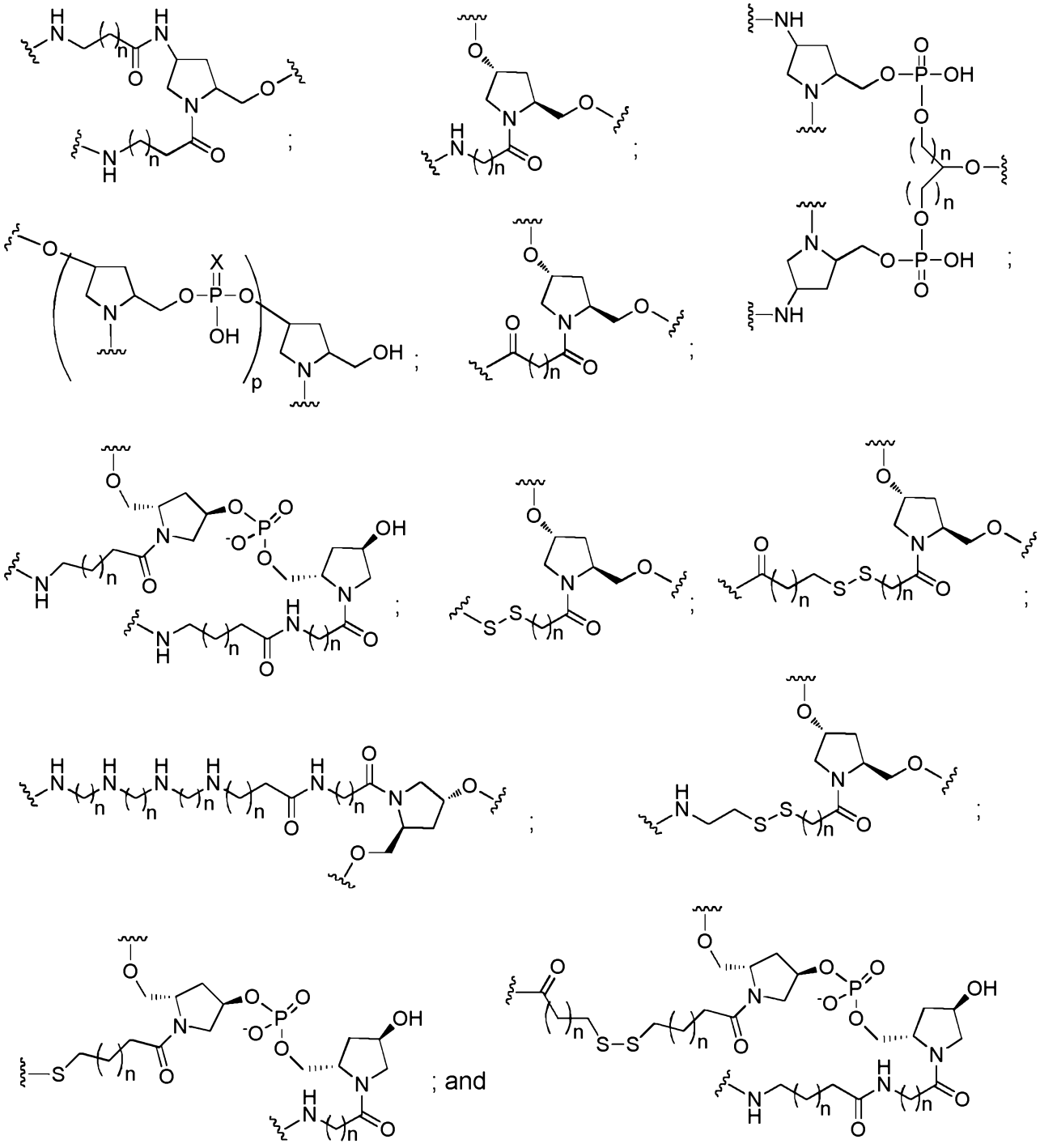
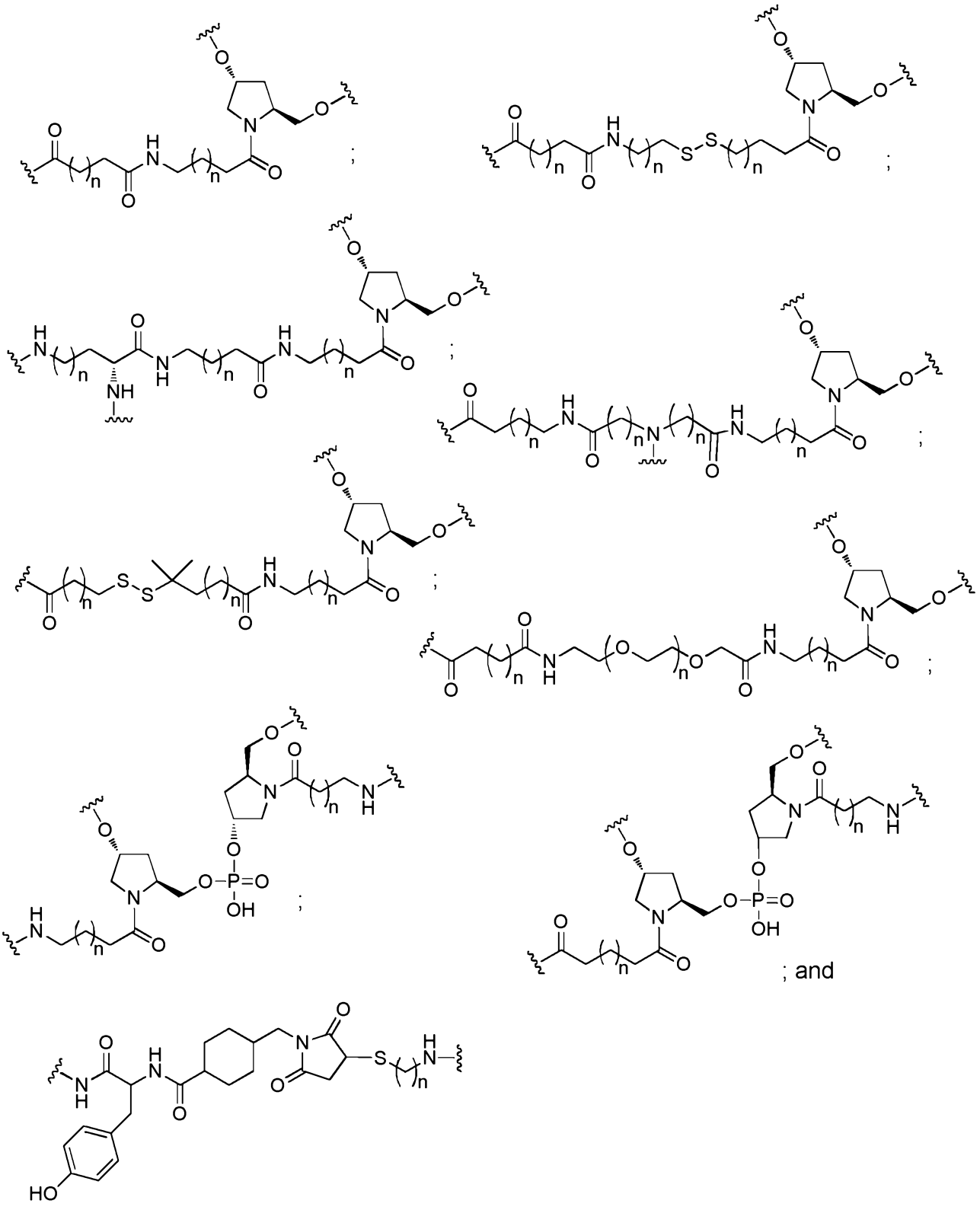
Embodiment 832. The conjugated antisense compound of any of embodiments 806 to 810, wherein the conjugate linker has a structure selected from among:



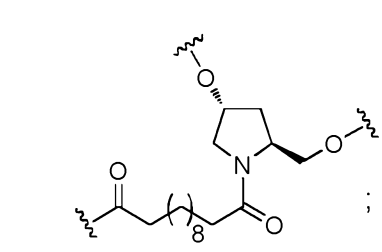
wherein each n is, independently, is from 1 to 20; and p is from 1 to 6.

Embodiment 833. The conjugated antisense compound of any of embodiments 806 to 810 wherein the conjugate linker has a structure selected from among:



wherein each n is, independently, from 1 to 20.

Embodiment 834. The conjugated antisense compound of any of embodiments 806 to 810 wherein the conjugate linker has a structure selected from among: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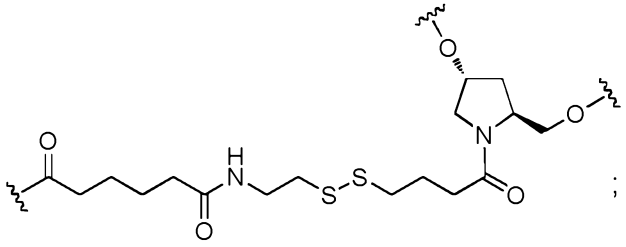
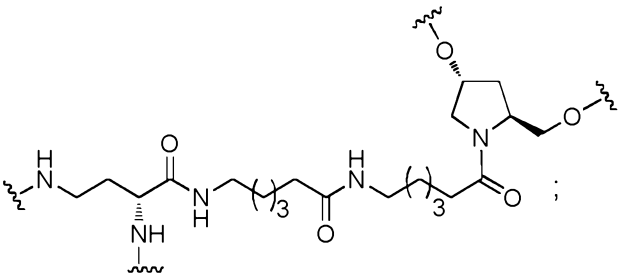
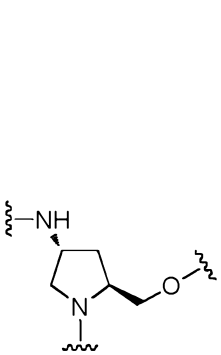
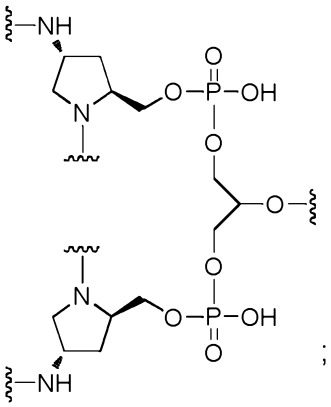

;


;

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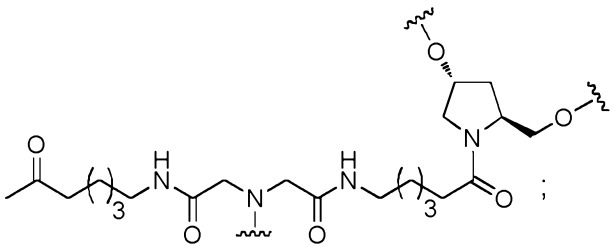
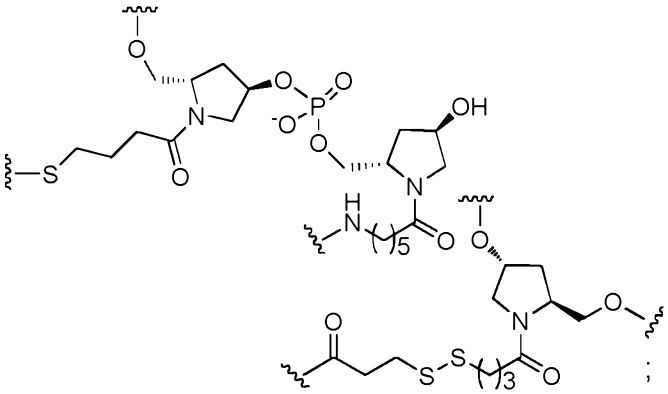

;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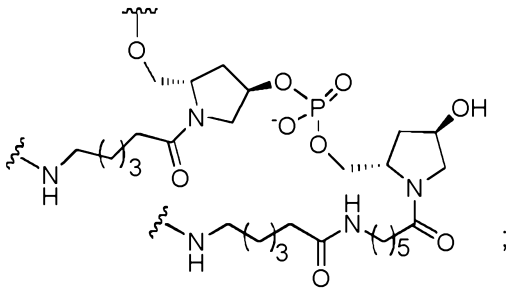
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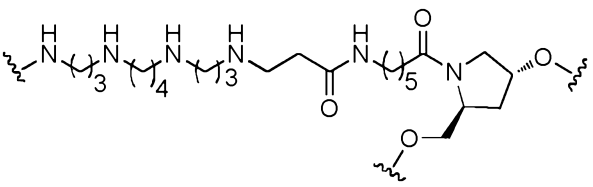
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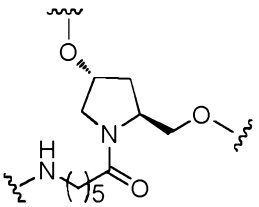
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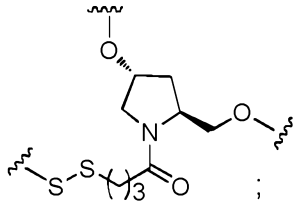
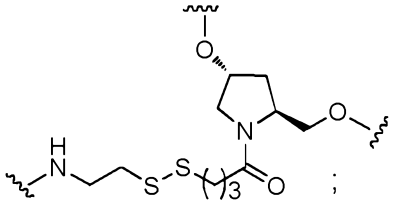
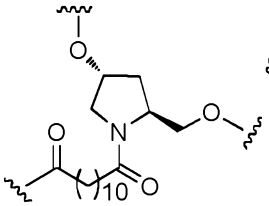
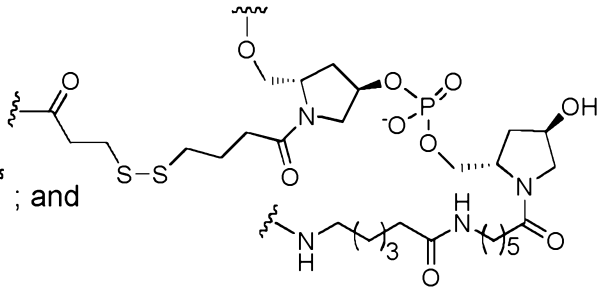
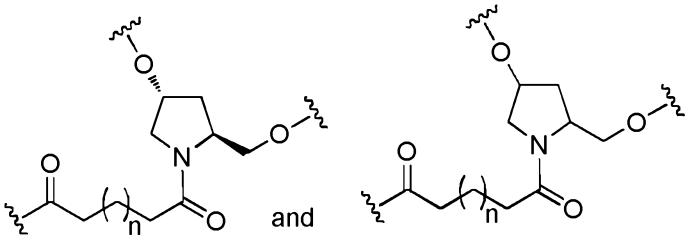

;


;


; and

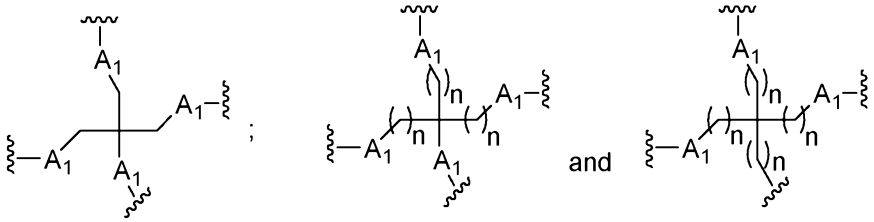

.

Embodiment 835. The conjugated antisense compound of any of embodiments 806 to 810 wherein the conjugate linker has a structure selected from among:



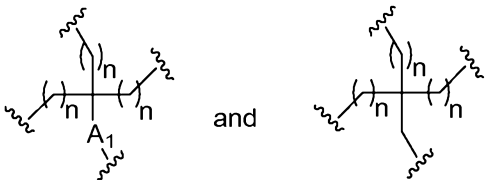
wherein n is from 1 to 20.

Embodiment 836. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has one of the following structures:



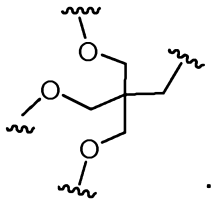
wherein each A_1 is independently, O, S, C=O or NH; and
each n is, independently, from 1 to 20.

Embodiment 837. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has one of the following structures:

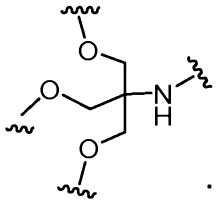


wherein each A_1 is independently, O, S, C=O or NH; and
each n is, independently, from 1 to 20.

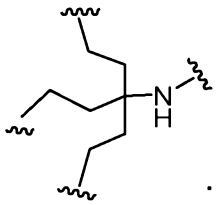
Embodiment 838. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:



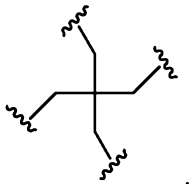
Embodiment 839. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:



Embodiment 840. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:

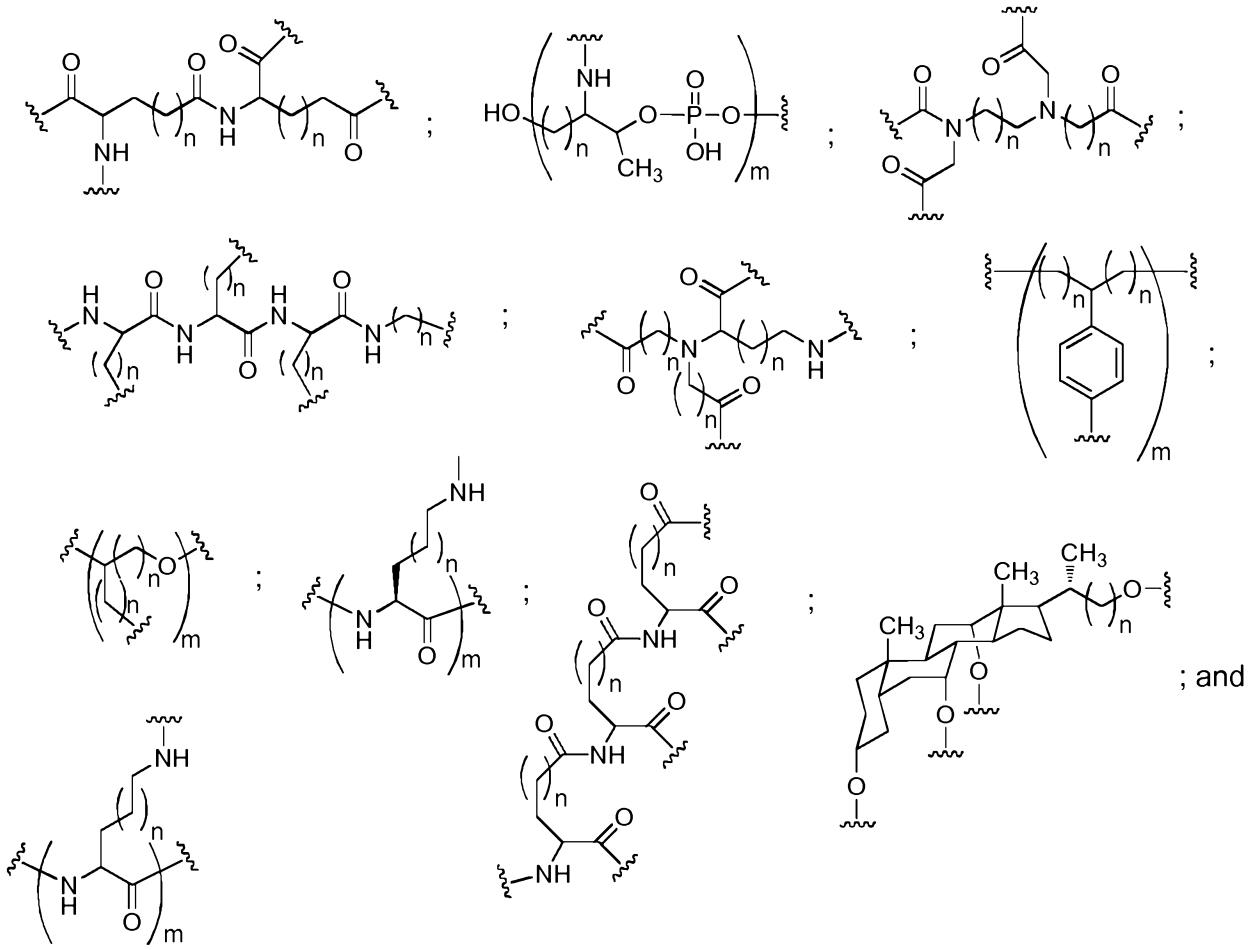


Embodiment 841. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:



Embodiment 842. The conjugated antisense compound of any of embodiments 806 to 835, wherein the branching group comprises an ether.

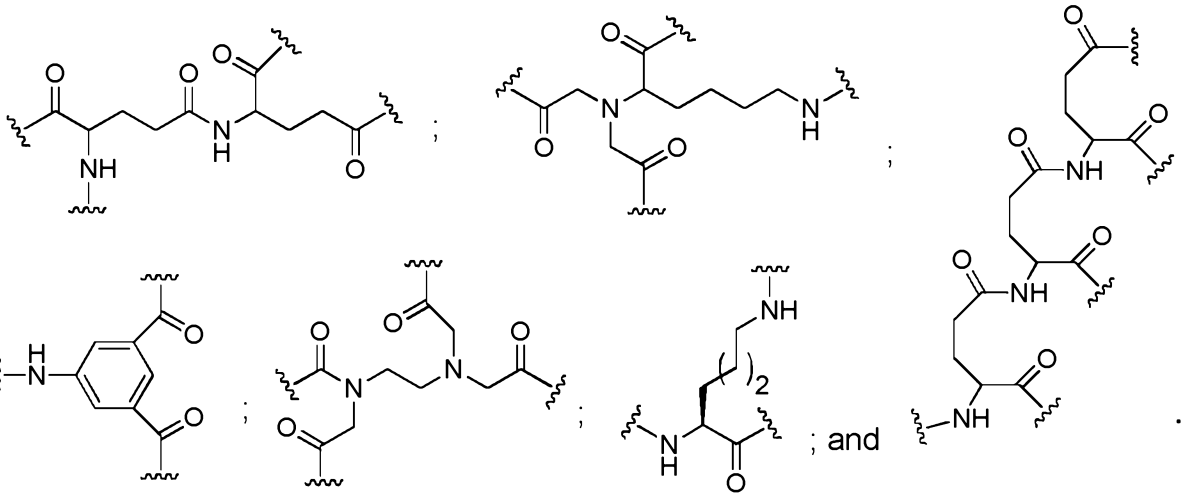
Embodiment 843. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:



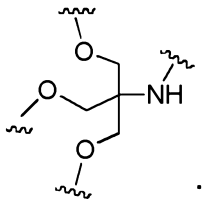
each n is, independently, from 1 to 20; and

m is from 2 to 6.

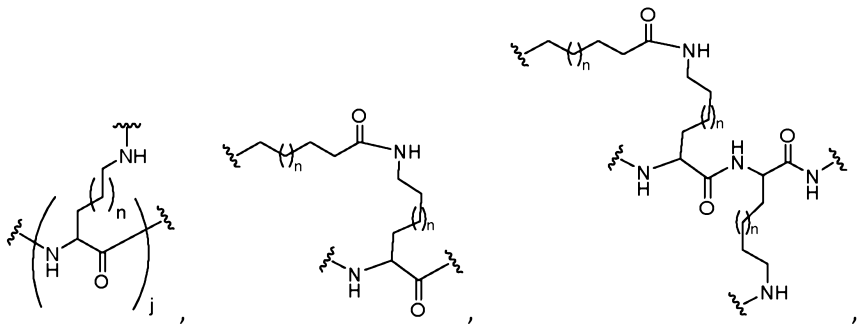
Embodiment 844. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:

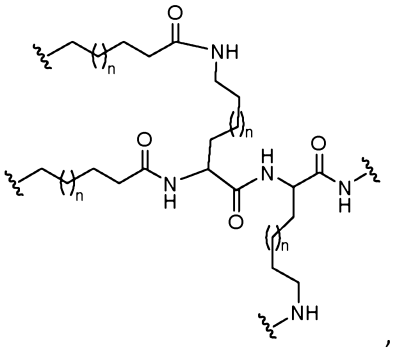
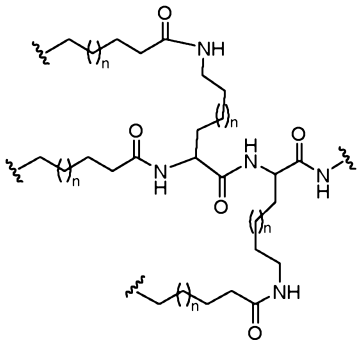


Embodiment 845. The conjugated antisense compound of embodiment 806 to 835, wherein the branching group has the following structure:



Embodiment 846. The conjugated antisense compound of any of embodiments 806 to 835, wherein the branching group comprises:

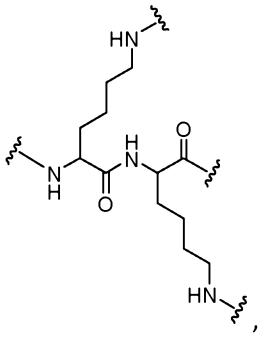
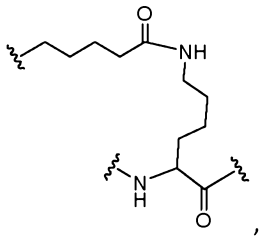
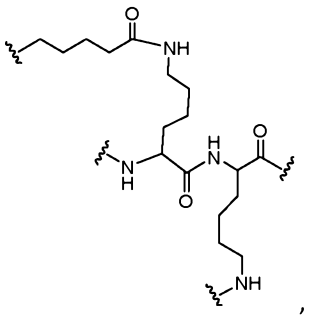
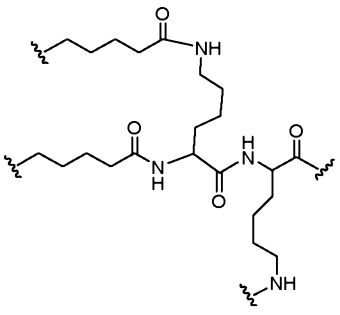
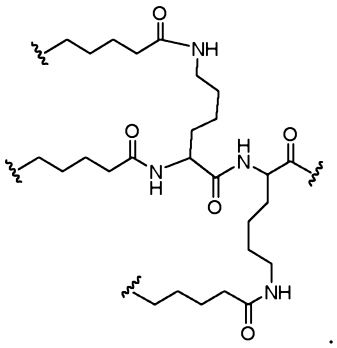



, or

;

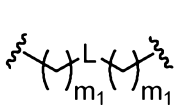
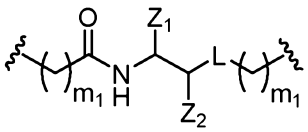
wherein each j is an integer from 1 to 3; and

wherein each n is an integer from 1 to 20.

Embodiment 847. The conjugated antisense compound of any of embodiments 806 to 835 wherein the branching group comprises:


,

,

,

, or

.

Embodiment 848. The conjugated antisense compound of embodiment 806 to 847, wherein each tether is selected from among:


and


wherein L is selected from a phosphorus linking group and a neutral linking group;

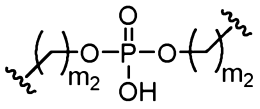
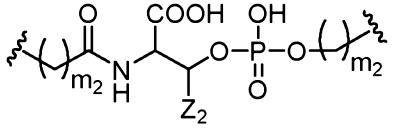
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 849. The conjugated antisense compound of embodiment 806 to 847, wherein each tether is selected from among:


and


wherein Z_2 is H or CH_3; and

each m_2 is, independently, from 0 to 20 wherein at least one m_2 is greater than 0 for each tether.

Embodiment 850. The conjugated antisense compound of any of embodiments 806 to 847, wherein at least one tether comprises PEG.

Embodiment 851. The conjugated antisense compound of any of embodiments 806 to 847, wherein at least one tether comprises an amide.

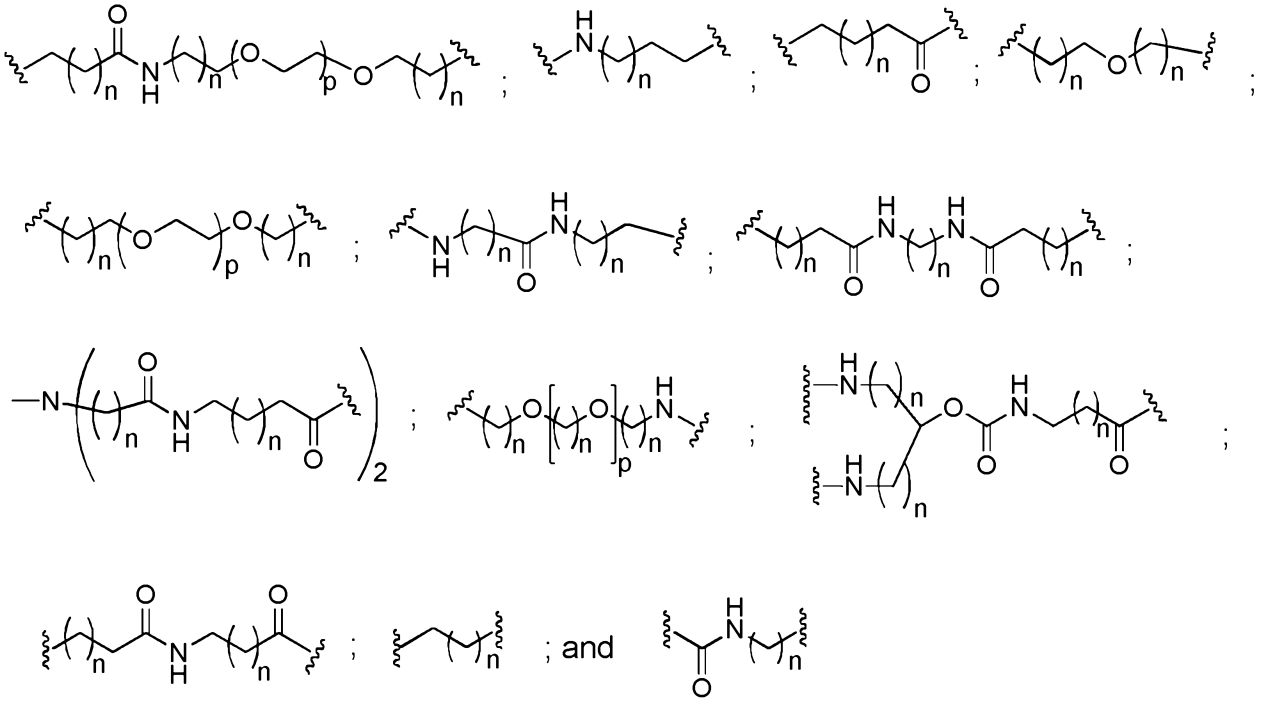
Embodiment 852. The conjugated antisense compound of any of embodiments 806 to 847, wherein at least one tether comprises a polyamide.

Embodiment 853. The conjugated antisense compound of any of embodiments 806 to 847, wherein at least one tether comprises an amine.

Embodiment 854. The conjugated antisense compound of any of embodiments 806 to 847, wherein at least two tethers are different from one another.

Embodiment 855. The conjugated antisense compound of any of embodiments 806 to 847, wherein all of the tethers are the same as one another.

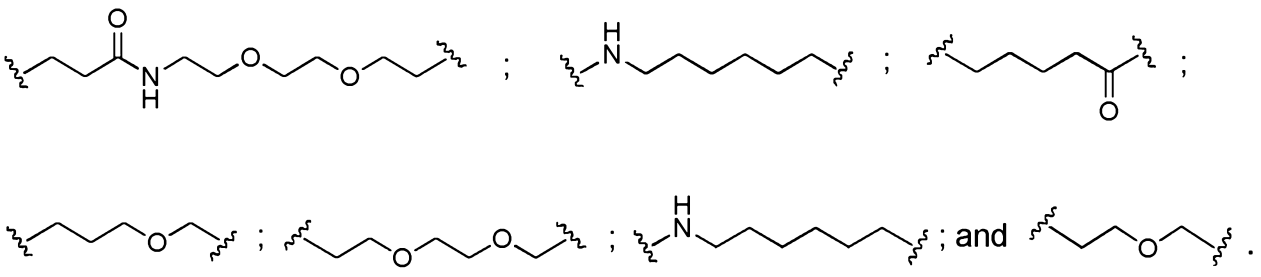
Embodiment 856. The conjugated antisense compound of any of embodiments 806 to 847, wherein each tether is selected from among:



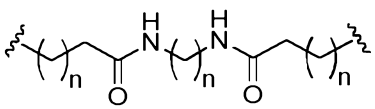
wherein each n is, independently, from 1 to 20; and

each p is from 1 to about 6.

Embodiment 857. The conjugated antisense compound of any of embodiments 806 to 847, wherein each tether is selected from among:

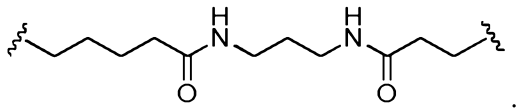


Embodiment 858. The conjugated antisense compound of any of embodiments 806 to 847, wherein each tether has the following structure:

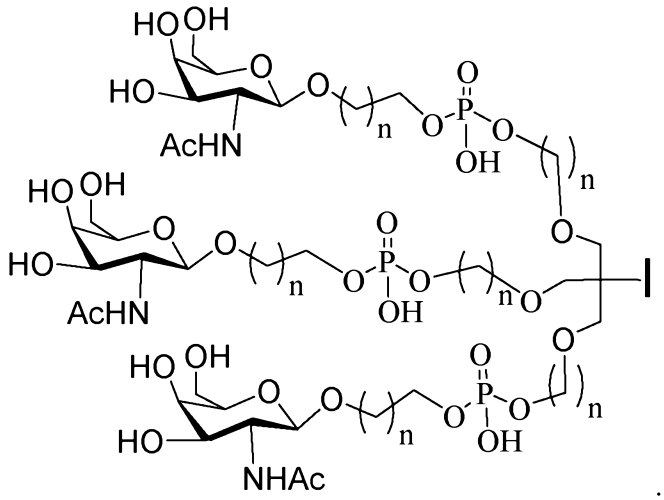


wherein each n is, independently, from 1 to 20.

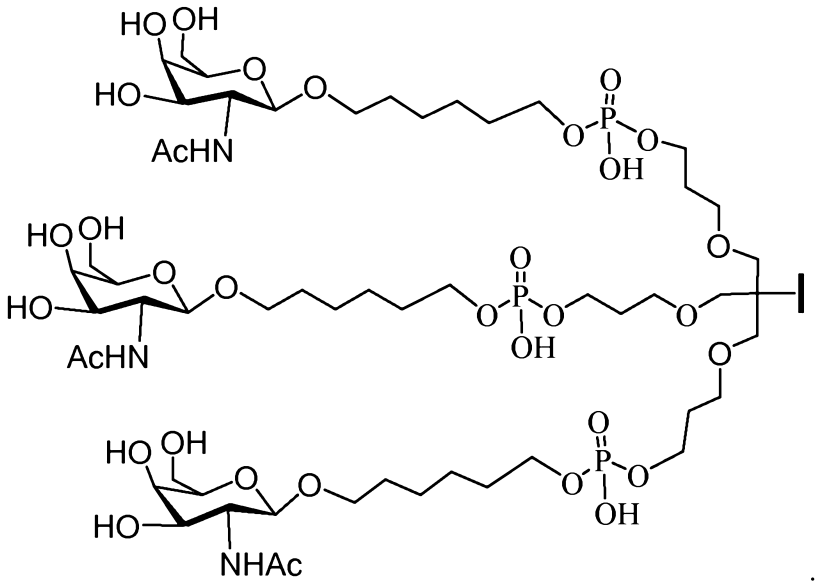
Embodiment 859. The conjugated antisense compound of any of embodiments 806 to 847, wherein each tether has the following structure:



Embodiment 860. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 861. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 862. The conjugated antisense compound of any of embodiments 806 to 859, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 863. The conjugated antisense compound of any of embodiments 806 to 859, wherein the cell-targeting moiety comprises one ligand.

Embodiment 864. The conjugated antisense compound of any of embodiments 806 to 859, wherein the targeting moiety comprises two ligands.

Embodiment 865. The conjugated antisense compound of any of embodiments 806 to 859, wherein the targeting moiety comprises three ligands.

Embodiment 866. The conjugated antisense compound of any of embodiments 806 to 859, wherein each ligand is covalently attached to each tether.

Embodiment 867. The conjugated antisense compound of any of embodiments 862 to 866, wherein at least one ligand is *N*-Acetylgalactosamine (GalNAc).

Embodiment 868. The conjugated antisense compound of any of embodiments 862 to 866, wherein each ligand is N-Acetylgalactosamine (GalNAc).

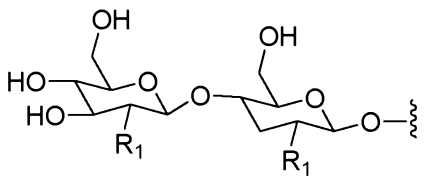
Embodiment 869. The conjugated antisense compound of any of embodiments 862 to 866, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a

mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

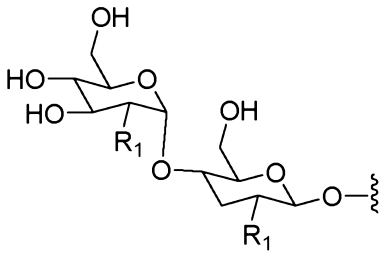
Embodiment 870. The conjugated antisense compound of any of embodiments 862 to 866, wherein the ligand is galactose.

Embodiment 871. The conjugated antisense compound of any of embodiments 862 to 866, wherein the ligand is mannose-6-phosphate.

Embodiment 872. The conjugated antisense compound of any of embodiments 862 to 866, wherein each ligand is selected from among:

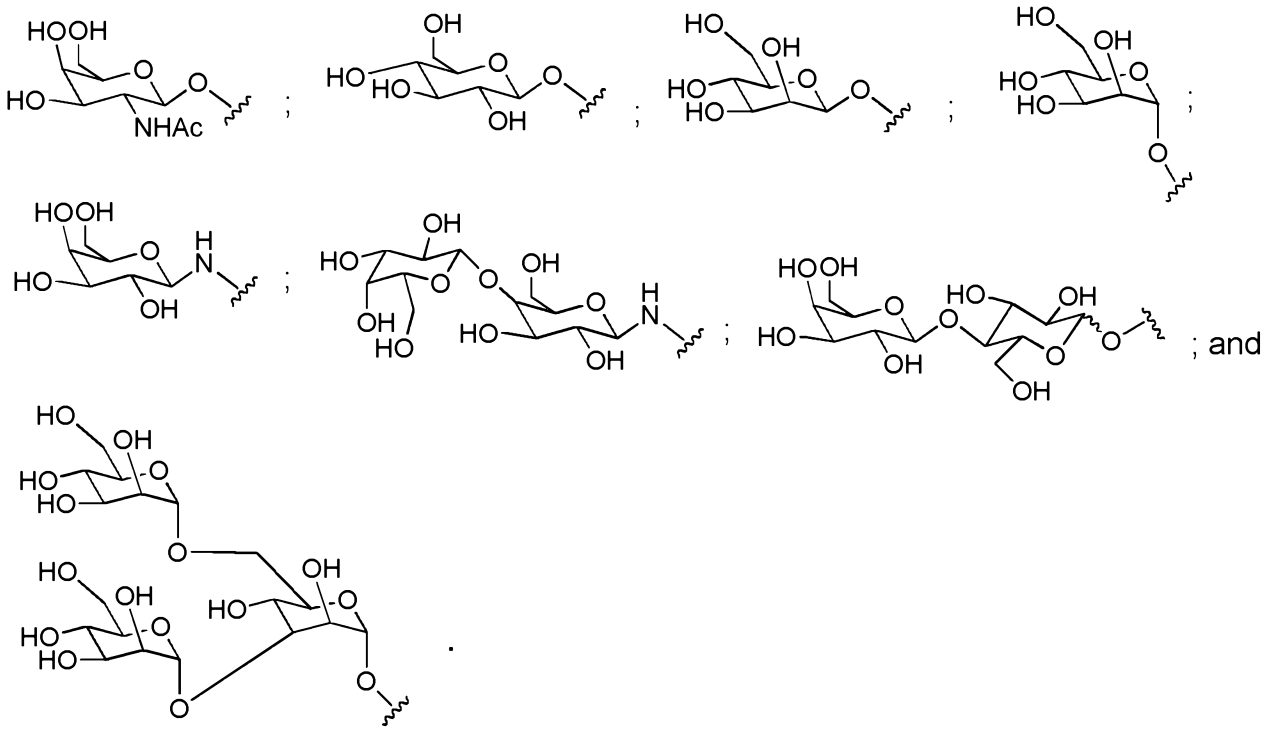


and

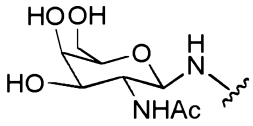


wherein each R_1 is selected from OH and NHCOOH.

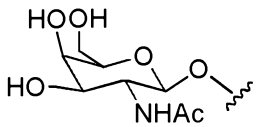
Embodiment 873. The conjugated antisense compound of any of embodiments 862 to 866, wherein each ligand is selected from among:



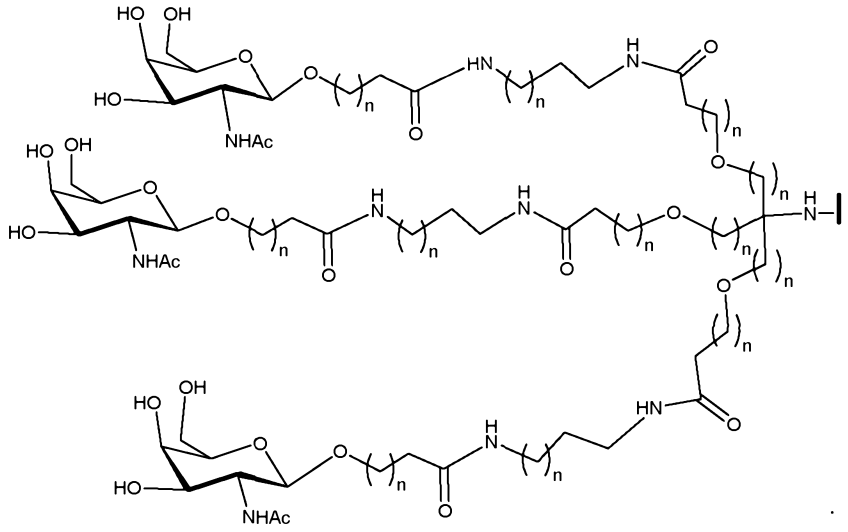
Embodiment 874. The conjugated antisense compound of any of embodiments 862 to 866, wherein each ligand has the following structure:



Embodiment 875. The conjugated antisense compound of any of embodiments 862 to 866, wherein each ligand has the following structure:

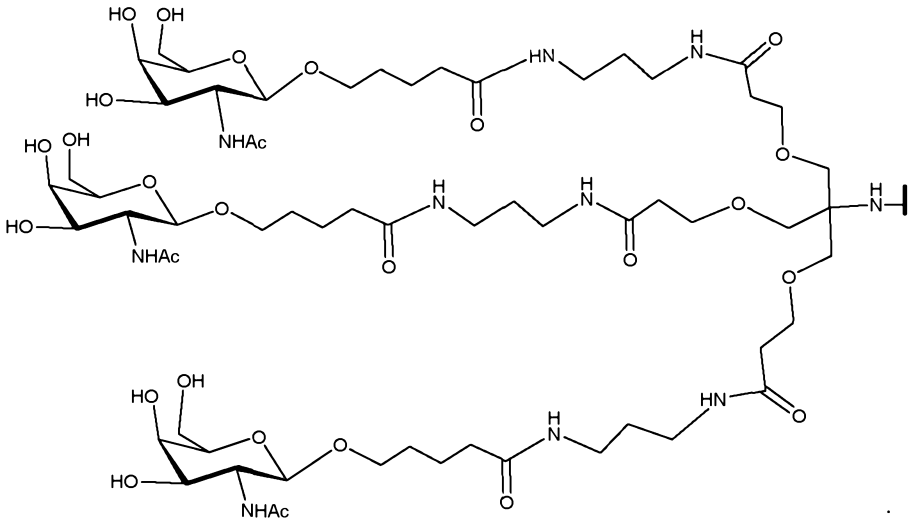


Embodiment 876. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:

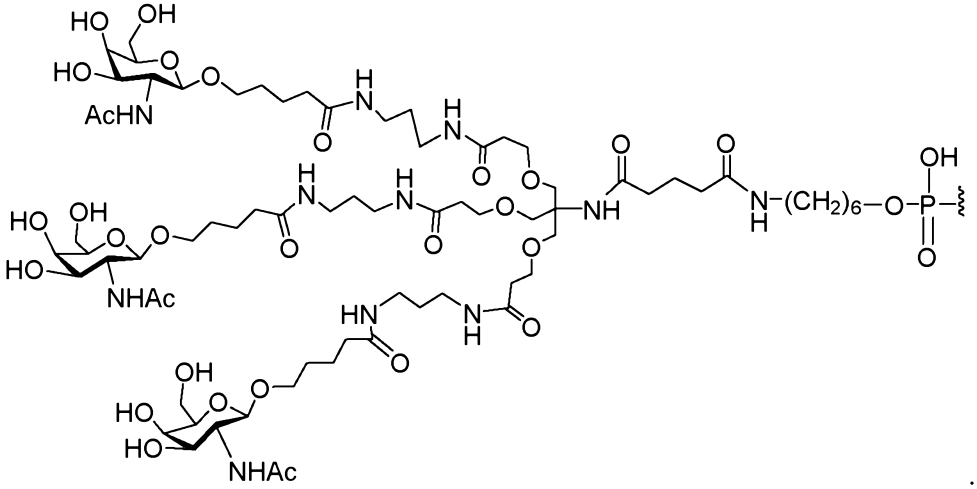


wherein each n is, independently, from 1 to 20.

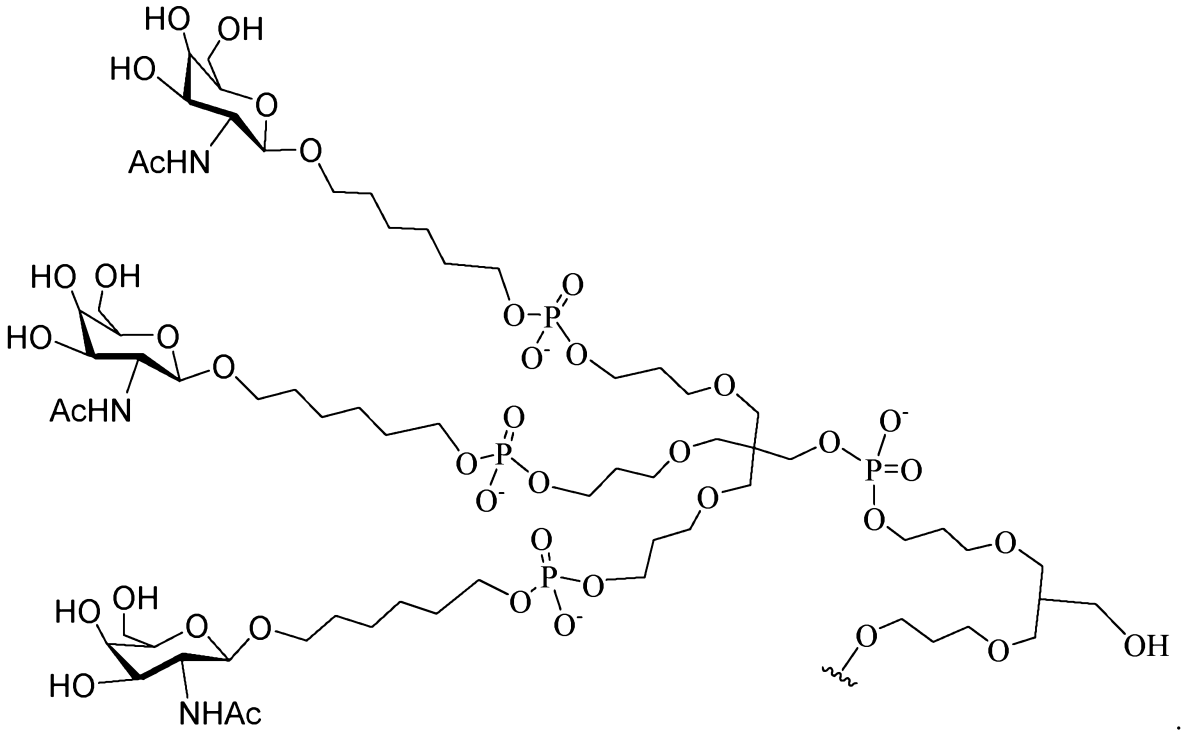
Embodiment 877. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



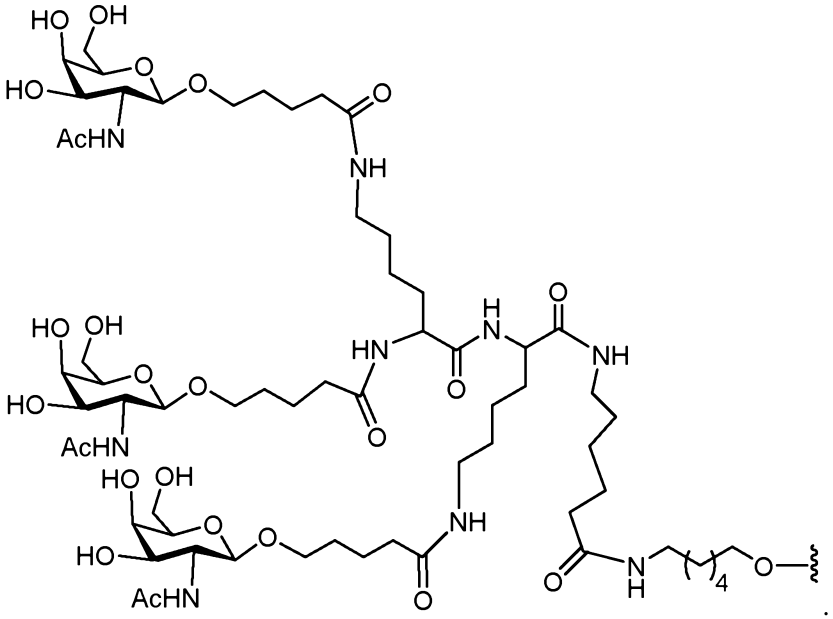
Embodiment 878. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



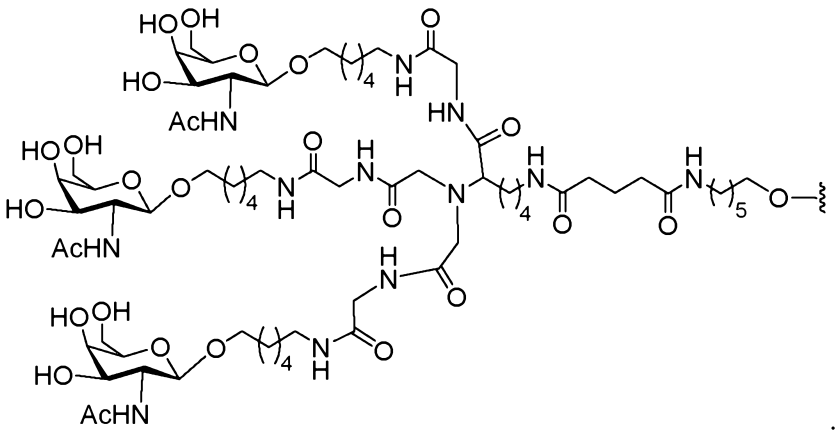
Embodiment 879. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



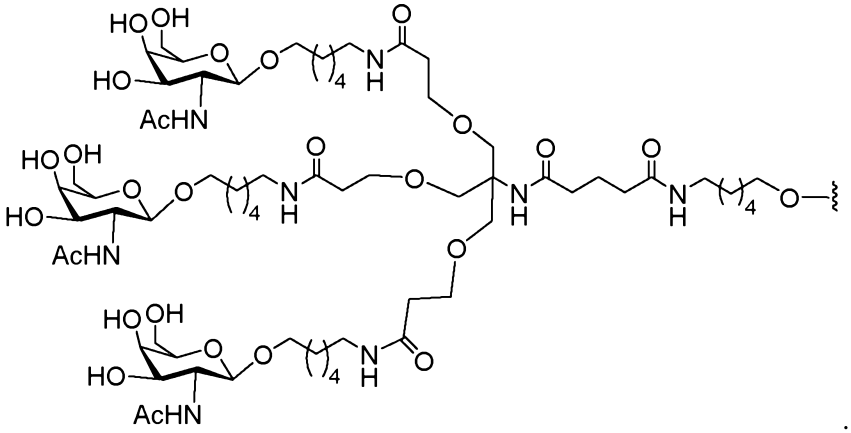
Embodiment 880. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



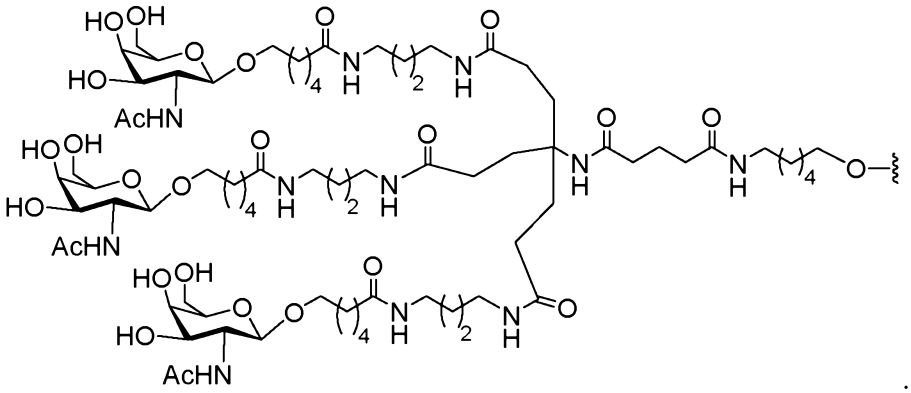
Embodiment 881. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



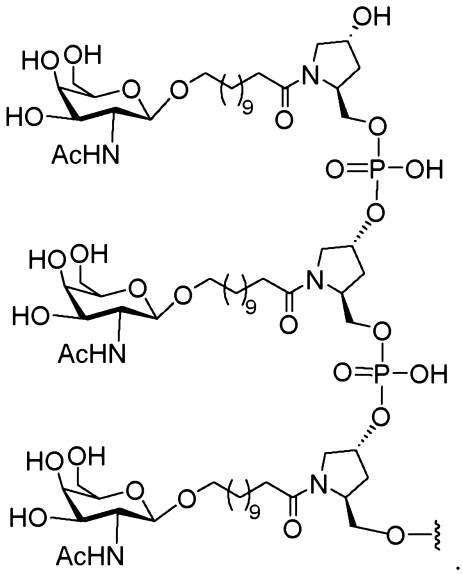
Embodiment 882. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



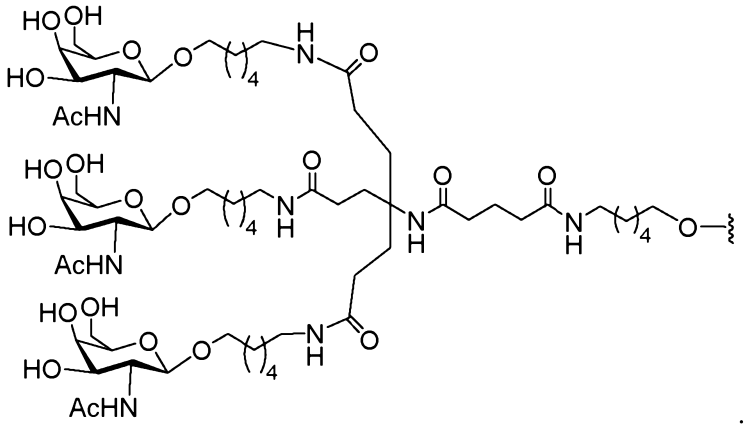
Embodiment 883. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



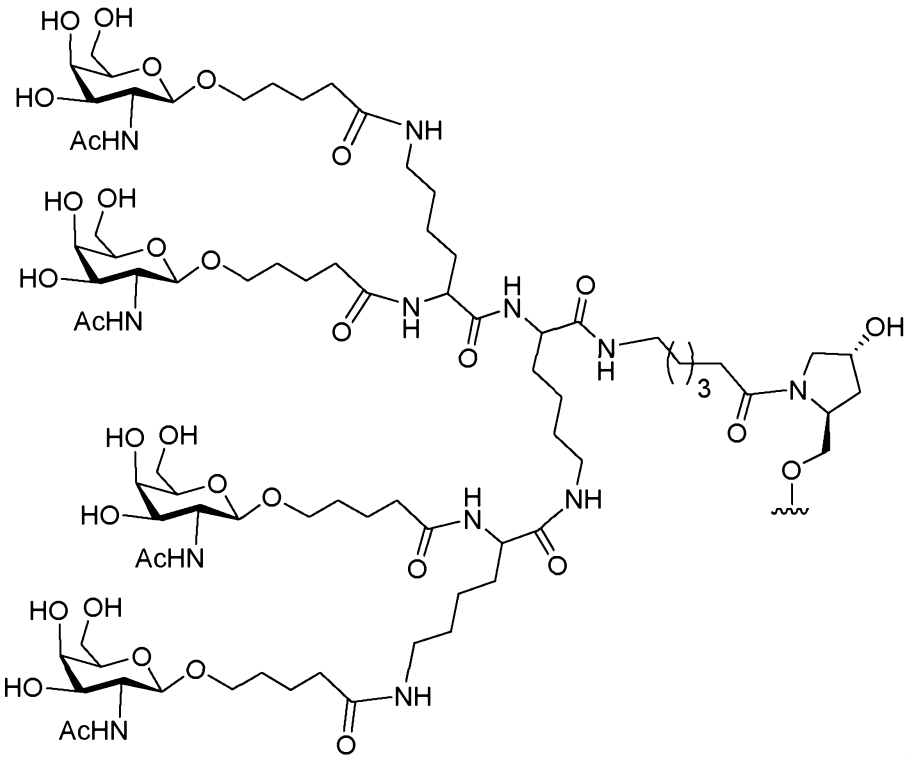
Embodiment 884. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



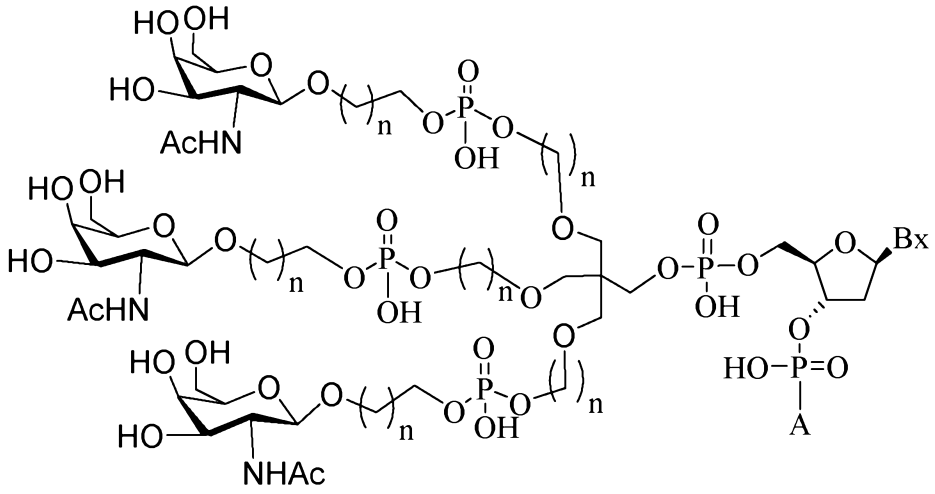
Embodiment 885. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 886. The conjugated antisense compound of any of embodiments 806 to 860, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 887. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:

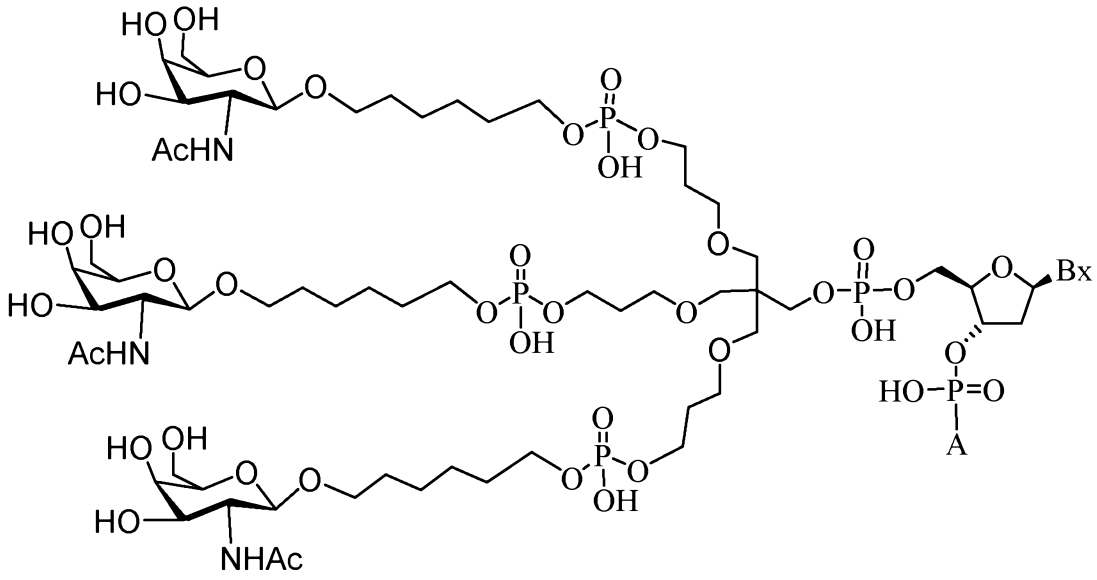


wherein each n is, independently, from 1 to 20;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 888. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:

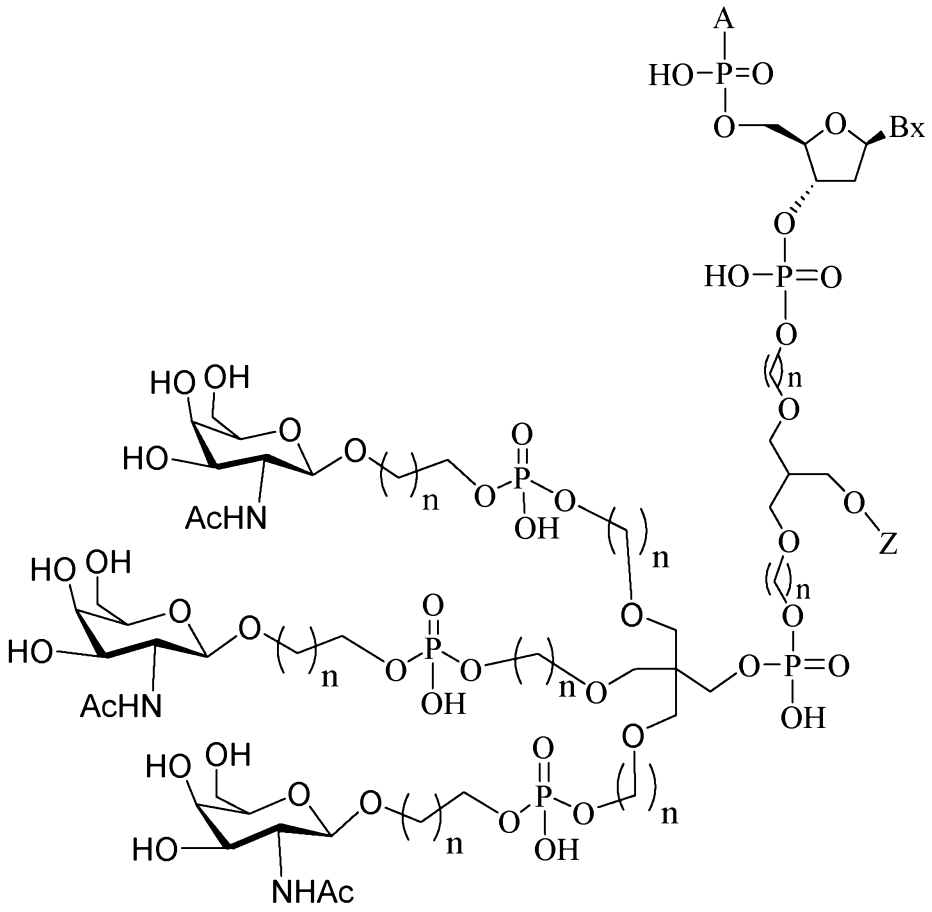


wherein each n is, independently, from 1 to 20;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 889. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



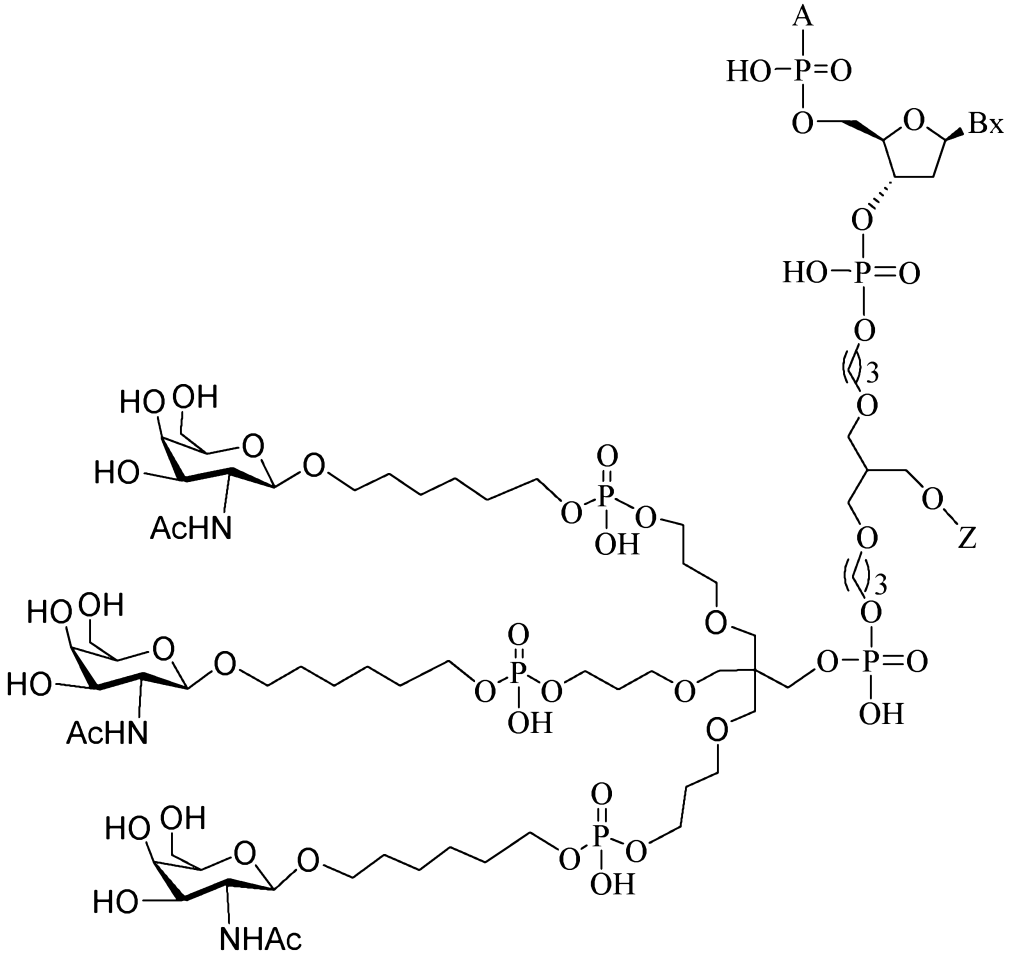
wherein each n is, independently, from 1 to 20;

A is the antisense oligonucleotide;

Z is H or a linked solid support; and

Bx is a heterocyclic base moiety.

Embodiment 890. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



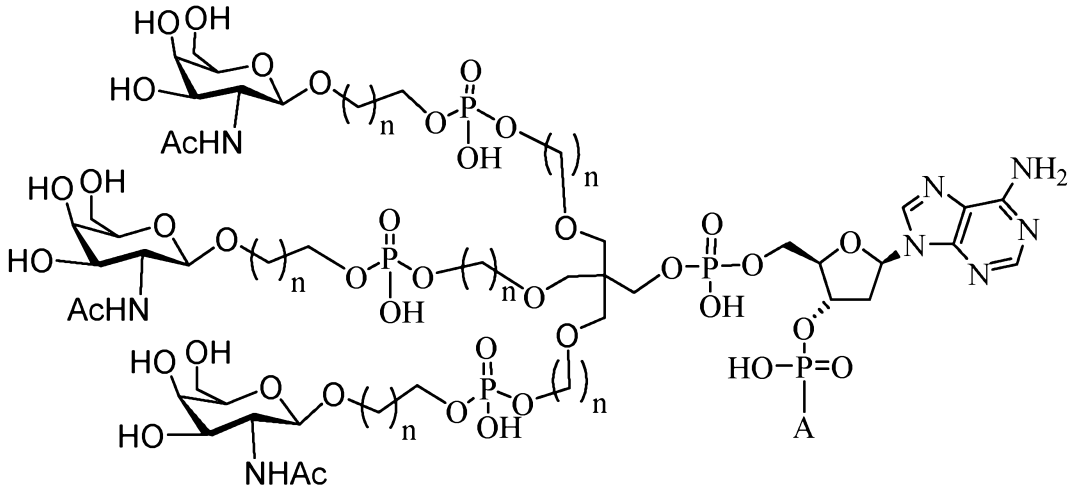
wherein each n is, independently, from 1 to 20;

A is the antisense oligonucleotide;

Z is H or a linked solid support; and

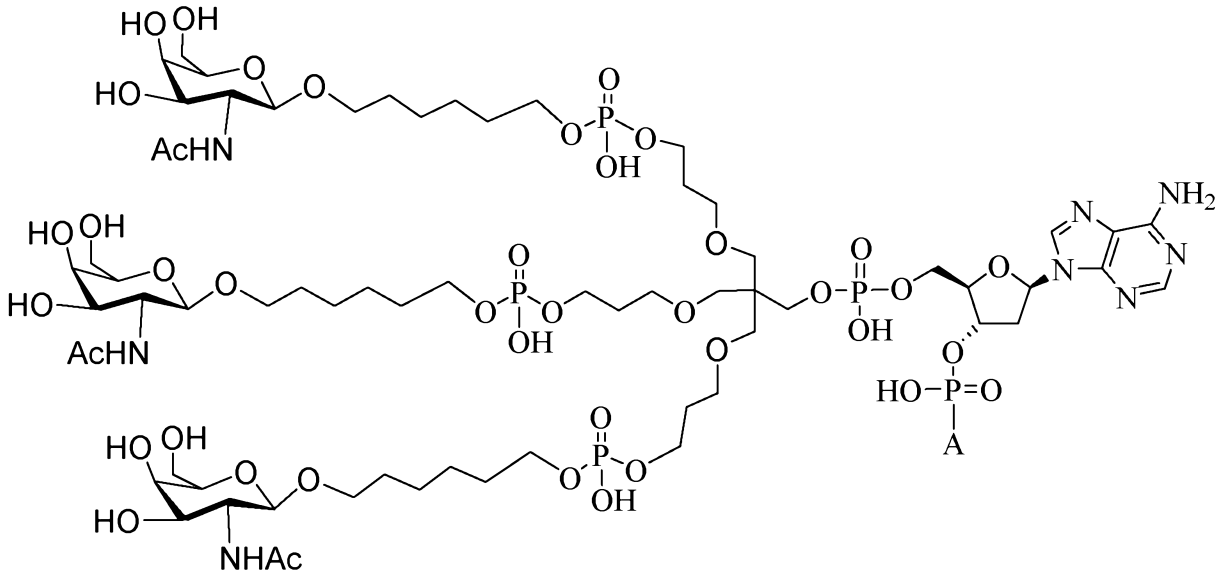
Bx is a heterocyclic base moiety.

Embodiment 891. The conjugated antisense compound of any of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



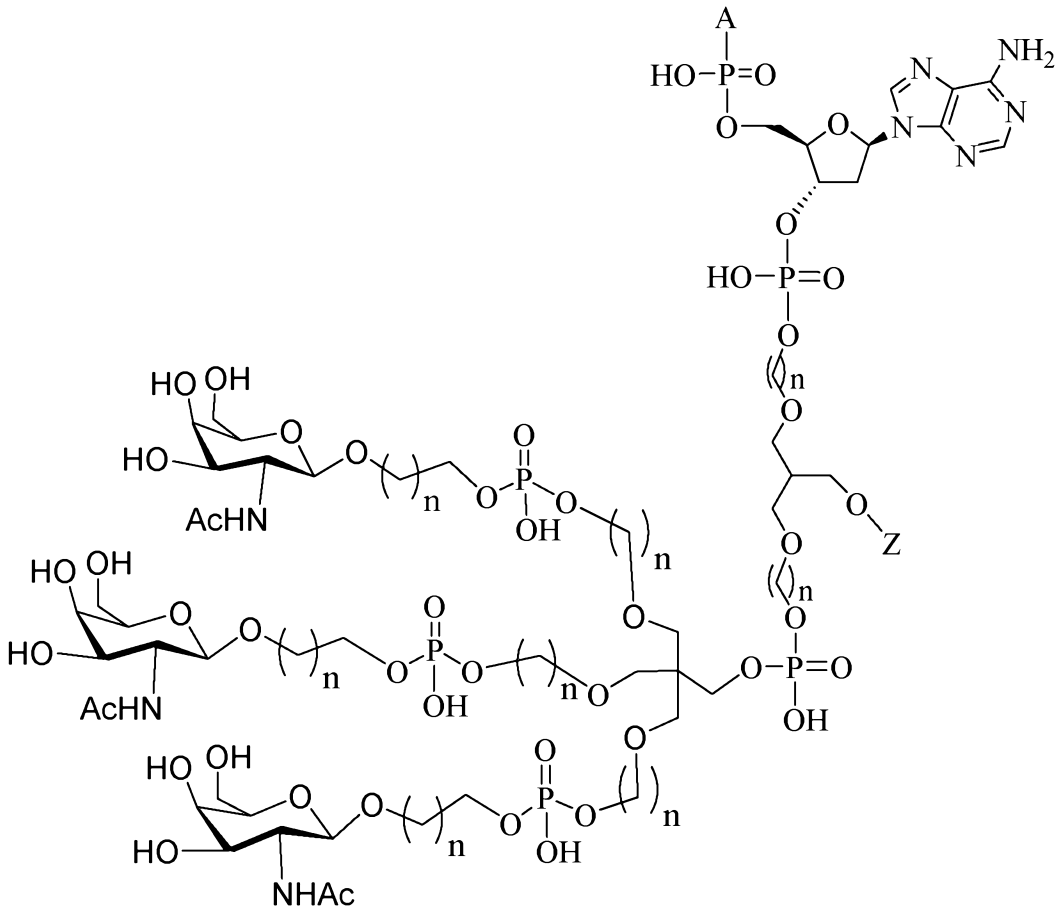
wherein A is the antisense oligonucleotide.

Embodiment 892. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



wherein A is the antisense oligonucleotide.

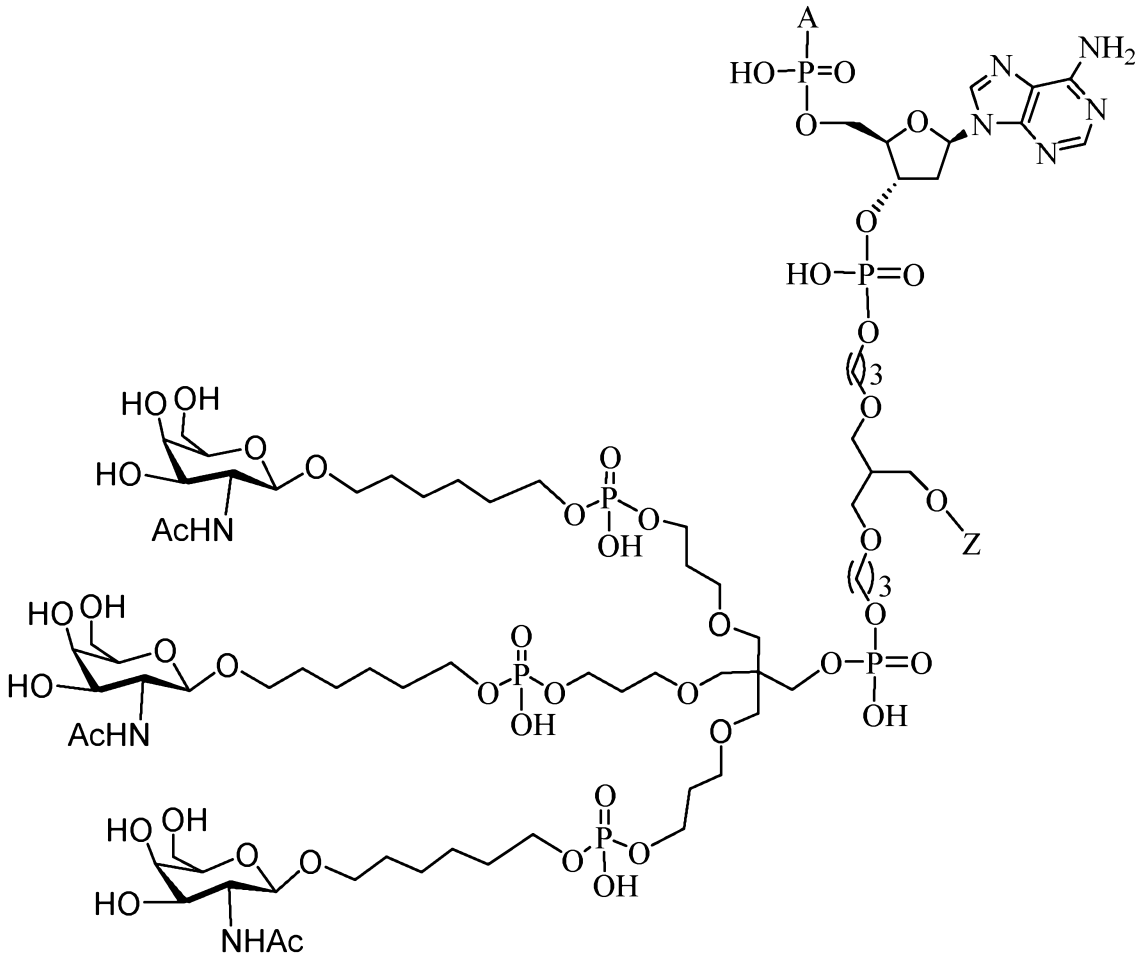
Embodiment 893. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



wherein A is the antisense oligonucleotide; and

Z is H or a linked solid support.

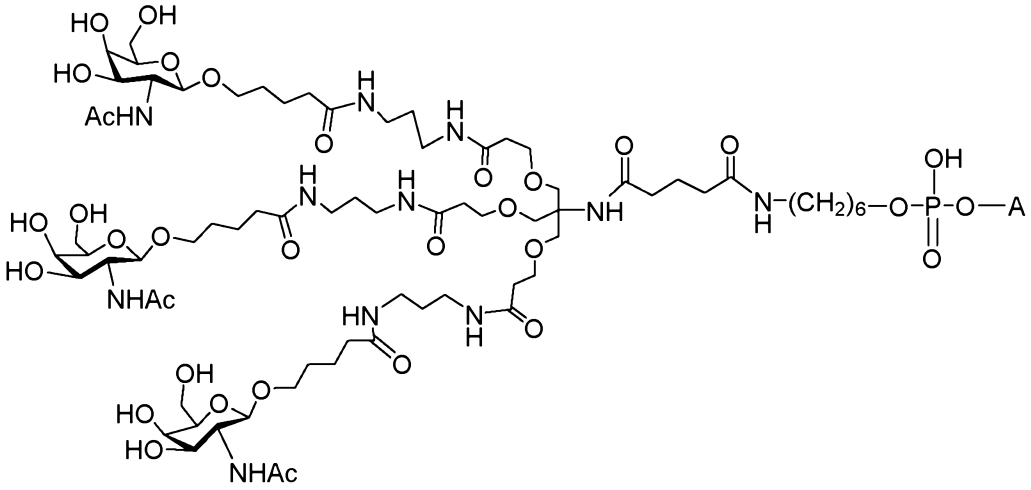
Embodiment 894. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



wherein A is the antisense oligonucleotide; and

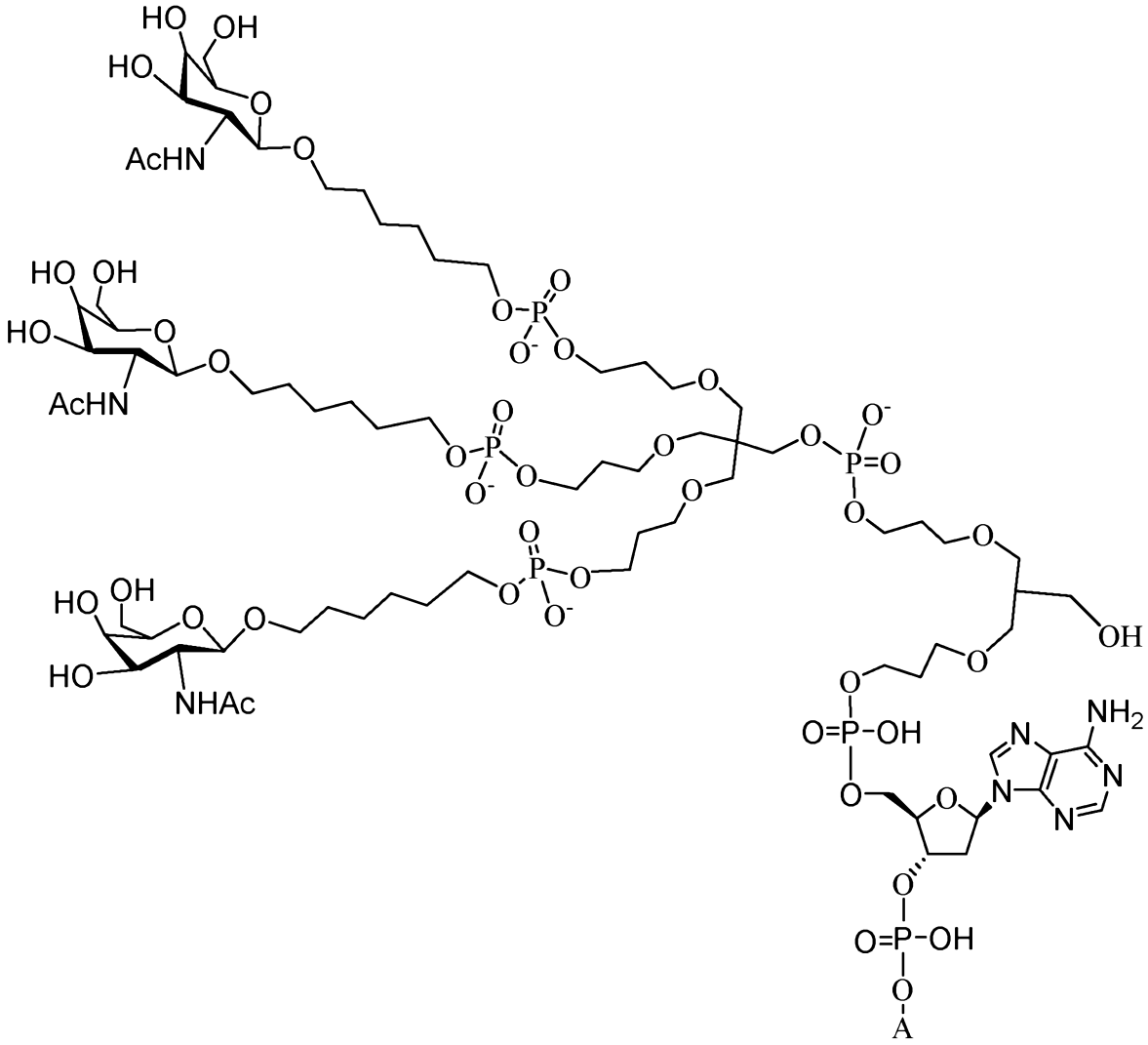
Z is H or a linked solid support.

Embodiment 895. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and wherein A is the antisense oligonucleotide.

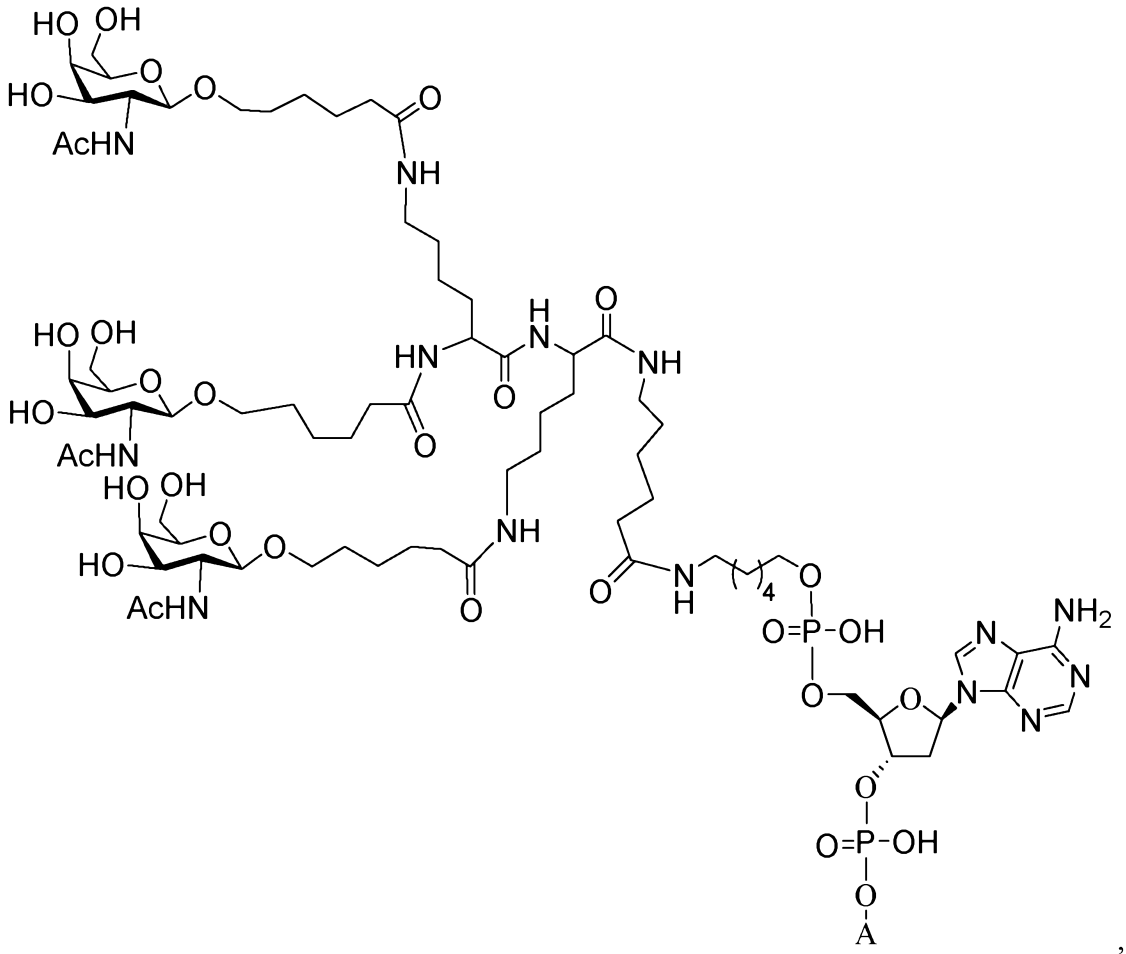
Embodiment 896. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and

wherein A is the antisense oligonucleotide.

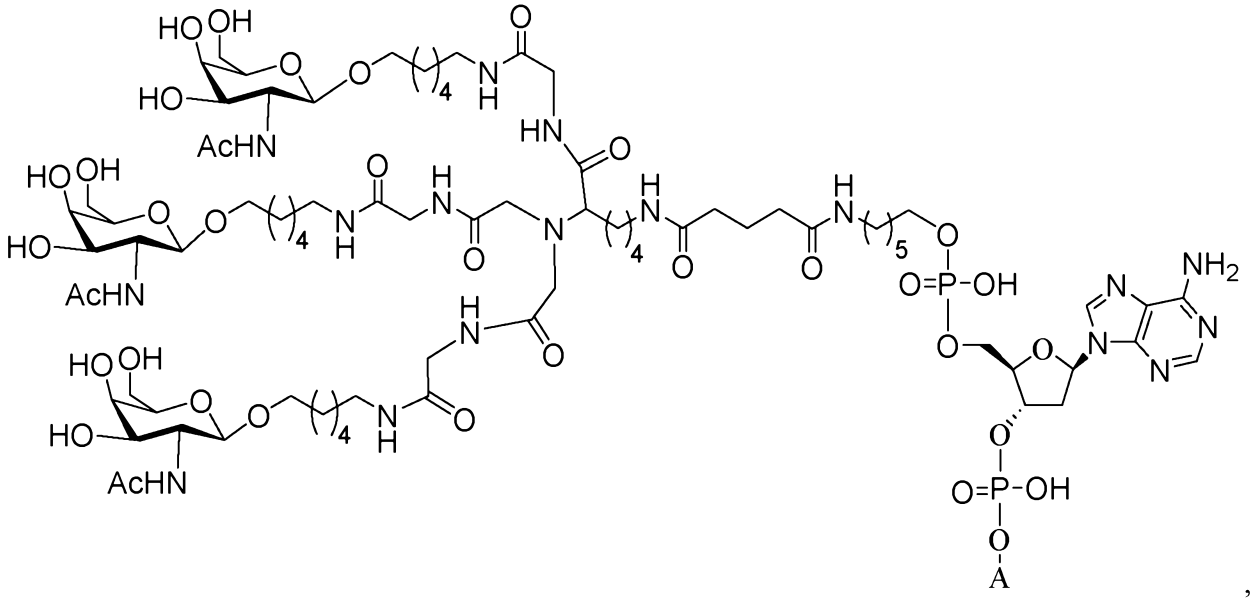
Embodiment 897. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and wherein

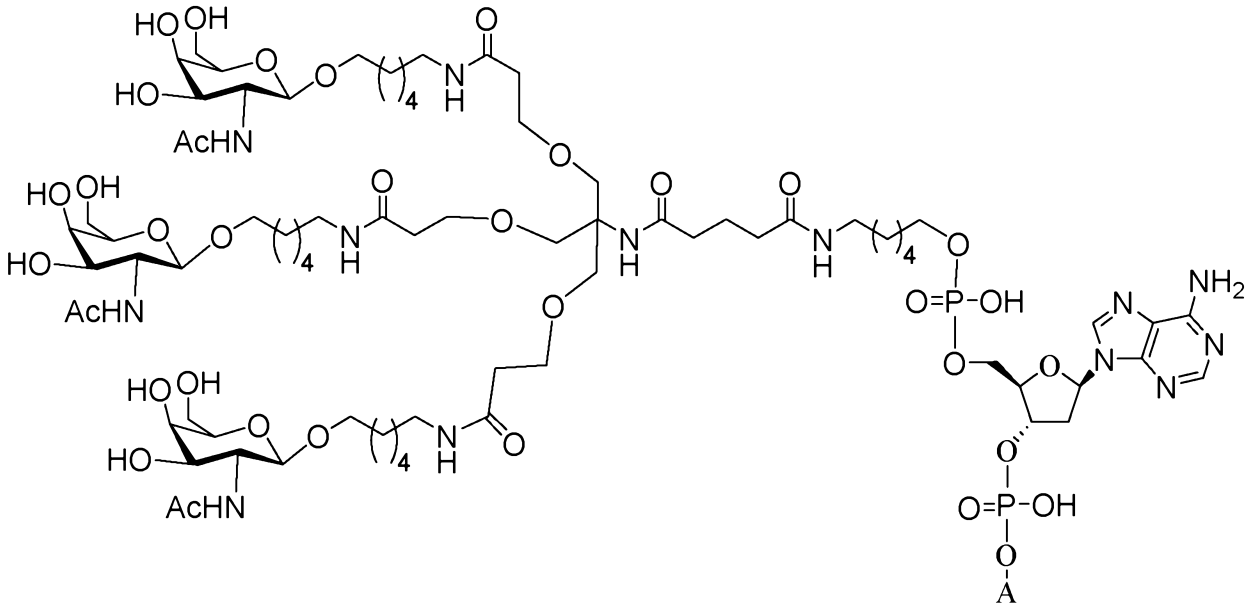
A is the antisense oligonucleotide.

Embodiment 898. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



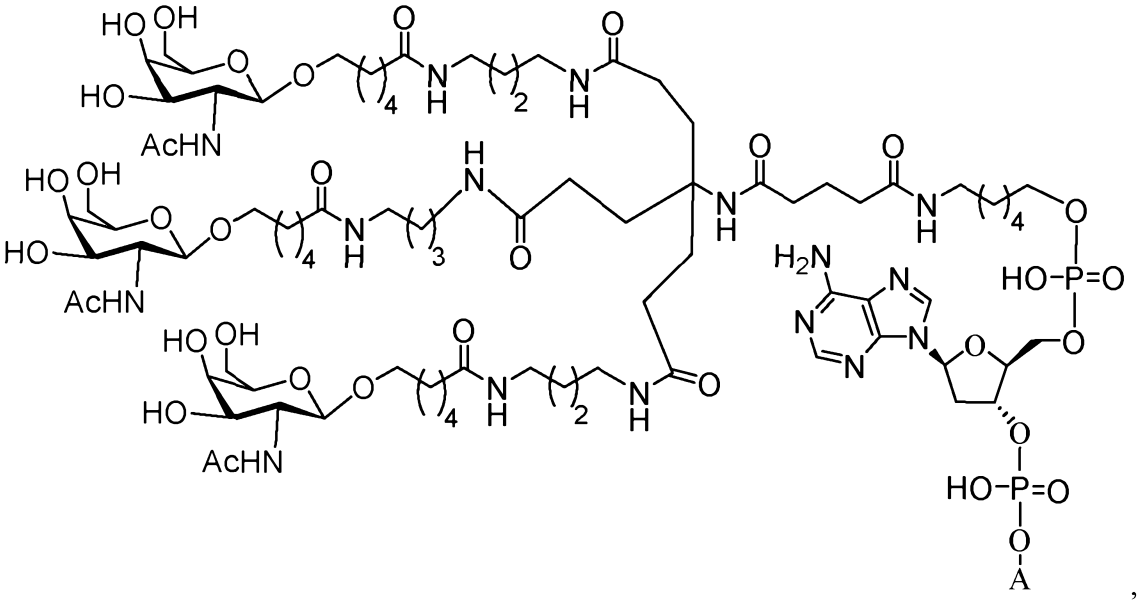
and wherein A is the antisense oligonucleotide.

Embodiment 899. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



and wherein A is the antisense oligonucleotide.

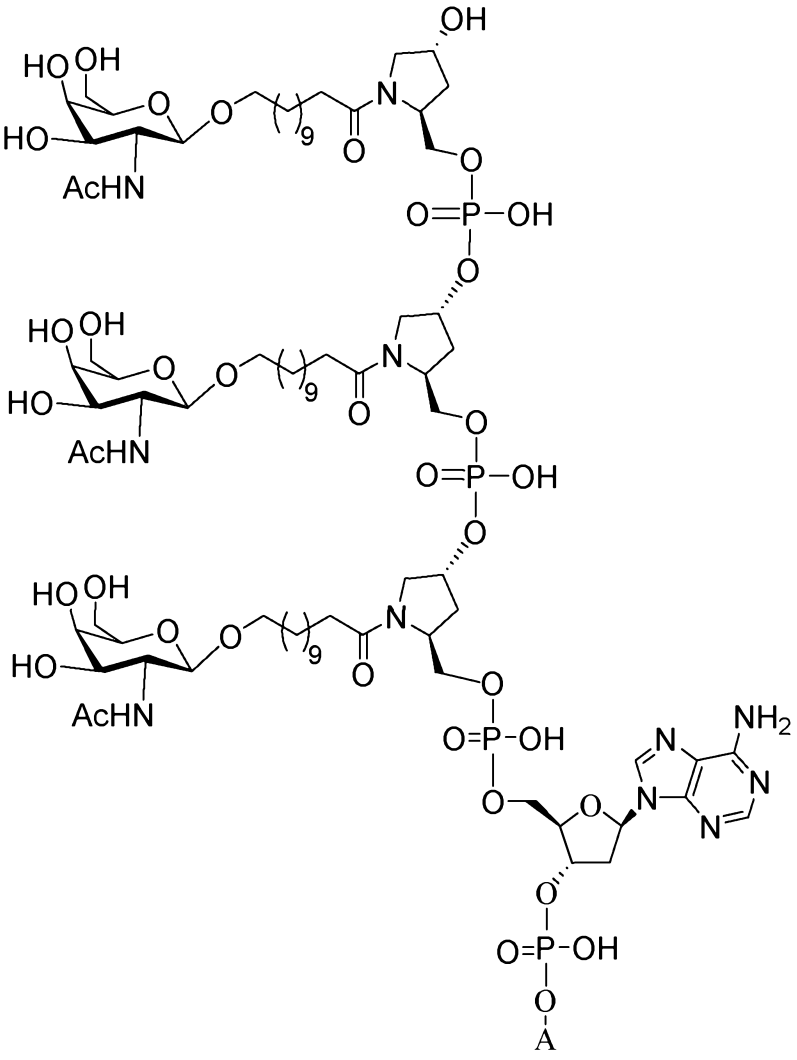
Embodiment 900. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and

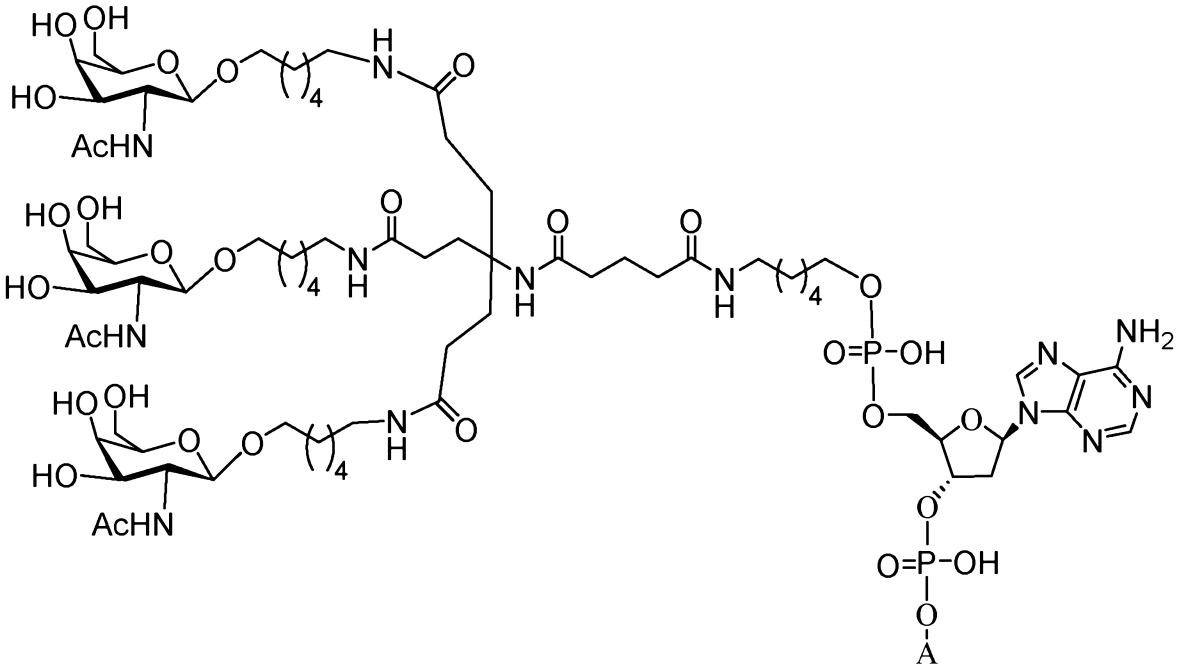
wherein A is the antisense oligonucleotide.

Embodiment 901. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and wherein A is the antisense oligonucleotide.

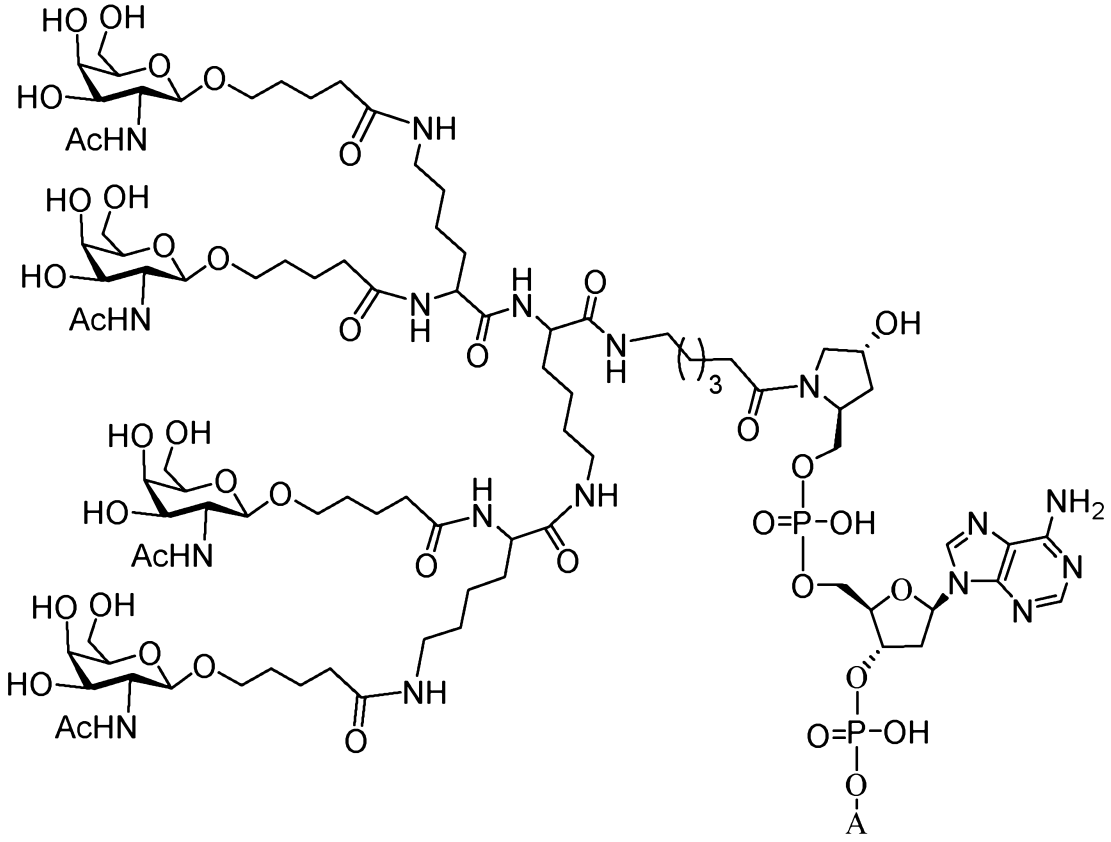
Embodiment 902. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and

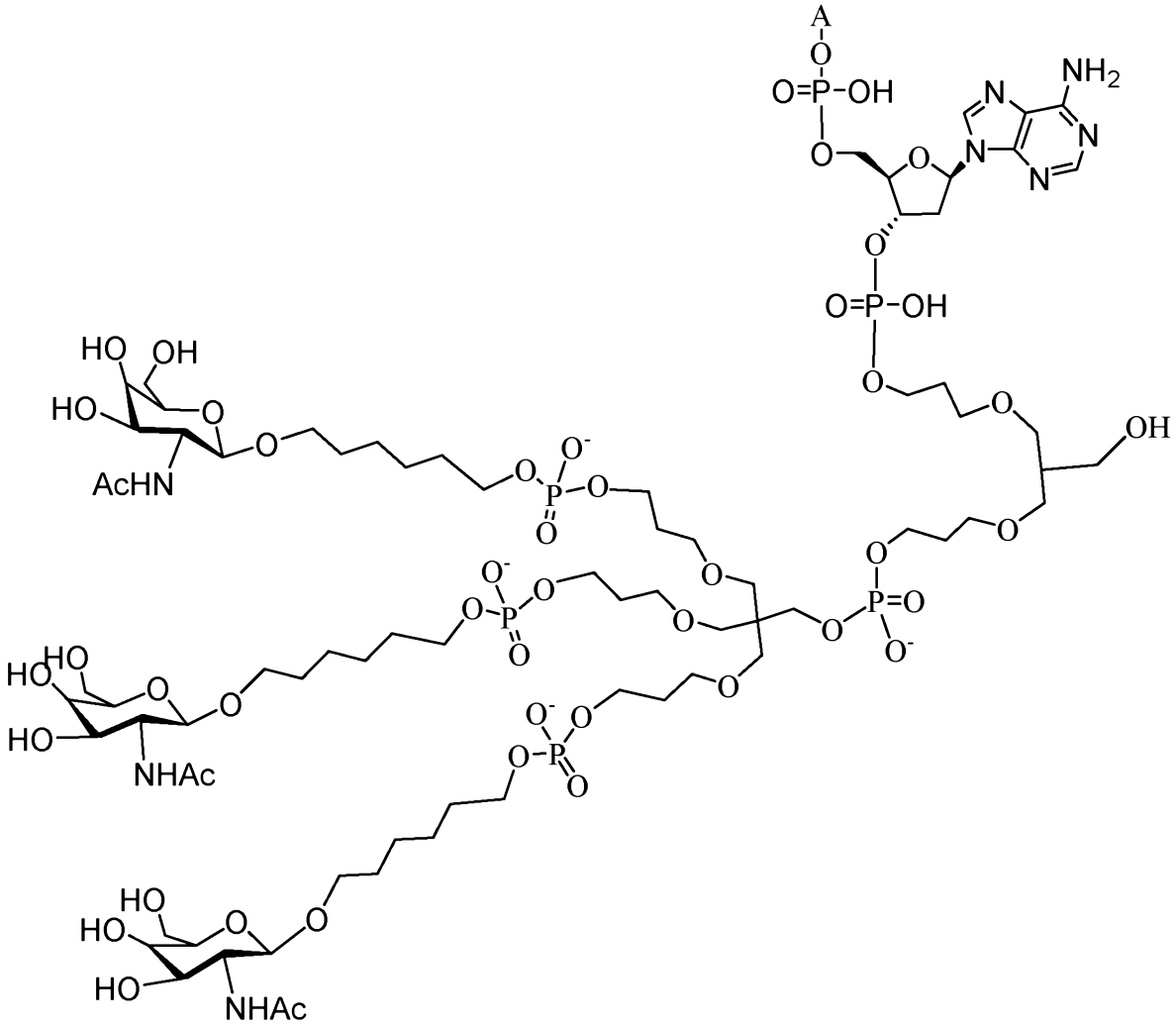
wherein A is the antisense oligonucleotide.

Embodiment 903. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and wherein A is the antisense oligonucleotide.

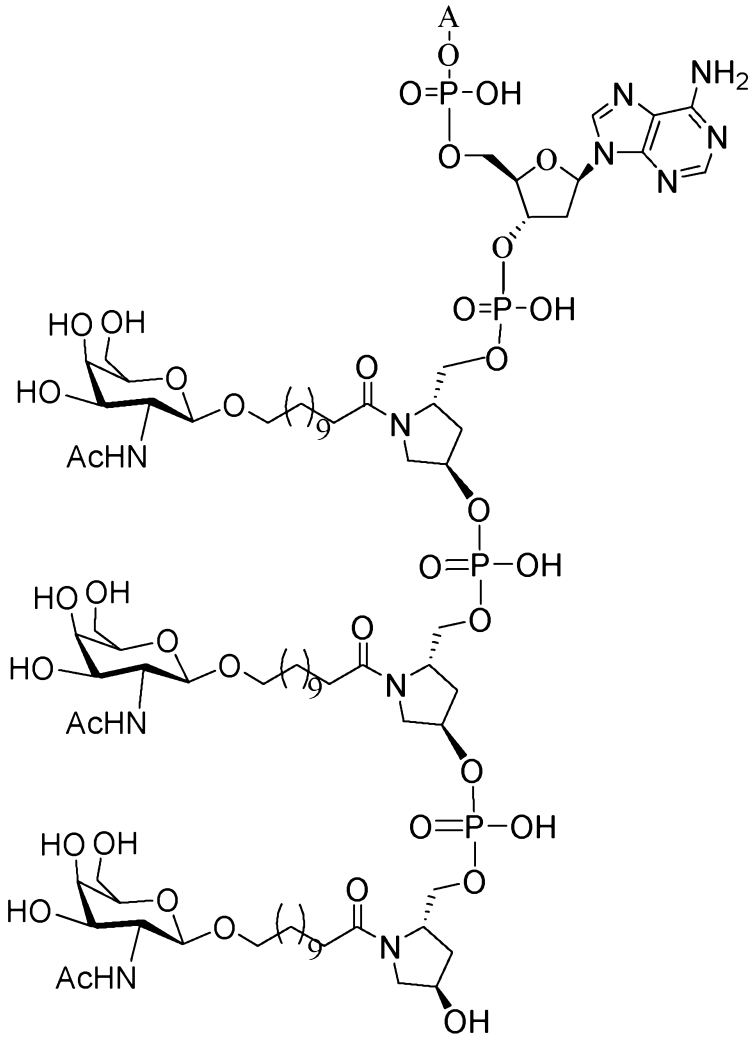
Embodiment 904. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and

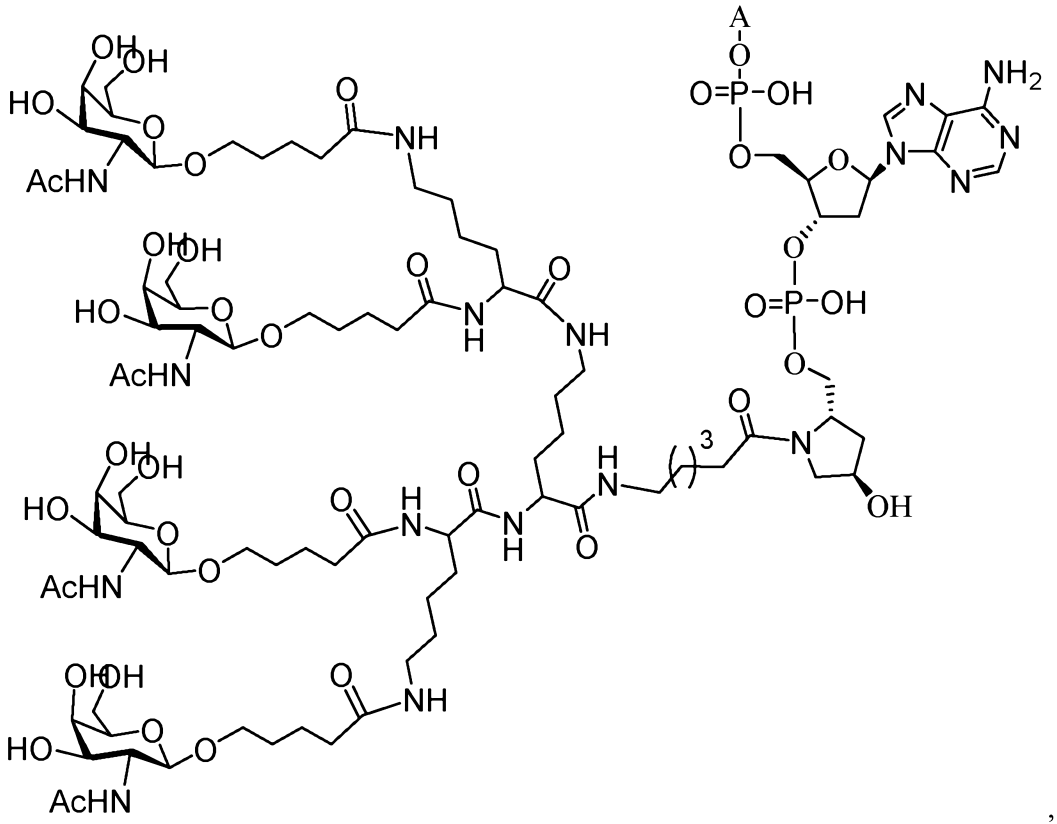
wherein A is the antisense oligonucleotide.

Embodiment 905. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and wherein A is the antisense oligonucleotide.

Embodiment 906. The conjugated antisense compound of any of embodiments 779 to 789, wherein the conjugate group has the following structure:



, and wherein A is the antisense oligonucleotide.

Embodiment 907. A conjugated oligonucleotide comprising an oligonucleotide and a conjugate group, wherein the conjugate group is any conjugate group of any of embodiments 779 to 907.

Embodiment 908. The conjugated oligonucleotide of embodiment 907 wherein the oligonucleotide comprises at least one modified nucleoside.

Embodiment 909. The conjugated oligonucleotide of embodiment 908 wherein the at least one modified nucleoside comprises a modified base.

Embodiment 910. The conjugated oligonucleotide of embodiment 908 or 909 wherein the at least one modified nucleoside comprises a sugar surrogate.

Embodiment 911. The conjugated oligonucleotide of embodiment 910 wherein the sugar surrogate is a tetrahydropyran.

Embodiment 912. The conjugated oligonucleotide of any of embodiment 911 wherein the tetrahydropyran is F-HNA.

Embodiment 913. The conjugated oligonucleotide of any of embodiments 908 to 912 wherein the remainder of the oligonucleotide comprises at least one nucleoside comprising a modified sugar.

Embodiment 914. The conjugated oligonucleotide of embodiment 913 wherein the at least one modified nucleoside comprising a modified sugar is selected from a bicyclic nucleoside and a 2'-modified nucleoside.

Embodiment 915. The conjugated oligonucleotide of embodiment 914 wherein the at least one modified nucleoside is a bicyclic nucleoside.

Embodiment 916. The conjugated oligonucleotide of embodiment 915 wherein the bicyclic nucleoside is a (4'-CH_2-O-2') BNA nucleoside.

Embodiment 917. The conjugated oligonucleotide of embodiment 915 wherein the bicyclic nucleoside is a (4'-$(CH_2)_2$-O-2') BNA nucleoside.

Embodiment 918. The conjugated oligonucleotide of embodiment 915 wherein the bicyclic nucleoside is a (4'-$C(CH_3)$H-O-2') BNA nucleoside.

Embodiment 919. The conjugated oligonucleotide of embodiment 914 wherein the at least one modified nucleoside is a 2'-modifed nucleoside.

Embodiment 920. The conjugated oligonucleotide of embodiment 919 wherein the at least one 2'-modified nucleoside is selected from a 2'-F nucleoside, a 2'-OCH_3 nucleoside, and a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 921. The conjugated oligonucleotide of embodiment 920 wherein the at least one 2'-modified nucleoside is a 2'-F nucleoside.

Embodiment 922. The conjugated oligonucleotide of embodiment 920 wherein the at least one 2'-modified nucleoside is a 2'-OCH_3 nucleoside.

Embodiment 923. The conjugated oligonucleotide of embodiment 920 wherein the at least one 2'-modified nucleoside is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 924. The conjugated oligonucleotide of any of embodiments 907-923 wherein the oligonucleotide comprises at least one unmodified nucleoside.

Embodiment 925. The conjugated oligonucleotide of embodiment 924 wherein the unmodified nucleoside is a ribonucleoside.

Embodiment 926. The conjugated oligonucleotide of embodiment 924 wherein the unmodified nucleoside is a deoxyribonucleoside.

Embodiment 927. The conjugated oligonucleotide of any of embodiments 907 to 926 wherein the oligonucleotide comprises at least two modified nucleosides.

Embodiment 928. The conjugated oligonucleotide of embodiment 927 wherein the at least two modified nucleosides comprise the same modification.

Embodiment 929. The conjugated oligonucleotide of embodiment 927 wherein the at least two modified nucleosides comprise different modifications.

Embodiment 930. The conjugated oligonucleotide of any of embodiments 927 to 929 wherein at least one of the at least two modified nucleosides comprises a sugar surrogate.

Embodiment 931. The conjugated oligonucleotide of any of embodiments 927 to 930 wherein at least one of the at least two modified nucleosides comprises a 2'-modification.

Embodiment 932. The conjugated oligonucleotide of embodiment 931 wherein each of the at least two modified nucleosides is independently selected from 2'-F nucleosides, 2'-OCH_3 nucleosides and 2'-$O(CH_2)_2OCH_3$ nucleosides.

Embodiment 933. The conjugated oligonucleotide of embodiment 932 wherein each of the at least two modified nucleosides is a 2'-F nucleoside.

Embodiment 934. The conjugated oligonucleotide of embodiment 932 wherein each of the at least two modified nucleosides is a 2'-OCH_3 nucleosides.

Embodiment 935. The conjugated oligonucleotide of embodiment 932 wherein each of the at least two modified nucleosides is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 936. The conjugated oligonucleotide of any of embodiments 907 to 935 wherein essentially every nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 937. The conjugated oligonucleotide of any of embodiments 907 to 927 or 930 to 936 wherein every nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 938. The conjugated oligonucleotide of any of embodiments 907 to 937 wherein the oligonucleotide is single-stranded.

Embodiment 939. The conjugated oligonucleotide of any of embodiments 907 to 937 wherein the oligonucleotide is double-stranded.

Embodiment 940. The conjugated oligonucleotide of any of embodiments 907 to 937, wherein the oligonucleotide is an antisense compound.

Embodiment 941. The conjugated oligonucleotide of any of embodiments 907 to 937, wherein the oligonucleotide is a RISC based oligonucleotide.

Embodiment 942. The conjugated oligonucleotide of any of embodiments 907 to 937, wherein the oligonucleotide activates the RISC pathway.

Embodiment 943. The conjugated oligonucleotide of any of embodiments 907 to 937, wherein the oligonucleotide is an RNase H based antisense compound.

Embodiment 944. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group is attached to the 5'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 945. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group is attached to the 3'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 946. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group is attached to an internal nucleoside of the antisense oligonucleotide.

Embodiment 947. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group increases uptake of the conjugated oligonucleotide compound into a hepatocyte relative to an unconjugated oligonucleotide compound.

Embodiment 948. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group increases the uptake of the conjugated oligonucleotide compound into a liver cell relative to an unconjugated oligonucleotide compound.

Embodiment 949. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group increases accumulation of the conjugated oligonucleotide compound in the liver relative to an unconjugated oligonucleotide compound.

Embodiment 950. The conjugated oligonucleotide compound of any of embodiments 907 to 943, wherein the conjugate group decreases accumulation of the conjugated oligonucleotide compound in the kidneys relative to an unconjugated oligonucleotide compound.

Embodiment 951. The conjugated oligonucleotide compound of embodiment 907 to 935 or 938 to 950, wherein the conjugated oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 952. The conjugated oligonucleotide compound of embodiment 951, wherein the 5'-region consists of 2 linked 5'-region nucleosides.

Embodiment 953. The conjugated oligonucleotide compound of embodiment 951, wherein the 5'-region consists of 3 linked 5'-region nucleosides.

Embodiment 954. The conjugated oligonucleotide compound of embodiment 951, wherein the 5'-region consists of 4 linked 5'-region nucleosides.

Embodiment 955. The conjugated oligonucleotide compound of embodiment 951, wherein the 5'-region consists of 5 linked 5'-region nucleosides.

Embodiment 956. The conjugated oligonucleotide compound of any of embodiments 951-955, wherein the 3'-region consists of 2 linked 3'-region nucleosides.

Embodiment 957. The conjugated oligonucleotide compound of any of embodiments 951-955, wherein the 3'-region consists of 3 linked 3'-region nucleosides.

Embodiment 958. The conjugated oligonucleotide compound of any of embodiments 951-955, wherein the 3'-region consists of 4 linked 3'-region nucleosides.

Embodiment 959. The conjugated oligonucleotide compound of any of embodiments 951-955, wherein the 3'-region consists of 5 linked 3'-region nucleosides.

Embodiment 960. The conjugated oligonucleotide compound of any of embodiments 951-959, wherein the central region consists of 5 linked central region nucleosides.

Embodiment 961. The conjugated oligonucleotide compound of any of embodiments 951-959, wherein the central region consists of 6 linked central region nucleosides.

Embodiment 962. The conjugated oligonucleotide compound of any of embodiments 951-959, wherein the central region consists of 7 linked central region nucleosides.

Embodiment 963. The conjugated oligonucleotide compound of any of embodiments 951-959, wherein the central region consists of 8 linked central region nucleosides.

Embodiment 964. The conjugated oligonucleotide compound of any of embodiments 951-959, wherein the central region consists of 9 linked central region nucleosides.

Embodiment 965. The conjugated oligonucleotide compound of any of embodiments 951-959, wherein the central region consists of 10 linked central region nucleosides.

Embodiment 966. The conjugated oligonucleotide compound of any of embodiments 951-965, wherein the conjugated oligonucleotide consists of 14 to 26 linked nucleosides.

Embodiment 967. The conjugated oligonucleotide compound of any of embodiments 951-965, wherein the conjugated oligonucleotide consists of 15 to 25 linked nucleosides.

Embodiment 968. The conjugated oligonucleotide compound of any of embodiments 951-965, wherein the conjugated oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 969. The conjugated oligonucleotide compound of any of embodiments 951-968, wherein each modified nucleoside independently comprises a 2'-substituted sugar moiety or a bicyclic sugar moiety.

Embodiment 970. The conjugated oligonucleotide compound of embodiment 969, wherein the at least one modified nucleoside comprises a 2'-substituted sugar moiety.

Embodiment 971. The conjugated oligonucleotide compound of embodiment 970, wherein each modified nucleoside comprising a 2'-substituted sugar moiety comprises a 2' substituent independently selected from among: halogen, optionally substituted allyl, optionally substituted amino, azido, optionally substituted SH, CN, OCN, CF3, OCF3, O, S, or N(Rm)-alkyl; O, S, or N(Rm)-alkenyl; O, S or N(Rm)-alkynyl; optionally substituted O-alkylenyl-O-alkyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted O-alkaryl, optionally substituted O-aralkyl, O(CH2)2SCH3, O-(CH2)2-O-N(Rm)(Rn) or O-CH2-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl;

wherein each optionally substituted group is optionally substituted with a substituent group independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

Embodiment 972. The conjugated oligonucleotide compound of embodiment 970, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-SCH_3, $O(CH_2)_2$-OCF_3, $O(CH_2)_3$-$N(R_1)(R_2)$, $O(CH_2)_2$-$ON(R_1)(R_2)$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_3)$-$(CH_2)_2$-$N(R_1)(R_2)$, and $O(CH_2)_2$-$N(R_3)$-$C(=NR_4)[N(R_1)(R_2)]$; wherein R_1, R_2, R_3 and R_4 are each, independently, H or C_1-C_6 alkyl.

Embodiment 973. The conjugated oligonucleotide compound of embodiment 970, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$.

Embodiment 974. The conjugated oligonucleotide compound of embodiment 970, wherein the at least one 2'-modified nucleoside comprises a 2'-MOE sugar moiety.

Embodiment 975. The conjugated oligonucleotide compound of embodiment 970, wherein the at least one 2'-modified nucleoside comprises a 2'-OMe sugar moiety.

Embodiment 976. The conjugated oligonucleotide compound of embodiment 970, wherein the at least one 2'-modified nucleoside comprises a 2'-F sugar moiety.

Embodiment 977. The conjugated oligonucleotide compound of any of embodiments 951-968, wherein the conjugated oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 978. The conjugated oligonucleotide compound of embodiment 977, wherein the modified nucleoside comprises an F-HNA sugar moiety.

Embodiment 979. The conjugated oligonucleotide compound of embodiment 977, wherein the modified nucleoside comprises an HNA sugar moiety.

Embodiment 980. The conjugated oligonucleotide compound of any of embodiments 951-968 wherein the conjugated oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 981. The conjugated oligonucleotide compound of embodiment 980, wherein the bicyclic sugar moiety is a cEt sugar moiety.

Embodiment 982. The conjugated oligonucleotide compound of embodiment 980, wherein bicyclic sugar moiety is an LNA sugar moiety.

Embodiment 983. The conjugated oligonucleotide compound of any of embodiments 907 to 982, wherein the conjugated oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 984. The conjugated oligonucleotide compound of embodiment 908, wherein each internucleoside linkage of the conjugated oligonucleotide is a modified internucleoside linkage.

Embodiment 985. The conjugated oligonucleotide compound of embodiment 983, wherein the conjugated oligonucleotide comprises at least one modified linkage and at least one unmodified phosphodiester internucleoside linkage.

Embodiment 986. The conjugated oligonucleotide compound of any of embodiments 983 to 985 wherein at least one modified internucleoside linkage is a phosphosphorothioate internucleoside linkage.

Embodiment 987. The conjugated oligonucleotide compound of any of embodiments 983 to 985, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 988. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 989. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 990. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 991. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 992. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 993. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 994. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 8 phosphodiester internucleoside linkages.

Embodiment 995. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 9 phosphodiester internucleoside linkages.

Embodiment 996. The conjugated oligonucleotide compound of any of embodiments 983 to 984, wherein the conjugated oligonucleotide comprises at least 10 phosphodiester internucleoside linkages.

Embodiment 997. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 16 phosphorothioate internucleoside linkages.

Embodiment 998. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 15 phosphorothioate internucleoside linkages.

Embodiment 999. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 14 phosphorothioate internucleoside linkages.

Embodiment 1000. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 13 phosphorothioate internucleoside linkages.

Embodiment 1001. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 12 phosphorothioate internucleoside linkages.

Embodiment 1002. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 11 phosphorothioate internucleoside linkages.

Embodiment 1003. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 10 phosphorothioate internucleoside linkages.

Embodiment 1004. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 9 phosphorothioate internucleoside linkages.

Embodiment 1005. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 8 phosphorothioate internucleoside linkages.

Embodiment 1006. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 7 phosphorothioate internucleoside linkages.

Embodiment 1007. The conjugated oligonucleotide compound of any of embodiments 983 or 985 to 996, wherein the conjugated oligonucleotide comprises fewer than 6 phosphorothioate internucleoside linkages.

Embodiment 1008. The conjugated oligonucleotide compound of any of embodiments 907 to 1007, wherein each terminal internucleoside linkage of the conjugated oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 1009. The conjugated oligonucleotide compound of any of embodiments 907 to 984 or 997 to 1008, wherein each internucleoside linkage linking two deoxynucleosides of the conjugated oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 1010. The conjugated oligonucleotide compound of any of embodiments 907 to 984 or 997 to 1009, wherein each non-terminal internucleoside linkage linking two modified nucleosides of the conjugated oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 1011. The conjugated oligonucleotide compound of any of embodiments 907 to 984 or 997 to 1010, wherein each non-terminal internucleoside linkage of the conjugated oligonucleotide that is 3' of a modified nucleoside is a phosphodiester internucleoside linkage.

Embodiment 1012. The conjugated oligonucleotide compound of any of embodiments 907 to 984 or 997 to 1011, wherein each internucleoside linkage of the conjugated oligonucleotide that is 3' of a deoxynucleoside is a phosphorothioate internucleoside linkage.

Embodiment 1013. The conjugated oligonucleotide compound of any of embodiments 907 to 984 or 997 to 1012 wherein the conjugated oligonucleotide has a chemical motif selected from among:

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

MsMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MsM
MsMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MyMsM
MsMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MyMyMsM
MsMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MyMyMyMsM
MsMyMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MsM
MsMyMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MyMsM
MsMyMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MyMyMsM; and
MsMyMyMyMy(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MyMyMyMsM;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each s is a phosphorothioate internucleoside linkage, and each y is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage, provided that at least one y is a phosphodiester internucleotide linkage.

Embodiment 1014. The conjugated oligonucleotide compound of any of embodiments 907 to 984 or 997 to 1012, wherein the conjugated oligonucleotides has a chemical motif selected from among:

MsMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMsM
MsMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMsM
MsMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMoMsM
MsMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MsM
MsMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMsM
MsMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMsM
MsMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMoMsM
MsMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MsM
MsMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMsM
MsMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMsM
MsMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMoMsM
MsMoMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MsM
MsMoMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMsM
MsMoMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMsM; and
MsMoMoMoMo(Ds)$_{0-1}$(DsDs)$_{(3-5)}$MoMoMoMsM;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each o is a phosphodiester internucleoside linkage, and each s is a phosphorothioate internucleoside linkage.

Embodiment 1015. The conjugated oligonucleotide compound of embodiment 1013 or 1014, wherein each M is independently selected from among: a 2'-MOE nucleoside and a bicyclic nucleoside.

Embodiment 1016. The conjugated oligonucleotide compound of embodiment 1015, wherein each M is independently selected from among a 2'-MOE nucleoside, a cEt nucleoside, and an LNA nucleoside.

Embodiment 1017. The conjugated oligonucleotide compound of embodiment 1015 or 1016, wherein each M is a 2'-MOE nucleoside.

Embodiment 1018. The conjugated oligonucleotide compound of embodiment 1015 or 1016, wherein each M is a cEt nucleoside.

Embodiment 1019. The conjugated oligonucleotide compound of embodiments 1015 or 1016, wherein each M is an LNA nucleoside.

Embodiment 1020. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 8 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1021. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 10 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1022. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 12 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1023. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 14 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1024. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 16 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1025. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 18 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1026. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide is at least 90% complementary to a target nucleic acid.

Embodiment 1027. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide is at least 95% complementary to a target nucleic acid.

Embodiment 1028. The conjugated oligonucleotide compound of any of embodiments 907 to 1019, wherein the conjugated oligonucleotide is 100% complementary to a target nucleic acid.

Embodiment 1029. The conjugated oligonucleotide compound of any of embodiments 1020 to 1028, wherein the target nucleic acid is a pre-mRNA.

Embodiment 1030. The conjugated oligonucleotide compound of any of embodiments 1020 to 1028, wherein the target nucleic acid is an mRNA.

Embodiment 1031. The conjugated oligonucleotide compound of any of embodiments 1020 to 1030, wherein the target nucleic acid is a micro RNA.

Embodiment 1032. The conjugated oligonucleotide compound of any of embodiments 1020 to 1030, wherein the target nucleic acid is expressed in the liver.

Embodiment 1033. The conjugated oligonucleotide compound of any of embodiments 1020 to 1030, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 1034. The conjugated oligonucleotide compound of any of embodiments 1020 to 1030, wherein the target nucleic encodes a protein selected from among: Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI, Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, SRB-1, and Transthyretin.

Embodiment 1035. The conjugated oligonucleotide compound of any of embodiments 1020 to 1031 wherein the target nucleic acid is a viral nucleic acid.

Embodiment 1036. The conjugated oligonucleotide compound of embodiment 1035, wherein the viral nucleic acid expressed in the liver.

Embodiment 1037. The conjugated oligonucleotide compound of embodiment 1036, wherein the target nucleic acid is a Hepatitis B viral nucleic acid.

Embodiment 1038. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NOs.: 17, 18, 19, 20, 21, 22, 23, or 24.

Embodiment 1039. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NO.: 25, 26, 27, 28, 29, or 30.

Embodiment 1040. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 31.

Embodiment 1041. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 32.

Embodiment 1042. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 33.

Embodiment 1043. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 34.

Embodiment 1044. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 35, 36, 37, 38, 39, 40, 41, 42, or 43.

Embodiment 1045. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 44, 45, 46, 47, or 48.

Embodiment 1046. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 1047. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 60, 61, 62, 63, 64, 65, 66, or 67.

Embodiment 1048. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NO.: 69, 70, 71, or 72.

Embodiment 1049. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 73.

Embodiment 1050. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 74, 75, 76, 77, 78, 79, 80, or 81.

Embodiment 1051. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 68.

Embodiment 1052. The conjugated oligonucleotide compound of any of embodiments 907 to 1030, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 82-103, 111, or 113.

Embodiment 1053. The conjugated oligonucleotide compound of any of embodiments 907 to 1052, wherein the conjugated oligonucleotide is an antisense oligonucleotide.

Embodiment 1054. A pharmaceutical composition comprising a compound or conjugated oligonucleotide according to any of embodiments 779 to 1053 and a pharmaceutically acceptable carrier or diluent.

Embodiment 1055. The pharmaceutical composition of embodiment 1054 wherein the pharmaceutically acceptable carrier or diluent is selected from among sterile water and sterile saline.

Embodiment 1056. A method of reducing the amount or activity of a target nucleic acid in a cell, comprising contacting a cell with a compound or conjugated antisense compound of any of embodiments 779 to 1053, or the pharmaceutical composition of embodiments 1054 to 1055.

Embodiment 1057. The method of embodiment 1056, wherein the cell is a liver cell.

Embodiment 1058. The method of embodiment 1056, wherein the cell is a hepatocyte.

Embodiment 1059. The method of any of embodiments 1056 to 1058 wherein the cell is in vitro.

Embodiment 1060. The method of any of embodiments 1056 to 1058, wherein the cell is in an animal.

Embodiment 1061. The method of embodiment 1060 wherein the animal is a mouse.

Embodiment 1062. The method of embodiment 1060 wherein the animal is a human.

Embodiment 1063. A method of treating a disease or condition in an animal comprising administering the pharmaceutical composition of embodiment 1054 or 1056 to the animal and thereby treating the disease or condition in the animal.

Embodiment 1064. The method of embodiment 1063 wherein the animal is a mouse.

Embodiment 1065. The method of embodiment 1063 wherein the animal is a human.

Embodiment 1066. The method of any of embodiments 1063 to 1065, wherein the disease or condition is a liver disease or condition.

Embodiment 1067. The method of any of embodiments 1063 to 1065 wherein the administration is parenteral.

Embodiment 1068. The method embodiment 1067 wherein the administration is by subcutaneous injection.

Embodiment 1069. The method of embodiment 1067 wherein the administration is by intravenous injection.

Embodiment 1070. The method of embodiment 1067 wherein the administration is by intramuscular injection.

Embodiment 1071. The method of any of embodiments 741 to 748 wherein the conjugated oligonucleotide is provided at a dose of 1-10 mg/kg.

Embodiment 1072. The method of any of embodiments 1056 to 1070 wherein the conjugated oligonucleotide is provided at a dose of less than 1 mg/kg.

Embodiment 1073. The method of any of embodiments 1056 to 1070 wherein the conjugated oligonucleotide is provided at a dose of greater than 10 mg/kg.

Embodiment 1074. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided for a dosing period of at least 2 months.

Embodiment 1075. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided for a dosing period of at least 4 months.

Embodiment 1076. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided for a dosing period of at least 6 months.

Embodiment 1077. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every week.

Embodiment 1078. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every two weeks.

Embodiment 1079. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every three weeks.

Embodiment 1080. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every four weeks.

Embodiment 1081. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every five weeks.

Embodiment 1082. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every six weeks.

Embodiment 1083. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every seven weeks.

Embodiment 1084. The method of any of embodiments 1056 to 1073 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every eight weeks.

Embodiment 1085. A conjugated antisense compound comprising: an antisense oligonucleotide comprising 12-30 linked nucleosides, and a conjugate group, wherein the conjugate group comprises at least one cell-targeting moiety.

Embodiment 1086. A method of reducing the activity or amount of an Apolipoprotein C-III protein in a cell, comprising contacting a cell with at least one conjugated antisense compound of any of embodiments 779 to 1055; and thereby reducing the activity or amount of the Apolipoprotein C-III protein in the cell.

Embodiment 1087. A method of decreasing total cholesterol, comprising contacting a cell with at least one compound of any of embodiments 779 to 1055; and thereby decreasing total cholesterol.

Embodiment 1088. A method of decreasing triglycerides, comprising contacting a cell with at least one compound of any of embodiments 779 to 1055; and thereby decreasing triglycerides.

Embodiment 1089. A method of lowering LDL, comprising contacting a cell with at least one compound of any of embodiments 779 to 1055; and thereby lowering LDL.

Embodiment 1090. A method of increasing HDL, comprising contacting a cell with at least one compound of any of embodiments 779 to 1055; and thereby increasing HDL.

Embodiment 1091. The method of any of embodiments 1086 to 1090, wherein the cell is in vitro.

Embodiment 1092. The method of any of embodiments 1086 to 1090, wherein the cell is in an animal.

Embodiment 1093. The method of any of embodiments 1086 to 1090, wherein the animal is a human.

Embodiment 1094. The compound or conjugated oligonucleotide of any of embodiments 1-1055 or a prodrug thereof.

Embodiment 1095. A method of manufacturing an antisense oligonucleotide of any of embodiments 1-1055.

Embodiment 1096. A method of preparing an antisense oligonucleotide of any of embodiments 1-1055.

Embodiment 1097. A process for manufacturing a conjugated antisense compound of any one of embodiments 1-1055, wherein the method includes formulating the conjugated antisense compound for human use, performing chromatogram analysis of the formulated conjugated antisense compound, and packaging the conjugated antisense compound ready for sale.

Embodiment 1098. A conjugate compound comprising at least one phosphorus linking group or neutral linking group and one or more ligands.

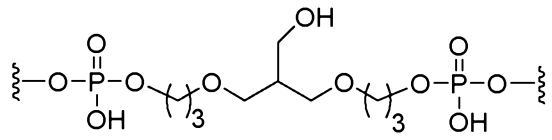
Embodiment 1099. The conjugate compound of claim 1098 comprising two or more ligands.

Embodiment 1100. The conjugate compound of claim 1098 comprising three ligands.

Embodiment 1101. The conjugate compound of any of claims 1098 to 1100, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

Embodiment 1102. The conjugate compound of any of claims 1098 to 1101, wherein the ligand is N-acetyl galactoseamine.

Embodiment 1103. The conjugate compound of any of claims 1098 to 1102, wherein conjugate group comprises a structure selected from among: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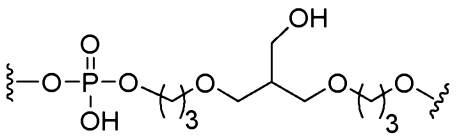
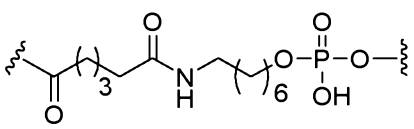
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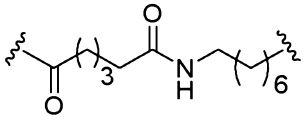
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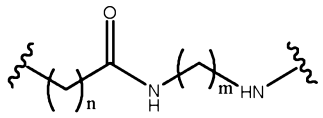
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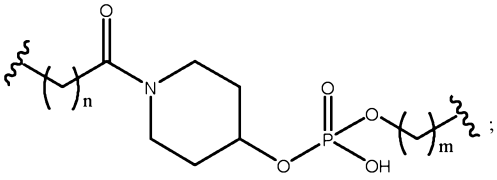
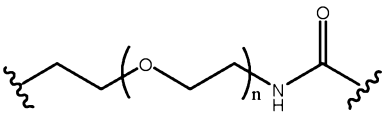
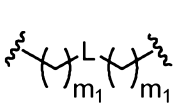
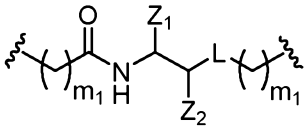

;

;

wherein n is from 1 to 12; and

wherein m is from 1 to 12.

Embodiment 1104. The conjugate compound of any of claims 1098 to 1102, wherein the conjugate compound has a tether having a structure selected from among:


and


wherein L is either a phosphorus linking group or a neutral linking group;

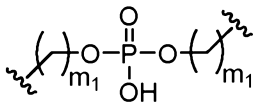
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

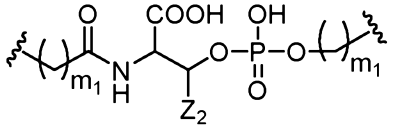
R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

Embodiment 1105. The conjugate compound of claim 1104, wherein the tether has a structure selected from among:



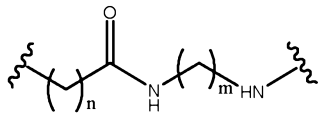
and



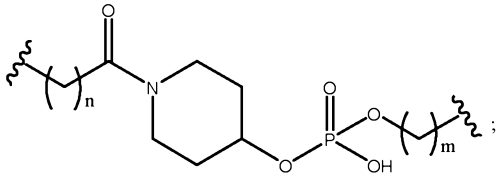
wherein Z_2 is H or CH_3; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

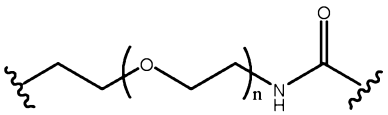
Embodiment 1106. The conjugate compound of any of claims 1098 to 1102, wherein the tether has a structure selected from among:



;



;



;

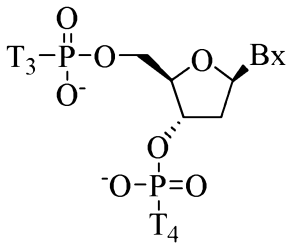
wherein n is from 1 to 12; and

wherein m is from 1 to 12.

Embodiment 1107. The conjugate compound of any of claims 1098 to 1106, wherein the conjugate compound is covalently attached to an oligonucleotide.

Embodiment 1108. An oligomeric compound comprising an oligonucleotide and at least one conjugate group, wherein at least one conjugate group is a conjugate compound of any of claims 1098 to 1108.

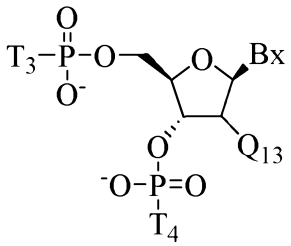
Embodiment 1109. A compound having the formula (V):



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, or $GalNAc_3$-22a.

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; and wherein Bx is a heterocyclic base moiety.

Embodiment 1110. A compound having the formula (Va):



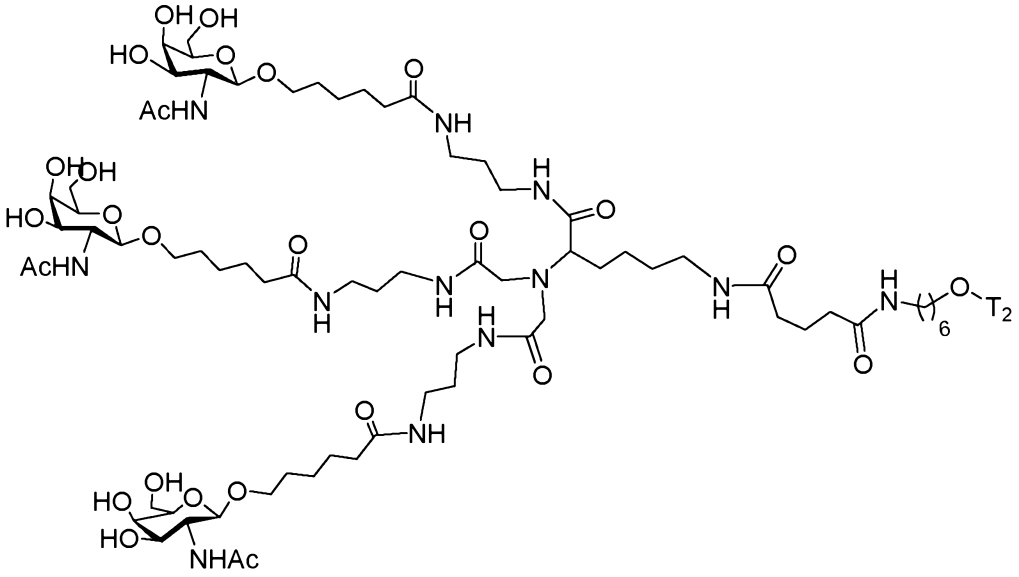
wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, or $GalNAc_3$-22a.

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety; and wherein Q_{13} is selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, OCH_2C(=O)-$N(H)CH_3$, OCH_2C(=O)-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-C(=NH)NH_2.

Embodiment 1111. The compound of claim 1109 or 1110, wherein B_x is selected from adenine, guanine, thymine, uracil, or cytosine.

Embodiment 1112. The compound of any of claims 1109 to 1111, wherein Q_{13} $O(CH_2)_2$-OCH_3.

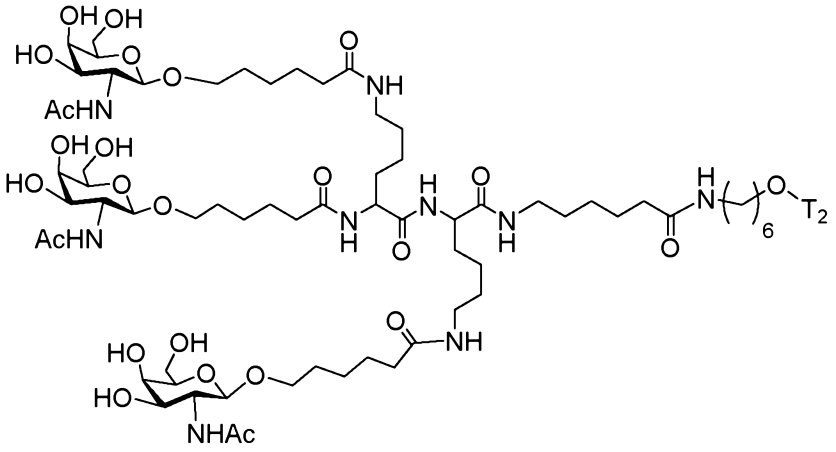
Embodiment 1113. A compound having the formula (XVI):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

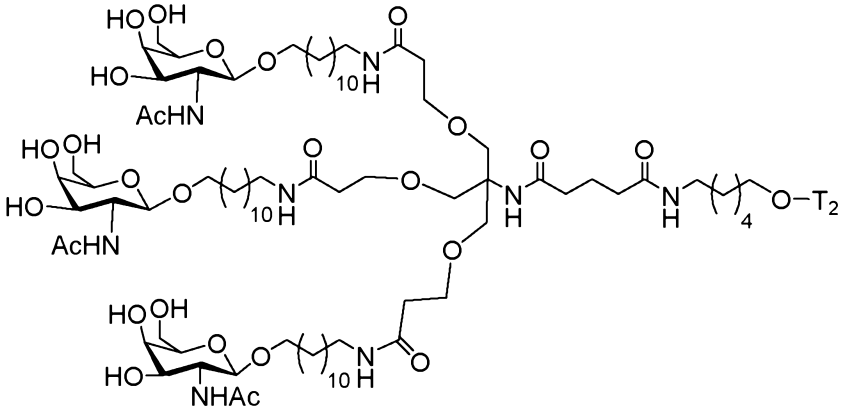
Embodiment 1114. A compound having the formula (XVII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

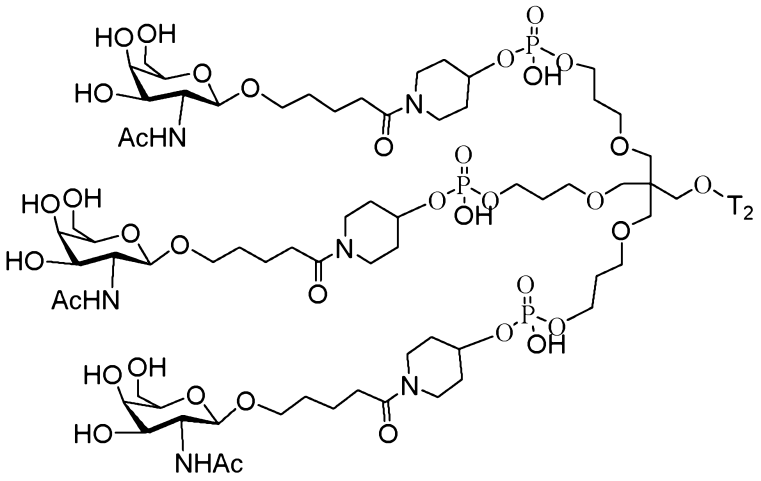
Embodiment 1115. A compound having the formula (XVIII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

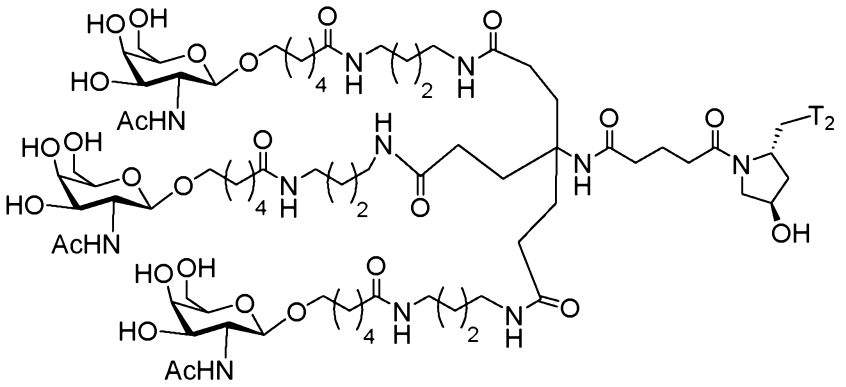
Embodiment 1116. A compound having the formula (XIX):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

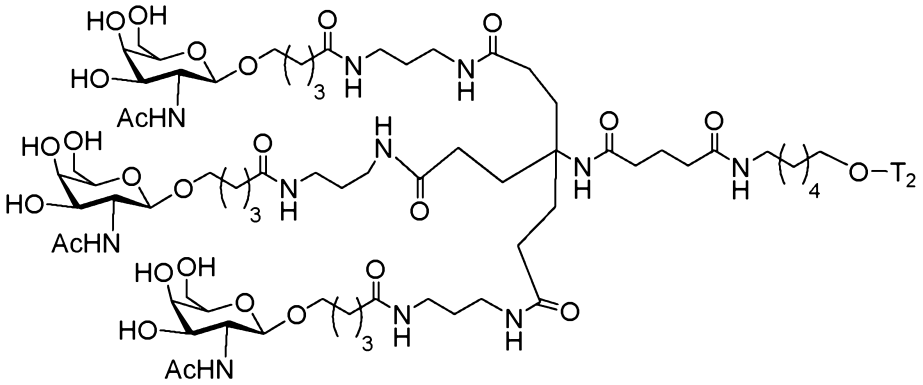
Embodiment 1117. A compound having the formula (XX):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

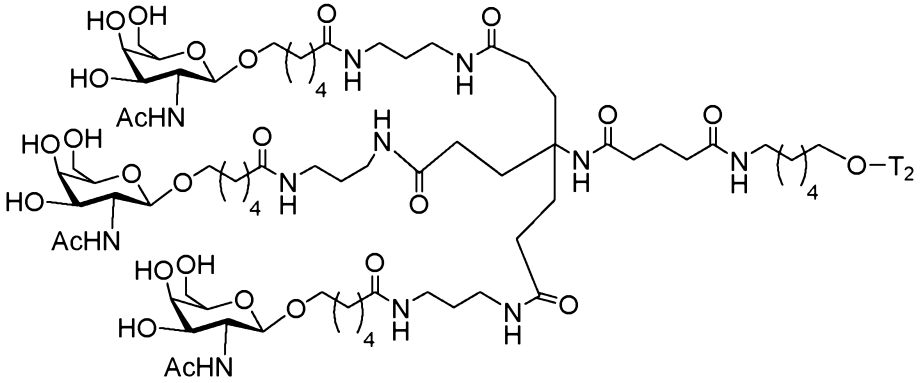
Embodiment 1118. A compound having the formula (XXI):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

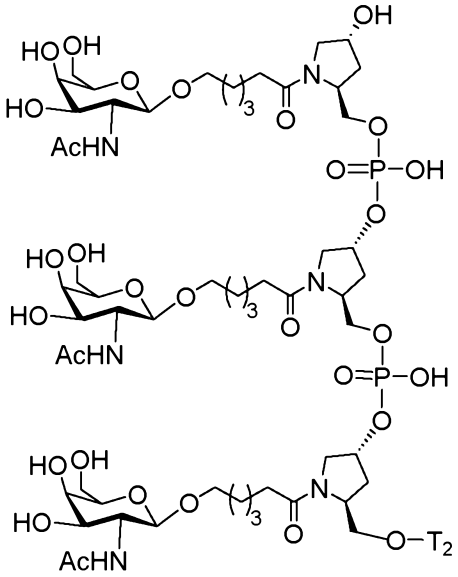
Embodiment 1119. A compound having the formula (XXII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

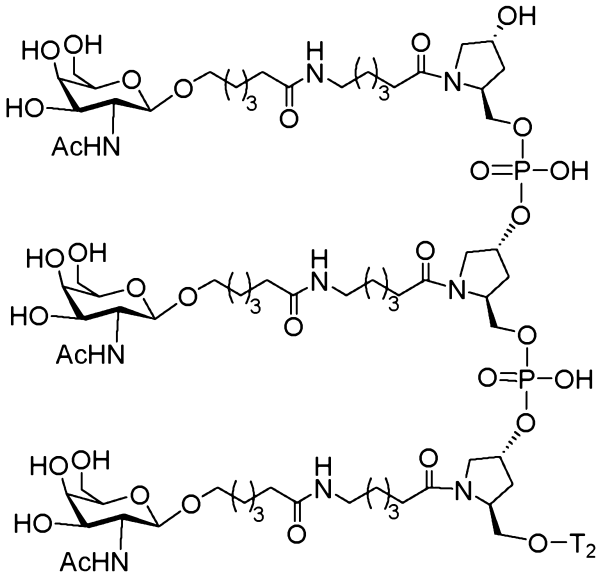
Embodiment 1120. A compound having the formula (XXIII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

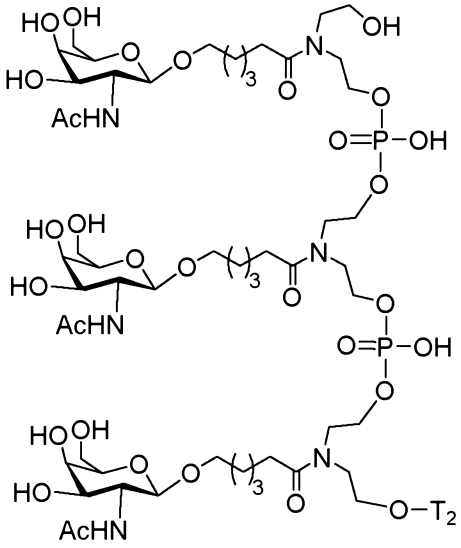
Embodiment 1121. A compound having the formula (XXIIIa):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

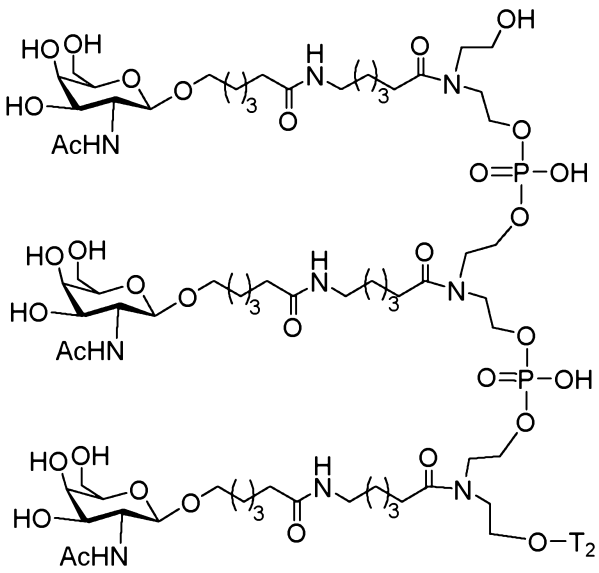
Embodiment 1122. A compound having the formula (XXIV):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

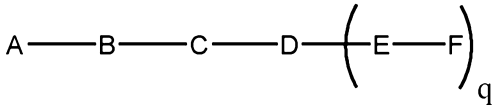
Embodiment 1123. A compound having the formula (XXIVa):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1124. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

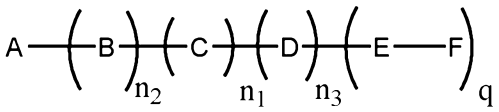
D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1125. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein:

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

D is the branching group

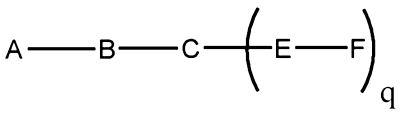
each E is a tether;

each F is a ligand;

n_1 is 0 or 1; and

q is an integer between 1 and 5.

Embodiment 1126. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety;

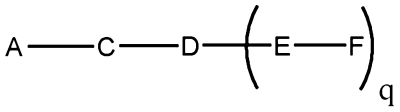
C is the conjugate linker;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1127. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

C is the conjugate linker;

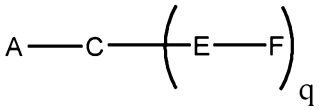
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1128. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

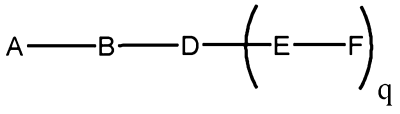
C is the conjugate linker;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1129. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety;

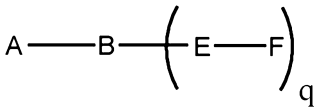
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1130. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

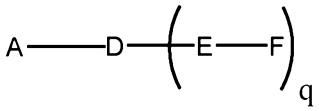
B is the cleavable moiety;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1131. A conjugated antisense compound, wherein the compound has a structure represented by the formula:



wherein

A is the antisense oligonucleotide;

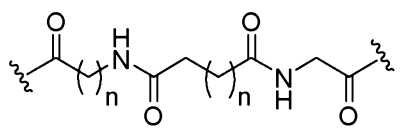
D is the branching group;

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

Embodiment 1132. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker has a structure selected from among: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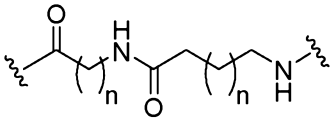
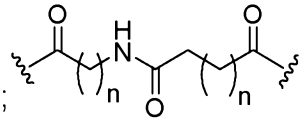
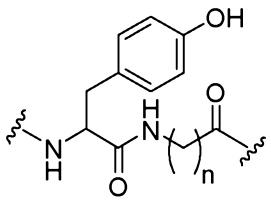
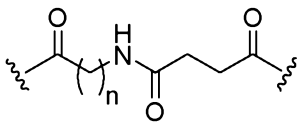
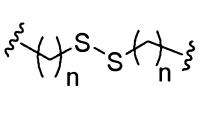
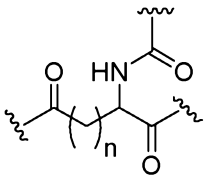

;

;

;

;

;

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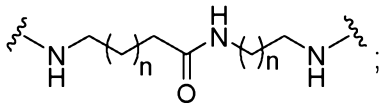
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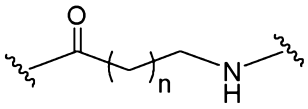
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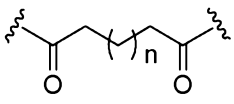
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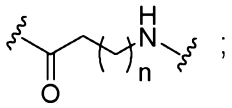
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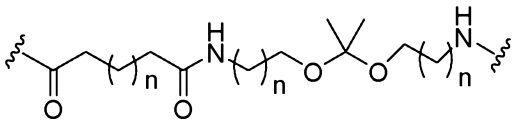
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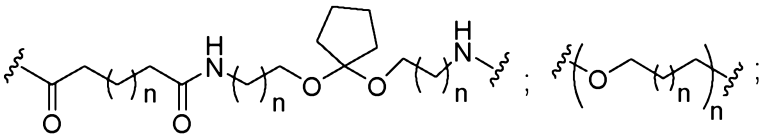
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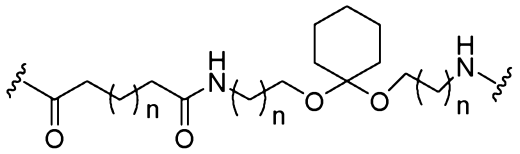
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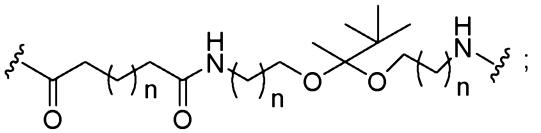
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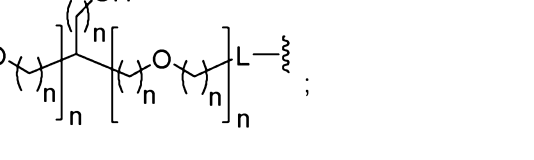
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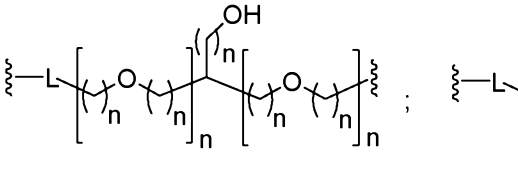
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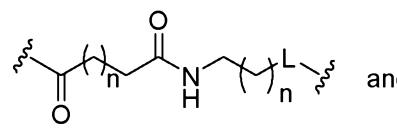
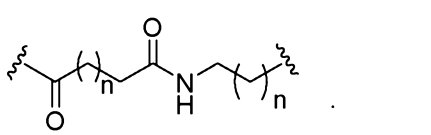
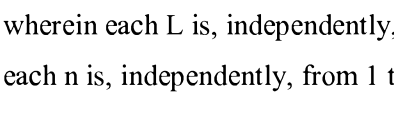
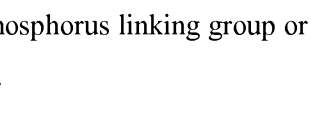
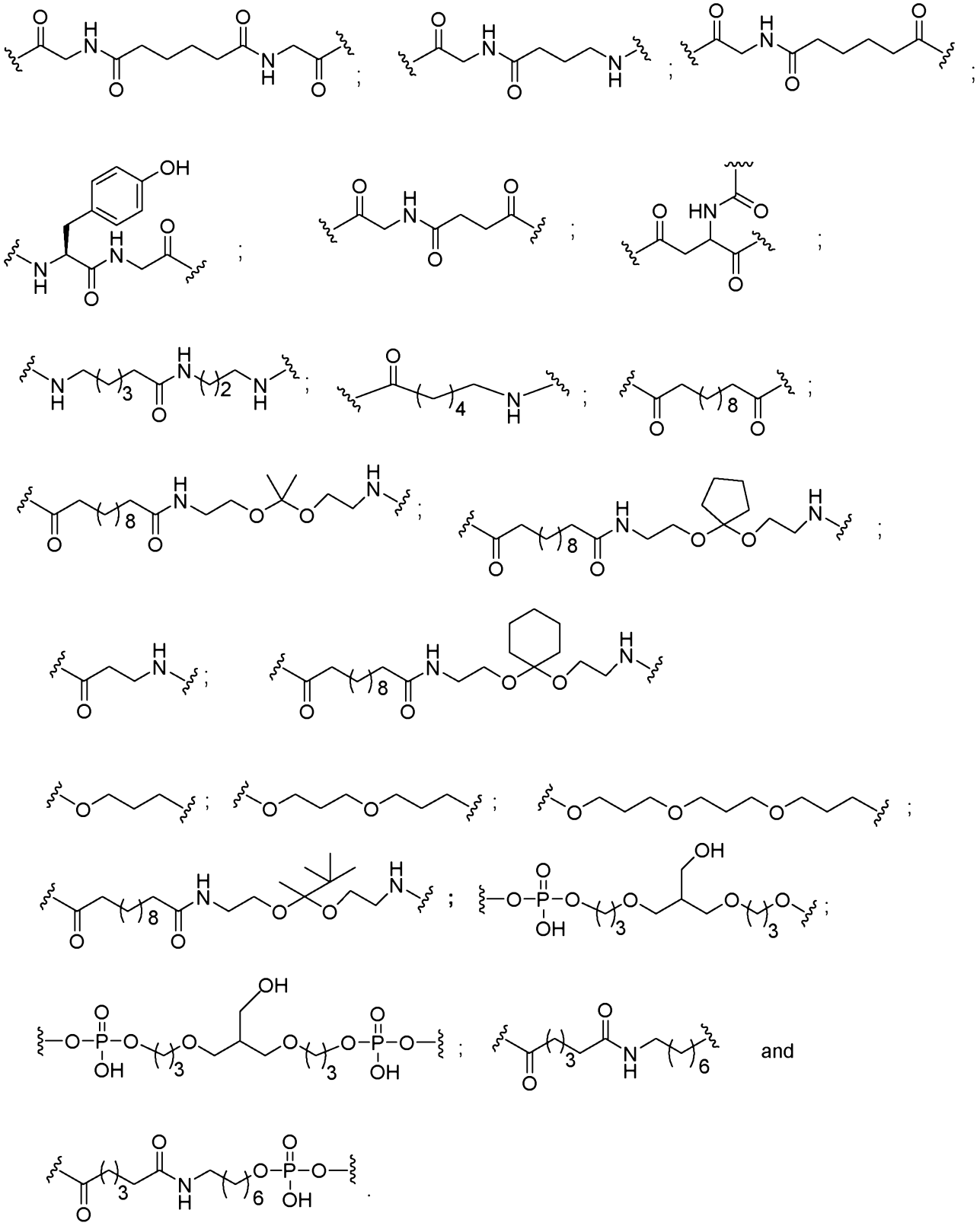

;

;

and

.

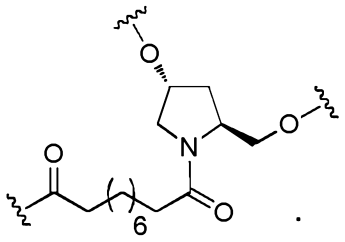
wherein each L is, independently, a phosphorus linking group or a neutral linking group; and each n is, independently, from 1 to 20.

Embodiment 1133. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker has a structure selected from among:

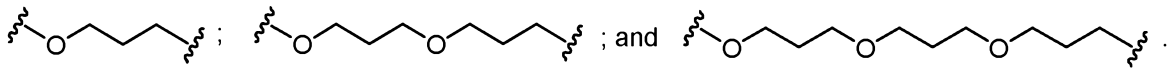


and

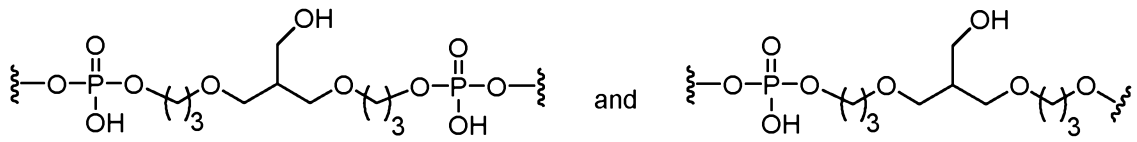
Embodiment 1134. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker has the structure:



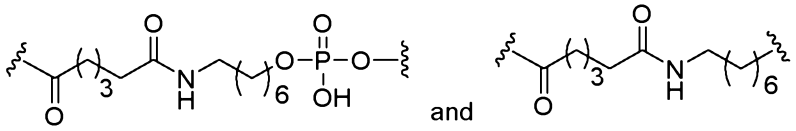
Embodiment 1135. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker has one of the structures selected from:



Embodiment 1136. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker has one of the structures selected from:



Embodiment 1137. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker has one of the structures selected from:



Embodiment 1138. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises a pyrrolidine.

Embodiment 1139. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker does not comprise a pyrrolidine.

Embodiment 1140. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises PEG.

Embodiment 1141. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises an amide.

Embodiment 1142. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker does not comprise an amide.

Embodiment 1143. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises a polyamide.

Embodiment 1144. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises an amine.

Embodiment 1145. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises one or more disulfide bonds.

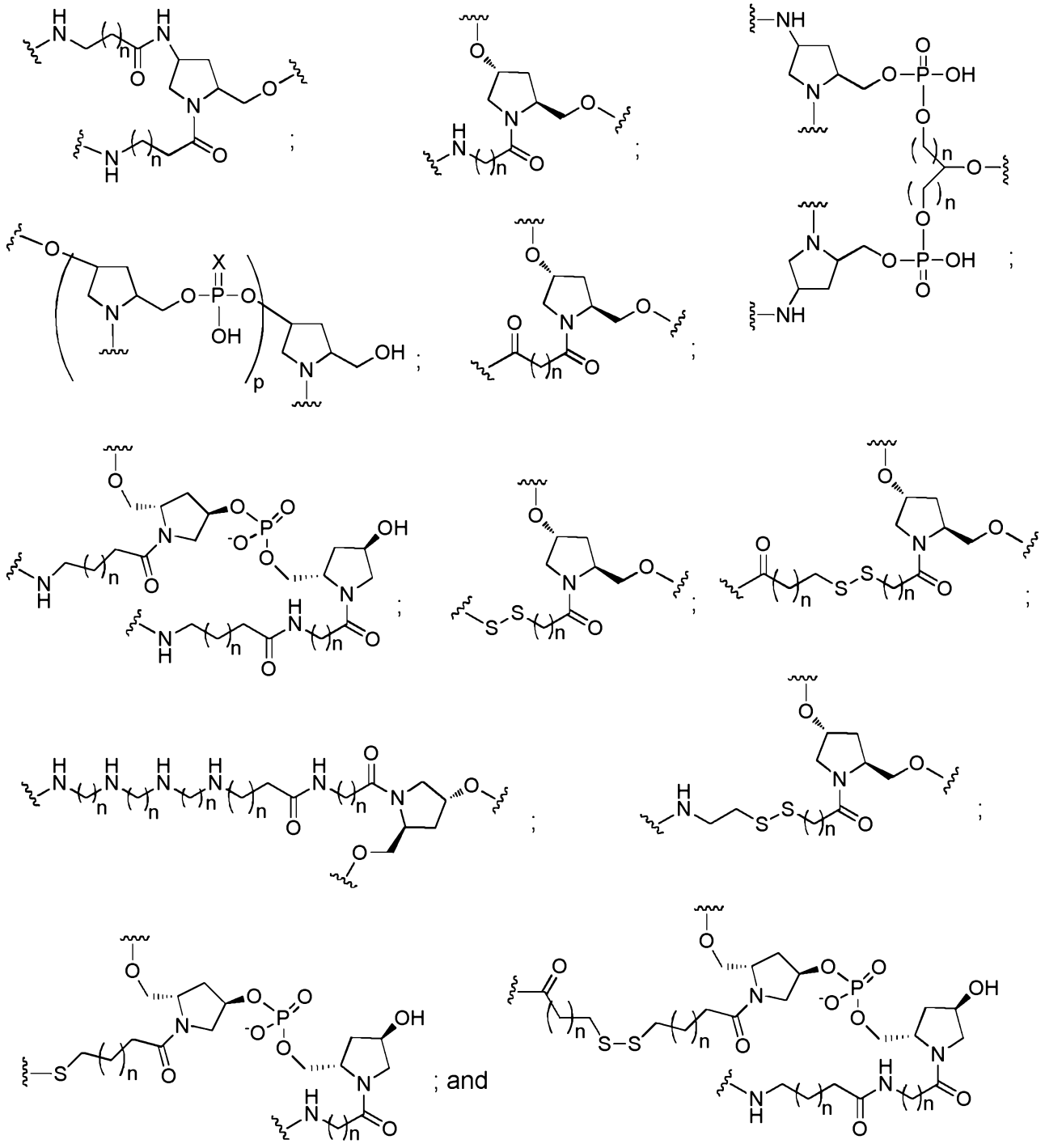
Embodiment 1146. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate linker comprises a protein binding moiety.

Embodiment 1147. The conjugated antisense compound of claim 1146, wherein the protein binding moiety comprises a lipid.

Embodiment 1148. The conjugated antisense compound of claim 1146, wherein the protein binding moiety is selected from among: cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), a vitamin (e.g., folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (e.g., monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, e.g., sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid.

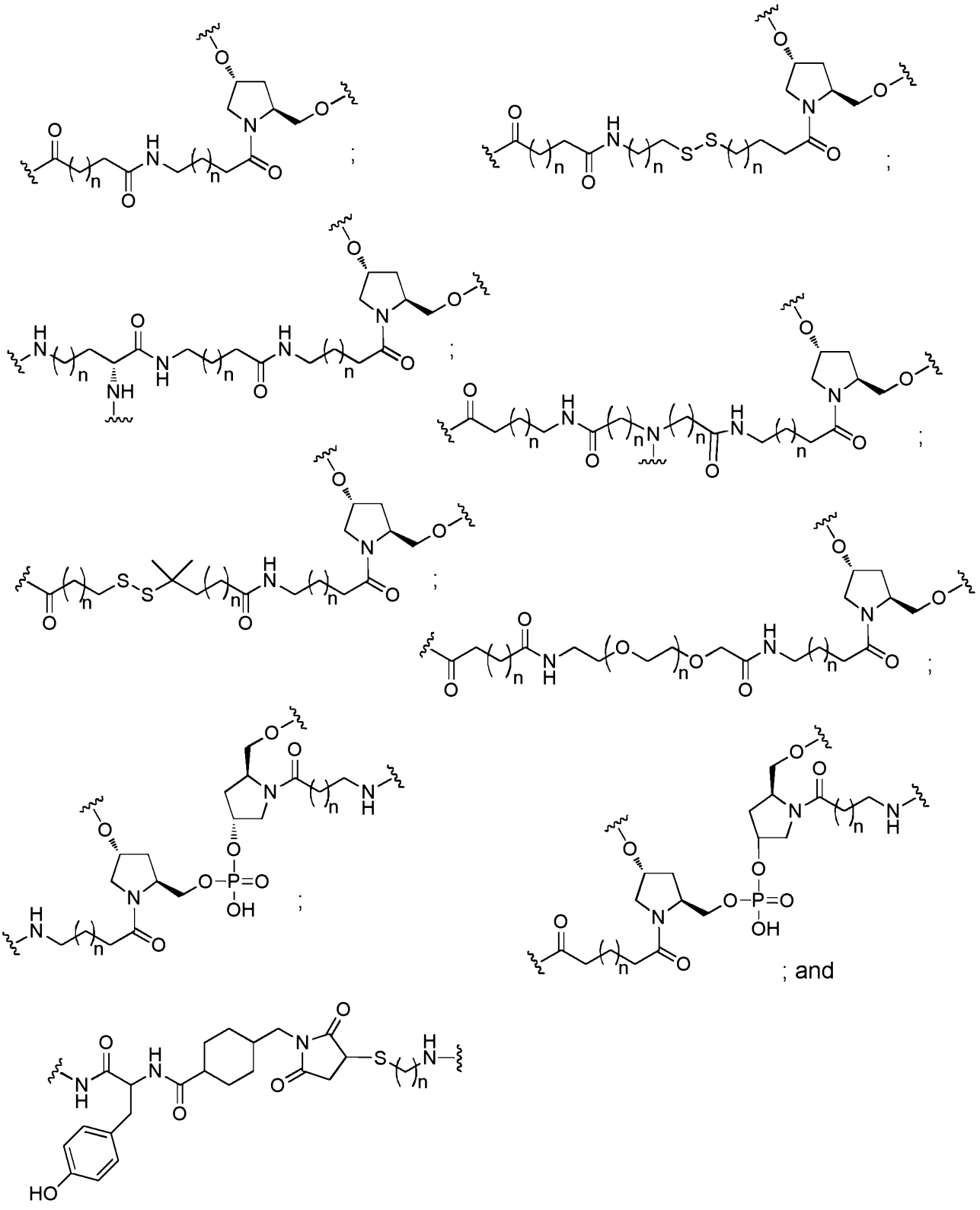
Embodiment 1149. The conjugated antisense compound of any of claims 1146 to 1147 wherein the protein binding moiety is a C16 to C22 long chain saturated or unsaturated fatty acid, cholesterol, cholic acid, vitamin E, adamantane or 1-pentafluoropropyl.

Embodiment 1150. The conjugated antisense compound of any of claims 1124 to 1128, wherein the conjugate linker has a structure selected from among:



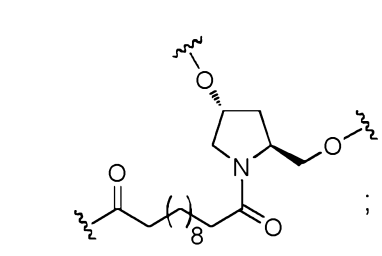
wherein each n is, independently, is from 1 to 20; and p is from 1 to 6.

Embodiment 1151. The conjugated antisense compound of any of claims 1124 to 1128 wherein the conjugate linker has a structure selected from among:



wherein each n is, independently, from 1 to 20.

Embodiment 1152. The conjugated antisense compound of any of claims 1124 to 1128 wherein the conjugate linker has a structure selected from among: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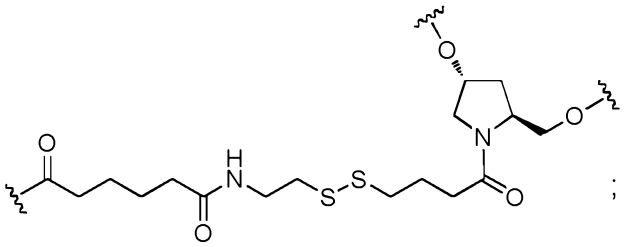
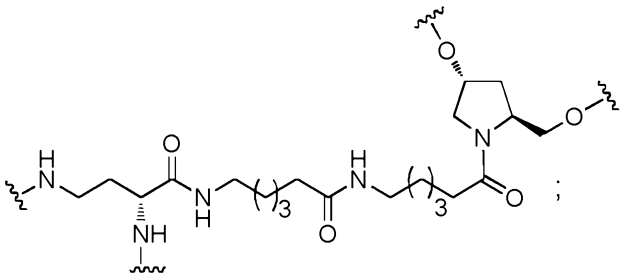
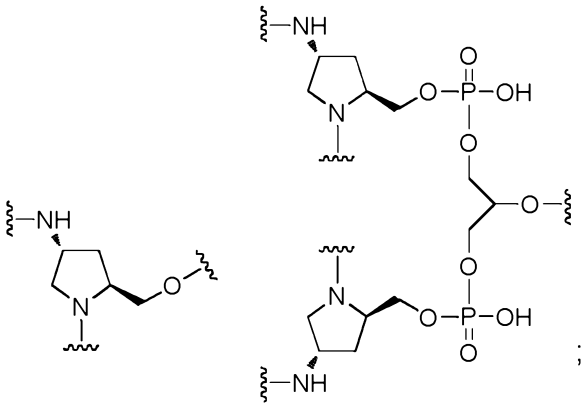

;


;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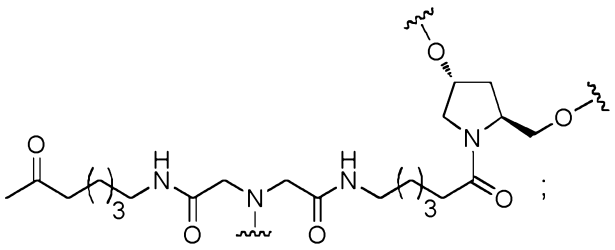
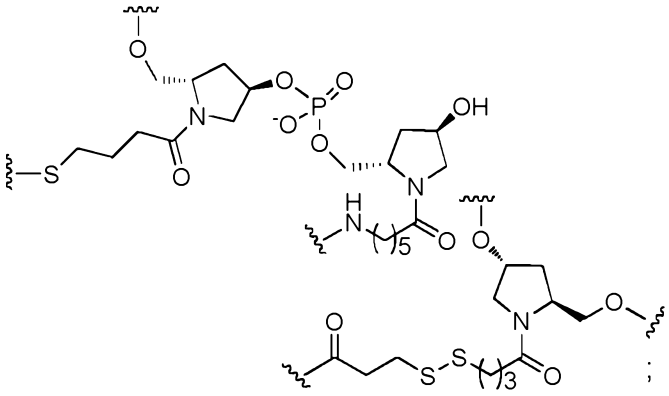

;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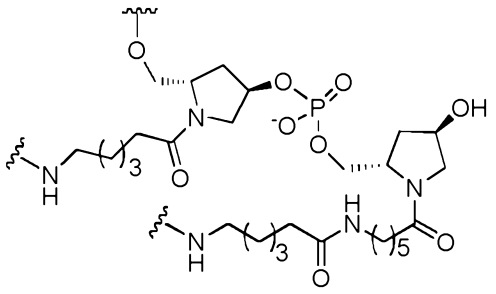
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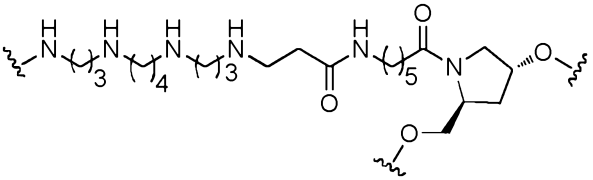
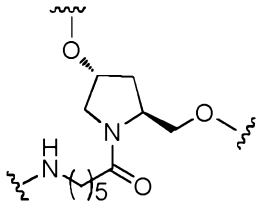
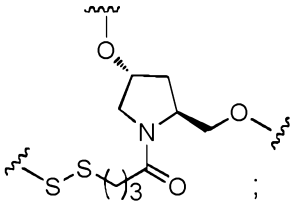
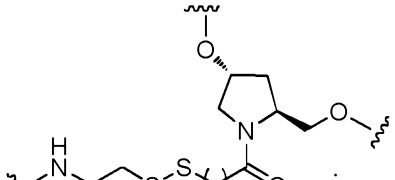
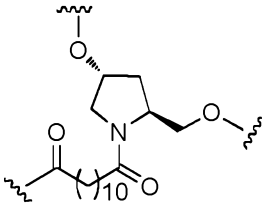
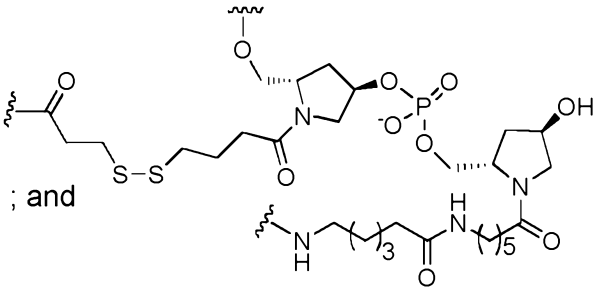

;


;

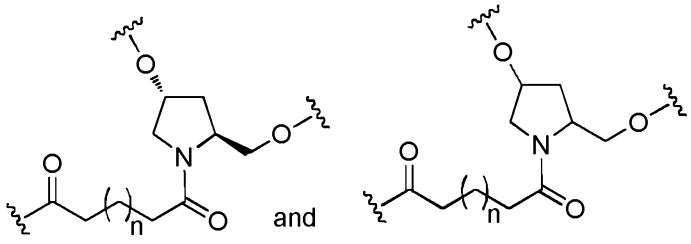

;


;


; and

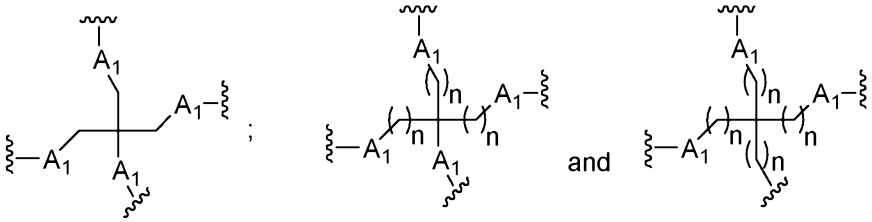

.

Embodiment 1153. The conjugated antisense compound of any of claims 1124 to 1128 wherein the conjugate linker has a structure selected from among:



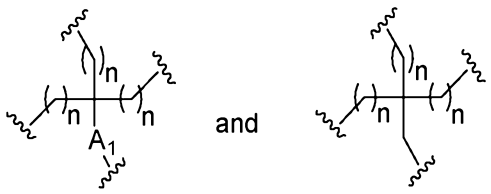
wherein n is from 1 to 20.

Embodiment 1154. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has one of the following structures:



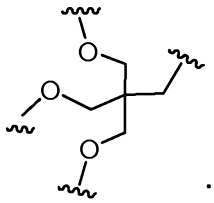
wherein each A_1 is independently, O, S, C=O or NH; and
each n is, independently, from 1 to 20.

Embodiment 1155. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has one of the following structures:

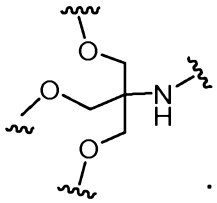


wherein each A_1 is independently, O, S, C=O or NH; and
each n is, independently, from 1 to 20.

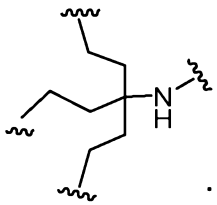
Embodiment 1156. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:



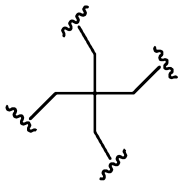
Embodiment 1157. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:



Embodiment 1158. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:

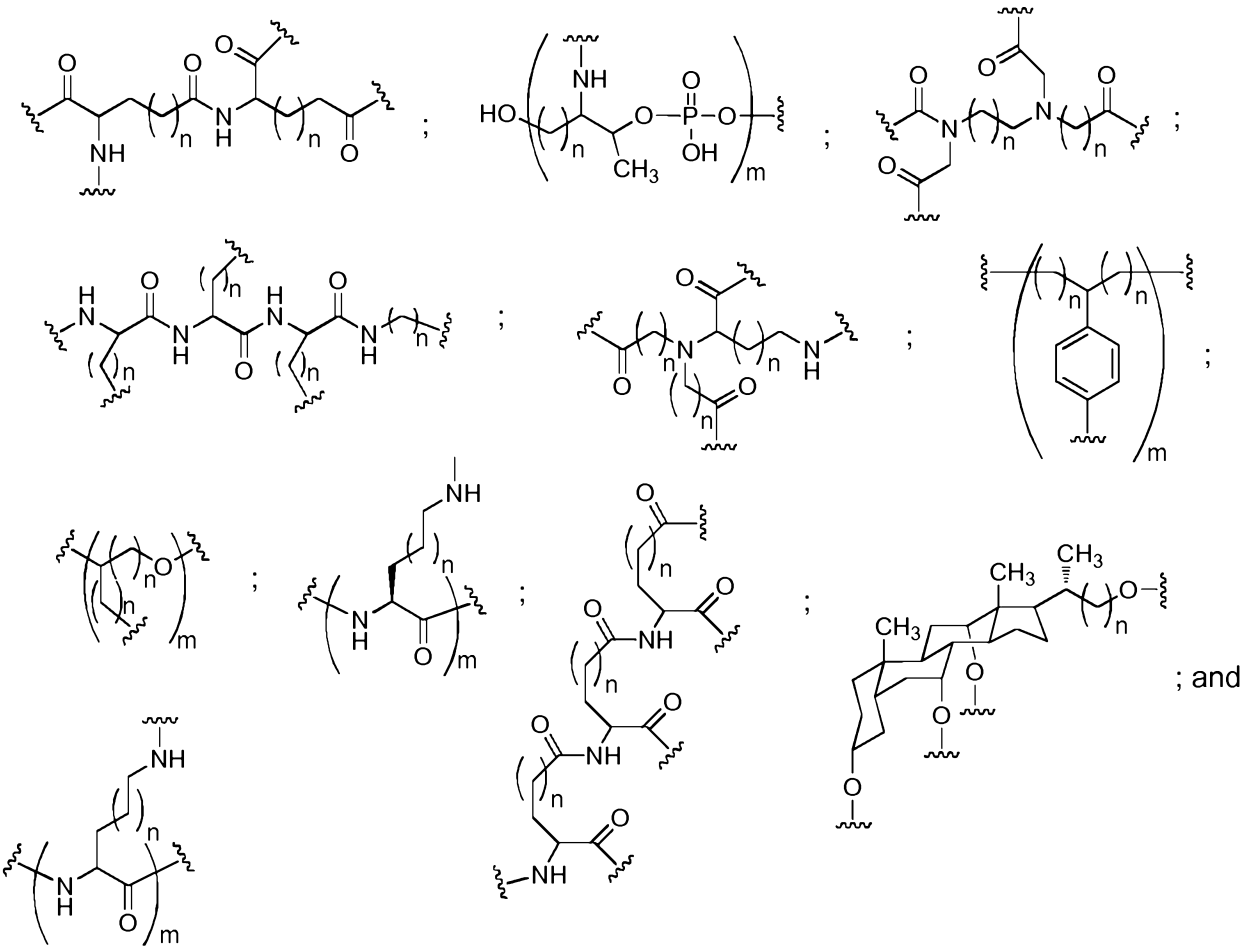


Embodiment 1159. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:



Embodiment 1160. The conjugated antisense compound of any of claims 1124 to 1154, wherein the branching group comprises an ether.

Embodiment 1161. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:

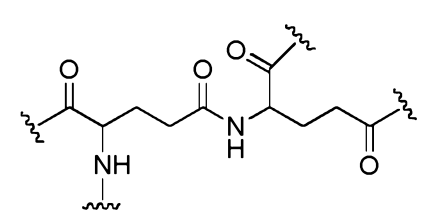
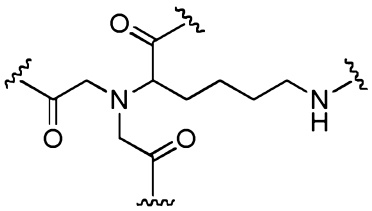
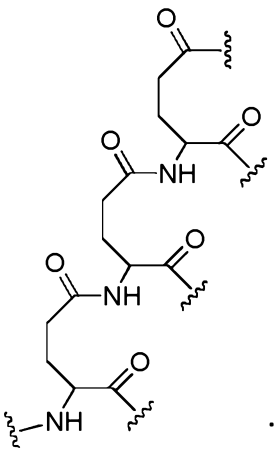
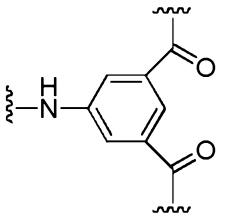
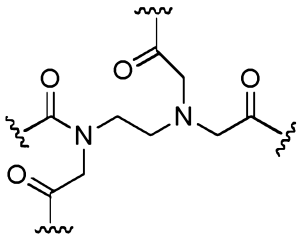
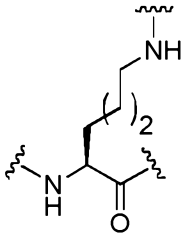


; and

each n is, independently, from 1 to 20; and

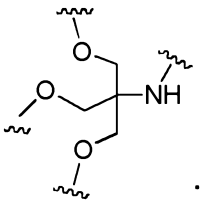
m is from 2 to 6.

Embodiment 1162. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:

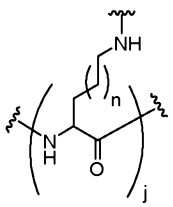
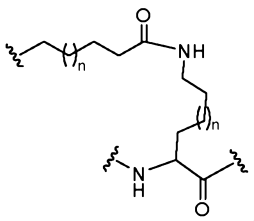
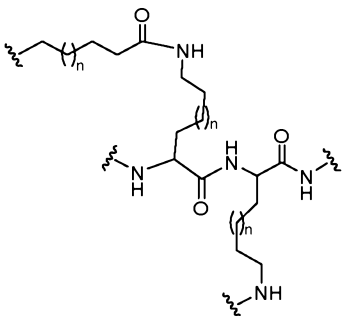

;

;


;

;

; and

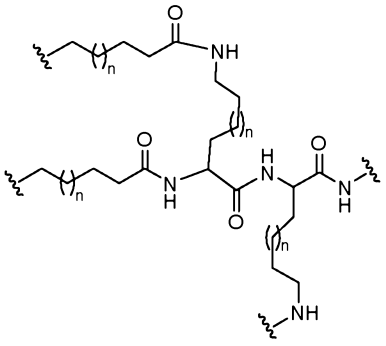
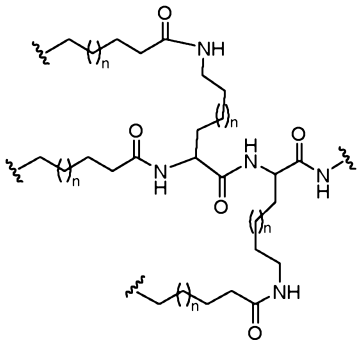
.

Embodiment 1163. The conjugated antisense compound of claim 1124 to 1154, wherein the branching group has the following structure:


.

Embodiment 1164. The conjugated antisense compound of any of claims 1124 to 1154, wherein the branching group comprises:

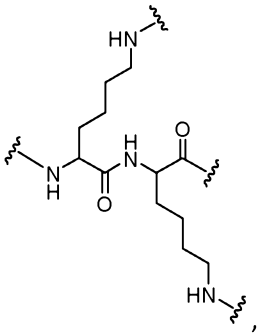
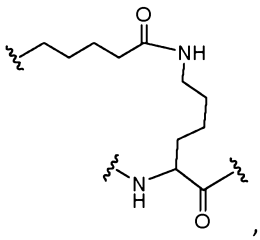
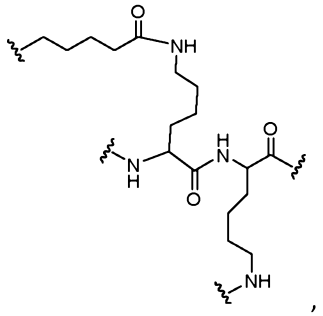
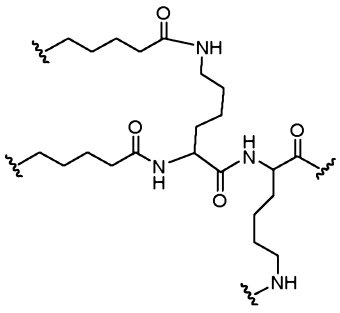
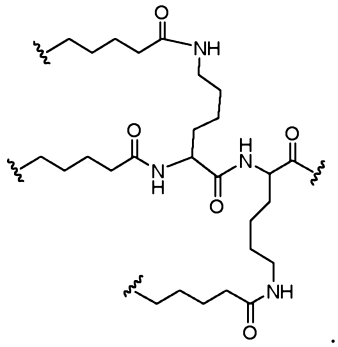

,

,

,


, or

;

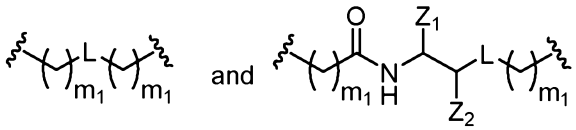
wherein each j is an integer from 1 to 3; and

wherein each n is an integer from 1 to 20.

Embodiment 1165. The conjugated antisense compound of any of claims 1124 to 1154 wherein the branching group comprises:


,

,

,

, or

.

Embodiment 1166. The conjugated antisense compound of claim 1124 to 1165, wherein each tether is selected from among:



wherein L is selected from a phosphorus linking group and a neutral linking group;

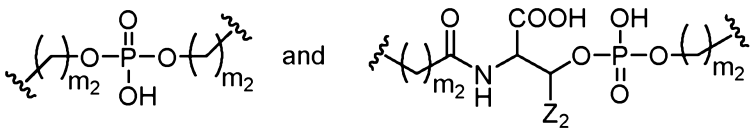
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

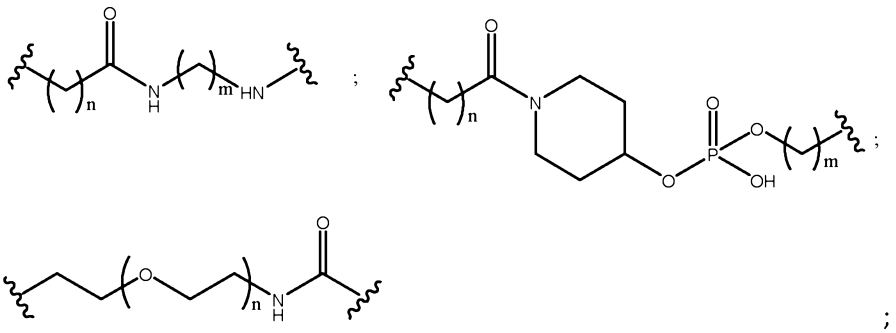
Embodiment 1167. The conjugated antisense compound of claim 1124 to 1165, wherein each tether is selected from among:



wherein Z_2 is H or CH_3; and

each m_2 is, independently, from 0 to 20 wherein at least one m_2 is greater than 0 for each tether.

Embodiment 1168. The conjugated antisense compound of claim 1124 to 1165, wherein each tether is selected from among:



wherein n is from 1 to 12; and

wherein m is from 1 to 12.

Embodiment 1169. The conjugated antisense compound of any of claims 1124 to 1165, wherein at least one tether comprises PEG.

Embodiment 1170. The conjugated antisense compound of any of claims 1124 to 1165, wherein at least one tether comprises an amide.

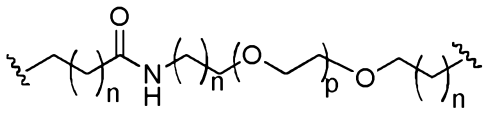
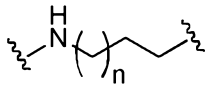
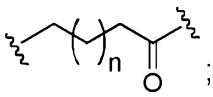
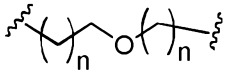
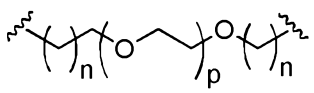
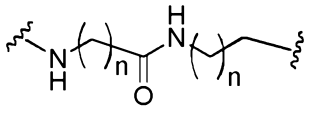
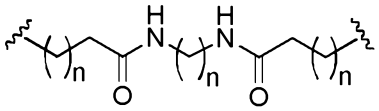
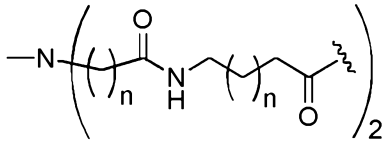
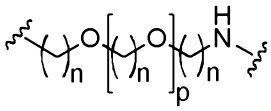
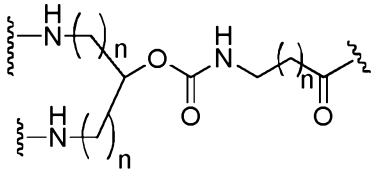
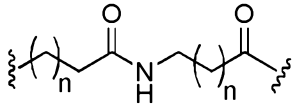
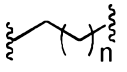
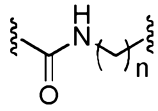
Embodiment 1171. The conjugated antisense compound of any of claims 1124 to 1165, wherein at least one tether comprises a polyamide.

Embodiment 1172. The conjugated antisense compound of any of claims 1124 to 1165, wherein at least one tether comprises an amine.

Embodiment 1173. The conjugated antisense compound of any of claims 1124 to 1165, wherein at least two tethers are different from one another.

Embodiment 1174. The conjugated antisense compound of any of claims 1124 to 1165, wherein all of the tethers are the same as one another.

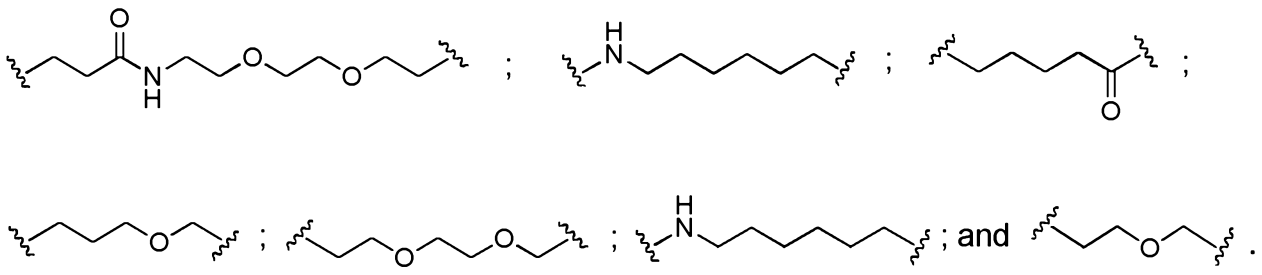
Embodiment 1175. The conjugated antisense compound of any of claims 1124 to 1165, wherein each tether is selected from among:


;

;

;

;

;

;

;

;

;

;

;

; and


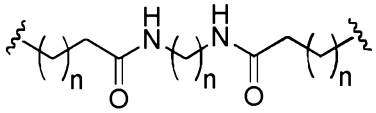
wherein each n is, independently, from 1 to 20; and

each p is from 1 to about 6.

Embodiment 1176. The conjugated antisense compound of any of claims 1124 to 1165, wherein each tether is selected from among:

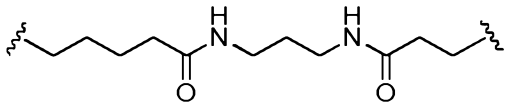


Embodiment 1177. The conjugated antisense compound of any of claims 1124 to 1165, wherein each tether has the following structure:



wherein each n is, independently, from 1 to 20.

Embodiment 1178. The conjugated antisense compound of any of claims 1124 to 1165, wherein each tether has the following structure:



Embodiment 1179. The conjugated antisense compound of any of claims 1124 to 1178, wherein the cell-targeting moiety comprises at least one ligand.

Embodiment 1180. The conjugated antisense compound of any of claims 1124 to 1178, wherein the cell-targeting moiety comprises one ligand.

Embodiment 1181. The conjugated antisense compound of any of claims 1124 to 1178, wherein the targeting moiety comprises two ligands.

Embodiment 1182. The conjugated antisense compound of any of claims 1124 to 1178, wherein the targeting moiety comprises three ligands.

Embodiment 1183. The conjugated antisense compound of any of claims 1179 to 1182, wherein each ligand is covalently attached to each tether.

Embodiment 1184. The conjugated antisense compound of any of claims 1179 to 1182, wherein at least one ligand is *N*-Acetylgalactosamine (GalNAc).

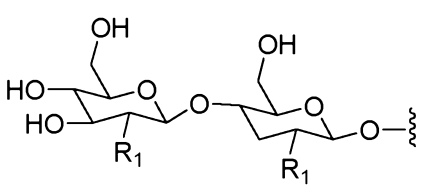
Embodiment 1185. The conjugated antisense compound of any of claims 1179 to 1182, wherein each ligand is N-Acetylgalactosamine (GalNAc).

Embodiment 1186. The conjugated antisense compound of any of claims 1179 to 1182, wherein the ligand is selected from among: a polysaccharide, modified polysaccharide, mannose, galactose, a mannose derivative, a galactose derivative, D-mannopyranose, L-Mannopyranose, D-Arabinose, L-Galactose, D-xylofuranose, L-xylofuranose, D-glucose, L-glucose, D-Galactose, L-Galactose, α-D-Mannofuranose, β-D-Mannofuranose, α-D-Mannopyranose, β-D-Mannopyranose, α-D-Glucopyranose, β-D-Glucopyranose, α-D-Glucofuranose, β-D-Glucofuranose, α-D-fructofuranose, α-D-fructopyranose, α-D-Galactopyranose, β -D-Galactopyranose, α-D-Galactofuranose, β -D-Galactofuranose, glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose, 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose, *N*-Glycoloyl-α-neuraminic acid, 5-thio-β-D-glucopyranose, methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside, 2,5-Anhydro-D-allononitrile, ribose, D-ribose, D-4-thioribose, L-ribose, L-4-thioribose.

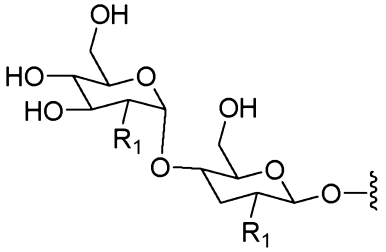
Embodiment 1187. The conjugated antisense compound of any of claims 1179 to 1182, wherein the ligand is galactose.

Embodiment 1188. The conjugated antisense compound of any of claims 1179 to 1182, wherein the ligand is mannose-6-phosphate.

Embodiment 1189. The conjugated antisense compound of any of claims 1179 to 1182, wherein each ligand is selected from among:

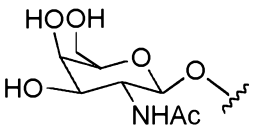


and

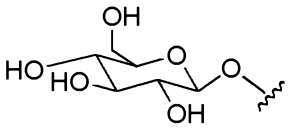


wherein each R_1 is selected from OH and NHCOOH.

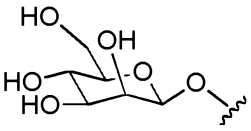
Embodiment 1190. The conjugated antisense compound of any of claims 1179 to 1182, wherein each ligand is selected from among:



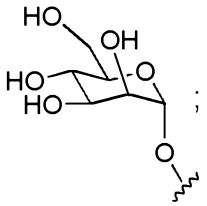
;



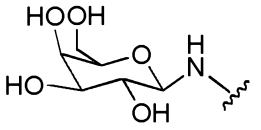
;



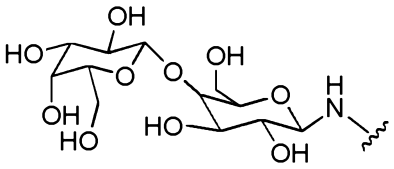
;



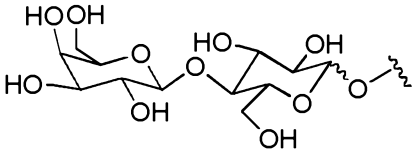
;



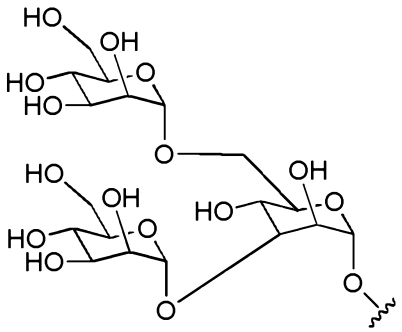
;



;

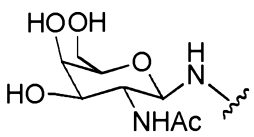


; and



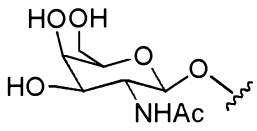
.

Embodiment 1191. The conjugated antisense compound of any of claims 1179 to 1182, wherein each ligand has the following structure:

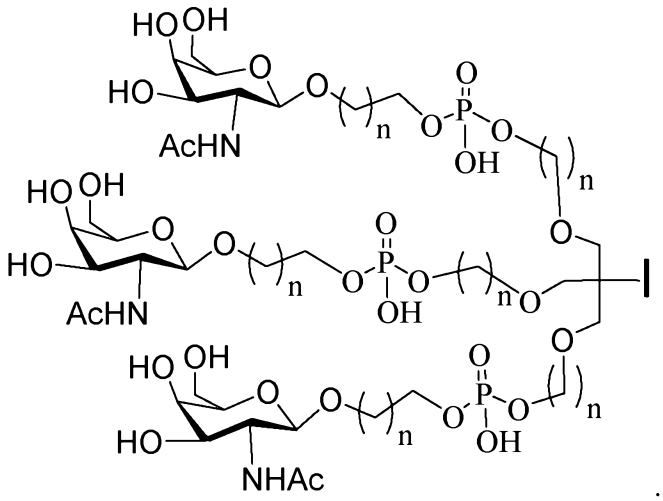


.

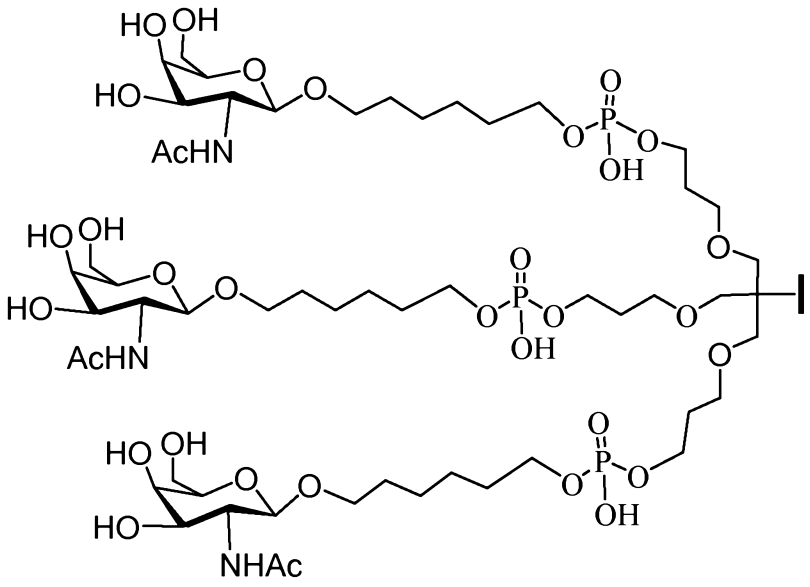
Embodiment 1192. The conjugated antisense compound of any of claims 1179 to 1182, wherein each ligand has the following structure:



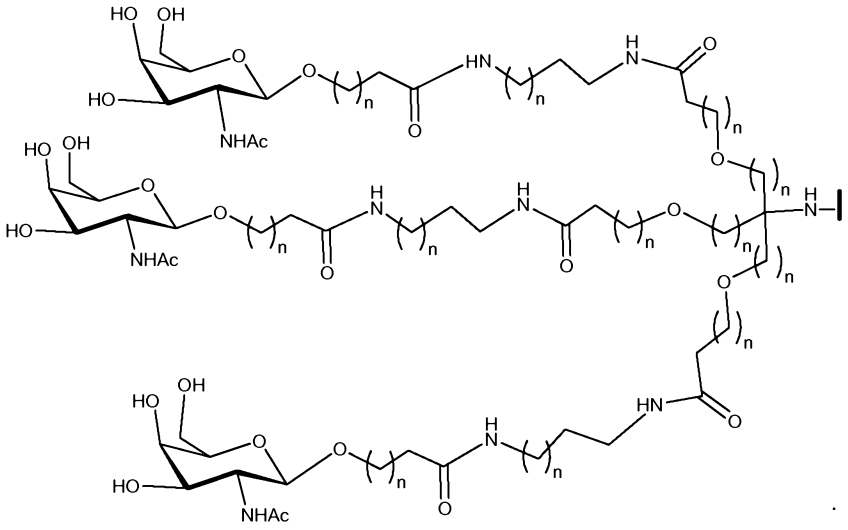
Embodiment 1193. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 1194. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:

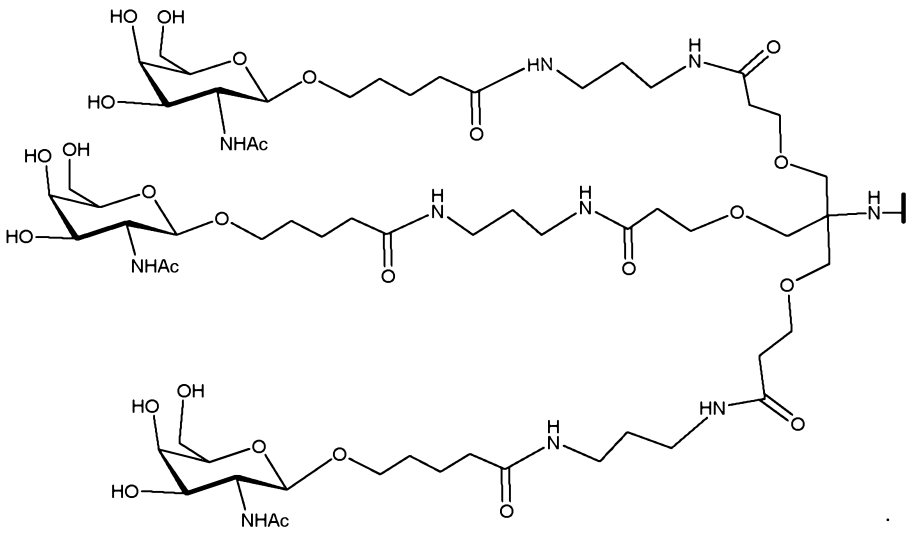


Embodiment 1195. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:

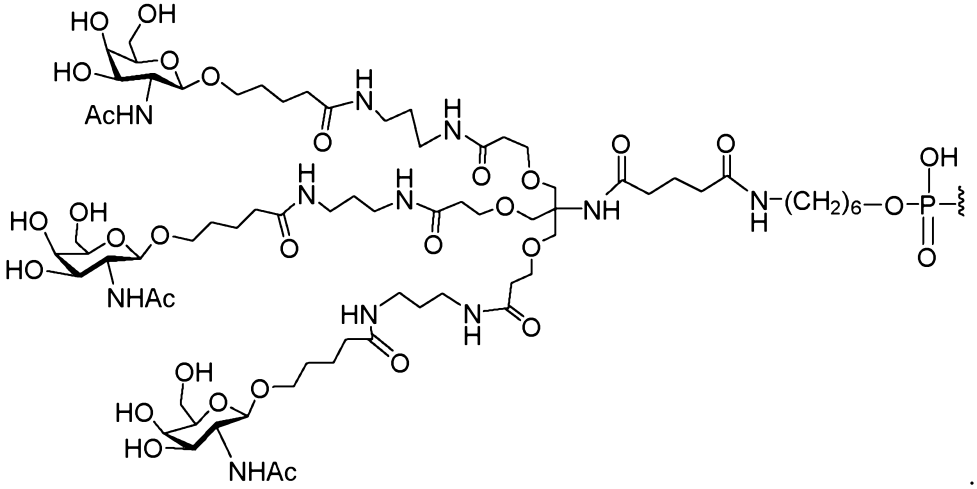


wherein each n is, independently, from 1 to 20.

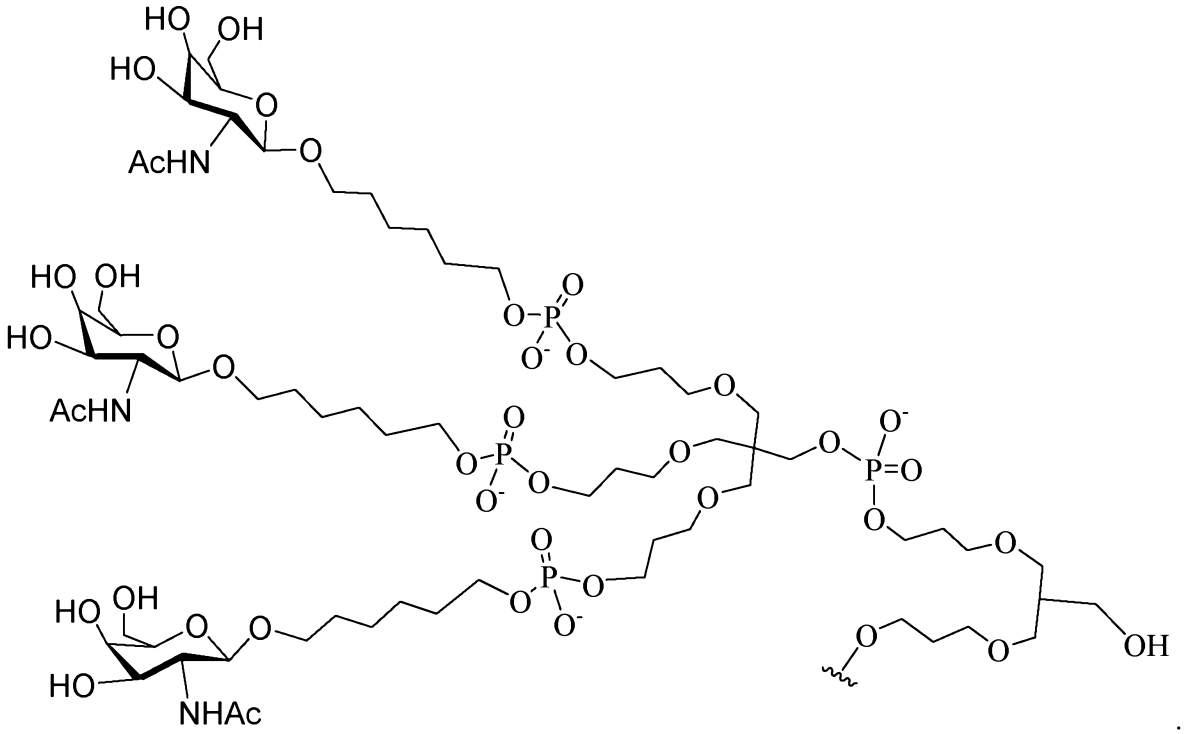
Embodiment 1196. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



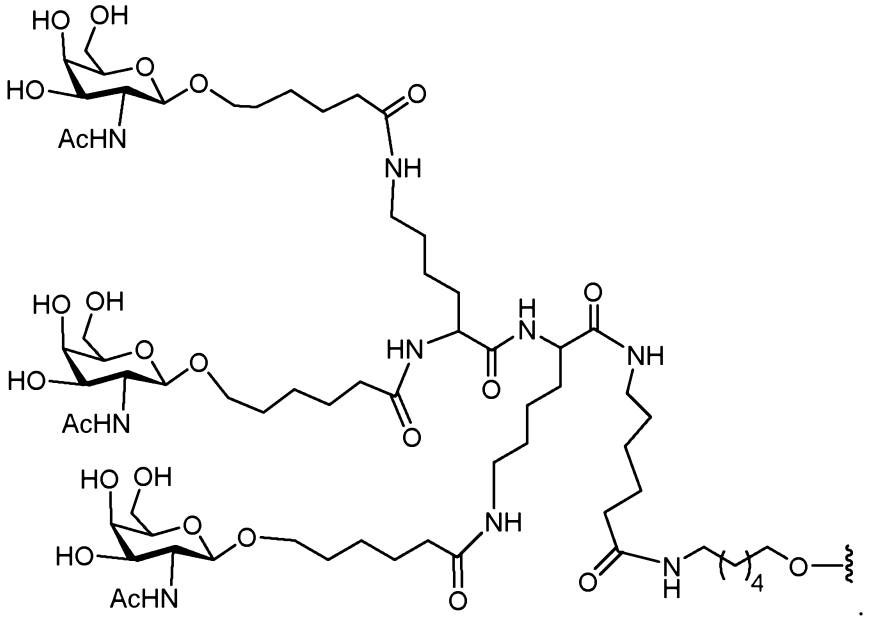
Embodiment 1197. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



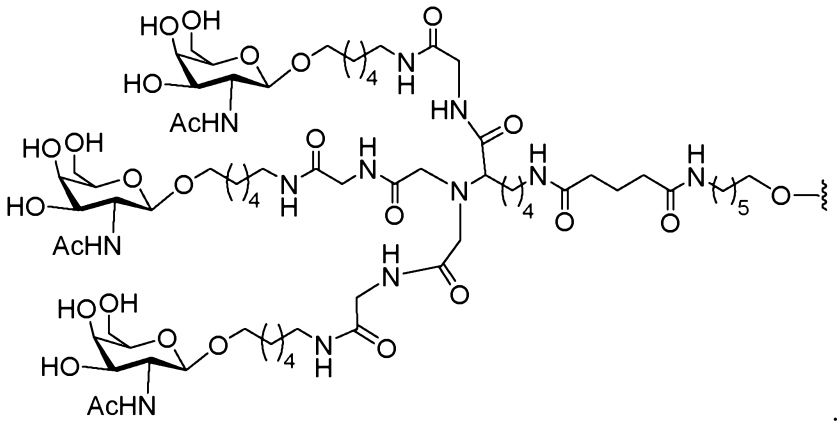
Embodiment 1198. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



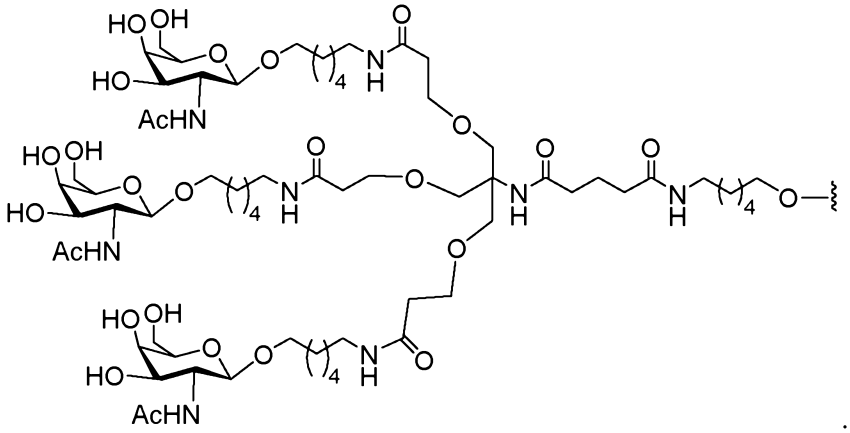
Embodiment 1199. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



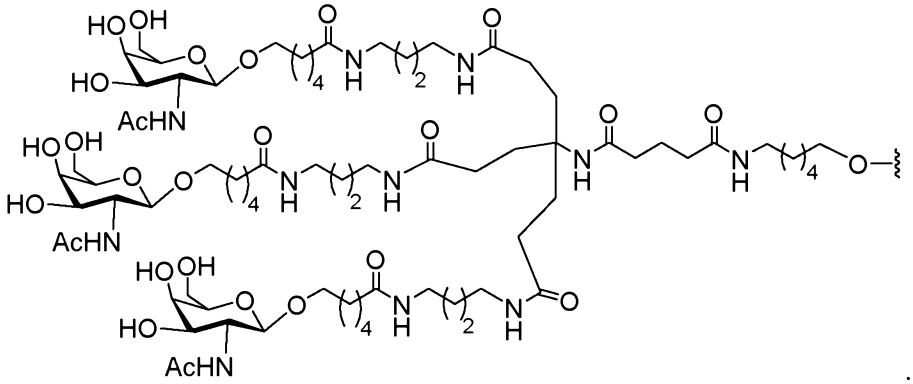
Embodiment 1200. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



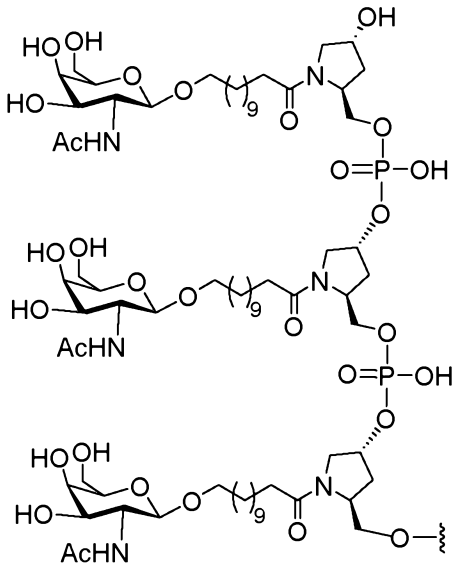
Embodiment 1201. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



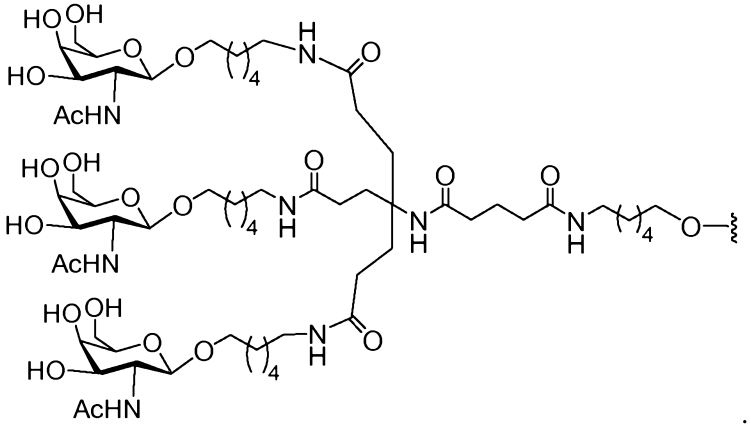
Embodiment 1202. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



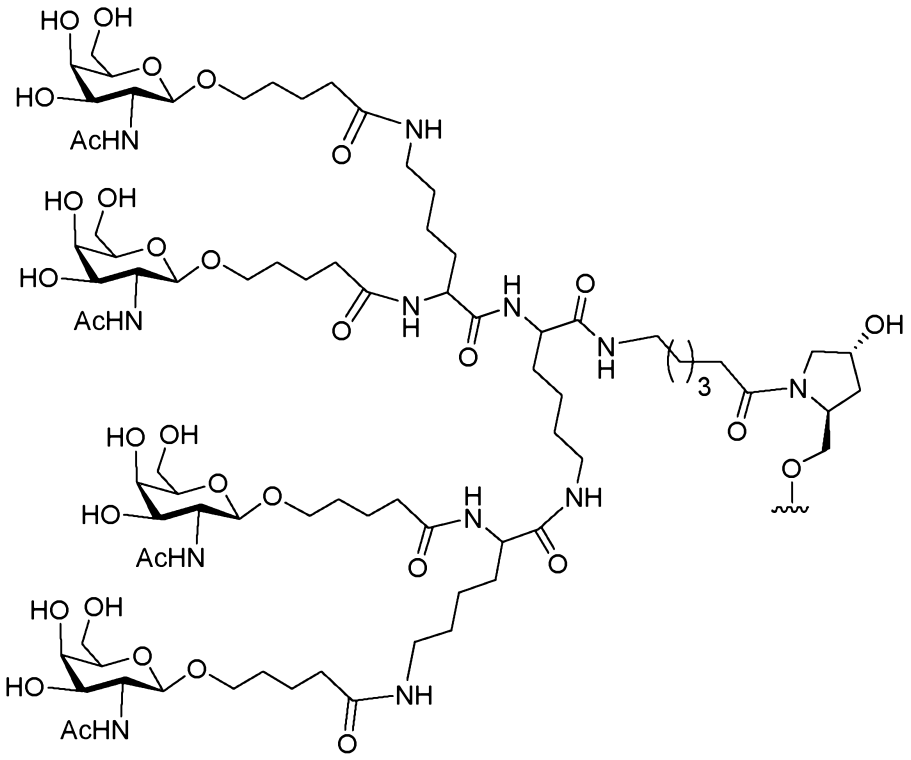
Embodiment 1203. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



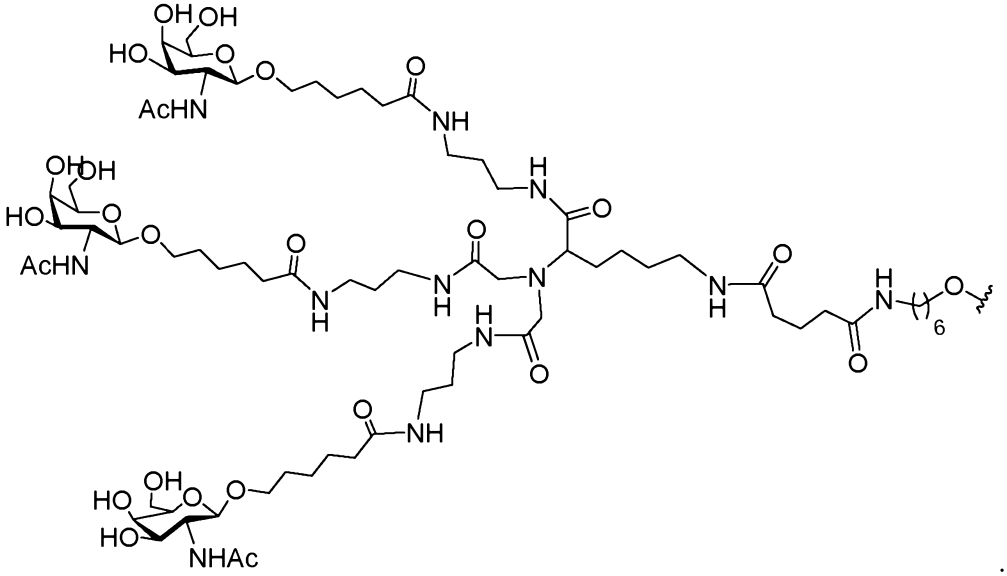
Embodiment 1204. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



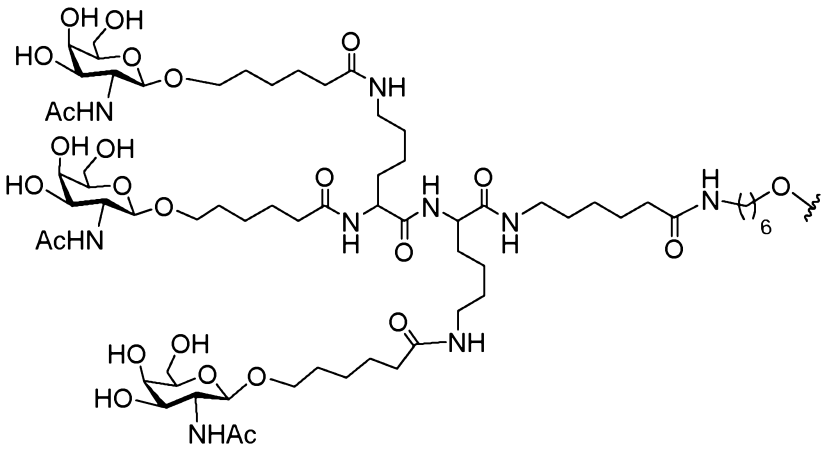
Embodiment 1205. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



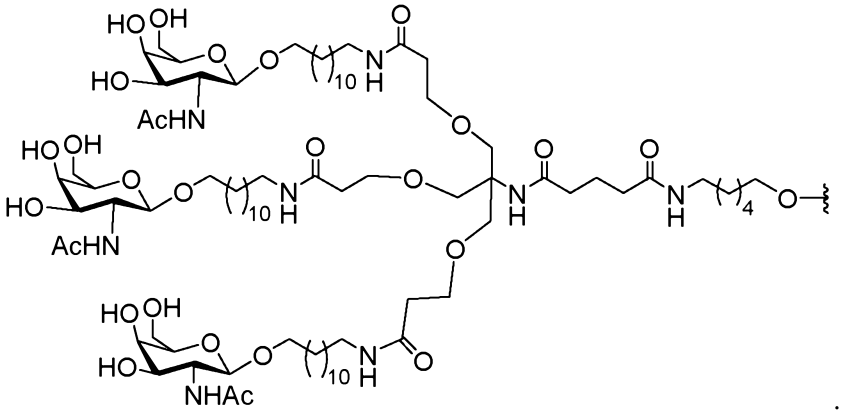
Embodiment 1206. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



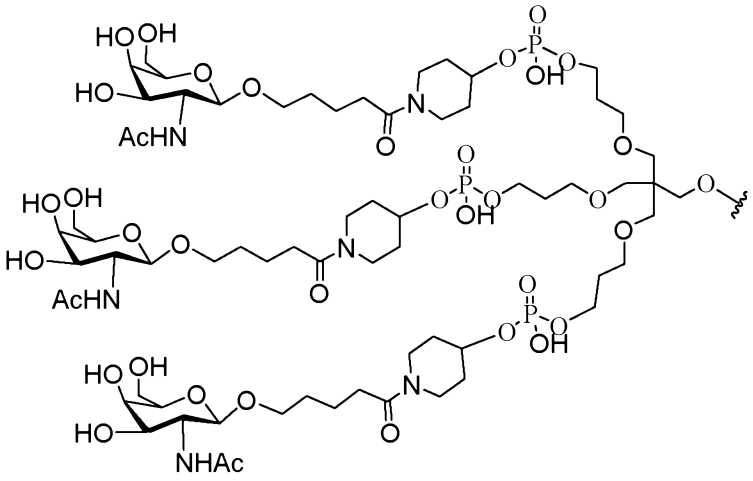
Embodiment 1207. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



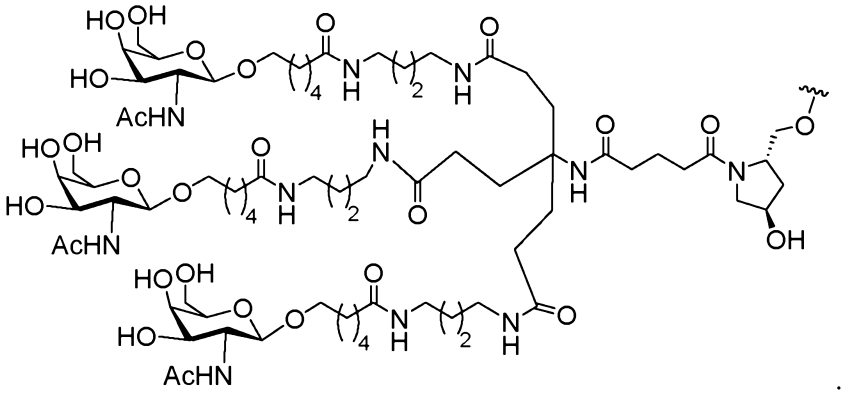
Embodiment 1208. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



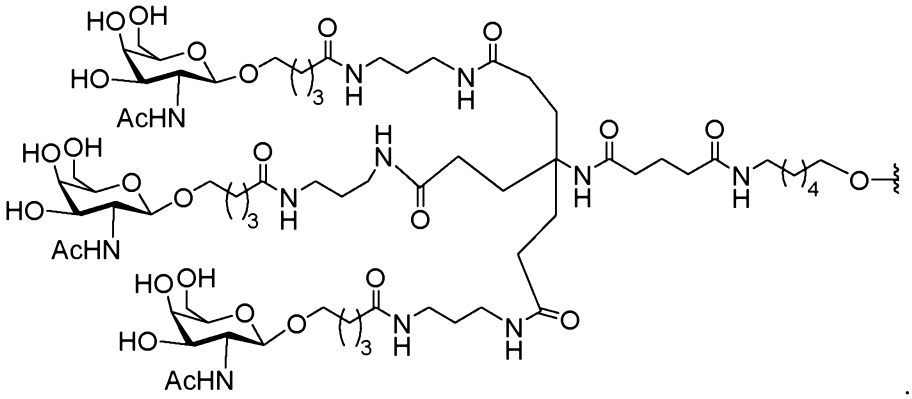
Embodiment 1209. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



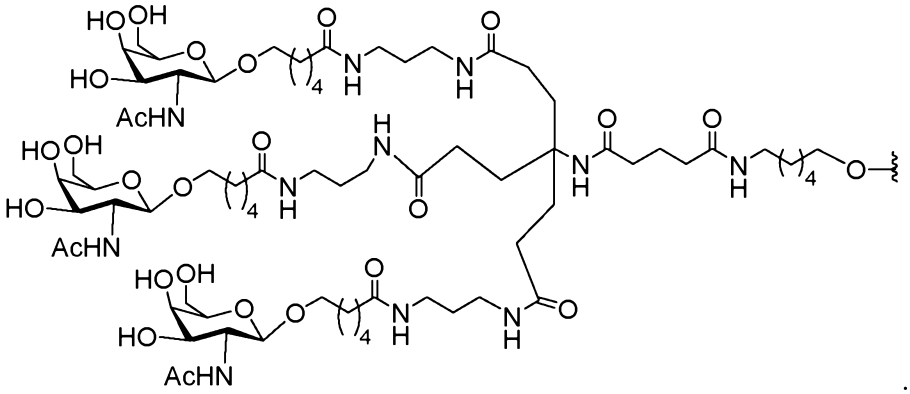
Embodiment 1210. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



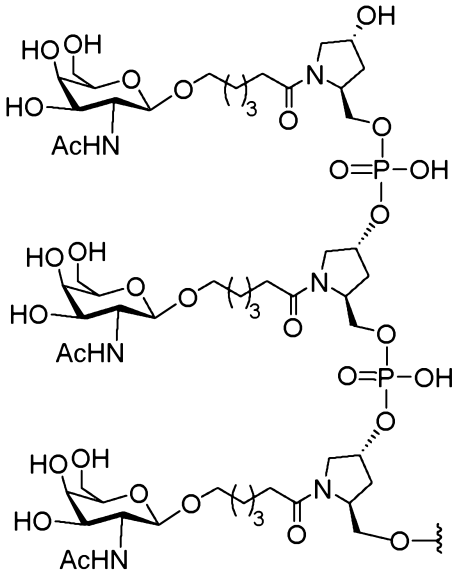
Embodiment 1211. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



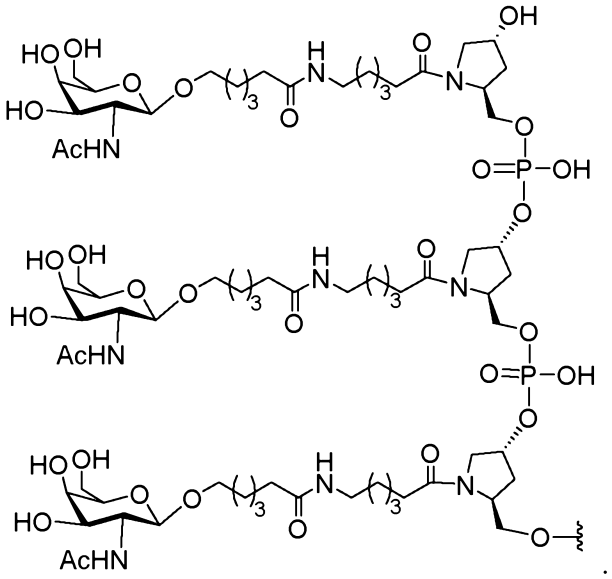
Embodiment 1212. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



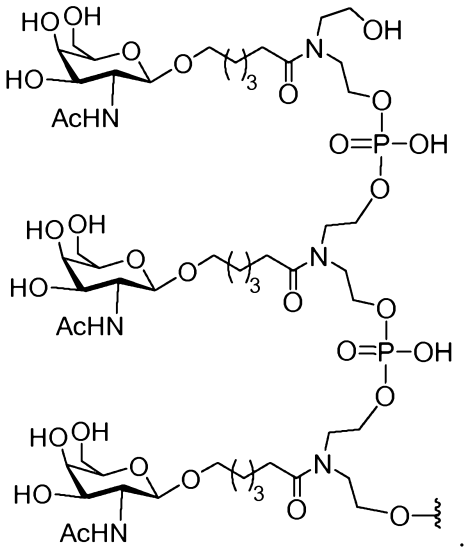
Embodiment 1213. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



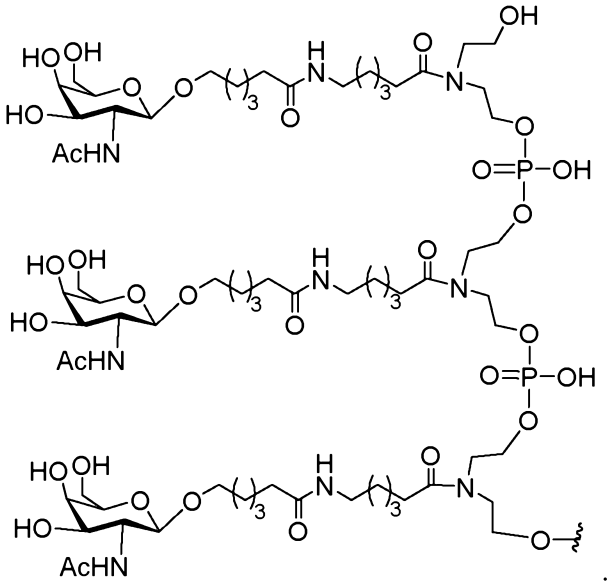
Embodiment 1214. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



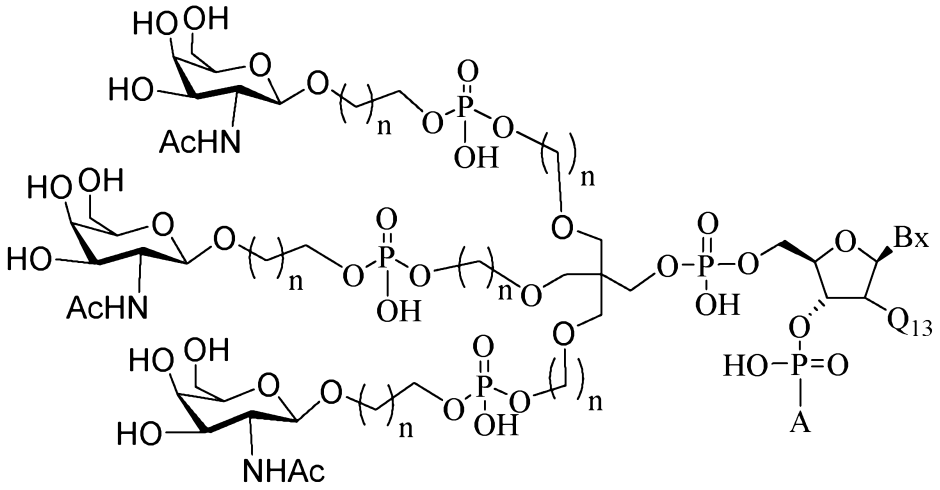
Embodiment 1215. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 1216. The conjugated antisense compound of any of claims 1124 to 1153, wherein the conjugate group comprises a cell-targeting moiety having the following structure:



Embodiment 1217. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:



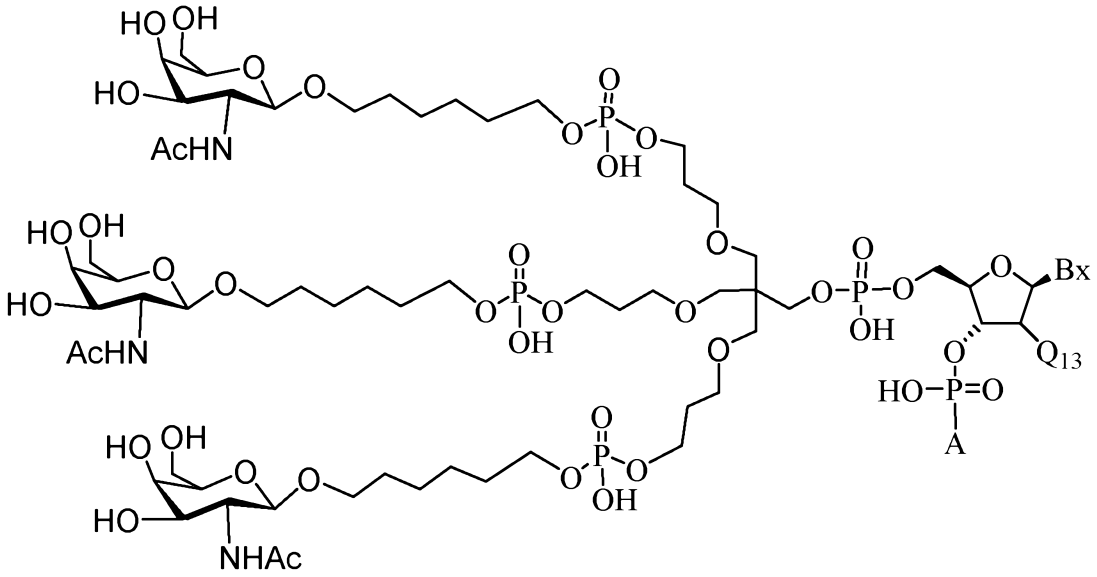
wherein each n is, independently, from 1 to 20;

Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1218. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:



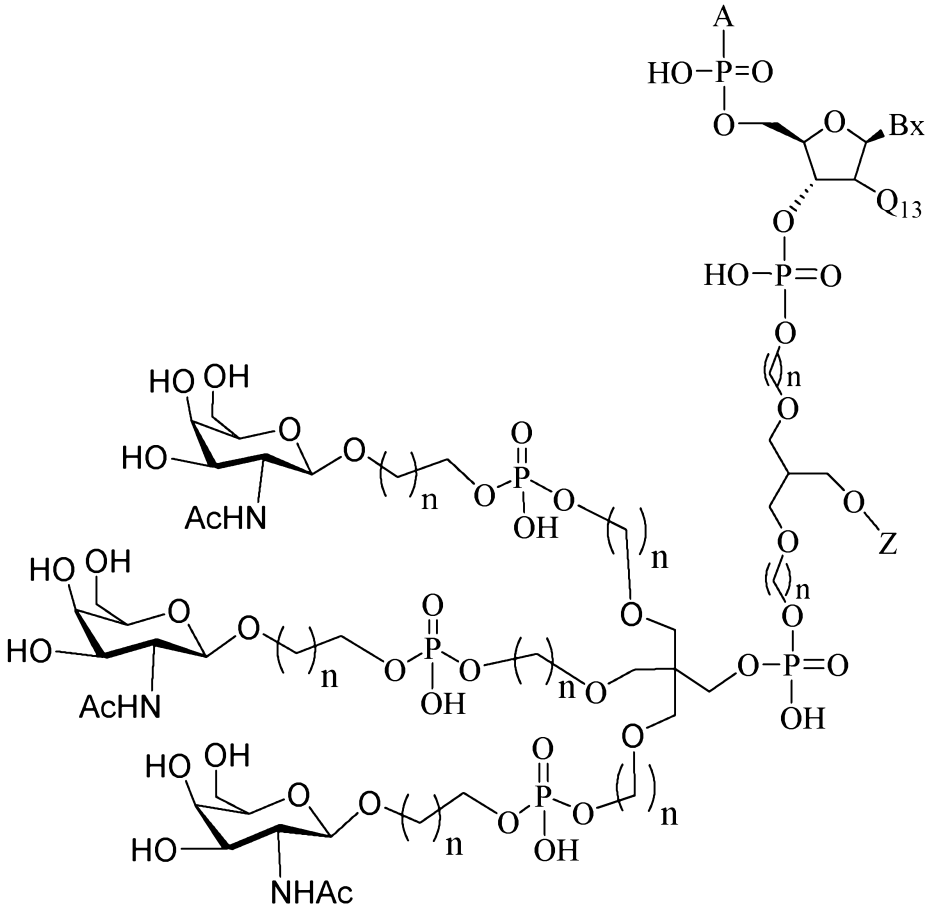
wherein each n is, independently, from 1 to 20;

Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1219. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:



wherein each n is, independently, from 1 to 20;

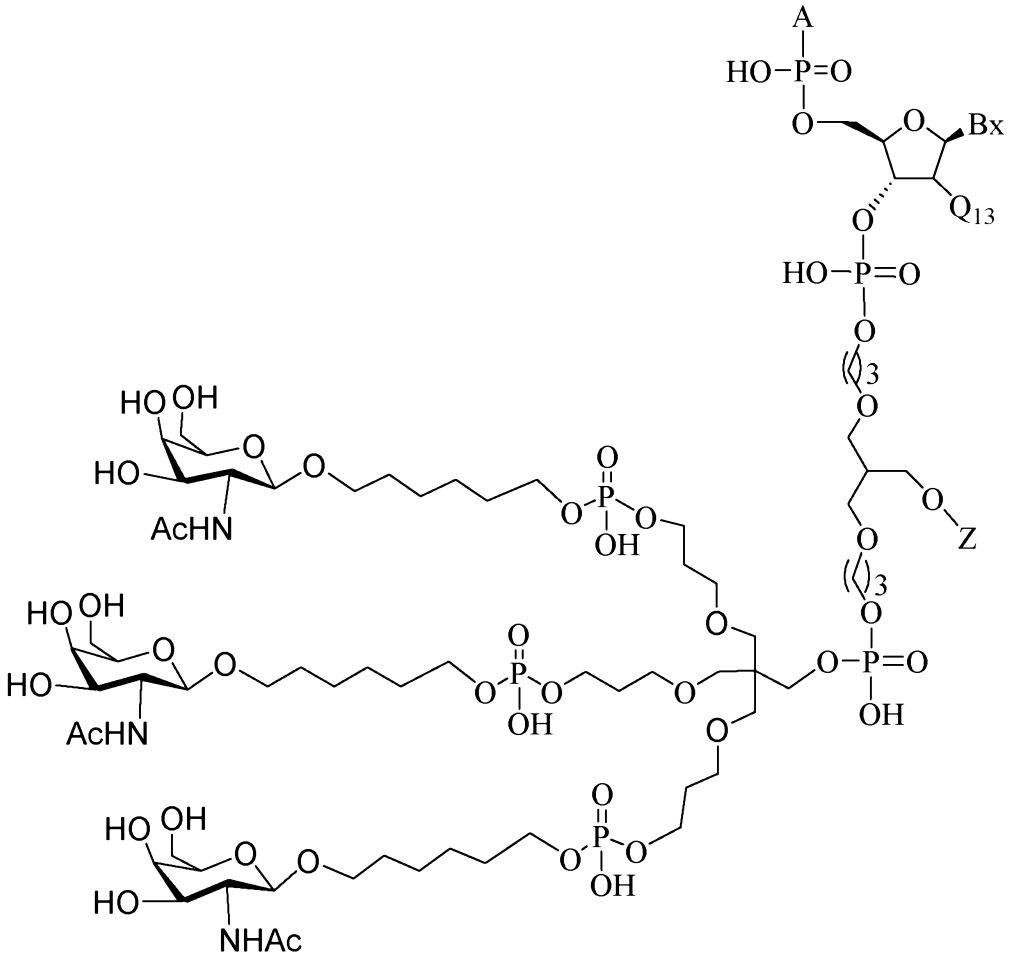
Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide;

Z is H or a linked solid support; and

Bx is a heterocyclic base moiety.

Embodiment 1220. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:



wherein each n is, independently, from 1 to 20;

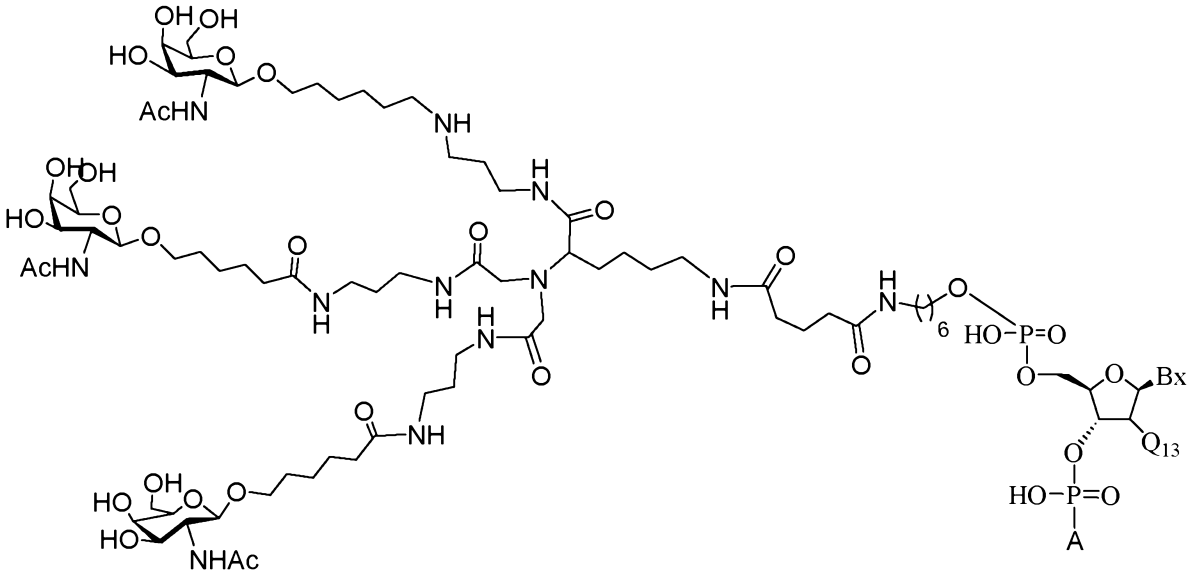
Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide;

Z is H or a linked solid support; and

Bx is a heterocyclic base moiety.

Embodiment 1221. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

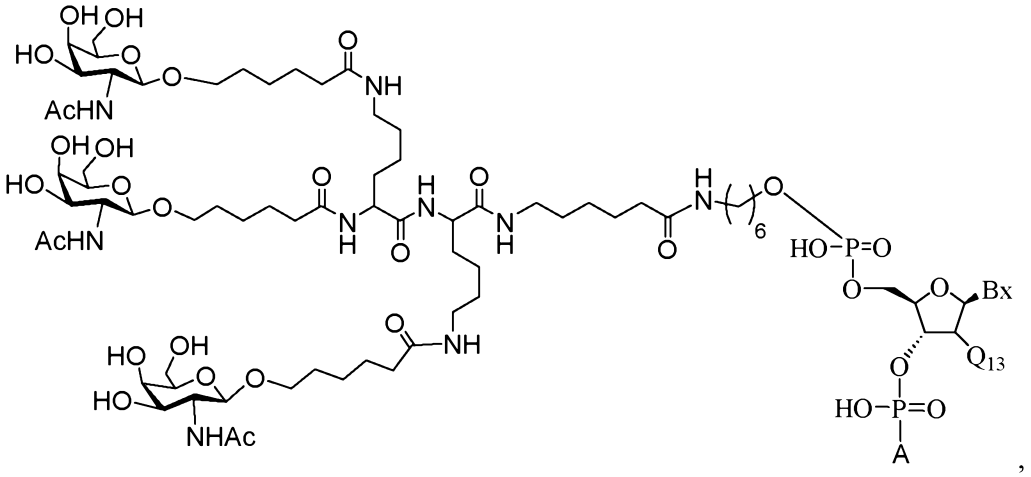


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide;and

Bx is a heterocyclic base moiety.

Embodiment 1222. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:



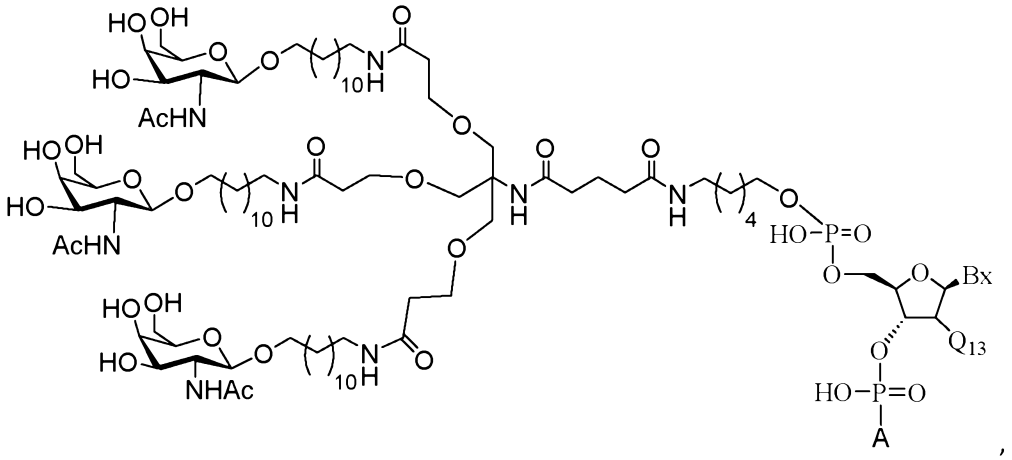
,

wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide;and

Bx is a heterocyclic base moiety.

Embodiment 1223. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

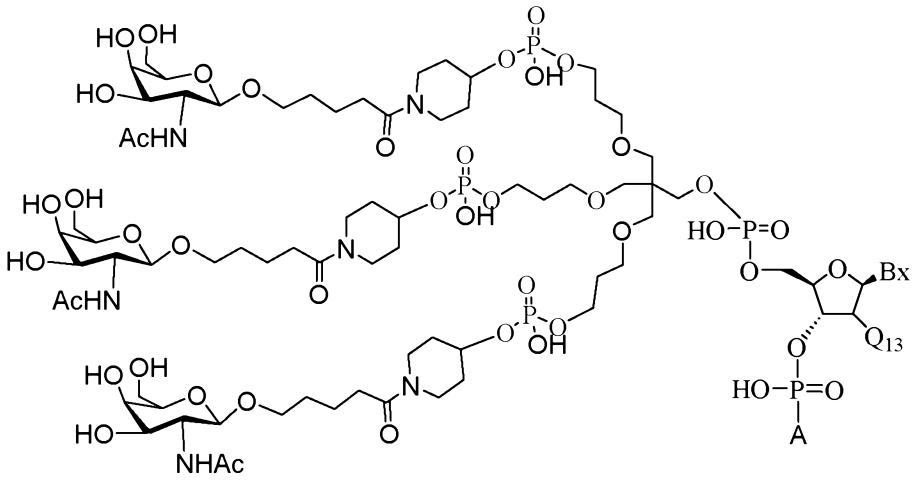


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1224. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

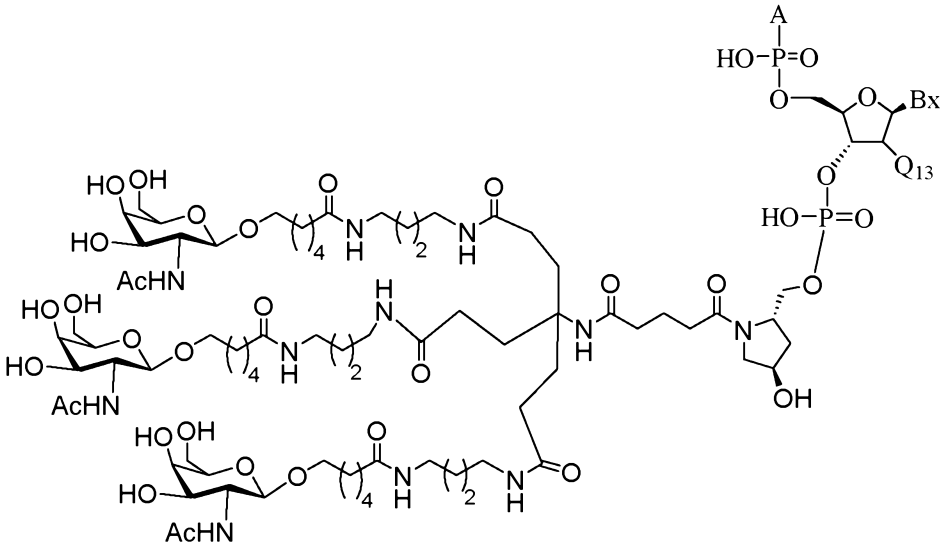


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1225. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

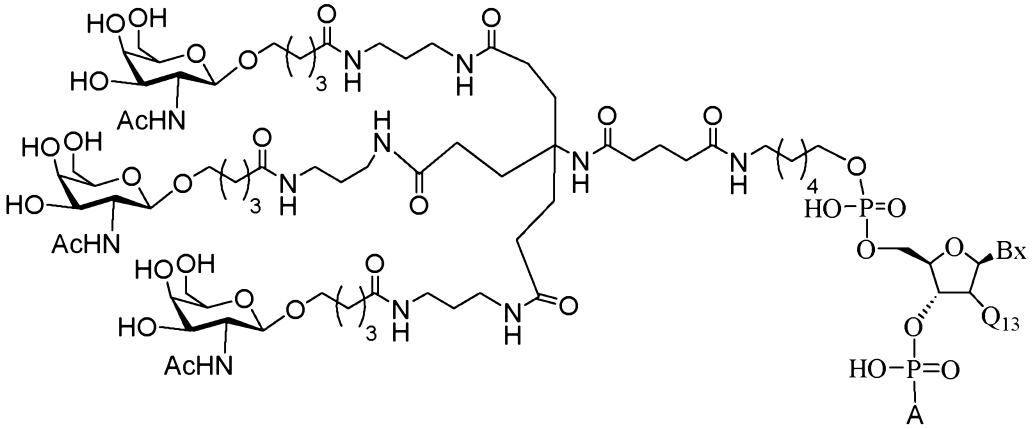


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1226. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

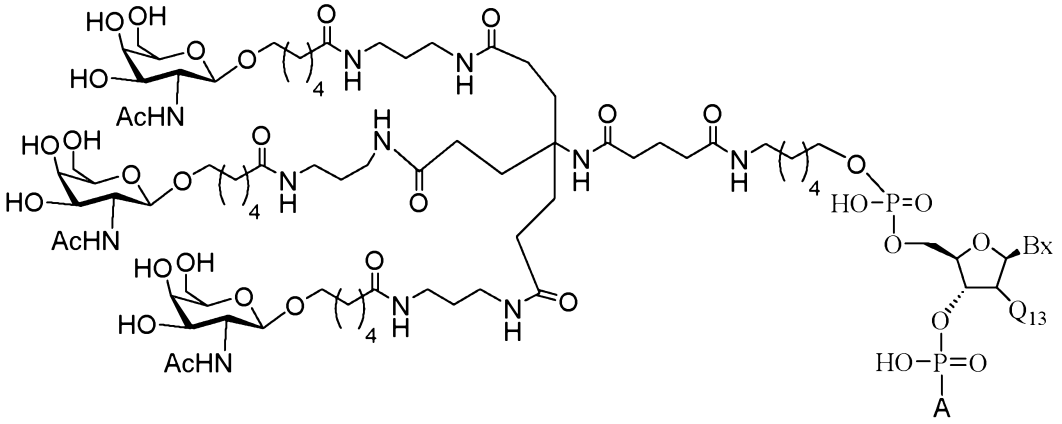


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1227. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

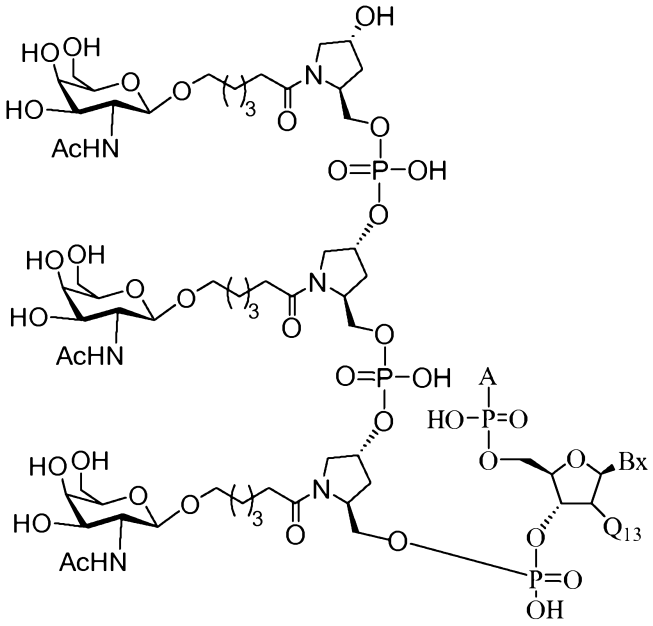


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1228. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

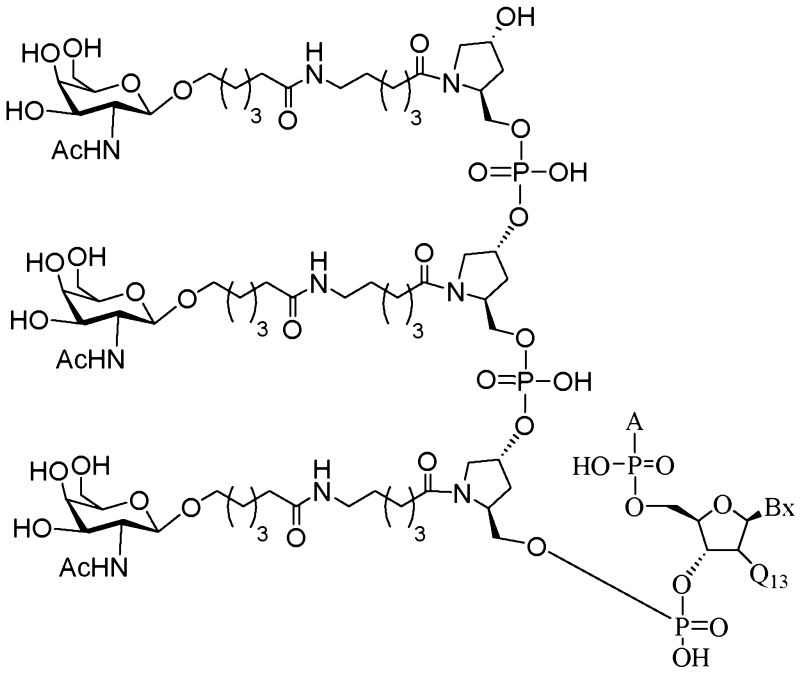


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1229. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

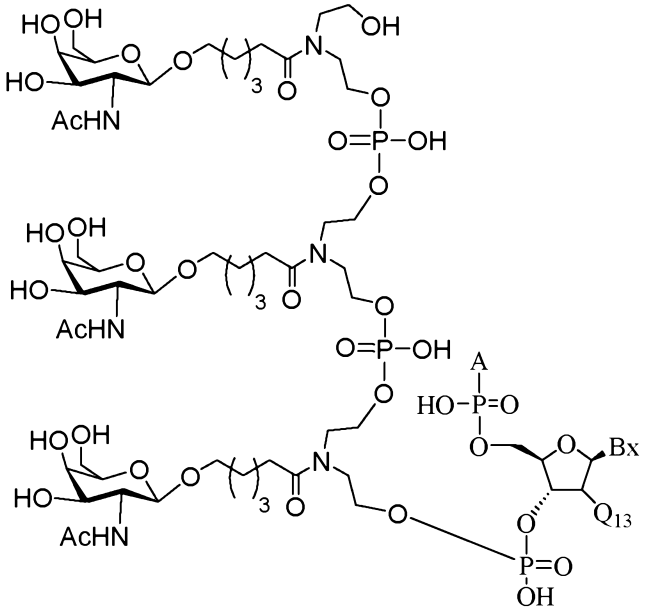


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1230. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:

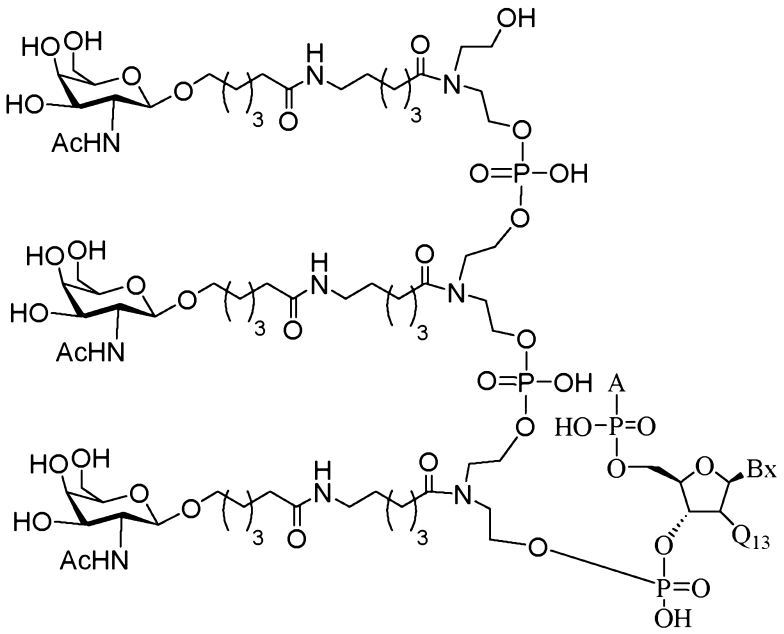


wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1231. The conjugated antisense compound of any of claims 1124 to 1131, wherein the conjugate group has the following structure:



wherein Q_{13} is H or $O(CH_2)_2$-OCH_3;

A is the antisense oligonucleotide; and

Bx is a heterocyclic base moiety.

Embodiment 1232. The compound of any of claims 1217 to 1231, wherein B_x is selected from among from adenine, guanine, thymine, uracil, or cytosine.

Embodiment 1233. The compound of any of claims1217 to 1231, wherein B_x is adenine.

Embodiment 1234. The compound of any of claims1217 to 1231, wherein B_x is thymine.

Embodiment 1235. The compound of any of claims 1217 to 1234, wherein Q_{13} is $O(CH_2)_2$-OCH_3.

Embodiment 1236. The compound of any of claims 1217 to 1234, wherein Q_{13} is H.

Embodiment 1237. A conjugated oligonucleotide comprising an oligonucleotide and a conjugate group, wherein the conjugate group is any conjugate group of any of claims 1098 to 1236.

Embodiment 1238. The conjugated oligonucleotide of claim 1237 wherein the oligonucleotide comprises at least one modified nucleoside.

Embodiment 1239. The conjugated oligonucleotide of claim 1237 wherein the at least one modified nucleoside comprises a modified base.

Embodiment 1240. The conjugated oligonucleotide of claim 1238 or 1239 wherein the at least one modified nucleoside comprises a sugar surrogate.

Embodiment 1241. The conjugated oligonucleotide of claim 1240 wherein the sugar surrogate is a tetrahydropyran.

Embodiment 1242. The conjugated oligonucleotide of any of claim 1241 wherein the tetrahydropyran is F-HNA.

Embodiment 1243. The conjugated oligonucleotide of any of claims 1238 to 1242 wherein the remainder of the oligonucleotide comprises at least one nucleoside comprising a modified sugar.

Embodiment 1244. The conjugated oligonucleotide of claim 1243 wherein the at least one modified nucleoside comprising a modified sugar is selected from a bicyclic nucleoside and a 2'-modified nucleoside.

Embodiment 1245. The conjugated oligonucleotide of claim 1244 wherein the at least one modified nucleoside is a bicyclic nucleoside.

Embodiment 1246. The conjugated oligonucleotide of claim 1245 wherein the bicyclic nucleoside is a (4'-CH_2-O-2') BNA nucleoside.

Embodiment 1247. The conjugated oligonucleotide of claim 1245 wherein the bicyclic nucleoside is a (4'-$(CH_2)_2$-O-2') BNA nucleoside.

Embodiment 1248. The conjugated oligonucleotide of claim 1245 wherein the bicyclic nucleoside is a (4'-$C(CH_3)$H-O-2') BNA nucleoside.

Embodiment 1249. The conjugated oligonucleotide of claim 1244 wherein the at least one modified nucleoside is a 2'-modifed nucleoside.

Embodiment 1250. The conjugated oligonucleotide of claim 1249 wherein the at least one 2'-modified nucleoside is selected from a 2'-F nucleoside, a 2'-OCH_3 nucleoside, and a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 1251. The conjugated oligonucleotide of claim 1250 wherein the at least one 2'-modified nucleoside is a 2'-F nucleoside.

Embodiment 1252. The conjugated oligonucleotide of claim 1250 wherein the at least one 2'-modified nucleoside is a 2'-OCH_3 nucleoside.

Embodiment 1253. The conjugated oligonucleotide of claim 1250 wherein the at least one 2'-modified nucleoside is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 1254. The conjugated oligonucleotide of any of claims 1237-1253 wherein the oligonucleotide comprises at least one unmodified nucleoside.

Embodiment 1255. The conjugated oligonucleotide of claim 1254 wherein the unmodified nucleoside is a ribonucleoside.

Embodiment 1256. The conjugated oligonucleotide of claim 1254 wherein the unmodified nucleoside is a deoxyribonucleoside.

Embodiment 1257. The conjugated oligonucleotide of any of claims 1237 to 1256 wherein the oligonucleotide comprises at least two modified nucleosides.

Embodiment 1258. The conjugated oligonucleotide of claim 1257 wherein the at least two modified nucleosides comprise the same modification.

Embodiment 1259. The conjugated oligonucleotide of claim 1257 wherein the at least two modified nucleosides comprise different modifications.

Embodiment 1260. The conjugated oligonucleotide of any of claims 1257 to 1259 wherein at least one of the at least two modified nucleosides comprises a sugar surrogate.

Embodiment 1261. The conjugated oligonucleotide of any of claims 1257 to 1260 wherein at least one of the at least two modified nucleosides comprises a 2'-modification.

Embodiment 1262. The conjugated oligonucleotide of claim 1261 wherein each of the at least two modified nucleosides is independently selected from 2'-F nucleosides, 2'-OCH_3 nucleosides and 2'-$O(CH_2)_2OCH_3$ nucleosides.

Embodiment 1263. The conjugated oligonucleotide of claim 1262 wherein each of the at least two modified nucleosides is a 2'-F nucleoside.

Embodiment 1264. The conjugated oligonucleotide of claim 1262 wherein each of the at least two modified nucleosides is a 2'-OCH_3 nucleosides.

Embodiment 1265. The conjugated oligonucleotide of claim 1262 wherein each of the at least two modified nucleosides is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 1266. The conjugated oligonucleotide of any of claims 1237 to 1265 wherein essentially every nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 1267. The conjugated oligonucleotide of any of claims 1237 to 1257 or 1260 to 1266 wherein every nucleoside of the oligonucleotide is a modified nucleoside.

Embodiment 1268. The conjugated oligonucleotide of any of claims 1237 to 1267 wherein the oligonucleotide is single-stranded.

Embodiment 1269. The conjugated oligonucleotide of any of claims 1237 to 1267 wherein the oligonucleotide is double-stranded.

Embodiment 1270. The conjugated oligonucleotide of any of claims 1237 to 1267, wherein the oligonucleotide is an antisense compound.

Embodiment 1271. The conjugated oligonucleotide of any of claims 1237 to 1267, wherein the oligonucleotide is a RISC based oligonucleotide.

Embodiment 1272. The conjugated oligonucleotide of any of claims 1237 to 1267, wherein the oligonucleotide activates the RISC pathway.

Embodiment 1273. The conjugated oligonucleotide of any of claims 1237 to 1267, wherein the oligonucleotide is an RNase H based antisense compound.

Embodiment 1274. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group is attached to the 5'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 1275. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group is attached to the 3'-terminal nucleoside of the antisense oligonucleotide.

Embodiment 1276. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group is attached to an internal nucleoside of the antisense oligonucleotide.

Embodiment 1277. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group increases uptake of the conjugated oligonucleotide compound into a hepatocyte relative to an unconjugated oligonucleotide compound.

Embodiment 1278. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group increases the uptake of the conjugated oligonucleotide compound into a liver cell relative to an unconjugated oligonucleotide compound.

Embodiment 1279. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group increases accumulation of the conjugated oligonucleotide compound in the liver relative to an unconjugated oligonucleotide compound.

Embodiment 1280. The conjugated oligonucleotide compound of any of claims 1237 to 1273, wherein the conjugate group decreases accumulation of the conjugated oligonucleotide compound in the kidneys relative to an unconjugated oligonucleotide compound.

Embodiment 1281. The conjugated oligonucleotide compound of claim 1237 to 1265 or 1268 to 1280, wherein the conjugated oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1282. The conjugated oligonucleotide compound of claim 1281, wherein the 5'-region consists of 2 linked 5'-region nucleosides.

Embodiment 1283. The conjugated oligonucleotide compound of claim 1281, wherein the 5'-region consists of 3 linked 5'-region nucleosides.

Embodiment 1284. The conjugated oligonucleotide compound of claim 1281, wherein the 5'-region consists of 4 linked 5'-region nucleosides.

Embodiment 1285. The conjugated oligonucleotide compound of claim 1281, wherein the 5'-region consists of 5 linked 5'-region nucleosides.

Embodiment 1286. The conjugated oligonucleotide compound of any of claims 1281-1285, wherein the 3'-region consists of 2 linked 3'-region nucleosides.

Embodiment 1287. The conjugated oligonucleotide compound of any of claims 1281-1285, wherein the 3'-region consists of 3 linked 3'-region nucleosides.

Embodiment 1288. The conjugated oligonucleotide compound of any of claims 1281-1285, wherein the 3'-region consists of 4 linked 3'-region nucleosides.

Embodiment 1289. The conjugated oligonucleotide compound of any of claims 1281-1285, wherein the 3'-region consists of 5 linked 3'-region nucleosides.

Embodiment 1290. The conjugated oligonucleotide compound of any of claims 1281-1289, wherein the central region consists of 5 linked central region nucleosides.

Embodiment 1291. The conjugated oligonucleotide compound of any of claims 1281-1289, wherein the central region consists of 6 linked central region nucleosides.

Embodiment 1292. The conjugated oligonucleotide compound of any of claims 1281-1289, wherein the central region consists of 7 linked central region nucleosides.

Embodiment 1293. The conjugated oligonucleotide compound of any of claims 1281-1289, wherein the central region consists of 8 linked central region nucleosides.

Embodiment 1294. The conjugated oligonucleotide compound of any of claims 1281-1289, wherein the central region consists of 9 linked central region nucleosides.

Embodiment 1295. The conjugated oligonucleotide compound of any of claims 1281-1289, wherein the central region consists of 10 linked central region nucleosides.

Embodiment 1296. The conjugated oligonucleotide compound of any of claims 1281-1295, wherein the conjugated oligonucleotide consists of 14 to 26 linked nucleosides.

Embodiment 1297. The conjugated oligonucleotide compound of any of claims 1281-1295, wherein the conjugated oligonucleotide consists of 15 to 25 linked nucleosides.

Embodiment 1298. The conjugated oligonucleotide compound of any of claims 1281-1295, wherein the conjugated oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1299. The conjugated oligonucleotide compound of any of claims 1281-1298, wherein each modified nucleoside independently comprises a 2'-substituted sugar moiety or a bicyclic sugar moiety.

Embodiment 1300. The conjugated oligonucleotide compound of claim 1299, wherein the at least one modified nucleoside comprises a 2'-substituted sugar moiety.

Embodiment 1301. The conjugated oligonucleotide compound of claim 1300, wherein each modified nucleoside comprising a 2'-substituted sugar moiety comprises a 2' substituent independently selected from among: halogen, optionally substituted allyl, optionally substituted amino, azido, optionally substituted SH, CN, OCN, CF3, OCF3, O, S, or N(Rm)-alkyl; O, S, or N(Rm)-alkenyl; O, S or N(Rm)-alkynyl; optionally substituted O-alkylenyl-O-alkyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted O-alkaryl, optionally substituted O-aralkyl, O(CH2)2SCH3, O-(CH2)2-O-N(Rm)(Rn) or O-CH2-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl;

wherein each optionally substituted group is optionally substituted with a substituent group independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

Embodiment 1302. The conjugated oligonucleotide compound of claim 1300, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-SCH_3, $O(CH_2)_2$-OCF_3, $O(CH_2)_3$-$N(R_1)(R_2)$, $O(CH_2)_2$-$ON(R_1)(R_2)$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_3)$-$(CH_2)_2$-$N(R_1)(R_2)$, and $O(CH_2)_2$-$N(R_3)$-$C(=NR_4)[N(R_1)(R_2)]$; wherein R_1, R_2, R_3 and R_4 are each, independently, H or C_1-C_6 alkyl.

Embodiment 1303. The conjugated oligonucleotide compound of claim 1300, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$.

Embodiment 1304. The conjugated oligonucleotide compound of claim 1300, wherein the at least one 2'-modified nucleoside comprises a 2'-MOE sugar moiety.

Embodiment 1305. The conjugated oligonucleotide compound of claim 1300, wherein the at least one 2'-modified nucleoside comprises a 2'-OMe sugar moiety.

Embodiment 1306. The conjugated oligonucleotide compound of claim 1300, wherein the at least one 2'-modified nucleoside comprises a 2'-F sugar moiety.

Embodiment 1307. The conjugated oligonucleotide compound of any of claims 1281-1298, wherein the conjugated oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 1308. The conjugated oligonucleotide compound of claim 1307, wherein the modified nucleoside comprises an F-HNA sugar moiety.

Embodiment 1309. The conjugated oligonucleotide compound of claim 1307, wherein the modified nucleoside comprises an HNA sugar moiety.

Embodiment 1310. The conjugated oligonucleotide compound of any of claims 1281-1298 wherein the conjugated oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 1311. The conjugated oligonucleotide compound of claim 1310, wherein the bicyclic sugar moiety is a cEt sugar moiety.

Embodiment 1312. The conjugated oligonucleotide compound of claim 1310, wherein bicyclic sugar moiety is an LNA sugar moiety.

Embodiment 1313. The conjugated oligonucleotide compound of any of claims 1237 to 1312, wherein the conjugated oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 1314. The conjugated oligonucleotide compound of claim 1238, wherein each internucleoside linkage of the conjugated oligonucleotide is a modified internucleoside linkage.

Embodiment 1315. The conjugated oligonucleotide compound of claim 1313, wherein the conjugated oligonucleotide comprises at least one modified linkage and at least one unmodified phosphodiester internucleoside linkage.

Embodiment 1316. The conjugated oligonucleotide compound of any of claims 1313 or 1315 wherein at least one modified internucleoside linkage is a phosphosphorothioate internucleoside linkage.

Embodiment 1317. The conjugated oligonucleotide compound of any of claims 1313 or 1315, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 1318. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 1319. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 1320. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 1321. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 1322. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 1323. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 1324. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 8 phosphodiester internucleoside linkages.

Embodiment 1325. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 9 phosphodiester internucleoside linkages.

Embodiment 1326. The conjugated oligonucleotide compound of any of claims 1313 or 1314, wherein the conjugated oligonucleotide comprises at least 10 phosphodiester internucleoside linkages.

Embodiment 1327. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 16 phosphorothioate internucleoside linkages.

Embodiment 1328. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 15 phosphorothioate internucleoside linkages.

Embodiment 1329. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 14 phosphorothioate internucleoside linkages.

Embodiment 1330. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 13 phosphorothioate internucleoside linkages.

Embodiment 1331. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 12 phosphorothioate internucleoside linkages.

Embodiment 1332. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 11 phosphorothioate internucleoside linkages.

Embodiment 1333. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 10 phosphorothioate internucleoside linkages.

Embodiment 1334. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 9 phosphorothioate internucleoside linkages.

Embodiment 1335. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 8 phosphorothioate internucleoside linkages.

Embodiment 1336. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 7 phosphorothioate internucleoside linkages.

Embodiment 1337. The conjugated oligonucleotide compound of any of claims 1313 or 1315 to 1326, wherein the conjugated oligonucleotide comprises fewer than 6 phosphorothioate internucleoside linkages.

Embodiment 1338. The conjugated oligonucleotide compound of any of claims 1237 to 1337, wherein each terminal internucleoside linkage of the conjugated oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 1339. The conjugated oligonucleotide compound of any of claims 1237 to 1314 or 1327 to 1338, wherein each internucleoside linkage linking two deoxynucleosides of the conjugated oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 1340. The conjugated oligonucleotide compound of any of claims 1237 to 1314 or 1327 to 1339, wherein each non-terminal internucleoside linkage linking two modified nucleosides of the conjugated oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 1341. The conjugated oligonucleotide compound of any of claims 1237 to 1314 or 1327 to 1340, wherein each non-terminal internucleoside linkage of the conjugated oligonucleotide that is 3' of a modified nucleoside is a phosphodiester internucleoside linkage.

Embodiment 1342. The conjugated oligonucleotide compound of any of claims 1237 to 1314 or 1327 to 1341, wherein each internucleoside linkage of the conjugated oligonucleotide that is 3' of a deoxynucleoside is a phosphorothioate internucleoside linkage.

Embodiment 1343. The conjugated oligonucleotide compound of any of claims 1237 to 1314 or 1327 to 1342 wherein the conjugated oligonucleotide has a chemical motif selected from among:

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$; and

$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each s is a phosphorothioate internucleoside linkage, and each y is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage, provided that at least one y is a phosphodiester internucleotide linkage.

Embodiment 1344. The conjugated oligonucleotide compound of any of claims 1237 to 1314 or 1327 to 1342, wherein the conjugated oligonucleotides has a chemical motif selected from among:

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$

$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$

$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$; and

$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each o is a phosphodiester internucleoside linkage, and each s is a phosphorothioate internucleoside linkage.

Embodiment 1345. The conjugated oligonucleotide compound of claim 1343 or 1344, wherein each M is independently selected from among: a 2'-MOE nucleoside and a bicyclic nucleoside.

Embodiment 1346. The conjugated oligonucleotide compound of claim 1345, wherein each M is independently selected from among a 2'-MOE nucleoside, a cEt nucleoside, and an LNA nucleoside.

Embodiment 1347. The conjugated oligonucleotide compound of claim 1345 or 1346, wherein each M is a 2'-MOE nucleoside.

Embodiment 1348. The conjugated oligonucleotide compound of claim 1345 or 1346, wherein each M is a cEt nucleoside.

Embodiment 1349. The conjugated oligonucleotide compound of claims 1345 or 1346, wherein each M is an LNA nucleoside.

Embodiment 1350. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 8 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1351. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 10 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1352. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 12 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1353. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 14 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1354. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 16 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1355. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide has a nucleobase sequence comprising an at least 18 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1356. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide is at least 90% complementary to a target nucleic acid.

Embodiment 1357. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide is at least 95% complementary to a target nucleic acid.

Embodiment 1358. The conjugated oligonucleotide compound of any of claims 1237 to 1349, wherein the conjugated oligonucleotide is 100% complementary to a target nucleic acid.

Embodiment 1359. The conjugated oligonucleotide compound of any of claims 1350 to 1358, wherein the target nucleic acid is a pre-mRNA.

Embodiment 1360. The conjugated oligonucleotide compound of any of claims 1350 to 1358, wherein the target nucleic acid is an mRNA.

Embodiment 1361. The conjugated oligonucleotide compound of any of claims 1350 to 1358, wherein the target nucleic acid is a micro RNA.

Embodiment 1362. The conjugated oligonucleotide compound of any of claims 1350 to 1358, wherein the target nucleic acid is expressed in the liver.

Embodiment 1363. The conjugated oligonucleotide compound of any of claims 1350 to 1358, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 1364. The conjugated oligonucleotide compound of any of claims 1350 to 1360, wherein the target nucleic encodes a protein selected from among: Alpha 1 antitrypsin, Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI, Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, SRB-1, and Transthyretin.

Embodiment 1365. The conjugated oligonucleotide compound of any of claims 1350 to 1361 wherein the target nucleic acid is a viral nucleic acid.

Embodiment 1366. The conjugated oligonucleotide compound of claim 1365, wherein the viral nucleic acid expressed in the liver.

Embodiment 1367. The conjugated oligonucleotide compound of claim 1366, wherein the target nucleic acid is a Hepatitis B viral nucleic acid.

Embodiment 1368. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NOs.: 17, 18, 19, 20, 21, 22, 23, or 24.

Embodiment 1369. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any one of SEQ ID NO.: 25, 26, 27, 28, 29, or 30.

Embodiment 1370. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 31.

Embodiment 1371. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 32.

Embodiment 1372. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 33.

Embodiment 1373. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 34.

Embodiment 1374. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 35, 36, 37, 38, 39, 40, 41, 42, or 43.

Embodiment 1375. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 44, 45, 46, 47, or 48.

Embodiment 1376. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 1377. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 60, 61, 62, 63, 64, 65, 66, or 67.

Embodiment 1378. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NO.: 69, 70, 71, or 72.

Embodiment 1379. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 73.

Embodiment 1380. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 74, 75, 76, 77, 78, 79, 80, or 81.

Embodiment 1381. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of SEQ ID NO.: 68.

Embodiment 1382. The conjugated oligonucleotide compound of any of claims 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 82-103, 111, or 113.

Embodiment 1383. The conjugated oligonucleotide compound of any of claims 1237 to 1382, wherein the conjugated oligonucleotide is an antisense oligonucleotide.

Embodiment 1384. A pharmaceutical composition comprising a compound or conjugated oligonucleotide according to any of claims 1098 to 1383 and a pharmaceutically acceptable carrier or diluent.

Embodiment 1385. The pharmaceutical composition of claim 1384 wherein the pharmaceutically acceptable carrier or diluent is selected from among sterile water and sterile saline.

Embodiment 1386. A method of reducing the amount or activity of a target nucleic acid in a cell, comprising contacting a cell with a compound or conjugated antisense compound of any of claims 1098 to 1383, or the pharmaceutical composition of claims 1384 to 1385.

Embodiment 1387. The method of claim 1386, wherein the cell is a liver cell.

Embodiment 1388. The method of claim 1386, wherein the cell is a hepatocyte.

Embodiment 1389. The method of any of claims 1386 to 1388 wherein the cell is in vitro.

Embodiment 1390. The method of any of claims 1386 to 1388, wherein the cell is in an animal.

Embodiment 1391. The method of claim 1060 wherein the animal is a mouse.

Embodiment 1392. The method of claim 1060 wherein the animal is a human.

Embodiment 1393. A method of treating a disease or condition in an animal comprising administering the pharmaceutical composition of claim 1384 or 1386 to the animal and thereby treating the disease or condition in the animal.

Embodiment 1394. The method of claim 1393 wherein the animal is a mouse.

Embodiment 1395. The method of claim 1393 wherein the animal is a human.

Embodiment 1396. The method of any of claims 1393 to 1395, wherein the disease or condition is a liver disease or condition.

Embodiment 1397. The method of any of claims 1393 to 1395 wherein the administration is parenteral.

Embodiment 1398. The method claim 1397 wherein the administration is by subcutaneous injection.

Embodiment 1399. The method of claim 1397 wherein the administration is by intravenous injection.

Embodiment 1400. The method of claim 1397 wherein the administration is by intramuscular injection.

Embodiment 1401. The method of any of claims 1393 to 1400 wherein the conjugated oligonucleotide is provided at a dose of 1-10 mg/kg.

Embodiment 1402. The method of any of claims 1393 to 1400 wherein the conjugated oligonucleotide is provided at a dose of less than 1 mg/kg.

Embodiment 1403. The method of any of claims 1393 to 1400 wherein the conjugated oligonucleotide is provided at a dose of greater than 10 mg/kg.

Embodiment 1404. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided for a dosing period of at least 2 months.

Embodiment 1405. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided for a dosing period of at least 4 months.

Embodiment 1406. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided for a dosing period of at least 6 months.

Embodiment 1407. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every week.

Embodiment 1408. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every two weeks.

Embodiment 1409. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of about one dose every three weeks.

Embodiment 1410. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every four weeks.

Embodiment 1411. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every five weeks.

Embodiment 1412. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every six weeks.

Embodiment 1413. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every seven weeks.

Embodiment 1414. The method of any of claims 1393 to 1403 wherein the conjugated oligonucleotide is provided at a dosing frequency of one dose every eight weeks.

Embodiment 1415. A conjugated antisense compound comprising: an antisense oligonucleotide comprising 12-30 linked nucleosides, and a conjugate group, wherein the conjugate group comprises at least one cell-targeting moiety.

Embodiment 1416. A method of reducing the activity or amount of an Apolipoprotein C-III protein in a cell, comprising contacting a cell with at least one conjugated antisense compound of any of claims 1098 to 1385; and thereby reducing the activity or amount of the Apolipoprotein C-III protein in the cell.

Embodiment 1417. A method of decreasing total cholesterol, comprising contacting a cell with at least one compound of any of claims 1098 to 1385; and thereby decreasing total cholesterol.

Embodiment 1418. A method of decreasing triglycerides, comprising contacting a cell with at least one compound of any of claims 1098 to 1385; and thereby decreasing triglycerides.

Embodiment 1419. A method of lowering LDL, comprising contacting a cell with at least one compound of any of claims 1098 to 1385; and thereby lowering LDL.

Embodiment 1420. A method of increasing HDL, comprising contacting a cell with at least one compound of any of claims 1098 to 1385; and thereby increasing HDL.

Embodiment 1421. The method of any of claims 1416 to 1420, wherein the cell is in vitro.

Embodiment 1422. The method of any of claims 1416 to 1420, wherein the cell is in an animal.

Embodiment 1423. The method of any of claims 1416 to 1420, wherein the animal is a human.

Embodiment 1424. The compound or conjugated oligonucleotide of any of claims 1-1385 or a prodrug thereof.

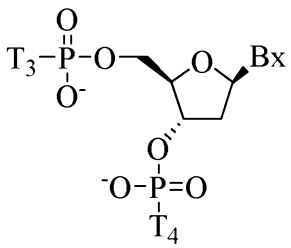
Embodiment 1425. A method of manufacturing an antisense oligonucleotide of any of claims 1-1385.

Embodiment 1426. A method of preparing an antisense oligonucleotide of any of claims 1-1385.

Embodiment 1427. A process for manufacturing a conjugated antisense compound of any one of claims 1-1385, wherein the method includes formulating the conjugated antisense compound for human use, performing chromatogram analysis of the formulated conjugated antisense compound, and packaging the conjugated antisense compound ready for sale.

Embodiment 1428. The conjugated oligonucleotide compound of any of embodiments 1237 to 1360, wherein the conjugated oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs.: 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, or 127.

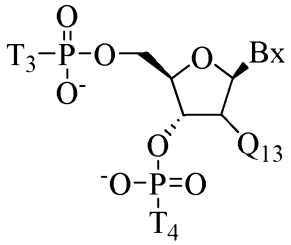
Embodiment 1429. A compound having the formula (V):



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, or GalNAc-23a.

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; and wherein Bx is a heterocyclic base moiety.

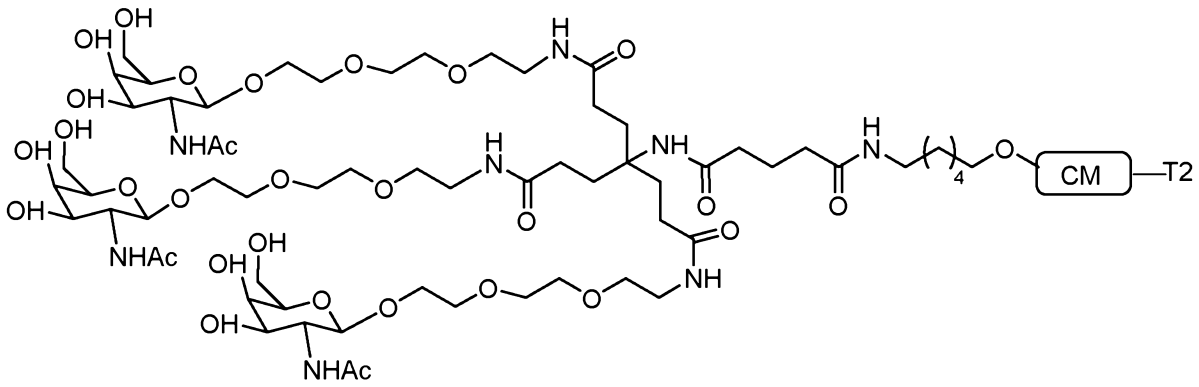
Embodiment 1430. A compound having the formula (Va):



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, or $GalNAc_3$-23a.

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety; and wherein Q_{13} is selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$.

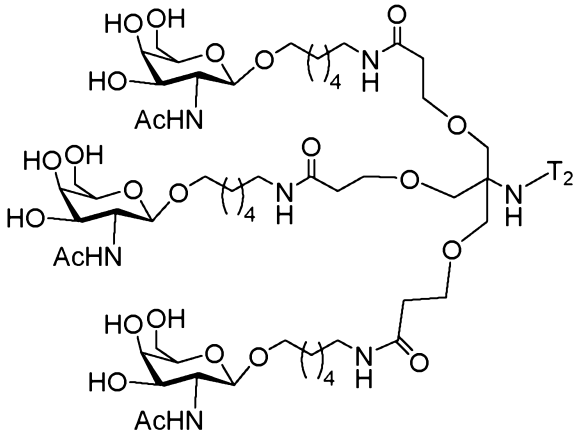
Embodiment 1431. A compound having the formula (XXV):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1432. A compound having the formula (XXVI):

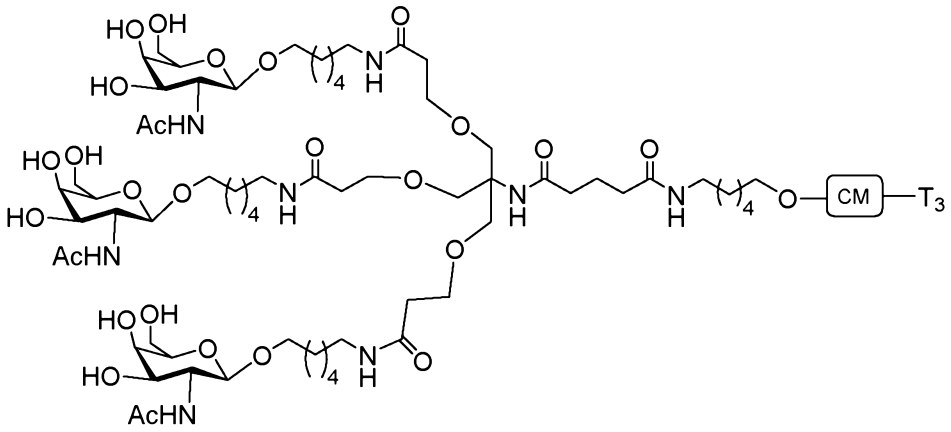


(XXVI)

wherein:

T_2 comprises a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1433. A compound having the formula (XXVII):

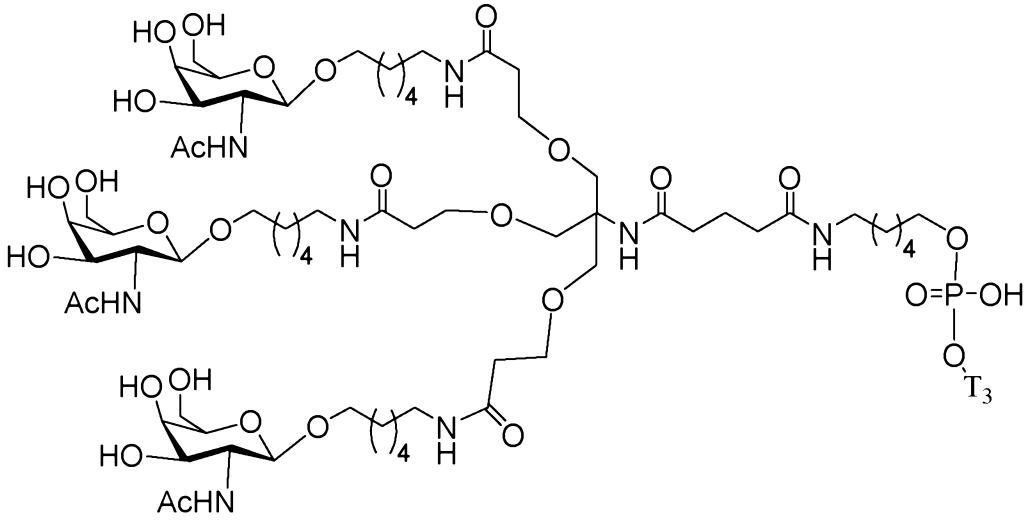


(XXVII)

wherein:

CM represents a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1434. A compound having the formula (XXVIII):

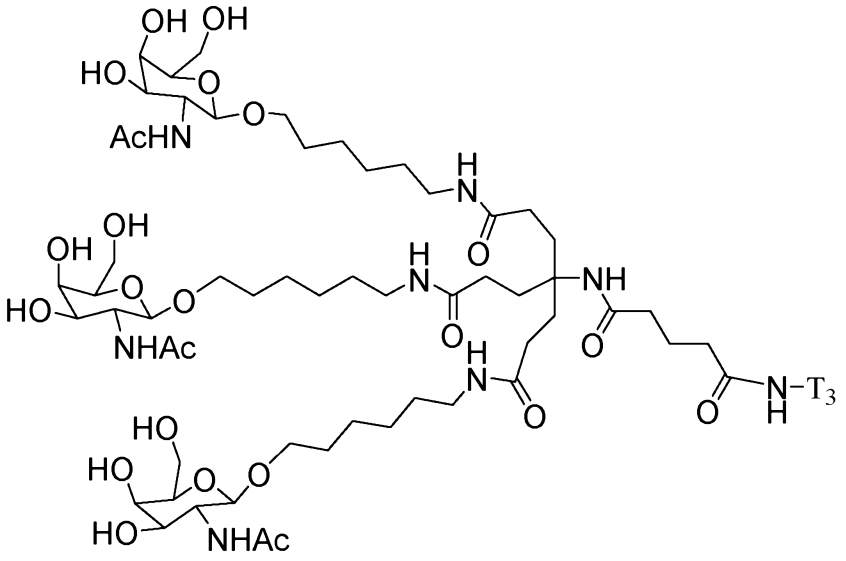


(XXVIII)

Wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1435. A compound having the formula (XXIX):

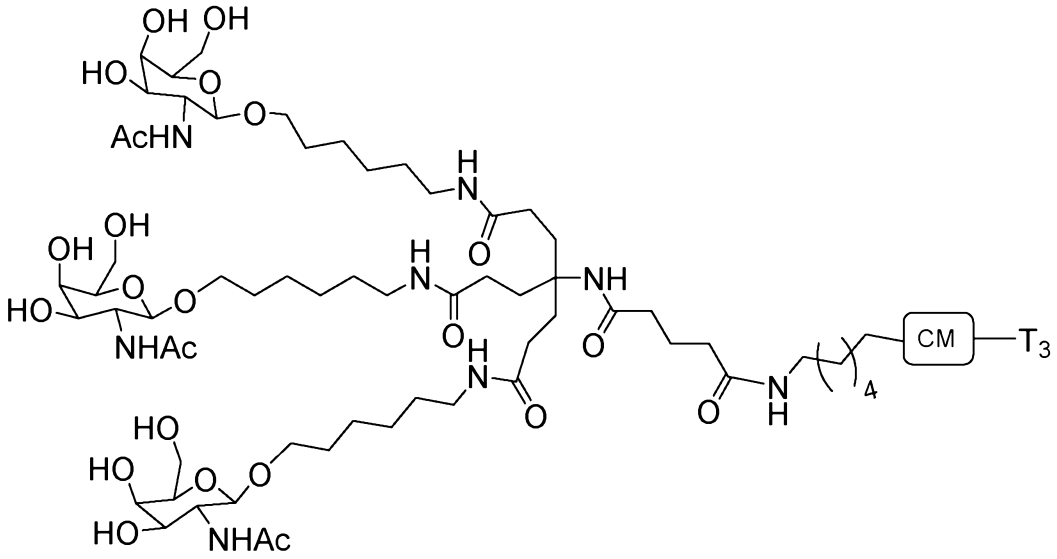


(XXIX)

wherein:

T_3 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1436. A compound having the formula (XXX):

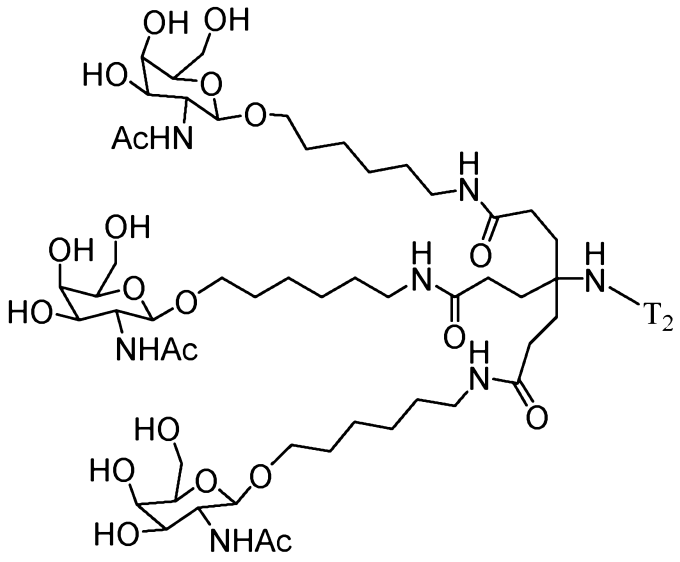


(XXX)

wherein:

CM represents a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1437. A compound having formula (XXXI):

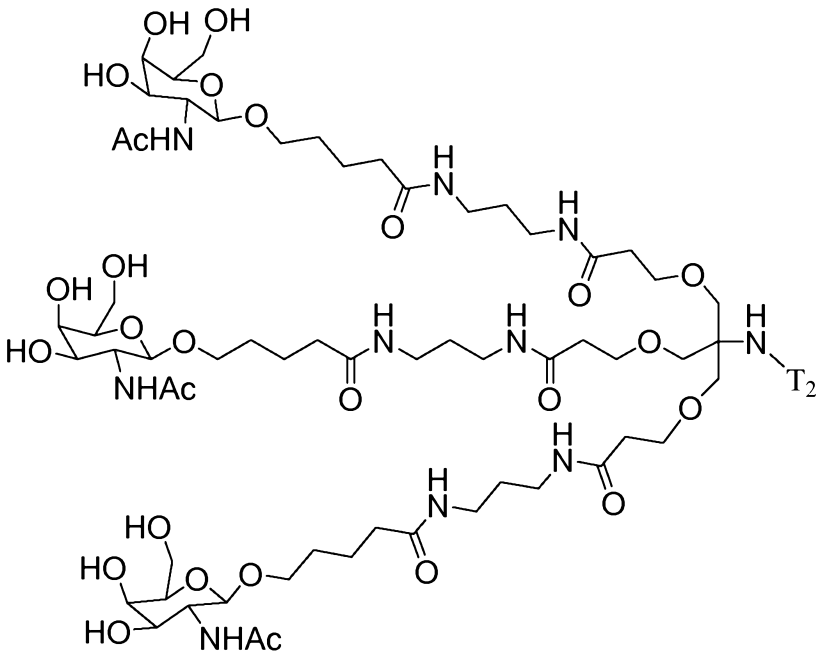


(XXXI)

wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1438. A compound having the formula (XXXII):

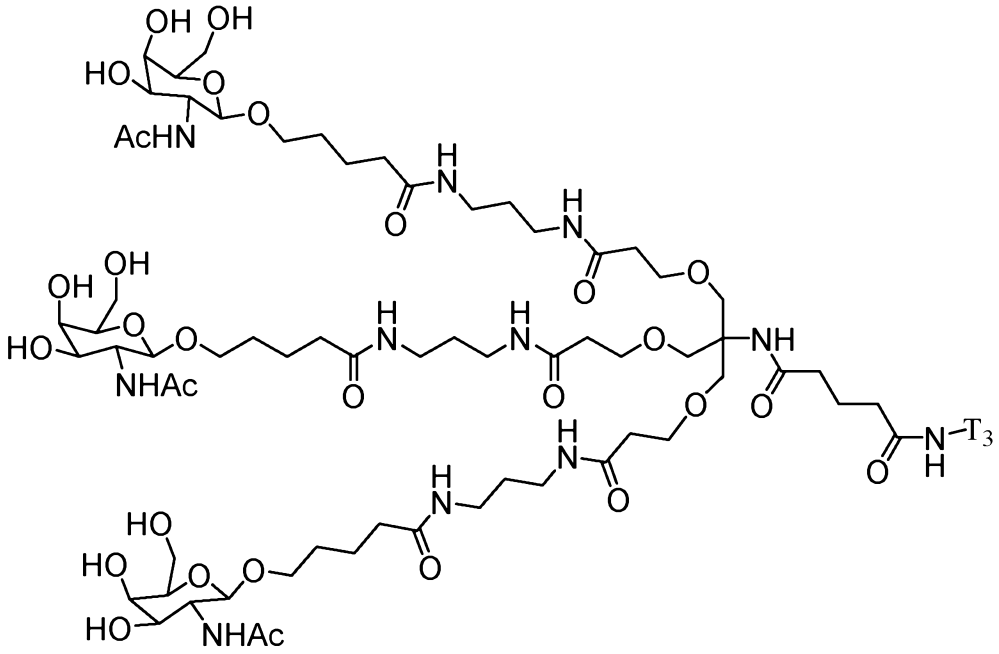


(XXXII)

wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1439. A compound having the formula (XXXIII):

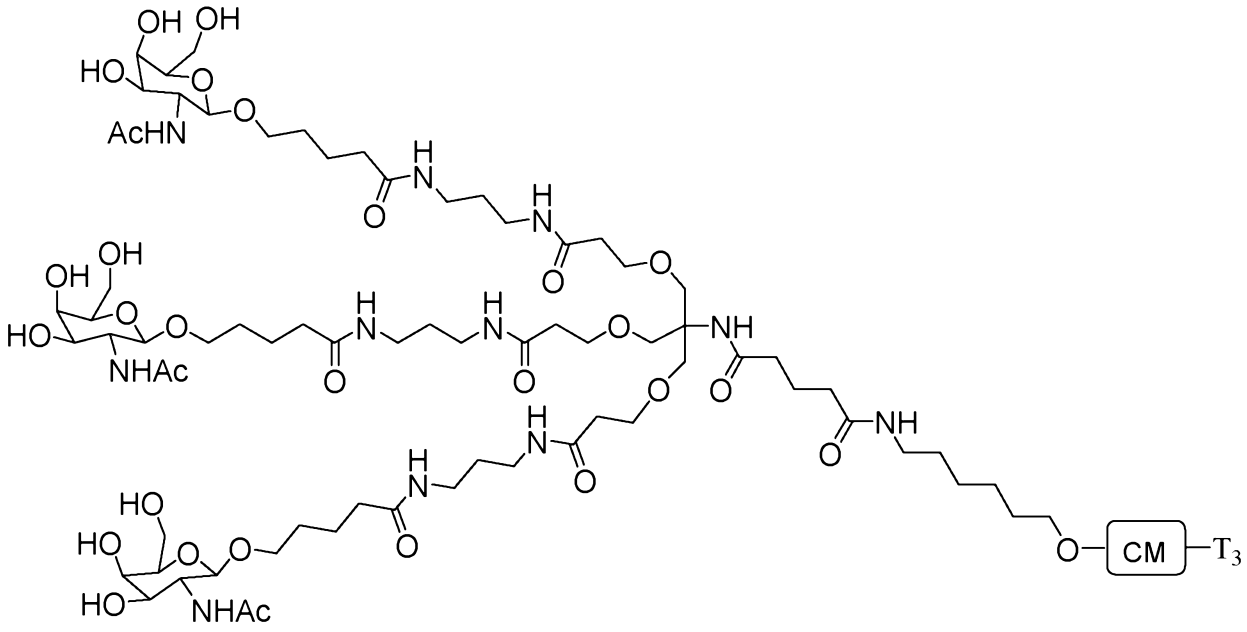


(XXXIII)

wherein:

T_3 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1440. A compound having formula (XXXIV):

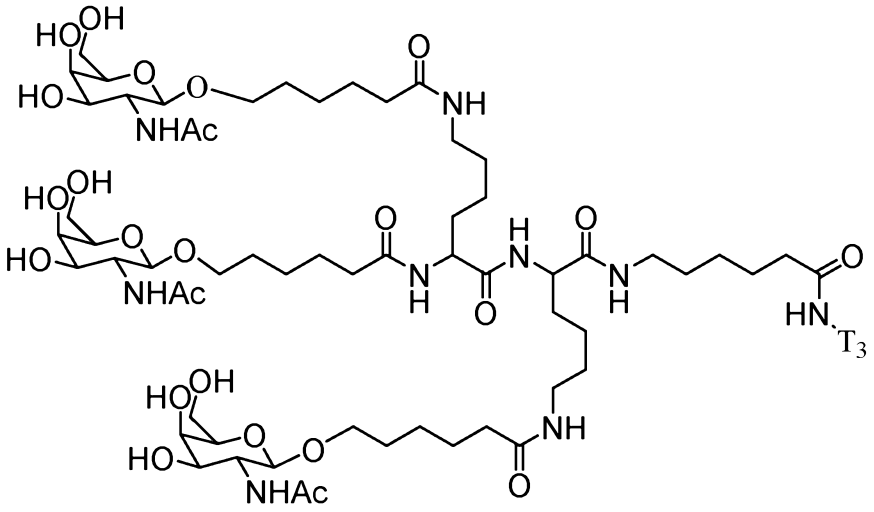


(XXXIV)

wherein:

CM represents a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1441. A compound having the formula (XXXV):

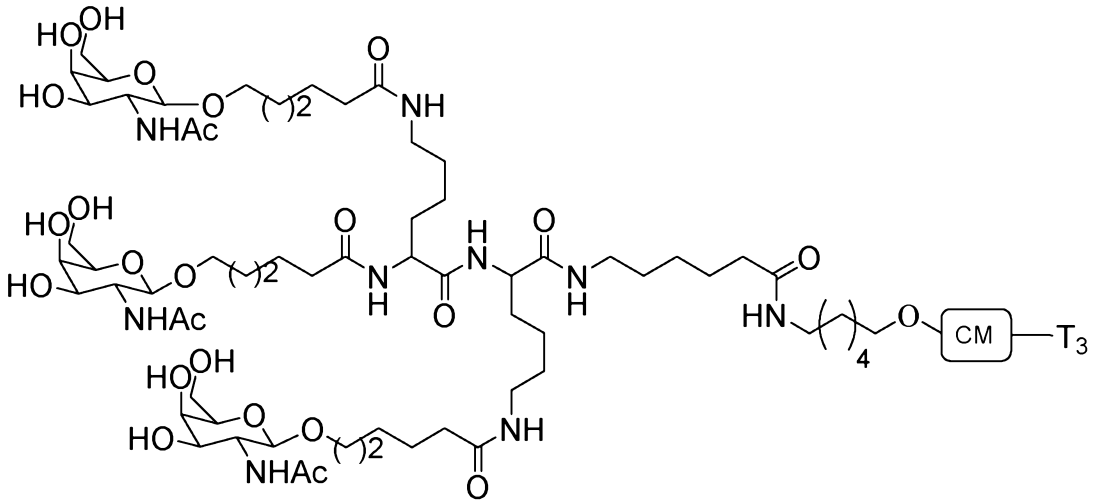


(XXXV)

wherein:

T_3 is a group comprising a linker, nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1442. A compound having the formula (XXXVI):

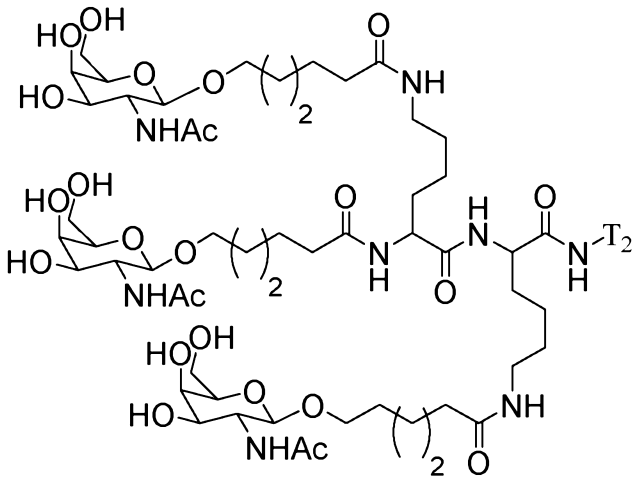


(XXXVI)

wherein:

CM represents a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1443. A compound having formula (XXXVII):

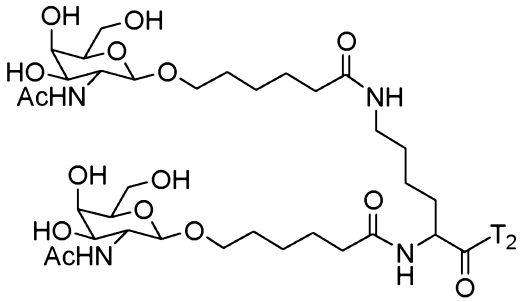


(XXXVII)

wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

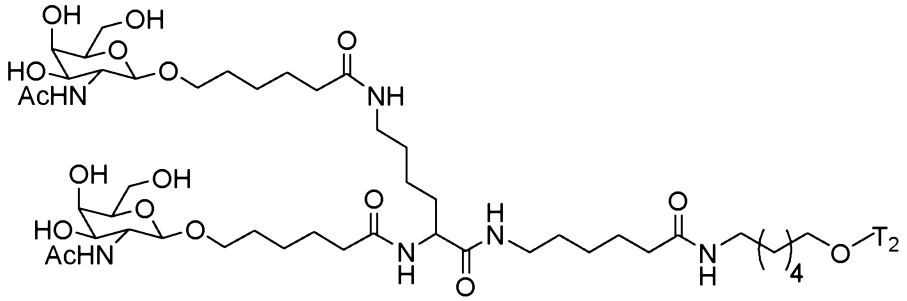
Embodiment 1444. A compound having formula (XXXVIII):



(XXXVIII)

wherein: T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

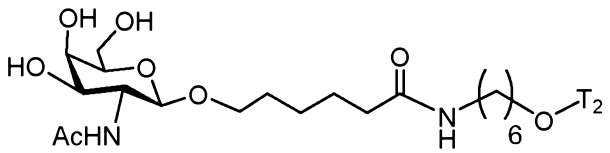
Embodiment 1445. A compound having formula (XXXIX):



(XXXIX)

wherein: T_2 is a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

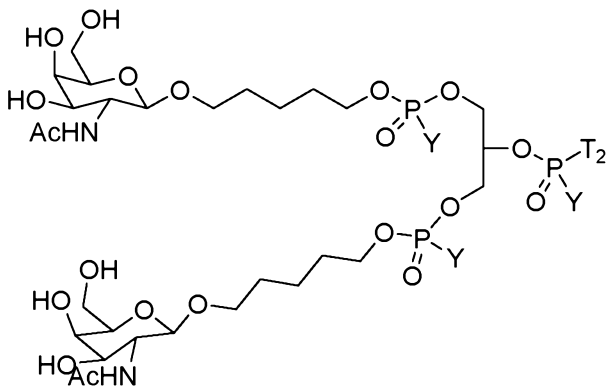
Embodiment 1446. A compound having formula (XL):



(XL)

wherein: T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1447. A compound having formula (XLI):

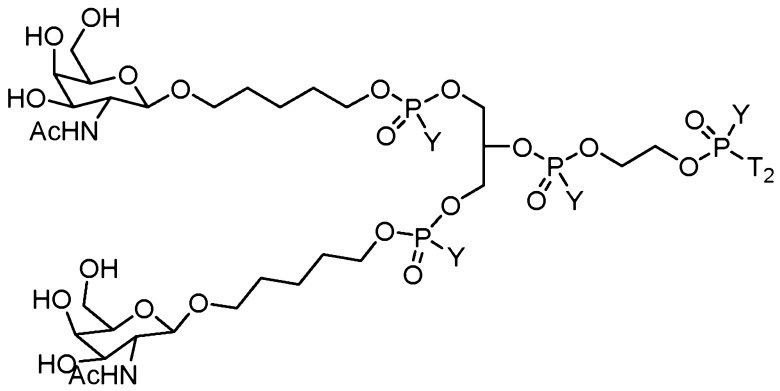


(XLI)

wherein each Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl;

and wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1448. A compound having formula (XLII):

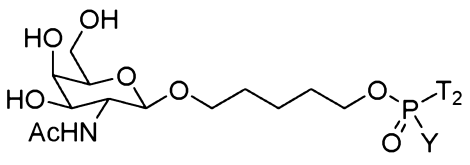


(XLII)

wherein each Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl;

and wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1449. A compound having formula (XLIII):

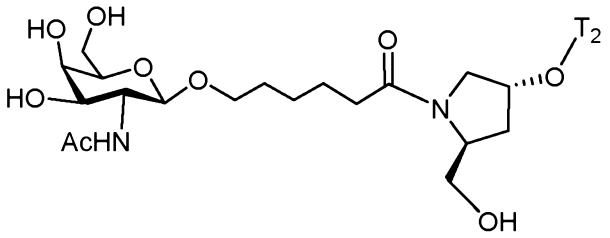


(XLIII)

wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl;

and wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

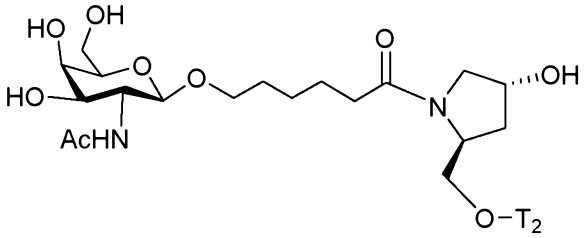
Embodiment 1450. A compound having formula (XLIV):



(XLIV)

wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

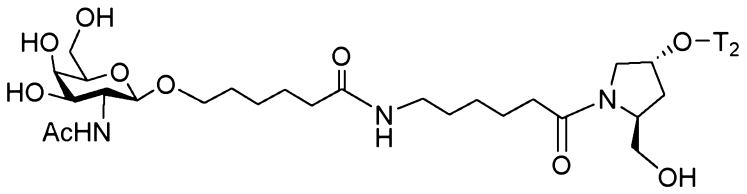
Embodiment 1451. A compound having formula (XLV):



(XLV)

wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

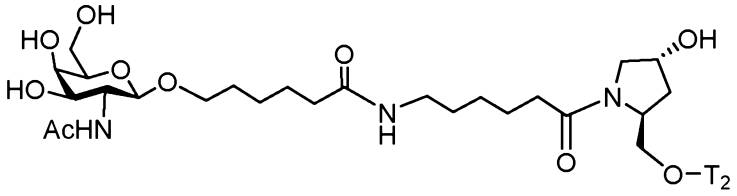
Embodiment 1452. A compound having formula (XLV):



(XLV)

wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

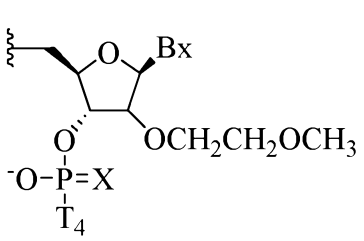
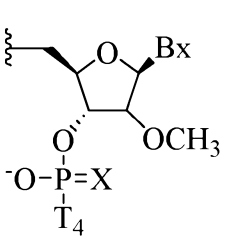
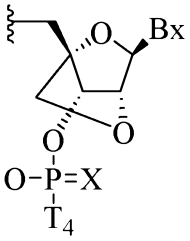
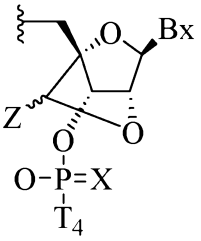
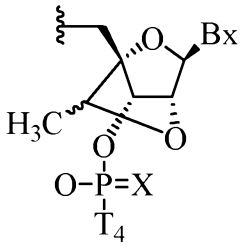
Embodiment 1453. A compound having formula (XLV):



(XLV)

wherein T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1454. The compound of any of embodiments 1432 to 1453, wherein T_2 or T_3 is selected from among:


,

,

,

, or

;

wherein:

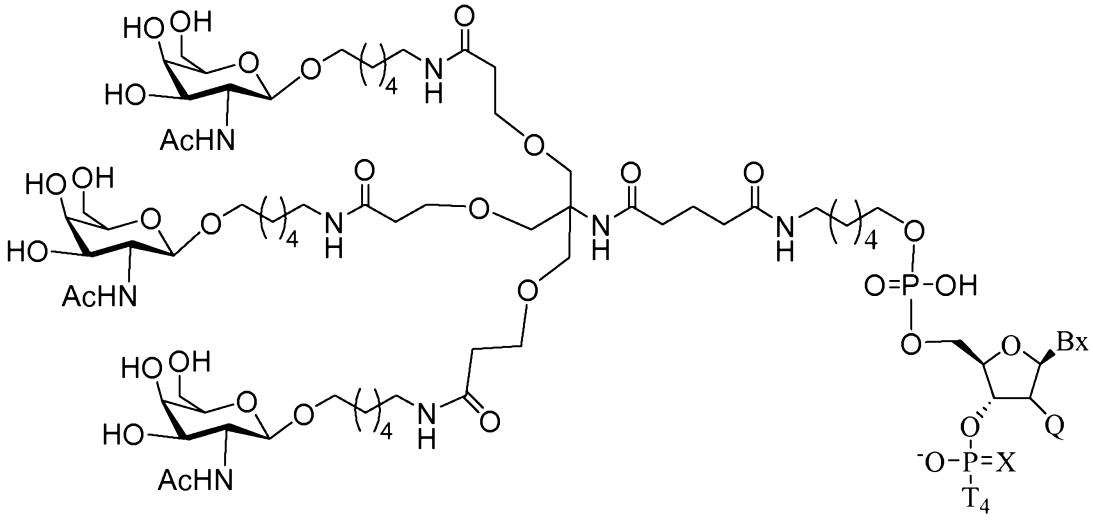
Bx is a heterocyclic base moiety;

T_4 is H, a hydroxyl protecting group or a reactive phosphorus group;

X is O or S;

Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, substituted amide, thiol or substituted thio; and wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1455. A compound having the formula:



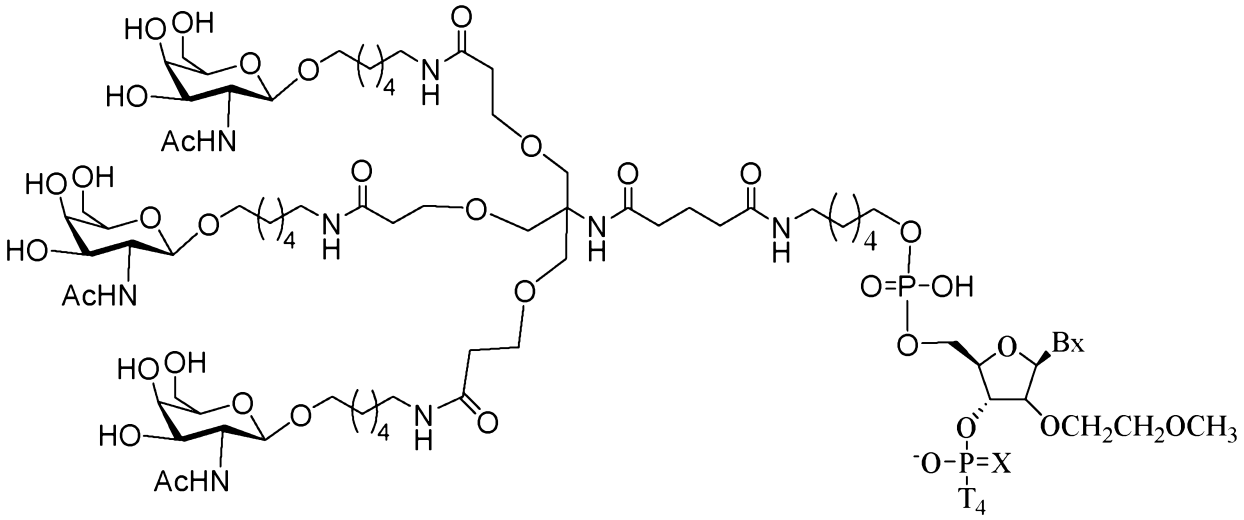
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Q is selected from among: H, a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH{=}CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$;

and wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1456. A compound having the formula:

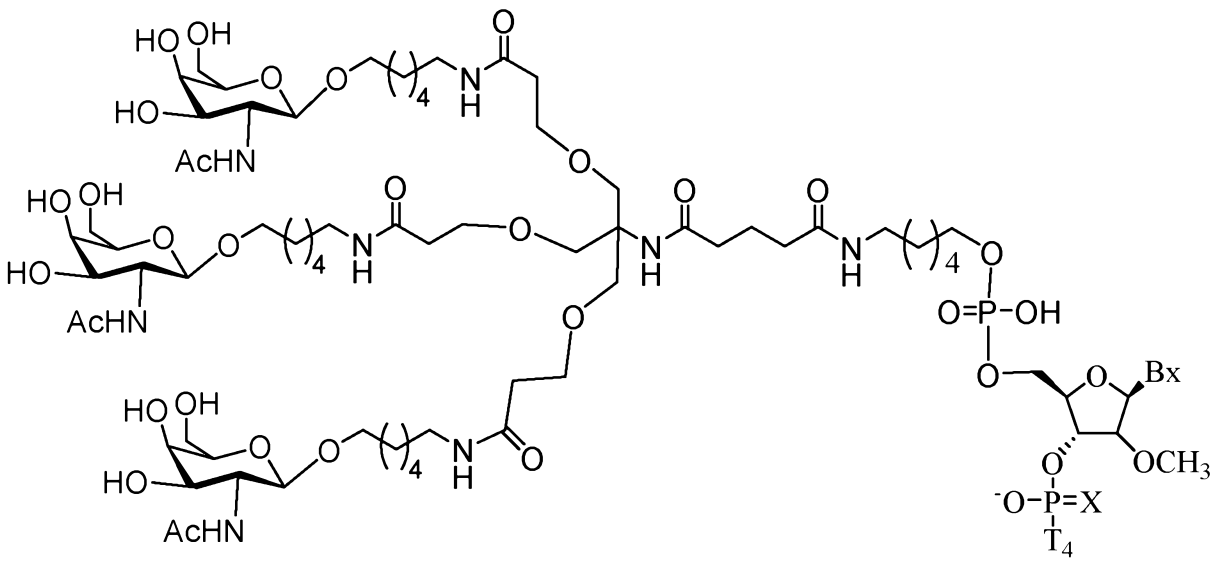


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

and wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1457. A compound having the formula:

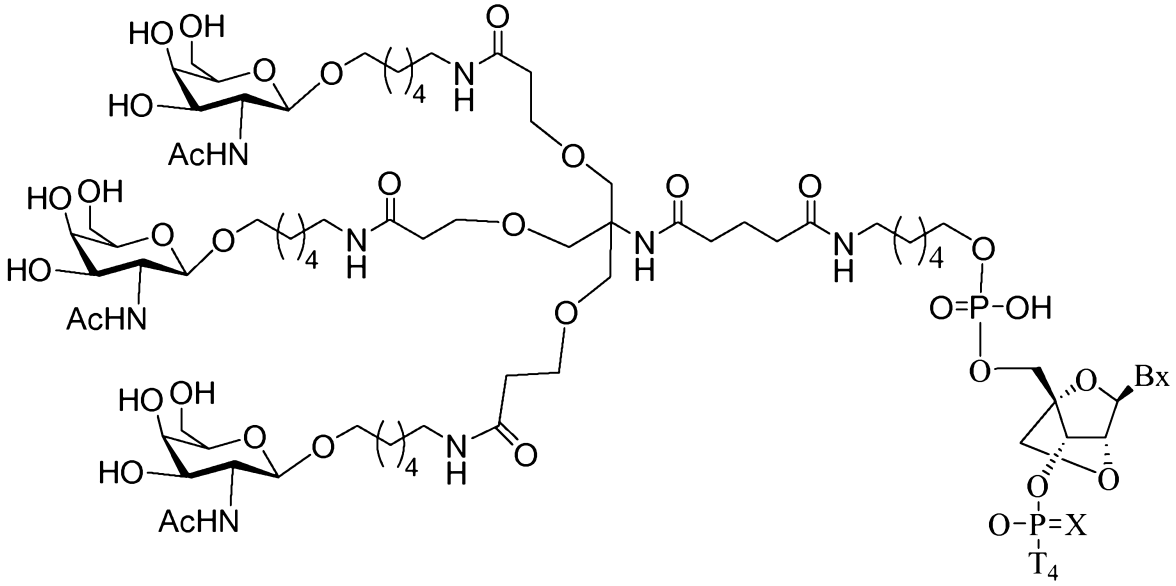


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1458. A compound having the formula :

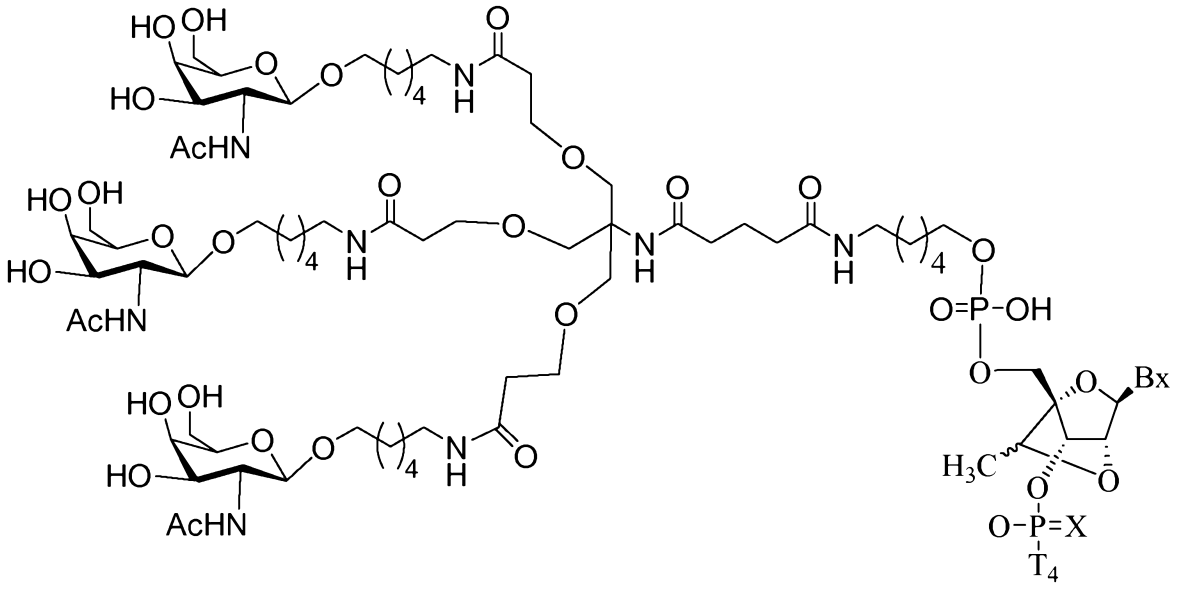


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1459. A compound having the formula :

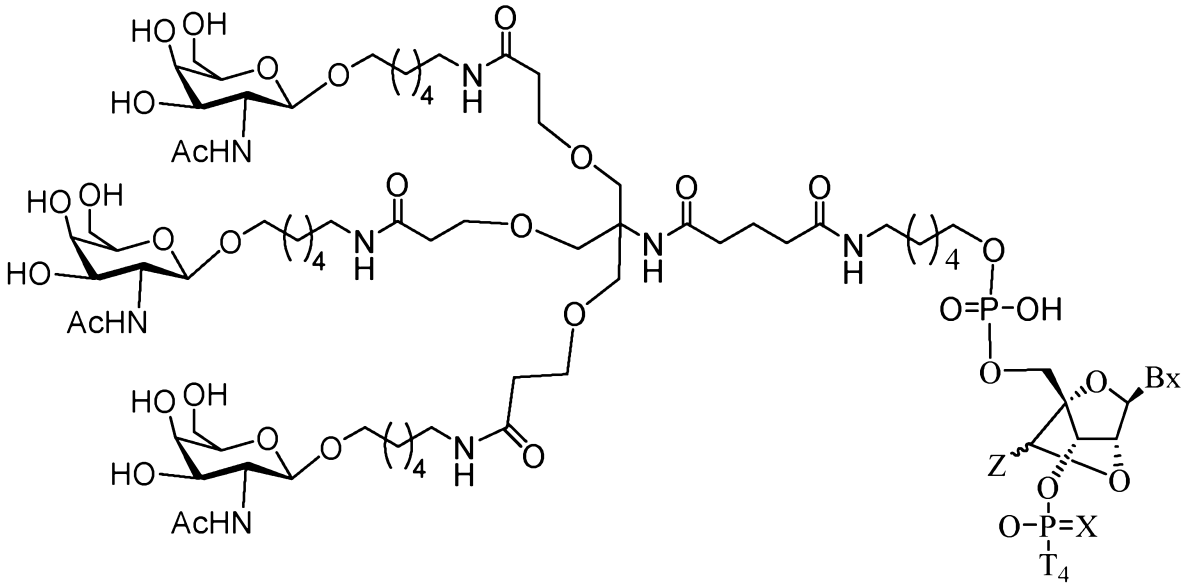


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1460. A compound having the formula :



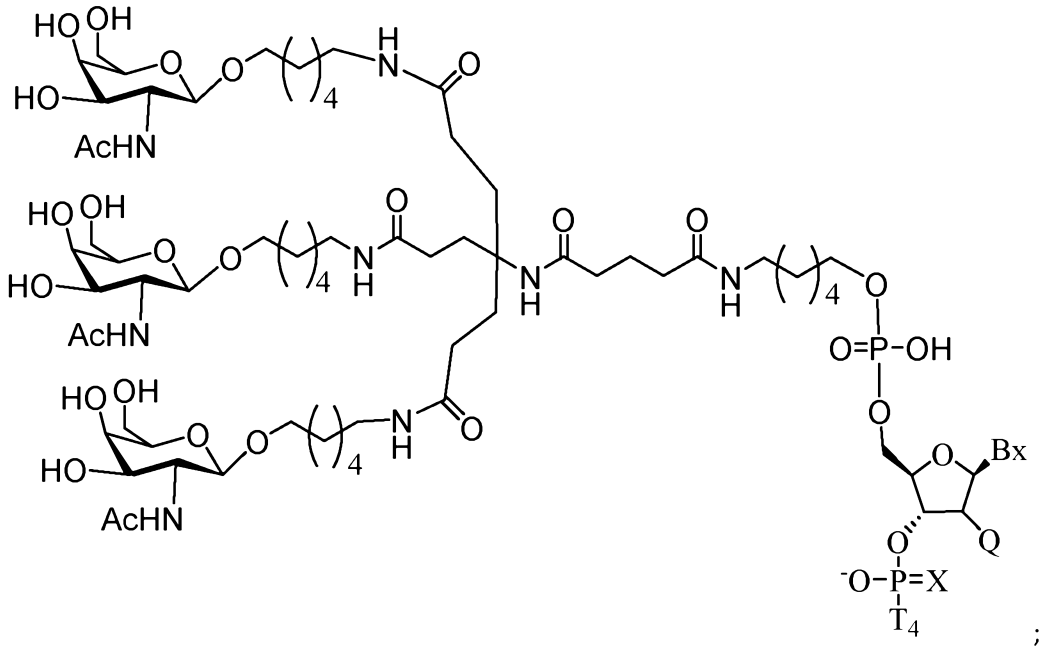
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, or substituted amide; and

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1461. A compound having the formula:



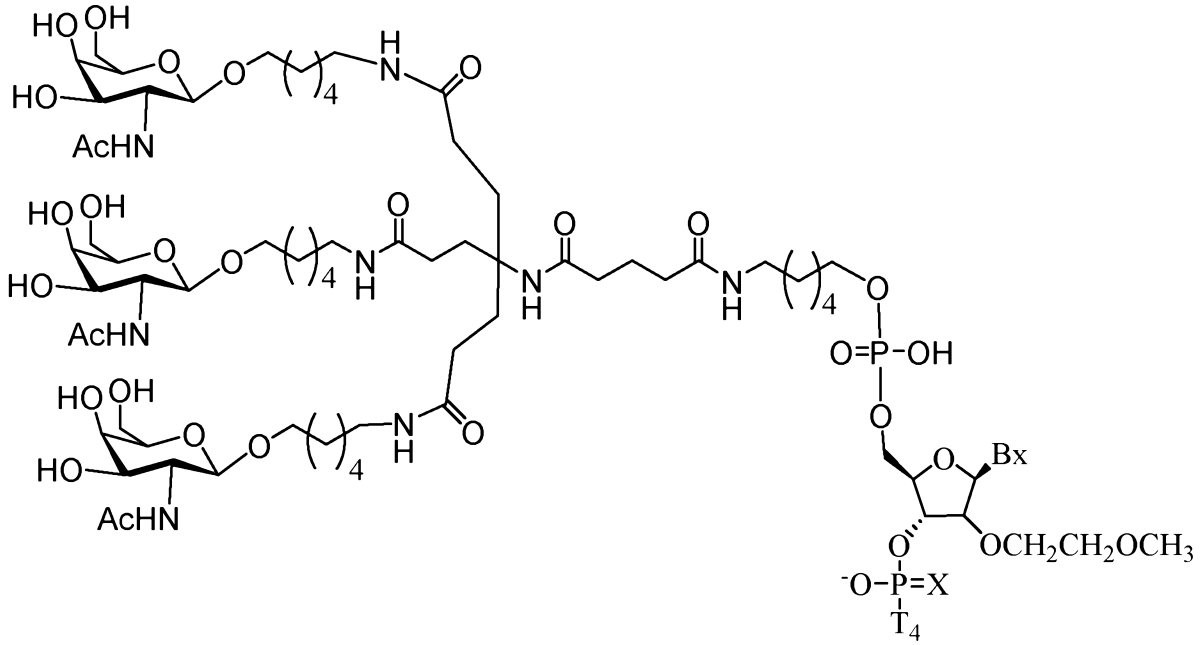
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Q is selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$ and

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1462. A compound having the formula:

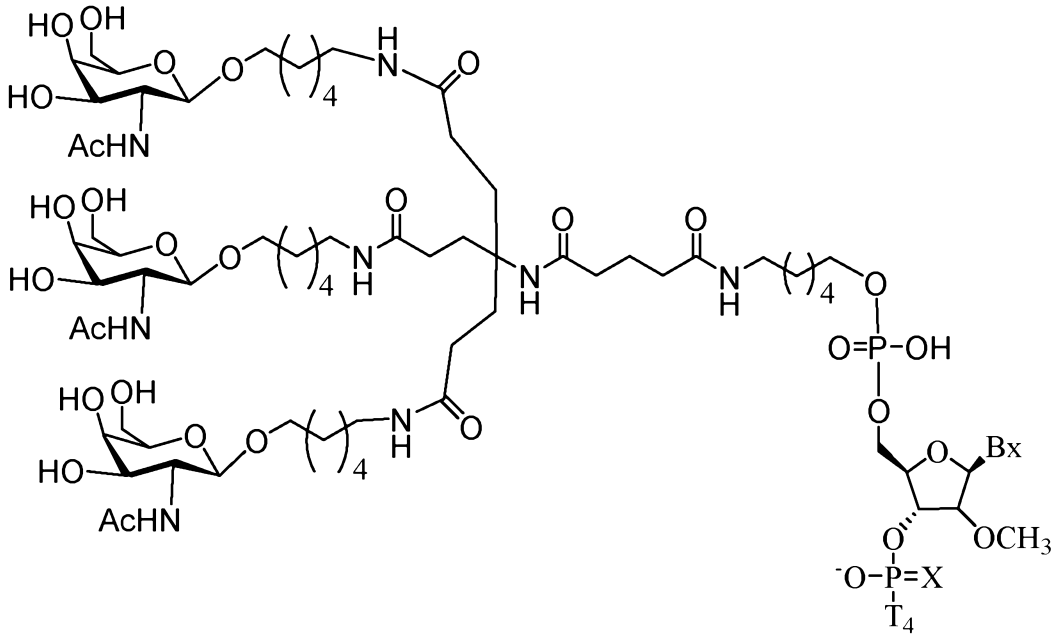


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1463. A compound having the formula:

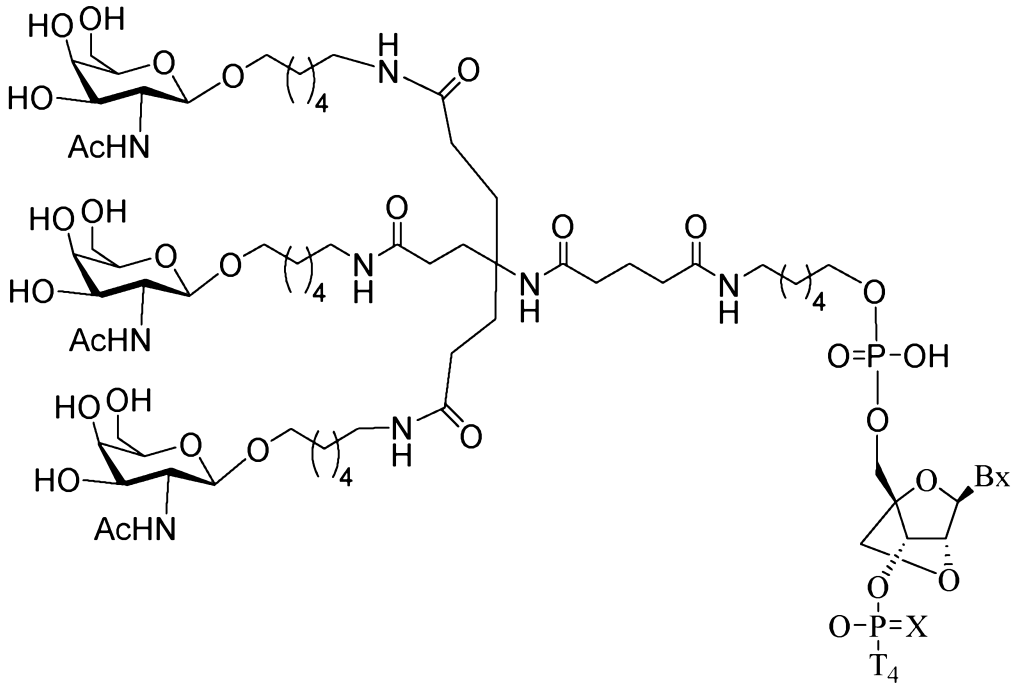


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1464. A compound having the formula:

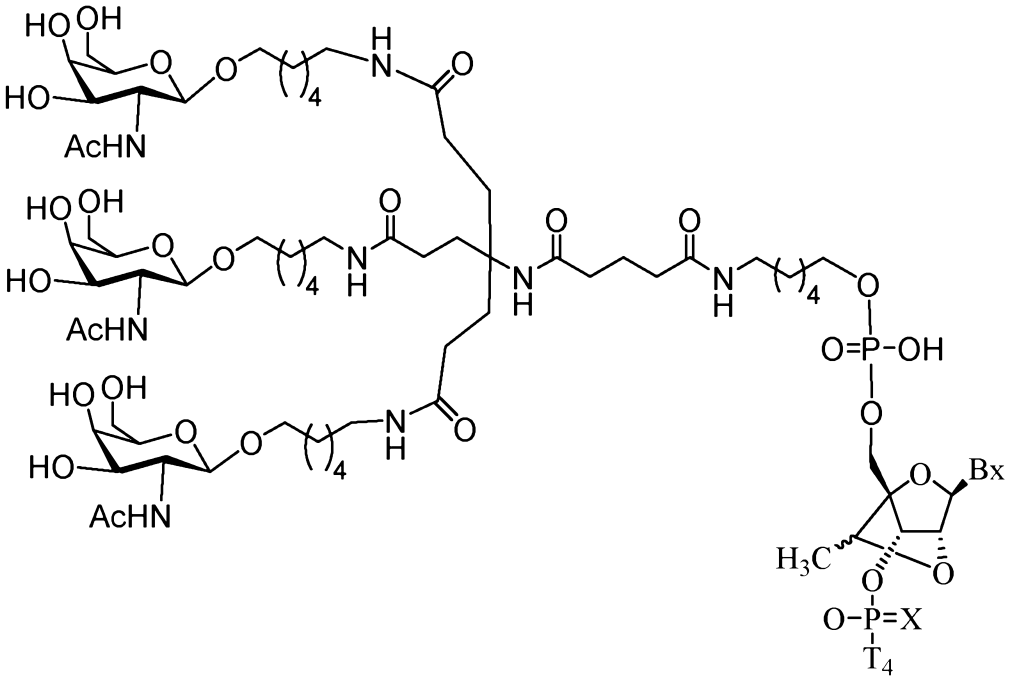


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1465. A compound having the formula:

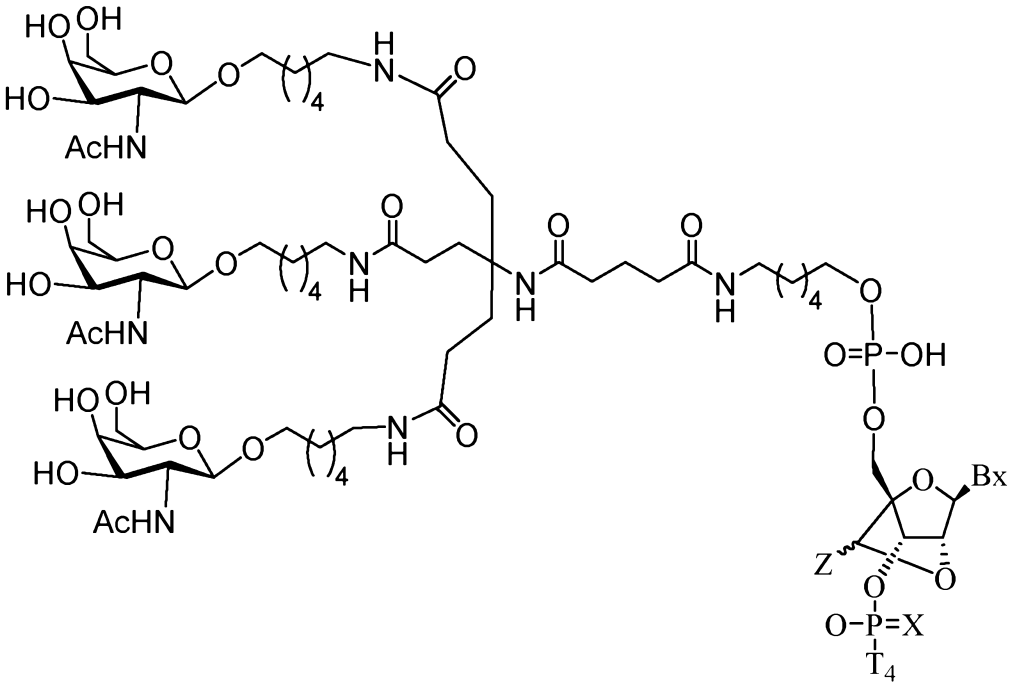


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1466. A compound having the formula:



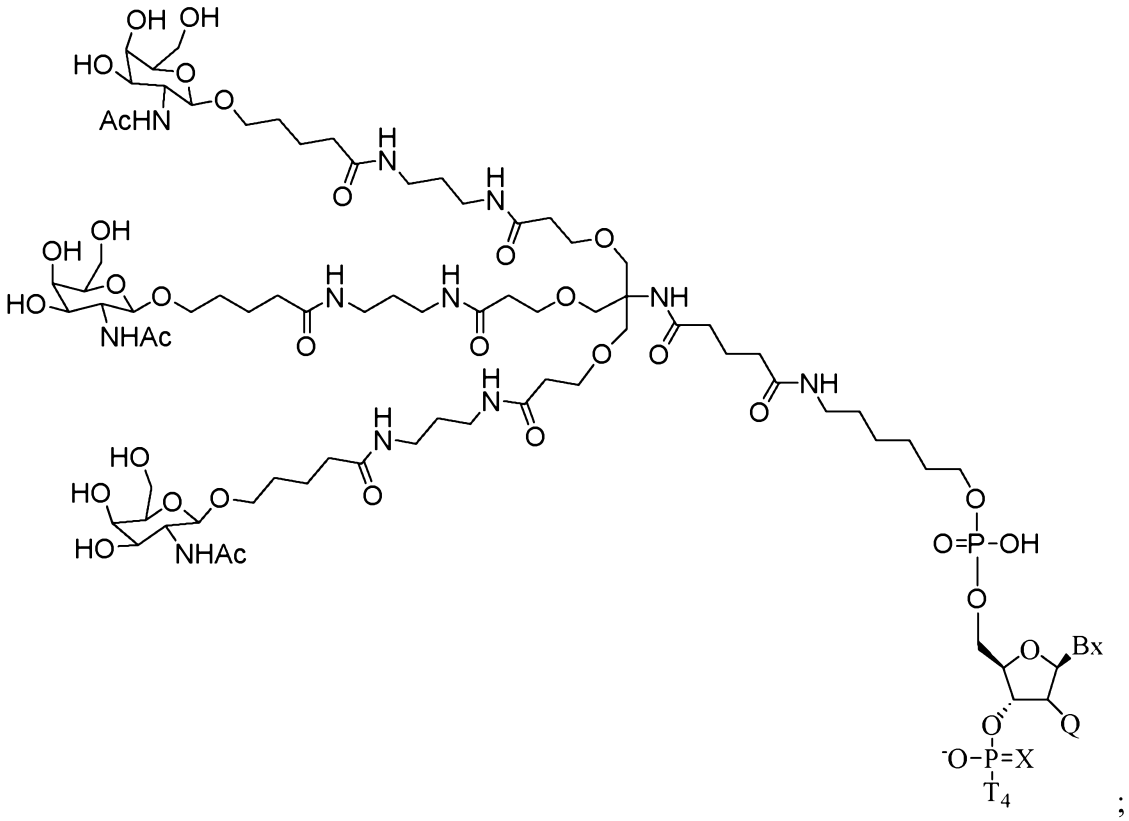
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, or substituted amide; and

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1467. A compound having the formula:



;

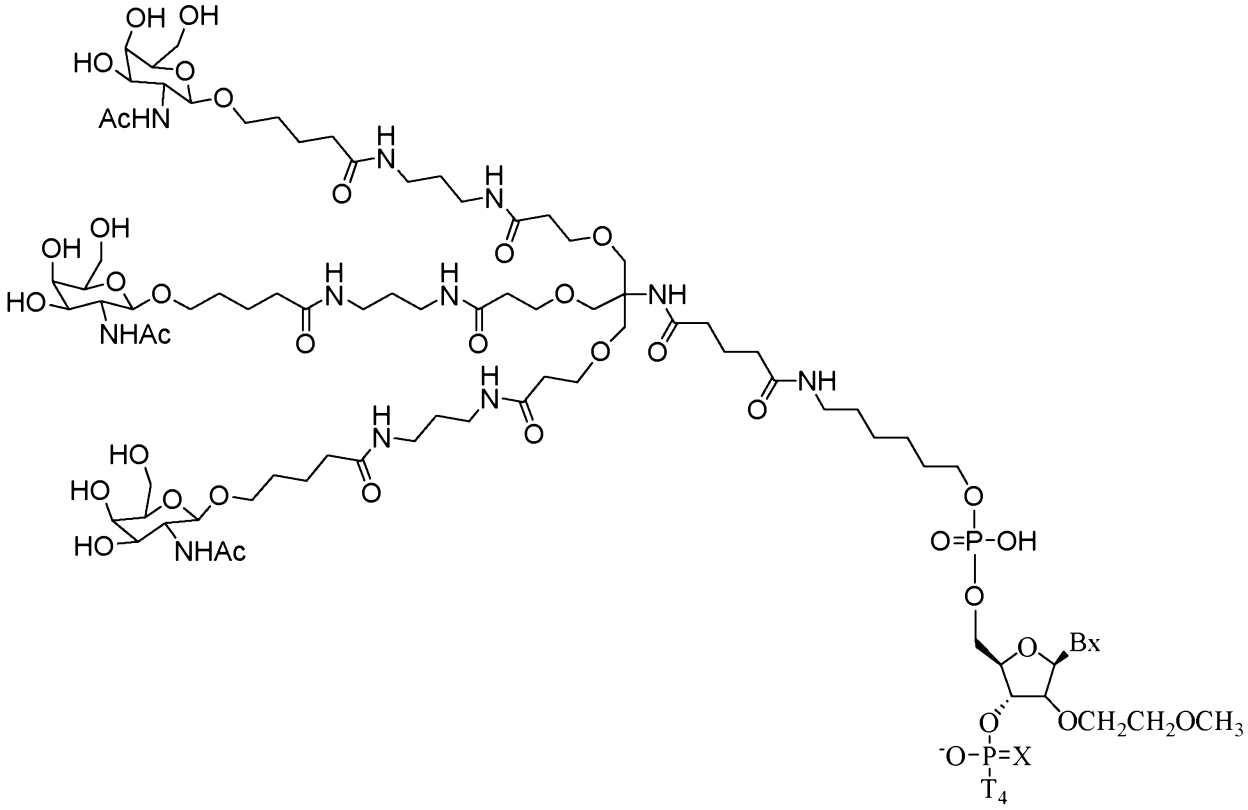
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Q is selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1468. A compound having the formula:

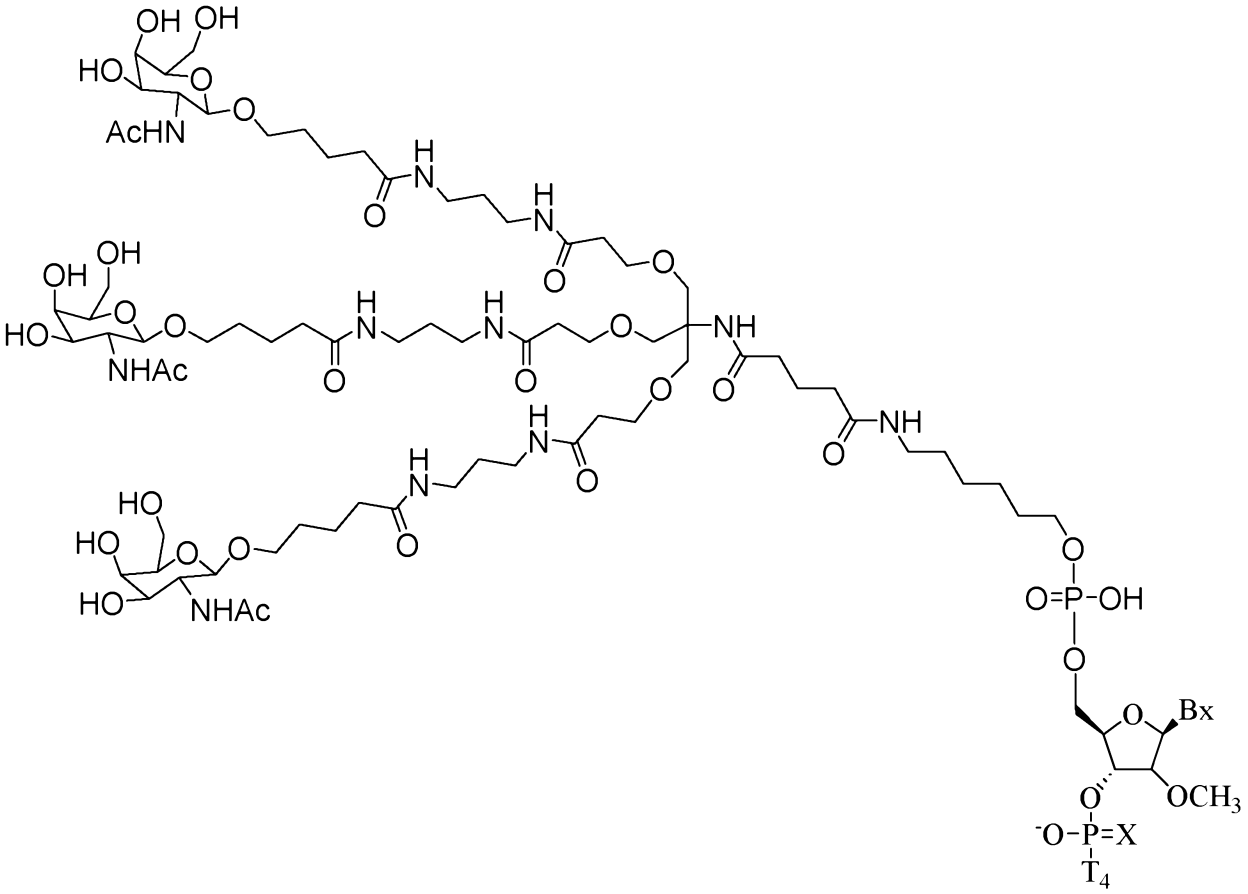


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1469. A compound having the formula:

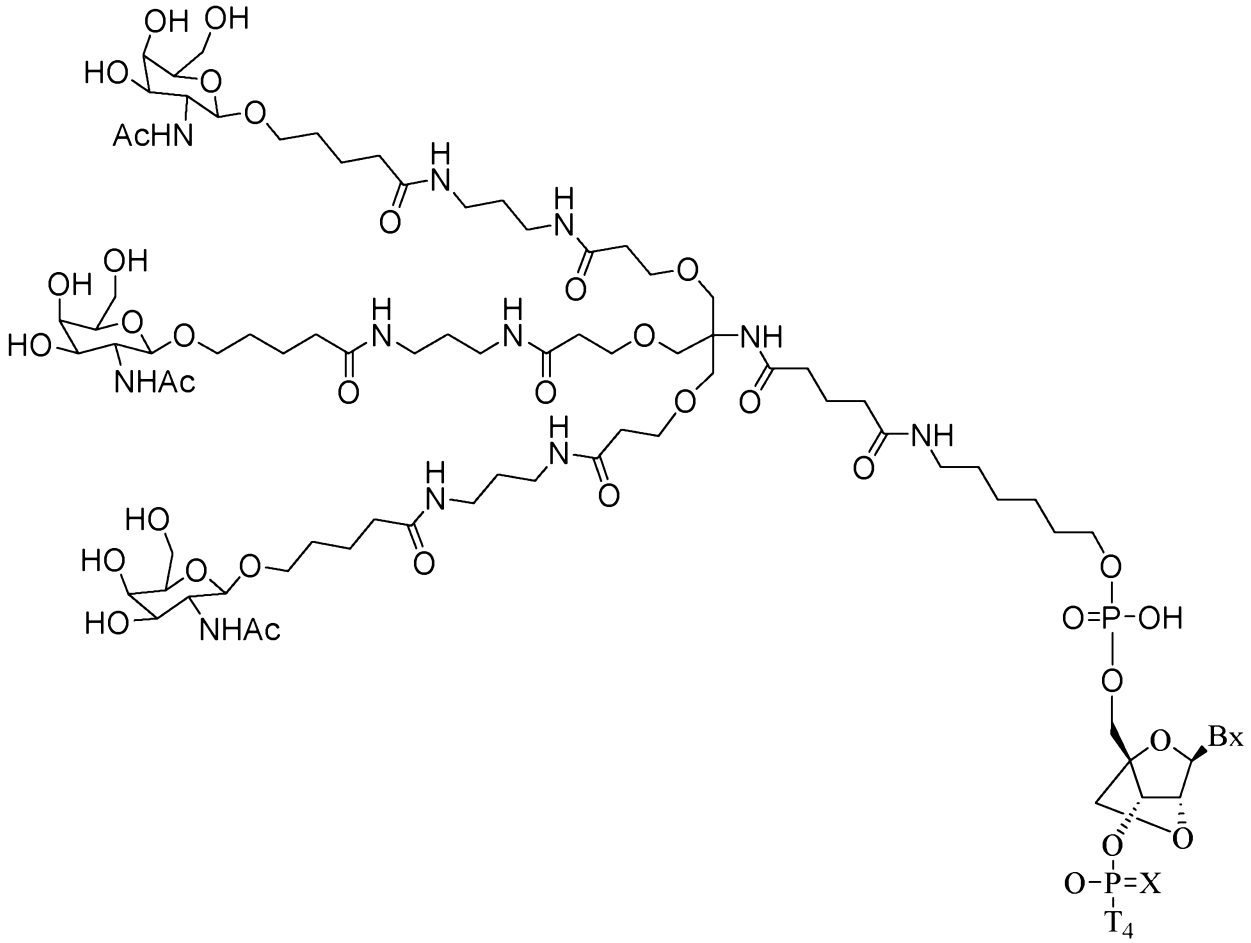


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1470. A compound having the formula:



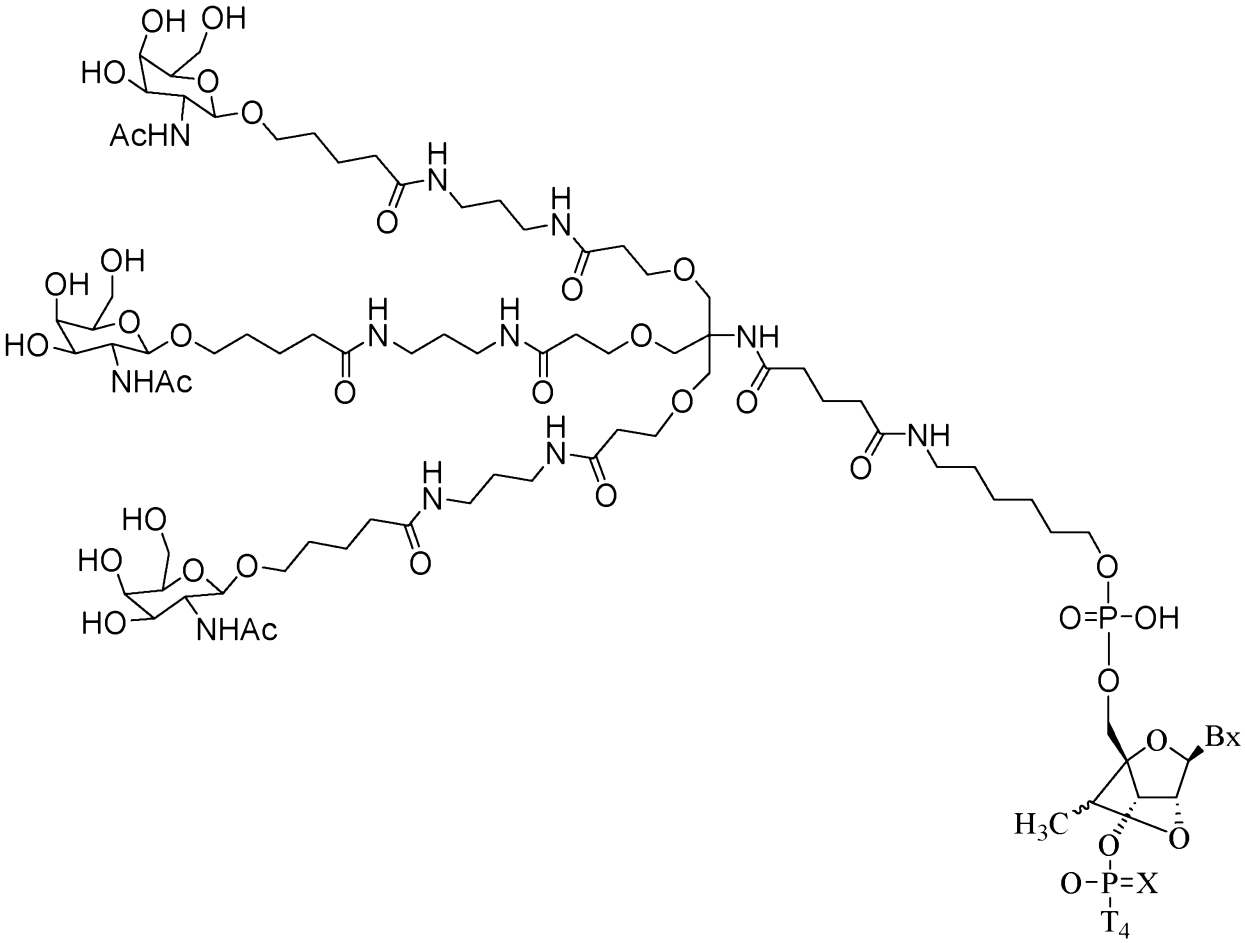
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, or substituted amide; and

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1471. A compound having the formula:

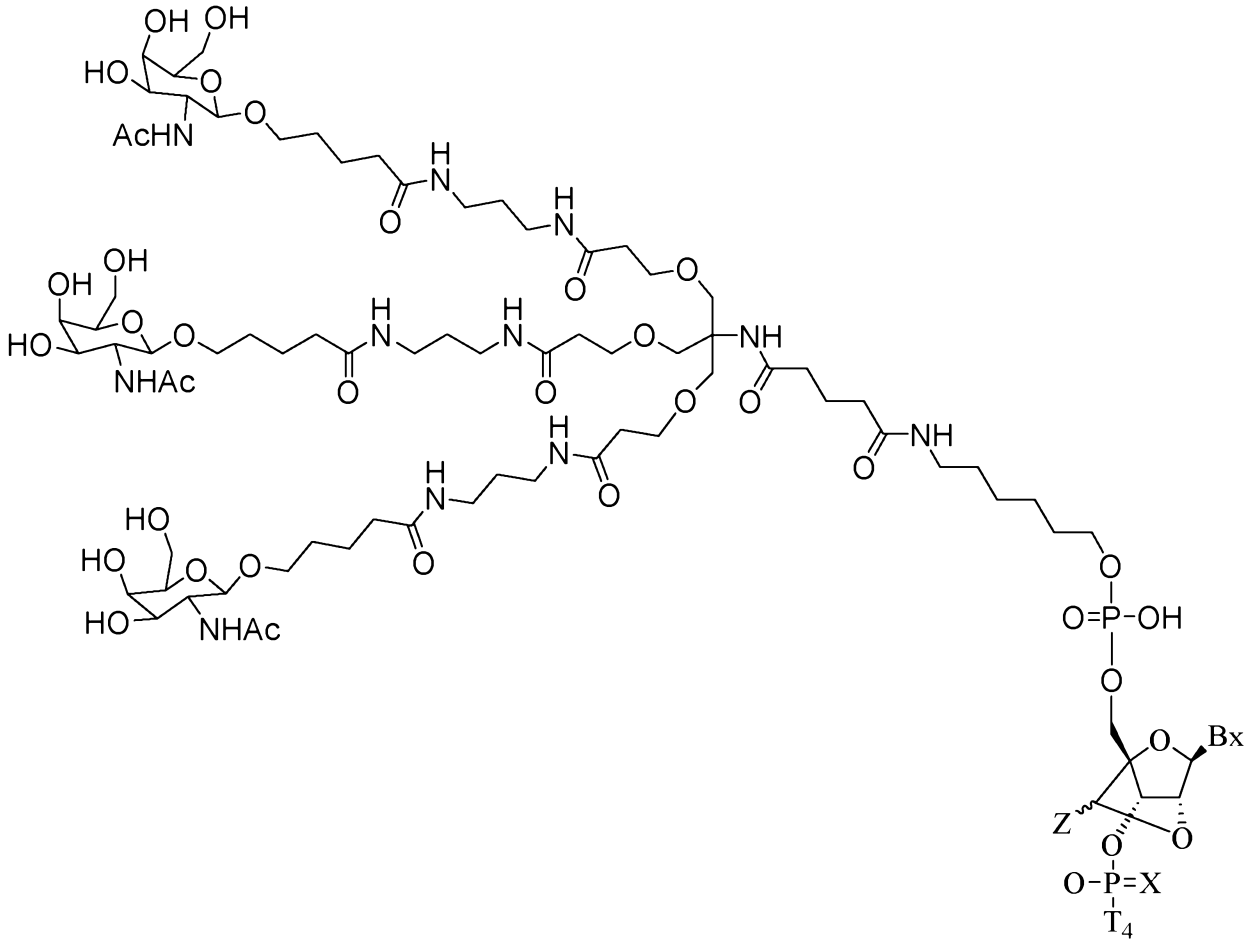


wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1472. A compound having the formula :



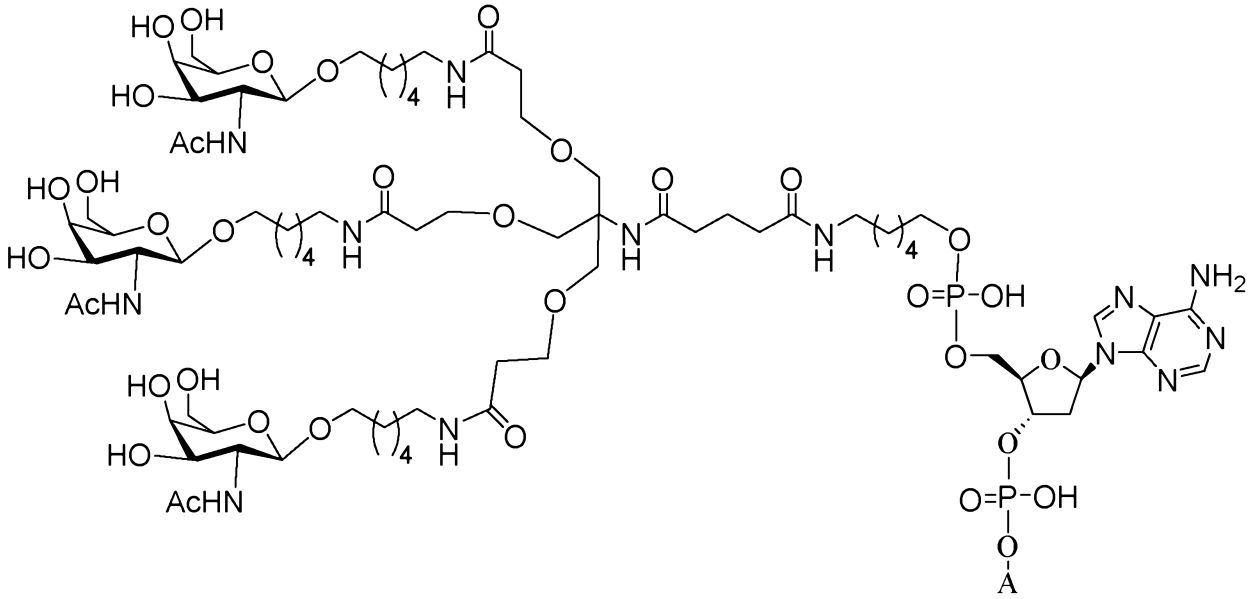
wherein X is O or S;

wherein Bx is a heterocyclic base moiety;

wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, or substituted amide; and

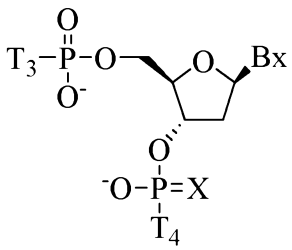
wherein T_4 is a nucleoside, a monomeric subunit, or an oligomeric compound.

Embodiment 1473. A compound having the formula:



, and wherein A is the modified oligonucleotide.

Embodiment 1474. A compound having the formula (V):

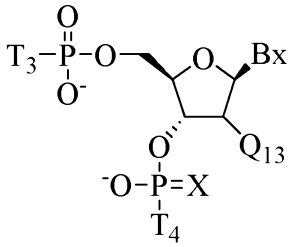


wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a.

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; and wherein Bx is a heterocyclic base moiety;

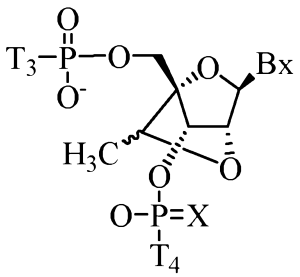
and where X is selected from among O or S.

Embodiment 1475. A compound having the formula (Va):



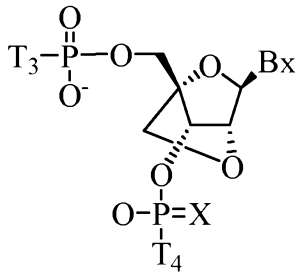
wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a, and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety; and wherein Q_{13} is selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-N(H)CH_3, $OCH_2C(=O)$-N(H)-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-N(H)-C(=NH)NH_2;
and where X is selected from among O or S.

Embodiment 1476. A compound having the formula:



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;
and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;
and where X is selected from among O or S.

Embodiment 1477. A compound having the formula:

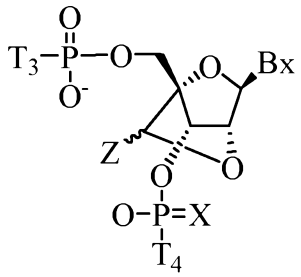


wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and where X is selected from among O or S.

Embodiment 1478. A compound having the formula:



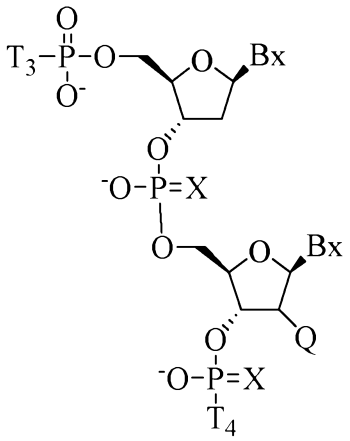
wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, acyl, substituted acyl, substituted amide, thiol or substituted thio;

one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and where X is selected from among O or S.

Embodiment 1479. A compound having the formula:



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; and wherein Bx is a heterocyclic base moiety;

and wherein Q is selected from among: a hydrogen, halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$;

and where X is selected from among O or S.

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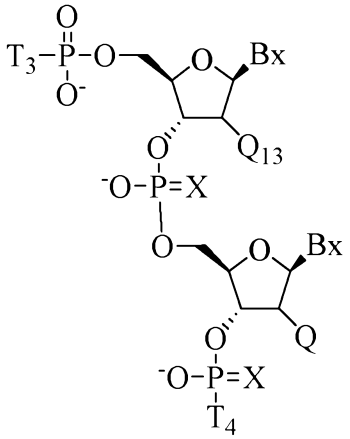
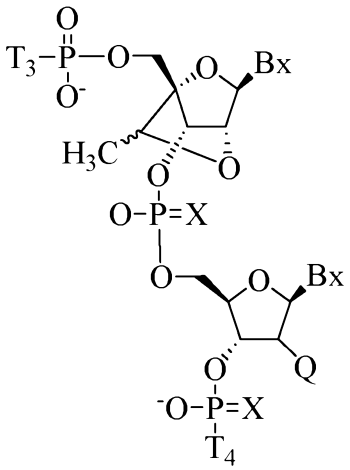
Embodiment 1480. A compound having the formula:



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a, and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety; and wherein Q or Q_{13} is selected from among: a hydrogen, halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-N(H)CH_3, $OCH_2C(=O)$-N(H)-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-N(H)-C(=NH)NH_2; and where X is selected from among O or S.

Embodiment 1481. A compound having the formula:



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a,

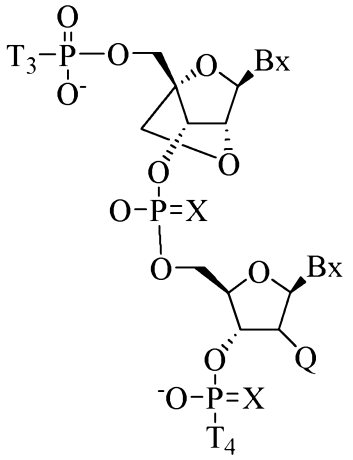
GalNAc$_3$-12a, GalNAc$_3$-13a, GalNAc$_3$-14a, GalNAc$_3$-15a, GalNAc$_3$-16a, GalNAc$_3$-17a, GalNAc$_3$-18a, GalNAc$_3$-19a, GalNAc$_3$-20a, GalNAc$_3$-21a, GalNAc$_3$-22a, GalNAc$_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and wherein Q is selected from among: a hydrogen, halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-N(H)CH_3, $OCH_2C(=O)$-N(H)-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-N(H)-C(=NH)NH_2;

and where X is selected from among O or S.

Embodiment 1482. A compound having the formula:



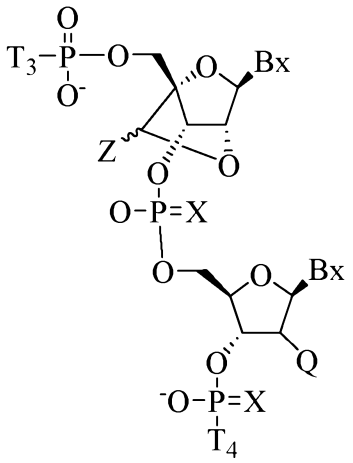
wherein one of T_3 or T_4 is selected from among: GalNAc$_3$-1a, GalNAc$_3$-2a, GalNAc$_3$-3a, GalNAc$_3$-4a, GalNAc$_3$-5a, GalNAc$_3$-6a, GalNAc$_3$-7a, GalNAc$_3$-8a, GalNAc$_3$-9a, GalNAc$_3$-10a, GalNAc$_3$-11a, GalNAc$_3$-12a, GalNAc$_3$-13a, GalNAc$_3$-14a, GalNAc$_3$-15a, GalNAc$_3$-16a, GalNAc$_3$-17a, GalNAc$_3$-18a, GalNAc$_3$-19a, GalNAc$_3$-20a, GalNAc$_3$-21a, GalNAc$_3$-22a, GalNAc$_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and wherein Q is selected from among: a hydrogen, halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-N(H)CH_3, $OCH_2C(=O)$-N(H)-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-N(H)-C(=NH)NH_2;

and where X is selected from among O or S.

Embodiment 1483. A compound having the formula:



wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, acyl, substituted acyl, substituted amide, thiol or substituted thio;

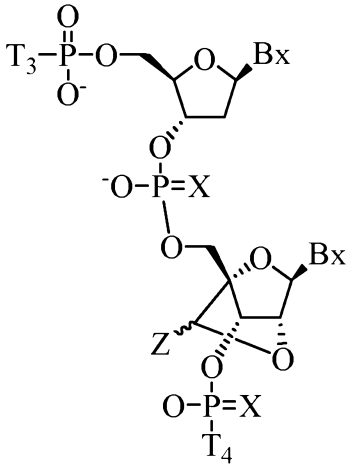
one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and wherein Q is selected from among: a hydrogen, halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$;

and where X is selected from among O or S.

Embodiment 1484. A compound having the formula:



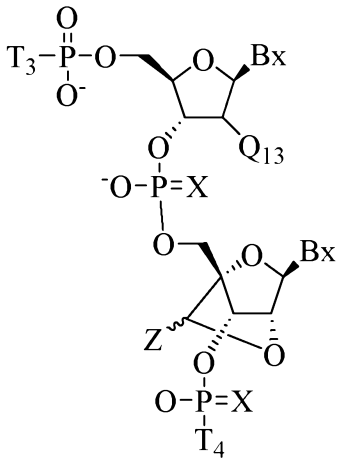
wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; and wherein Bx is a heterocyclic base moiety;

and where X is selected from among O or S

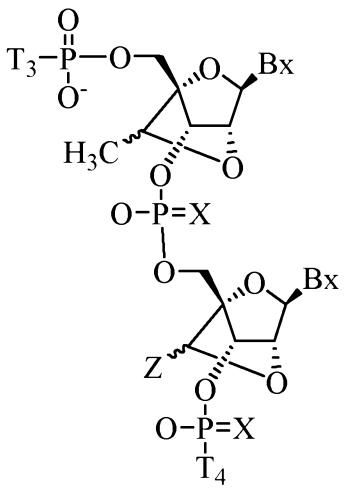
and where Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, hydrogen, acyl, substituted acyl, substituted amide, thiol or substituted thio.

Embodiment 1485. A compound having the formula:



wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a; and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety; and wherein Q_{13} is selected from among: a hydrogen, halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-N(H)-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-N(H)-C(=NH)NH_2;
and where X is selected from among O or S
and where Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, hydrogen, acyl, substituted acyl, substituted amide, thiol or substituted thio.

Embodiment 1486. A compound having the formula:

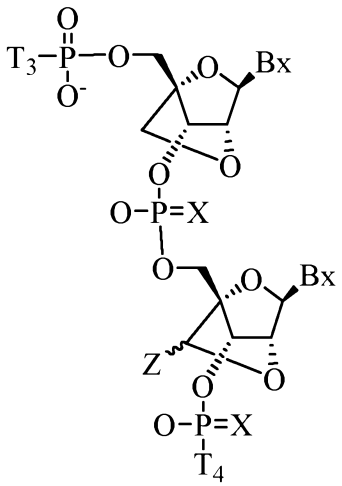


wherein one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a; and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and where X is selected from among O or S

and where Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, hydrogen, acyl, substituted acyl, substituted amide, thiol or substituted thio.

Embodiment 1487. A compound having the formula:



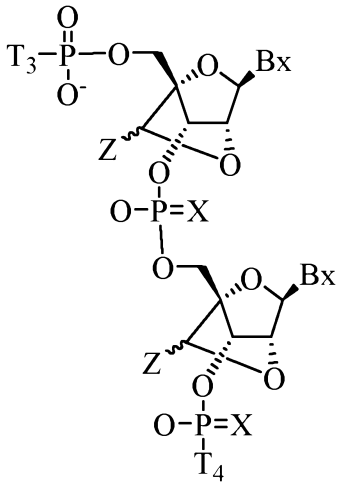
wherein one of T_3 or T_4 is selected from among: GalNAc$_3$-1a, GalNAc$_3$-2a, GalNAc$_3$-3a, GalNAc$_3$-4a, GalNAc$_3$-5a, GalNAc$_3$-6a, GalNAc$_3$-7a, GalNAc$_3$-8a, GalNAc$_3$-9a, GalNAc$_3$-10a, GalNAc$_3$-11a, GalNAc$_3$-12a, GalNAc$_3$-13a, GalNAc$_3$-14a, GalNAc$_3$-15a, GalNAc$_3$-16a, GalNAc$_3$-17a, GalNAc$_3$-18a, GalNAc$_3$-19a, GalNAc$_3$-20a, GalNAc$_3$-21a, GalNAc$_3$-22a, GalNAc$_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

and where X is selected from among O or S.

and where Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, hydrogen, acyl, substituted acyl, substituted amide, thiol or substituted thio.

Embodiment 1488. A compound having the formula:



wherein Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, acyl, substituted acyl, substituted amide, thiol or substituted thio;

one of T_3 or T_4 is selected from among: $GalNAc_3$-1a, $GalNAc_3$-2a, $GalNAc_3$-3a, $GalNAc_3$-4a, $GalNAc_3$-5a, $GalNAc_3$-6a, $GalNAc_3$-7a, $GalNAc_3$-8a, $GalNAc_3$-9a, $GalNAc_3$-10a, $GalNAc_3$-11a, $GalNAc_3$-12a, $GalNAc_3$-13a, $GalNAc_3$-14a, $GalNAc_3$-15a, $GalNAc_3$-16a, $GalNAc_3$-17a, $GalNAc_3$-18a, $GalNAc_3$-19a, $GalNAc_3$-20a, $GalNAc_3$-21a, $GalNAc_3$-22a, $GalNAc_3$-23a, GalNAc-24a, GalNAc-25a, GalNAc-26a, GalNAc-27a, GalNAc-28a, GalNAc-29a, GalNAc-30a, GalNAc-31a, and GalNAc-32a;

and the other of T_3 or T_4 is selected from among: a hydroxyl, a hydroxyl protecting group, a nucleoside, an oligonucleotide, a monomeric subunit, or an oligomeric compound; wherein Bx is a heterocyclic base moiety;

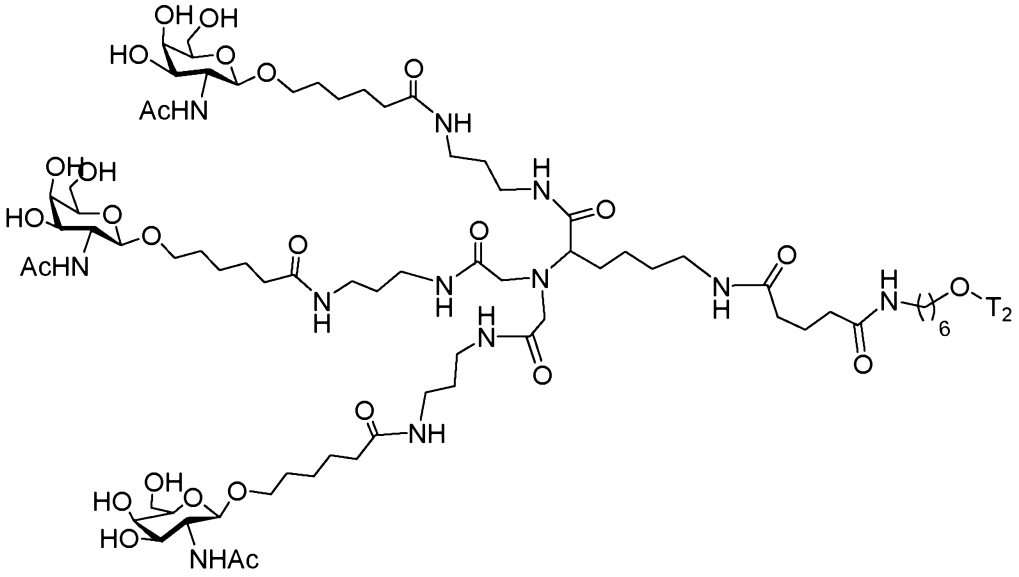
and where X is O or S;

and where Z is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, halogen, hydrogen, acyl, substituted acyl, substituted amide, thiol or substituted thio.

Embodiment 1489. The compound of any of embodiments 1474 to 1488, wherein B_x is selected from adenine, guanine, thymine, uracil, cytosine, or 5-methyl cytosine.

Embodiment 1490. The compound of any of embodiments 1474 to 1483 or 1485, wherein Q or Q_{13} is $O(CH_2)_2$-OCH_3.

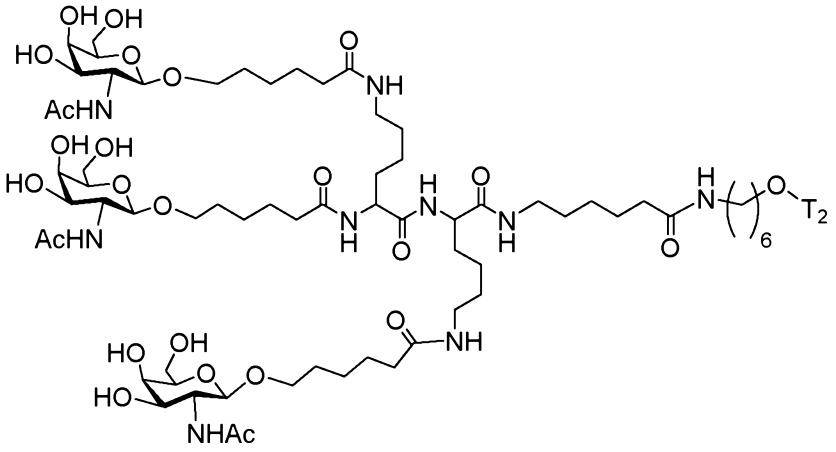
Embodiment 1491. A compound having the formula (XVI):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

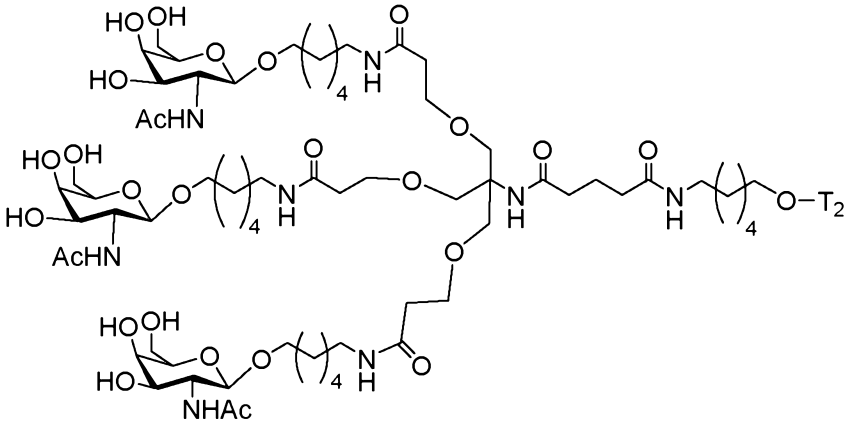
Embodiment 1492. A compound having the formula (XVII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

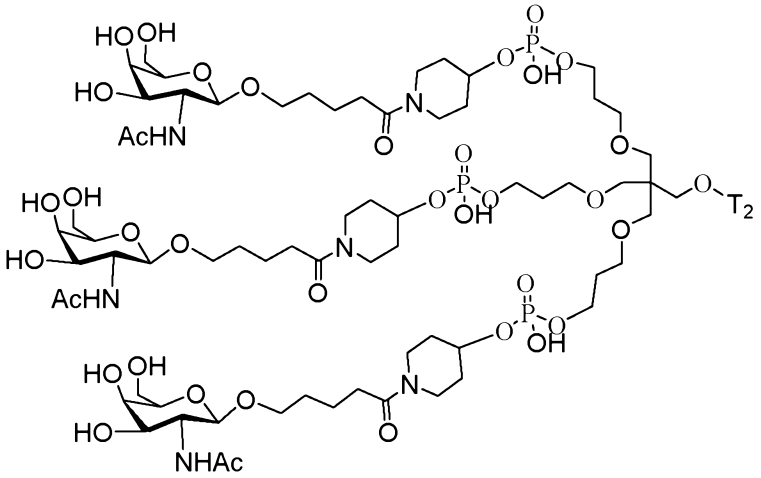
Embodiment 1493. A compound having the formula (XVIII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

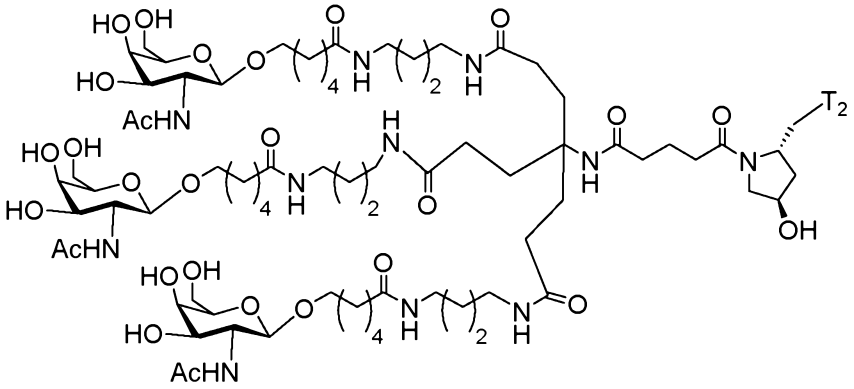
Embodiment 1494. A compound having the formula (XIX):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

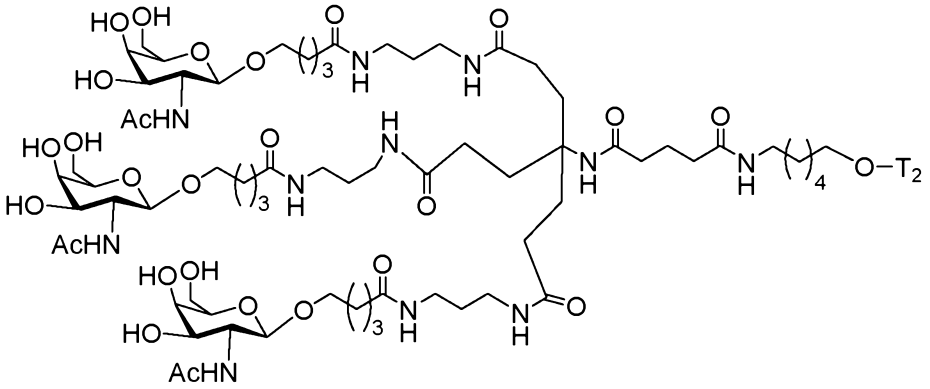
Embodiment 1495. A compound having the formula (XX):



wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

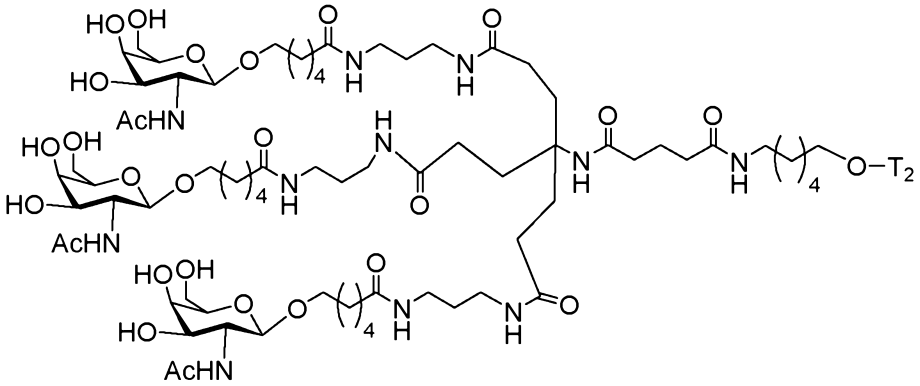
Embodiment 1496. A compound having the formula (XXI):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

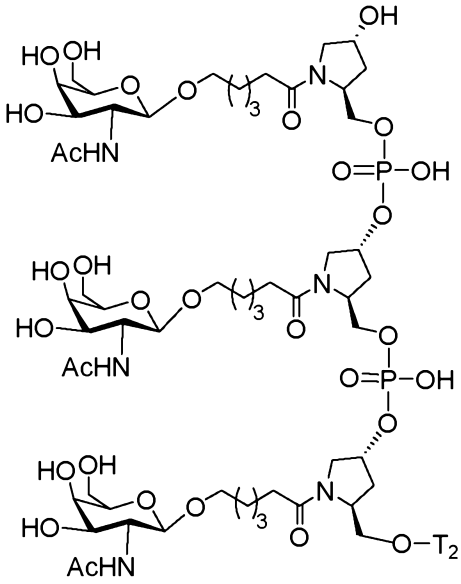
Embodiment 1497. A compound having the formula (XXII):



wherein:

T_2 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

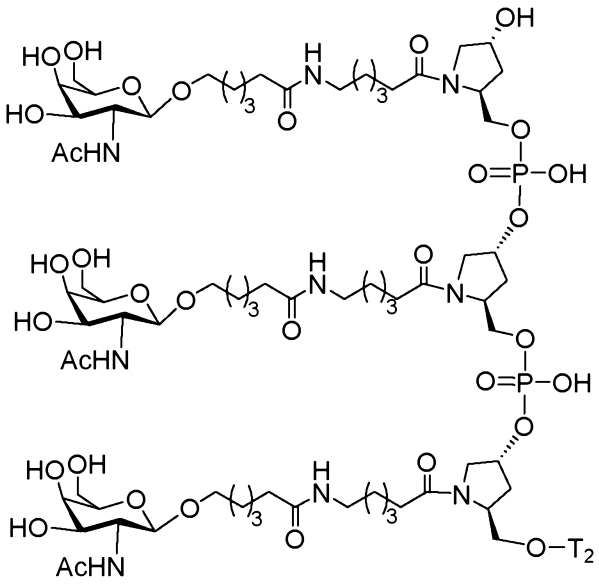
Embodiment 1498. A compound having the formula (XXIII):



wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

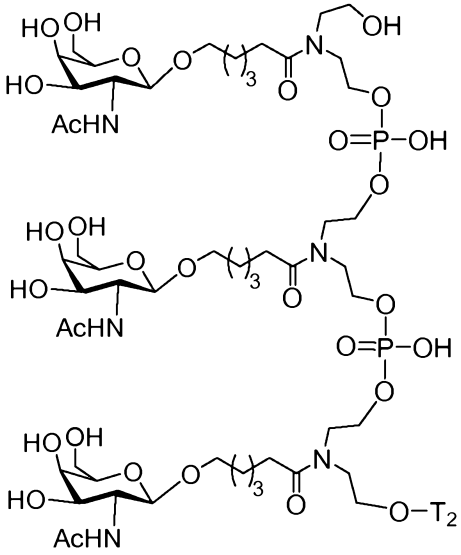
Embodiment 1499. A compound having the formula (XXIIIa):



wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

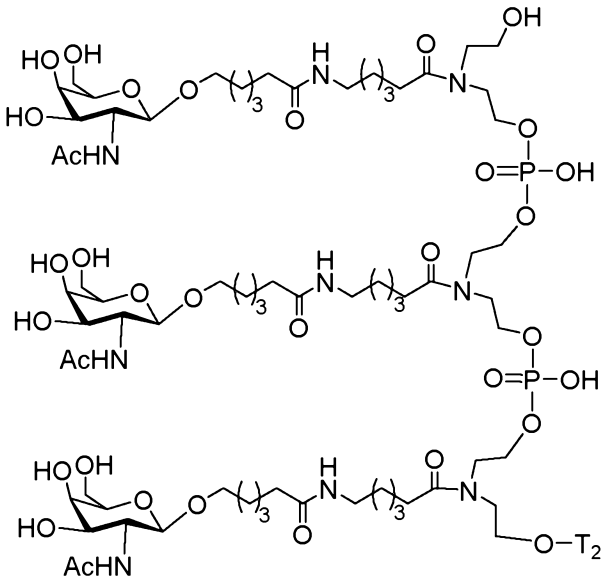
Embodiment 1500. A compound having the formula (XXIV):



wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1501. A compound having the formula (XXIVa):



wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1502. The compound of any of embodiments 1432 to 1502, wherein the oligomeric compound is a modified oligonucleotide.

Embodiment 1503. The compound of embodiment 1502, wherein the modified oligonucleotide is a gapmer.

Embodiment 1504. The compound of embodiment 1502, wherein the modified oligonucleotide activates RNase H when bound to a complementary target nucleic acid.

Embodiment 1505. The compound of any of embodiments 1502 to 1504, wherein the modified oligonucleotide comprises at least one modified nucleoside.

Embodiment 1506. The compound of embodiment 1505 wherein the at least one modified nucleoside comprises a modified base.

Embodiment 1507. The compound of embodiment 1505 or 1506 wherein the at least one modified nucleoside comprises a sugar surrogate.

Embodiment 1508. The compound of embodiment 1507 wherein the sugar surrogate is a tetrahydropyran.

Embodiment 1509. The compound of embodiment 1508 wherein the tetrahydropyran is F-HNA.

Embodiment 1510. The compound of any of embodiments 1505 to 1509 wherein the remainder of the modified oligonucleotide comprises at least one nucleoside comprising a modified sugar.

Embodiment 1511. The compound of embodiment any of embodiments 1502 to 1510 wherein the modified oligonucleotide comprises at least one nucleoside comprising a modified sugar.

Embodiment 1512. The compound of embodiment 1511 wherein the at least one modified nucleoside comprising a modified sugar is selected from a bicyclic nucleoside and a 2'-modified nucleoside.

Embodiment 1513. The compound of embodiment 1512 wherein the at least one modified nucleoside is a bicyclic nucleoside.

Embodiment 1514. The compound of embodiment 1513 wherein the bicyclic nucleoside is a (4'-CH_2-O-2') BNA nucleoside.

Embodiment 1515. The compound of embodiment 1513 wherein the bicyclic nucleoside is a (4'-$(CH_2)_2$-O-2') BNA nucleoside.

Embodiment 1516. The compound of embodiment 1513 wherein the bicyclic nucleoside is a (4'-$C(CH_3)H$-O-2') BNA nucleoside.

Embodiment 1517. The compound of embodiment 1513 wherein the at least one modified nucleoside is a 2'-modifed nucleoside.

Embodiment 1518. The compound of embodiment 1512 wherein the at least one 2'-modified nucleoside is selected from a 2'-F nucleoside, a 2'-OCH_3 nucleoside, and a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 1519. The compound of embodiment 1518 wherein the at least one 2'-modified nucleoside is a 2'-F nucleoside.

Embodiment 1520. The compound of embodiment 1518 wherein the at least one 2'-modified nucleoside is a 2'-OCH_3 nucleoside.

Embodiment 1521. The compound of embodiment 1518 wherein the at least one 2'-modified nucleoside is a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 1522. The compound of any of embodiments 1502 to 1521 wherein the modified oligonucleotide comprises at least one unmodified nucleoside.

Embodiment 1523. The compound of embodiment 1522 wherein the unmodified nucleoside is a ribonucleoside.

Embodiment 1524. The compound of embodiment 1522 wherein the unmodified nucleoside is a deoxyribonucleoside.

Embodiment 1525. The compound of any of embodiments 1502 to 1524 wherein the modified oligonucleotide comprises at least two modified nucleosides.

Embodiment 1526. The compound of embodiment 1525 wherein the at least two modified nucleosides comprise the same modification.

Embodiment 1527. The compound of embodiment 1525 wherein the at least two modified nucleosides comprise different modifications.

Embodiment 1528. The compound of any of embodiments 1525 to 1527 wherein at least one of the at least two modified nucleosides comprises a sugar surrogate.

Embodiment 1529. The compound of any of embodiments 1525 to 1528 wherein at least one of the at least two modified nucleosides comprises a 2'-modification.

Embodiment 1530. The compound of embodiment 1529 wherein each of the at least two modified nucleosides is independently selected from 2'-F nucleosides, 2'-OCH_3 nucleosides and 2'-$O(CH_2)_2OCH_3$ nucleosides.

Embodiment 1531. The compound of embodiment 1530 wherein each of the at least two modified nucleosides is a 2'-F nucleoside.

Embodiment 1532. The compound of embodiment 1530 wherein each of the at least two modified nucleosides is a 2'-OCH_3 nucleosides.

Embodiment 1533. The compound of embodiment 1530 wherein each of the at least two modified nucleosides are a 2'-$O(CH_2)_2OCH_3$ nucleoside.

Embodiment 1534. The compound of any of embodiments 1502 to 1533, wherein essentially every nucleoside of the modified oligonucleotide is a modified nucleoside.

Embodiment 1535. The compound of any of embodiments 1502 to 1522 or 1525 to 1534 wherein every nucleoside of the modified oligonucleotide is a modified nucleoside.

Embodiment 1536. The compound of any of embodiments 1502 to 1533, wherein at least 4 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1537. The compound of any of embodiments 1520 to 1533, wherein at least 5 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1538. The compound of any of embodiments 1502 to 1533, wherein at least 6 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1539. The compound of any of embodiments 1502 to 1533, wherein at least 7 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1540. The compound of any of embodiments 1502 to 1533, wherein at least 8 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1541. The compound of any of embodiments 1502 to 1533, wherein at least 9 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1542. The compound of any of embodiments 1502 to 1533, wherein at least 10 nucleosides of the modified oligonucleotide are deoxyribonucleosides.

Embodiment 1543. The compound of any of embodiments 1536 to 1542, wherein each of the deoxyribonucleosides of the modified oligonucleotide are consecutively linked by internucleoside linkages.

Embodiment 1544. The compound of any of embodiments 1502 to 1543, wherein the modified oligonucleotide is single-stranded.

Embodiment 1545. The compound of any of embodiments 1502 to 1543, wherein the modified oligonucleotide is double-stranded.

Embodiment 1546. The compound of any of embodiments 1502 to 1543, wherein the modified oligonucleotide is an antisense compound.

Embodiment 1547. The compound of any of embodiments 1502 to 1543, wherein the modified oligonucleotide is a RISC based oligonucleotide.

Embodiment 1548. The compound of any of embodiments 1502 to 1543, wherein the modified oligonucleotide activates the RISC pathway.

Embodiment 1549. The compound of any of embodiments 1502 to 1547, wherein the oligonucleotide is an RNase H based antisense compound.

Embodiment 1550. The compound of any of embodiments 1502 to 1534 or 1536 to 1546, wherein the compound has a sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1551. The compound of embodiment 1550, wherein the 5'-region consists of 2 linked 5'-region nucleosides.

Embodiment 1552. The compound of embodiment 1550, wherein the 5'-region consists of 3 linked 5'-region nucleosides.

Embodiment 1553. The compound of embodiment 1550, wherein the 5'-region consists of 4 linked 5'-region nucleosides.

Embodiment 1554. The compound of embodiment 1550, wherein the 5'-region consists of 5 linked 5'-region nucleosides.

Embodiment 1555. The compound of any of embodiments 1550 to 1554, wherein the 3'-region consists of 2 linked 3'-region nucleosides.

Embodiment 1556. The compound of any of embodiments 1550 to 1554, wherein the 3'-region consists of 3 linked 3'-region nucleosides.

Embodiment 1557. The compound of any of embodiments 1550 to 1554, wherein the 3'-region consists of 4 linked 3'-region nucleosides.

Embodiment 1558. The compound of any of embodiments 1550 to 1554, wherein the 3'-region consists of 5 linked 3'-region nucleosides.

Embodiment 1559. The compound of any of embodiments 1550 to 1558, wherein the central region consists of 5 linked central region nucleosides.

Embodiment 1560. The compound of any of embodiments 1550 to 1558, wherein the central region consists of 6 linked central region nucleosides.

Embodiment 1561. The compound of any of embodiments 1550 to 1558, wherein the central region consists of 7 linked central region nucleosides.

Embodiment 1562. The compound of any of embodiments 1550 to 1558, wherein the central region consists of 8 linked central region nucleosides.

Embodiment 1563. The compound of any of embodiments 1550 to 1558, wherein the central region consists of 9 linked central region nucleosides.

Embodiment 1564. The compound of any of embodiments 1550 to 1558, wherein the central region consists of 10 linked central region nucleosides.

Embodiment 1565. The compound of any of embodiments 1550 to 1564, wherein the compound consists of 14 to 26 linked nucleosides.

Embodiment 1566. The compound of any of embodiments 1550 to 1564, wherein the compound consists of 15 to 25 linked nucleosides.

Embodiment 1567. The compound of any of embodiments 1550 to 1564, wherein the compound consists of 16 to 20 linked nucleosides.

Embodiment 1568. The compound of any of embodiments 1550 to 1567, wherein each modified nucleoside independently comprises a 2'-substituted sugar moiety or a bicyclic sugar moiety.

Embodiment 1569. The compound of embodiment 1568, wherein the at least one modified nucleoside comprises a 2'-substituted sugar moiety.

Embodiment 1570. The compound of embodiment 1569, wherein each modified nucleoside comprising a 2'-substituted sugar moiety comprises a 2' substituent independently selected from among: halogen, optionally substituted allyl, optionally substituted amino, azido, optionally substituted SH, CN, OCN, CF3, OCF3, O, S, or N(Rm)-alkyl; O, S, or N(Rm)-alkenyl; O, S or N(Rm)-alkynyl; optionally substituted O-alkylenyl-O-alkyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted aralkyl, optionally substituted O-alkaryl, optionally substituted O-aralkyl, O(CH2)2SCH3, O-(CH2)2-O-N(Rm)(Rn) or O-CH2-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl;
wherein each optionally substituted group is optionally substituted with a substituent group independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO_2), thiol, thioalkoxy (S-alkyl), halogen, alkyl, aryl, alkenyl and alkynyl.

Embodiment 1571. The compound of embodiment 1569, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_3, $O(CH_2)_2F$, OCH_2CHF_2,

OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-SCH_3, $O(CH_2)_2$-OCF_3, $O(CH_2)_3$-$N(R_1)(R_2)$, $O(CH_2)_2$-$ON(R_1)(R_2)$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_1)(R_2)$, $OCH_2C(=O)$-$N(R_3)$-$(CH_2)_2$-$N(R_1)(R_2)$, and $O(CH_2)_2$-$N(R_3)$-$C(=NR_4)[N(R_1)(R_2)]$; wherein R_1, R_2, R_3 and R_4 are each, independently, H or C_1-C_6 alkyl.

Embodiment 1572. The compound of embodiment 1569, wherein each 2' substituent is independently selected from among: a halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-CH=CH_2, $O(CH_2)_2$-OCH_3 (MOE), $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$, and OCH_2-$N(H)$-$C(=NH)NH_2$.

Embodiment 1573. The compound of embodiment 1569, wherein the at least one 2'-modified nucleoside comprises a 2'-MOE sugar moiety.

Embodiment 1574. The compound of embodiment 1569, wherein the at least one 2'-modified nucleoside comprises a 2'-OMe sugar moiety.

Embodiment 1575. The compound of embodiment 1569, wherein the at least one 2'-modified nucleoside comprises a 2'-F sugar moiety.

Embodiment 1576. The compound of any of embodiments 1550 to 1575, wherein the compound comprises at least one modified nucleoside comprising a sugar surrogate.

Embodiment 1577. The compound of embodiment 1576, wherein the modified nucleoside comprises an F-HNA sugar moiety.

Embodiment 1578. The compound of embodiment 1576, wherein the modified nucleoside comprises an HNA sugar moiety.

Embodiment 1579. The compound of any of embodiments 1550 to 1578 wherein the compound comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

Embodiment 1580. The compound of embodiment 1579, wherein the bicyclic sugar moiety is a cEt sugar moiety.

Embodiment 1581. The compound of embodiment 1579, wherein bicyclic sugar moiety is an LNA sugar moiety.

Embodiment 1582. The compound of any of embodiments 1502 to 1581, wherein the compound comprises at least one modified internucleoside linkage.

Embodiment 1583. The compound of embodiment 1582, wherein each internucleoside linkage of the compound is a modified internucleoside linkage.

Embodiment 1584. The compound of embodiment 1582, wherein the compound comprises at least one modified linkage and at least one unmodified phosphodiester internucleoside linkage.

Embodiment 1585. The compound of any of embodiments 1582 or 1584 wherein at least one modified internucleoside linkage is a phosphosphorothioate internucleoside linkage.

Embodiment 1586. The compound of any of embodiments 1584 or 1585, wherein each modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 1587. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 1588. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 1589. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 1590. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 1591. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 1592. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 1593. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 8 phosphodiester internucleoside linkages.

Embodiment 1594. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 9 phosphodiester internucleoside linkages.

Embodiment 1595. The compound of any of embodiments 1584 or 1585, wherein the compound comprises at least 10 phosphodiester internucleoside linkages.

Embodiment 1596. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 16 phosphorothioate internucleoside linkages.

Embodiment 1597. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 15 phosphorothioate internucleoside linkages.

Embodiment 1598. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 14 phosphorothioate internucleoside linkages.

Embodiment 1599. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 13 phosphorothioate internucleoside linkages.

Embodiment 1600. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 12 phosphorothioate internucleoside linkages.

Embodiment 1601. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 11 phosphorothioate internucleoside linkages.

Embodiment 1602. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 10 phosphorothioate internucleoside linkages.

Embodiment 1603. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 9 phosphorothioate internucleoside linkages.

Embodiment 1604. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 8 phosphorothioate internucleoside linkages.

Embodiment 1605. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 7 phosphorothioate internucleoside linkages.

Embodiment 1606. The compound of any of embodiments 1584 or 1595, wherein the compound comprises fewer than 6 phosphorothioate internucleoside linkages.

Embodiment 1607. The compound of any of embodiments 1502 to 1605, wherein each terminal internucleoside linkage of the compound is a phosphorothioate internucleoside linkage.

Embodiment 1608. The compound of any of embodiments 1502 to 1605, wherein each internucleoside linkage linking two deoxynucleosides of the compound is a phosphorothioate internucleoside linkage.

Embodiment 1609. The compound of any of embodiments 1502 to 1605, wherein each non-terminal internucleoside linkage linking two modified nucleosides of the compound is a phosphodiester internucleoside linkage.

Embodiment 1610. The compound of any of embodiments 1502 to 1605, wherein each non-terminal internucleoside linkage of the compound that is 3' of a modified nucleoside is a phosphodiester internucleoside linkage.

Embodiment 1611. The compound of any of embodiments 1502 to 1605, wherein each internucleoside linkage of the compound that is 3' of a deoxynucleoside is a phosphorothioate internucleoside linkage.

Embodiment 1612. The compound of any of embodiments 1502 to 1588, wherein the compound has a chemical motif selected from among:

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$

$MsMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMsM$
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMsM$; and
$MsMyMyMyMy(Ds)_{0-1}(DsDs)_{(3-5)}MyMyMyMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each s is a phosphorothioate internucleoside linkage, and each y is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage, provided that at least one y is a phosphodiester internucleotide linkage.

Embodiment 1613. The compound of any of embodiments 1502 to 1588, wherein the compounds has a chemical motif selected from among:

$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$
$MsMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMsM$
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMsM$; and
$MsMoMoMoMo(Ds)_{0-1}(DsDs)_{(3-5)}MoMoMoMsM$;

wherein each M is independently a modified nucleoside, each D is a deoxynucleoside; each o is a phosphodiester internucleoside linkage, and each s is a phosphorothioate internucleoside linkage.

Embodiment 1614. The compound of embodiment 1612 or 1613, wherein each M is independently selected from among: a 2'-MOE nucleoside and a bicyclic nucleoside.

Embodiment 1615. The compound of embodiment 1614, wherein each M is independently selected from among a 2'-MOE nucleoside, a cEt nucleoside, and an LNA nucleoside.

Embodiment 1616. The compound of embodiment 1612 or 1613, wherein each M is a 2'-MOE nucleoside.

Embodiment 1617. The compound of embodiment 1612 or 1613, wherein each M is a cEt nucleoside.

Embodiment 1618. The compound of embodiments 1612 or 1613, wherein each M is an LNA nucleoside.

Embodiment 1619. The compound of any of embodiments 1502 to 1618, wherein the compound has a nucleobase sequence comprising an at least 8 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1620. The compound of any of embodiments 1502 to 1618, wherein the compound has a nucleobase sequence comprising an at least 10 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1621. The compound of any of embodiments 1502 to 1618, wherein the compound has a nucleobase sequence comprising an at least 12 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1622. The compound of any of embodiments 1502 to 1618, wherein the compound has a nucleobase sequence comprising an at least 14 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1623. The compound of any of embodiments 1502 to 1618, wherein the compound has a nucleobase sequence comprising an at least 16 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1624. The compound of any of embodiments 1502 to 1618, wherein the compound has a nucleobase sequence comprising an at least 18 nucleobase portion complementary to an equal length portion of a target nucleic acid.

Embodiment 1625. The compound of any of embodiments 1502 to 1618, wherein the compound is at least 90% complementary to a target nucleic acid.

Embodiment 1626. The compound of any of embodiments 1502 to 1618, wherein the compound is at least 95% complementary to a target nucleic acid.

Embodiment 1627. The compound of any of embodiments 1502 to 1618, wherein the compound is 100% complementary to a target nucleic acid.

Embodiment 1628. The compound of embodiment 1627, wherein the target nucleic acid is a pre-mRNA.

Embodiment 1629. The compound of embodiment 1627, wherein the target nucleic acid is an mRNA.

Embodiment 1630. The compound of embodiment 1627, wherein the target nucleic acid is a micro RNA.

Embodiment 1631. The compound of embodiment 1627, wherein the target nucleic acid is expressed in the liver.

Embodiment 1632. The compound of embodiment 1627, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 1633. The compound of embodiment 1627, wherein the target nucleic encodes a protein selected from among: Alpha 1 antitrypsin, Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI, Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, SRB-1, and Transthyretin.

Embodiment 1634. The compound of embodiment 1627, wherein the target nucleic acid is a viral nucleic acid.

Embodiment 1635. The compound of embodiment 1634, wherein the viral nucleic acid expressed in the liver.

Embodiment 1636. The compound of embodiment 1634, wherein the target nucleic acid is a Hepatitis B viral nucleic acid.

Embodiment 1637. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any one of SEQ ID NOs.: 17, 18, 19, 20, 21, 22, 23, or 24.

Embodiment 1638. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any one of SEQ ID NO.: 25, 26, 27, 28, 29, or 30.

Embodiment 1639. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 31.

Embodiment 1640. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 32.

Embodiment 1641. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 33.

Embodiment 1642. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 34.

Embodiment 1643. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any of SEQ ID NOs.: 35, 36, 37, 38, 39, 40, 41, 42, or 43.

Embodiment 1644. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 44, 45, 46, 47, or 48.

Embodiment 1645. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any of SEQ ID NOs.: 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 1646. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any of SEQ ID NOs.: 60, 61, 62, 63, 64, 65, 66, or 67.

Embodiment 1647. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any of SEQ ID NO.: 69, 70, 71, or 72.

Embodiment 1648. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 73.

Embodiment 1649. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any of SEQ ID NOs.: 74, 75, 76, 77, 78, 79, 80, or 81.

Embodiment 1650. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of SEQ ID NO.: 68.

Embodiment 1651. The compound of any of embodiments 1502 to 1627, wherein the compound comprises the nucleobase sequence of any of SEQ ID NOs.: 82-103, 111, or 113.

Embodiment 1652. The compound of any of embodiments 1502 to 1627, wherein the compound is an antisense oligonucleotide.

Embodiment 1653. A pharmaceutical composition comprising a compound or compound according to any of embodiments 1502 to 1652 and a pharmaceutically acceptable carrier or diluent.

Embodiment 1654. The pharmaceutical composition of embodiment 1653 wherein the pharmaceutically acceptable carrier or diluent is selected from among sterile water and sterile saline.

Embodiment 1655. A method of reducing the amount or activity of a target nucleic acid in a cell, comprising contacting a cell with a compound or conjugated antisense compound of any of embodiments 1498 to 1648, or the pharmaceutical composition of embodiments 1653to 1654.

Embodiment 1656. The method of embodiment 1655, wherein the cell is a liver cell.

Embodiment 1657. The method of embodiment 1655, wherein the cell is a hepatocyte.

Embodiment 1658. The method of any of embodiments 1655 to 1657, wherein the cell is in vitro.

Embodiment 1659. The method of any of embodiments 1655 to 1657, wherein the cell is in an animal.

Embodiment 1660. The method of embodiment 1659 wherein the animal is a mouse.

Embodiment 1661. The method of embodiment 1659 wherein the animal is a human.

Embodiment 1662. A method of treating a disease or condition in an animal comprising administering the pharmaceutical composition of embodiment 1653 or 1654 to the animal and thereby treating the disease or condition in the animal.

Embodiment 1663. The method of embodiment 1662 wherein the animal is a mouse.

Embodiment 1664. The method of embodiment 1662 wherein the animal is a human.

Embodiment 1665. The method of any of embodiments 1662 to 1664, wherein the disease or condition is a liver disease or condition.

Embodiment 1666. The method of any of embodiments 1662 to 1665, wherein the administration is parenteral.

Embodiment 1667. The method of any of embodiments 1662 to 1665, wherein the administration is by subcutaneous injection.

Embodiment 1668. The method of any of embodiments 1662 to 1665, wherein the administration is by intravenous injection.

Embodiment 1669. The method of any of embodiments 1662 to 1665, wherein the administration is by intramuscular injection.

Embodiment 1670. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dose of 1-10 mg/kg.

Embodiment 1671. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dose of less than 1 mg/kg.

Embodiment 1672. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dose of greater than 10 mg/kg.

Embodiment 1673. The method of any of embodiments 1662 to 1669, wherein the compound is provided for a dosing period of at least 2 months.

Embodiment 1674. The method of any of embodiments 1662 to 1669, wherein the compound is provided for a dosing period of at least 4 months.

Embodiment 1675. The method of any of embodiments 1662 to 1669, wherein the compound is provided for a dosing period of at least 6 months.

Embodiment 1676. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of about one dose every week.

Embodiment 1677. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of about one dose every two weeks.

Embodiment 1678. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of about one dose every three weeks.

Embodiment 1679. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of one dose every four weeks.

Embodiment 1680. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of one dose every five weeks.

Embodiment 1681. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of one dose every six weeks.

Embodiment 1682. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of one dose every seven weeks.

Embodiment 1683. The method of any of embodiments 1662 to 1669, wherein the compound is provided at a dosing frequency of one dose every eight weeks.

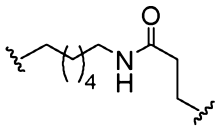
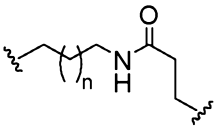
Embodiment 1684. The compound or compound of any of embodiments 1 to 1652, or a prodrug thereof.

Embodiment 1685. A method of manufacturing an antisense oligonucleotide of any of embodiments 1 to 1652.

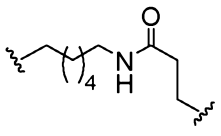
Embodiment 1686. A method of preparing an antisense oligonucleotide of any of embodiments 1 to 1652.

Embodiment 1687. A process for manufacturing a conjugated antisense compound of any one of embodiments 1 to 1652, wherein the method includes formulating the conjugated antisense compound for human use, performing chromatogram analysis of the formulated conjugated antisense compound, and packaging the conjugated antisense compound ready for sale.

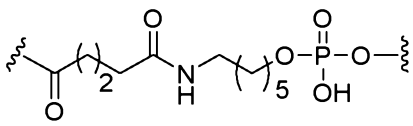
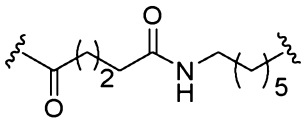
Embodiment 1688. The conjugated antisense compound of any of embodiments 1179 to 1182, wherein the tether has a structure selected from among:

 , or  ; wherein each n is independently, 0, 1, 2, 3, 4, 5, 6, or 7.

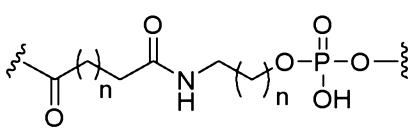
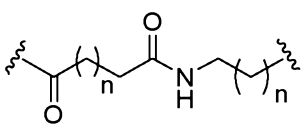
Embodiment 1689. The conjugated antisense compound of any of embodiments 1179 to 1182, wherein the tether has the structure:

 .

Embodiment 1690. The conjugated antisense compound of any of embodiments 1179 to 1182 or 1688 to 1689, wherein the linker has a structure selected from among:

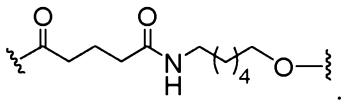
 and  .

Embodiment 1691. The conjugated antisense compound of any of embodiments 1179 to 1182 or 1688 to 1689, wherein the linker has a structure selected from among:

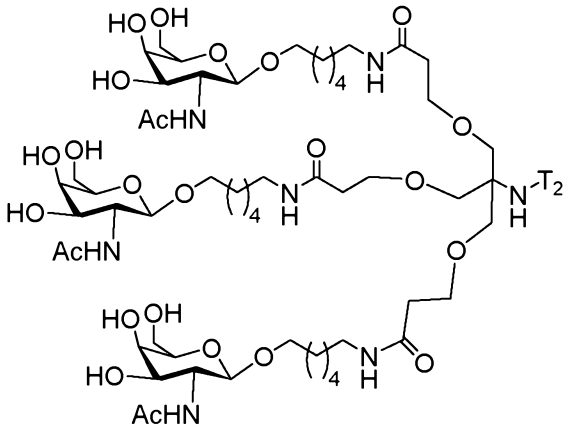
 and  ;

wherein each n is independently, 0, 1, 2, 3, 4, 5, 6, or 7.

Embodiment 1692. The conjugated antisense compound of any of embodiments 1179 to 1182 or 1688 to 1689, wherein the linker has the structure:



Embodiment 1693. A compound having the formula (XXVI):



(XXVI)

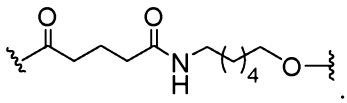
wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

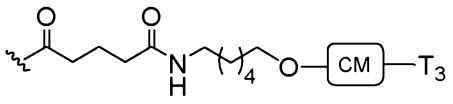
Embodiment 1694. The compound of embodiment 1693, wherein the linker comprises an amine, an amide, an ester, an ether, a pyrrolidine, PEG, a polyamide, or a disulfide bond.

Embodiment 1695. The compound of embodiment 1693 or 1694, wherein the linker does not comprise a pyrrolidine.

Embodiment 1696. The compound of any of embodiments 1693 to 1695, wherein the linker has the formula:



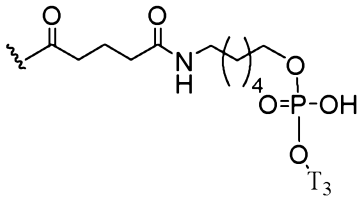
Embodiment 1697. The compound of any of embodiments 1693 to 1696, wherein T_2 has the formula:



wherein:

CM is a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1698. The compound of any of embodiments 1693 to 1697, wherein T_2 has the formula:



wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1699. The compound of any of embodiments 1693 to 1698, wherein T_2 or T_3 is a group comprising an oligomeric compound, and wherein the oligomeric compound is a modified oligonucleotide.

Embodiment 1700. The compound of embodiment 1699, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides wherein at least one nucleoside is a modified nucleoside.

Embodiment 1701. The compound of embodiment 1699 or 1700, wherein the modified oligonucleotide comprises at least one modified nucleoside selected from among: a 2'-MOE nucleoside, a 2'-OMe nucleoside, a 2'-F nucleoside, a (4'-CH_2-O-2') bicyclic nucleoside, a (4'-$(CH_2)_2$-O-2') bicyclic nucleoside, a (4'-$C(CH_3)$H-O-2') bicyclic nucleoside; and a morpholino.

Embodiment 1702. The compound of any of embodiments 1699 to1701, wherein the modified oligonucleotide has a gapmer sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1703. The compound of embodiment 1702, wherein each 5'-region nucleoside is a modified nucleoside; each 3'-region nucleoside is a modified nucleoside; and each central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1704. The compound of any of embodiments 1702 to 1704, wherein the 5'-region consists of 2-5 linked 5'-region nucleosides; the 3'-region consists of 2-5 linked 3'-region nucleosides; and the central region consists of 8-10 central region nucleosides.

Embodiment 1705. The compound of any of embodiments 1699 to 1704, wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage.

Embodiment 1706. The compound of any of embodiments 1699 to 1705, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1707. The compound of any of embodiments 1699 to 1706, wherein each internucleoside linkage of the modified oligonucleotide is either phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

Embodiment 1708. The compound of any of embodiments 1699 to 1707, wherein the modified oligonucleotide is attached to the remainder of the compound at the 5'-end of the modified oligonucleotide.

Embodiment 1709. The compound of any of embodiments 1699 to 1707, wherein the modified oligonucleotide is attached to the remainder of the compound at the 3'-end of the modified oligonucleotide.

Embodiment 1710. The compound of any of embodiments 1699 to 1709, wherein the modified oligonucleotide is an antisense oligonucleotide.

Embodiment 1711. The compound of embodiment any of embodiments 1699 to 1710, wherein the modified oligonucleotide is single-stranded.

Embodiment 1712. The compound of any of embodiments 1699 to 1710, wherein the modified oligonucleotide is double-stranded.

Embodiment 1713. The compound of any of embodiments 1699 to 1712, wherein the modified oligonucleotide activates the RISC pathway.

Embodiment 1714. The compound of any of embodiments 1699 to 1712, wherein the modified oligonucleotide is an RNase H based antisense compound.

Embodiment 1715. The compound of any of embodiments 1699 to 1712, wherein the modified oligonucleotide alters splicing of a target pre-mRNA.

Embodiment 1716. The compound of any of embodiments 1699 to 1715, wherein the modified oligonucleotide is complementary to a target nucleic acid.

Embodiment 1717. The compound of embodiment 1716, wherein the target nucleic acid is selected from among: pre-mRNA, micro-RNA, or long non-coding RNA.

Embodiment 1718. The compound of any of embodiments 1699 to 1717, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Embodiment 1719. The compound of any of embodiments 1699 to 1717, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides.

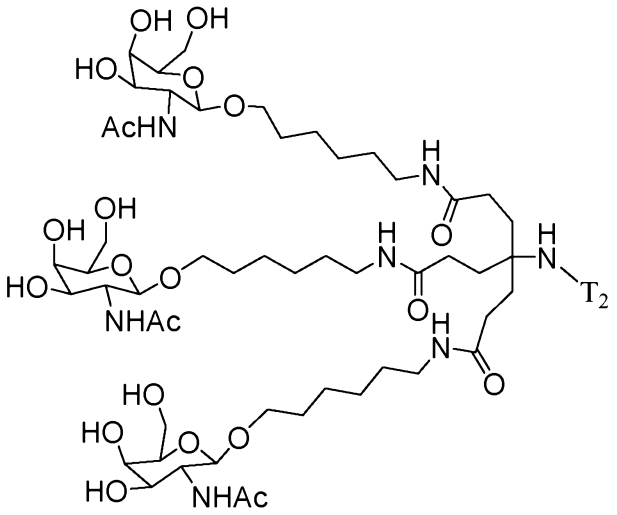
Embodiment 1720. The compound of any of embodiments 1699 to 1717, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1721. A method of administering the compound of any of embodiments 1693 to 1720 to an animal.

Embodiment 1722. A method of treating a metabolic disorder comprising administering the compound of any of embodiments 1693 to 1720 to a subject in need thereof.

Embodiment 1723. A method of treating a cardiovascular disorder comprising administering the compound of any of embodiments 1693 to 1720 to a subject in need thereof.

Embodiment 1724. A compound having the formula (XXXI):



(XXXI)

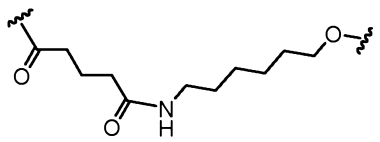
wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1725. The compound of embodiment 1724, wherein the linker comprises an amine, an amide, an ester, an ether, a pyrrolidine, PEG, a polyamide, or a disulfide bond.

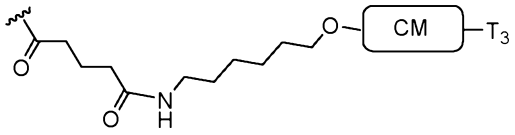
Embodiment 1726. The compound of embodiment 1724 or 1725, wherein the linker does not comprise a pyrrolidine.

Embodiment 1727. The compound of any of embodiments 1724 to 1726, wherein the linker is:



.

Embodiment 1728. The compound of any of embodiments 1724 to 1727, wherein T_2 has the formula:

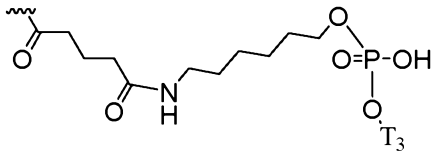


wherein:

CM represents a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or

an oligomeric compound.

Embodiment 1729. The compound of any of embodiments 1724 to 1728, wherein T_2 has the formula:



wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1730. The compound of any of embodiments 1724 to 1729, wherein T_2 or T_3 is a group comprising an oligomeric compound, and wherein the oligomeric compound is a modified oligonucleotide.

Embodiment 1731. The compound of embodiment 1730, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides wherein at least one nucleoside is a modified nucleoside.

Embodiment 1732. The compound of embodiment 1730 or 1731, wherein the modified oligonucleotide comprises at least one modified nucleoside selected from among: a 2'-MOE nucleoside, a 2'-OMe nucleoside, a 2'-F nucleoside, a (4'-CH_2-O-2') bicyclic nucleoside, a (4'-$(CH_2)_2$-O-2') bicyclic nucleoside, a (4'-$C(CH_3)$H-O-2') bicyclic nucleoside; and a morpholino.

Embodiment 1733. The compound of any of embodiments 1730 to 1732, wherein the modified oligonucleotide has a gapmer sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1734. The compound of embodiment 1733, wherein each 5'-region nucleoside is a modified nucleoside; each 3'-region nucleoside is a modified nucleoside; and each central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1735. The compound of any of embodiments 1733 to 1734, wherein the 5'-region consists of 2-5 linked 5'-region nucleosides; the 3'-region consists of 2-5 linked 3'-region nucleosides; and the central region consists of 8-10 central region nucleosides.

Embodiment 1736. The compound of any of embodiments 1730 to 1735, wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage.

Embodiment 1737. The compound of any of embodiments 1730 to 1736, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1738. The compound of any of embodiments 1730 to 1737, wherein each internucleoside linkage of the modified oligonucleotide is either phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

Embodiment 1739. The compound of any of embodiments 1730 to 1738, wherein the modified oligonucleotide is attached to the remainder of the compound at the 5'-end of the modified oligonucleotide.

Embodiment 1740. The compound of any of embodiments 1730 to 1738, wherein the modified oligonucleotide is attached to the remainder of the compound at the 3'-end of the modified oligonucleotide.

Embodiment 1741. The compound of any of embodiments 1730 to 1740, wherein the modified oligonucleotide is an antisense oligonucleotide.

Embodiment 1742. The compound of embodiment any of embodiments 1730 to 1741, wherein the modified oligonucleotide is single-stranded.

Embodiment 1743. The compound of any of embodiments 1730 to 1741, wherein the modified oligonucleotide is double-stranded.

Embodiment 1744. The compound of any of embodiments 1730 to 1743, wherein the modified oligonucleotide activates the RISC pathway.

Embodiment 1745. The compound of any of embodiments 1730 to 1743, wherein the modified oligonucleotide is an RNase H based antisense compound.

Embodiment 1746. The compound of any of embodiments 1730 to 1743, wherein the modified oligonucleotide alters splicing of a target pre-mRNA.

Embodiment 1747. The compound of any of embodiments 1730 to 1746, wherein the modified oligonucleotide is complementary to a target nucleic acid.

Embodiment 1748. The compound of embodiment 1747, wherein the target nucleic acid is selected from among: pre-mRNA, micro-RNA, or long non-coding RNA.

Embodiment 1749. The compound of any of embodiments 1730 to 1748, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Embodiment 1750. The compound of any of embodiments 1730 to 1748, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides.

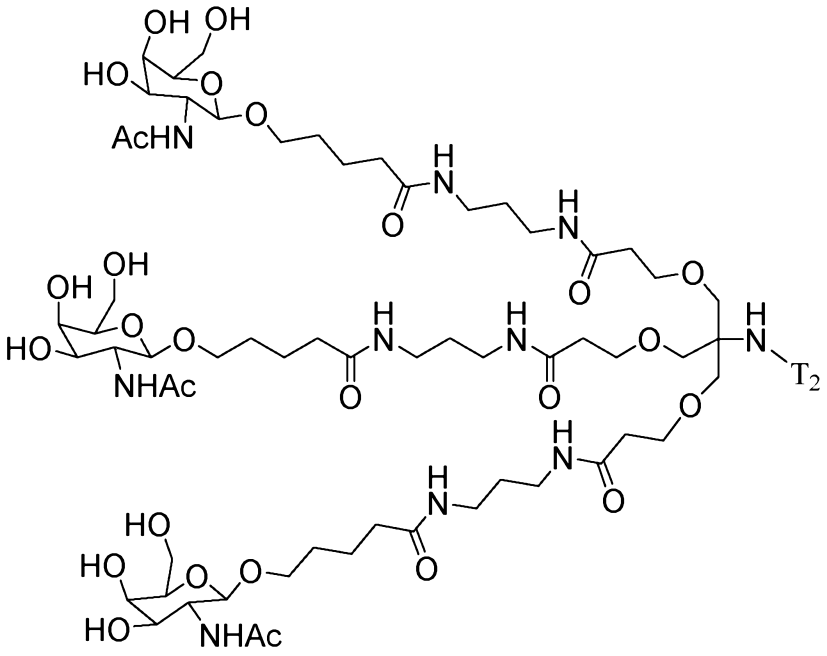
Embodiment 1751. The compound of any of embodiments 1730 to 1748, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1752. A method of administering the compound of any of embodiments 1724 to 1751 to an animal.

Embodiment 1753. A method of treating a metabolic disorder comprising administering the compound of any of embodiments 1724 to 1751 to a subject in need thereof.

Embodiment 1754. A method of treating a cardiovascular disorder comprising administering the compound of any of embodiments 1724 to 1751 to a subject in need thereof.

Embodiment 1755. A compound having the formula (XXXII):



(XXXII)

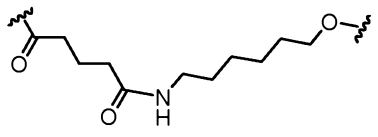
wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1756. The compound of embodiment 1755, wherein the linker comprises an amine, an amide, an ester, an ether, a pyrrolidine, PEG, a polyamide, or a disulfide bond.

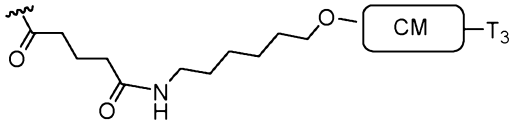
Embodiment 1757. The compound of embodiment 1755 or 1756, wherein the linker does not comprise a pyrrolidine.

Embodiment 1758. The compound of any of embodiments 1755 to 1757, wherein the linker is:



.

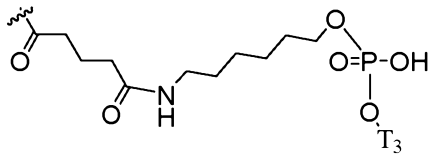
Embodiment 1759. The compound of any of embodiments 1755 to 1758, wherein T_2 has the formula:



wherein:

CM is a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1760. The compound of any of embodiments 1755 to 1759, wherein T_2 has the formula:



wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1761. The compound of any of embodiments 1755 to 1760, wherein T_2 or T_3 is a group comprising an oligomeric compound, and wherein the oligomeric compound is a modified oligonucleotide.

Embodiment 1762. The compound of embodiment 1761, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides wherein at least one nucleoside is a modified nucleoside.

Embodiment 1763. The compound of embodiment 1761 or 1762, wherein the modified oligonucleotide comprises at least one modified nucleoside selected from among: a 2'-MOE nucleoside, a 2'-OMe nucleoside, a 2'-F nucleoside, a (4'-CH_2-O-2') bicyclic nucleoside, a (4'-$(CH_2)_2$-O-2') bicyclic nucleoside, a (4'-$C(CH_3)$H-O-2') bicyclic nucleoside; and a morpholino.

Embodiment 1764. The compound of any of embodiments 1761 to 1763, wherein the modified oligonucleotide has a gapmer sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1765. The compound of embodiment 1764, wherein each 5'-region nucleoside is a modified nucleoside; each 3'-region nucleoside is a modified nucleoside; and each central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1766. The compound of any of embodiments 1764 to 1765, wherein the 5'-region consists of 2-5 linked 5'-region nucleosides; the 3'-region consists of 2-5 linked 3'-region nucleosides; and the central region consists of 8-10 central region nucleosides.

Embodiment 1767. The compound of any of embodiments 1761 to 1766, wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage.

Embodiment 1768. The compound of any of embodiments 1761 to 1767, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1769. The compound of any of embodiments 1761 to 1768, wherein each internucleoside linkage of the modified oligonucleotide is either phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

Embodiment 1770. The compound of any of embodiments 1761 to 1769, wherein the modified oligonucleotide is attached to the remainder of the compound at the 5'-end of the modified oligonucleotide.

Embodiment 1771. The compound of any of embodiments 1761 to 1769, wherein the modified oligonucleotide is attached to the remainder of the compound at the 3'-end of the modified oligonucleotide.

Embodiment 1772. The compound of any of embodiments 1761 to 1771, wherein the modified oligonucleotide is an antisense oligonucleotide.

Embodiment 1773. The compound of embodiment any of embodiments 1761 to 1772, wherein the modified oligonucleotide is single-stranded.

Embodiment 1774. The compound of any of embodiments 1761 to 1772, wherein the modified oligonucleotide is double-stranded.

Embodiment 1775. The compound of any of embodiments 1761 to 1774, wherein the modified oligonucleotide activates the RISC pathway.

Embodiment 1776. The compound of any of embodiments 1761 to 1774, wherein the modified oligonucleotide is an RNase H based antisense compound.

Embodiment 1777. The compound of any of embodiments 1761 to 1774, wherein the modified oligonucleotide alters splicing of a target pre-mRNA.

Embodiment 1778. The compound of any of embodiments 1761 to 1777, wherein the modified oligonucleotide is complementary to a target nucleic acid.

Embodiment 1779. The compound of embodiment 1779, wherein the target nucleic acid is selected from among: pre-mRNA, micro-RNA, or long non-coding RNA.

Embodiment 1780. The compound of any of embodiments 1761 to 1779, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Embodiment 1781. The compound of any of embodiments 1761 to 1779, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides.

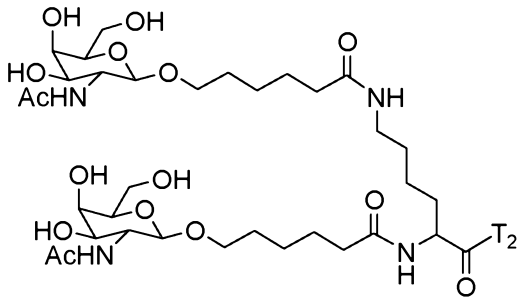
Embodiment 1782. The compound of any of embodiments 1761 to 1779, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1783. A method of administering the compound of any of embodiments 1755 to 1782 to an animal.

Embodiment 1784. A method of treating a metabolic disorder comprising administering the compound of any of embodiments 1755 to 1782 to a subject in need thereof.

Embodiment 1785. A method of treating a cardiovascular disorder comprising administering the compound of any of embodiments 1755 to 1782 to a subject in need thereof.

Embodiment 1786. A compound having the formula(XXXVIII):



(XXXVIII)

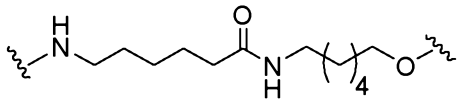
wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

Embodiment 1787. The compound of embodiment 1786, wherein the linker comprises an amine, an amide, an ester, an ether, a pyrrolidine, PEG, a polyamide, or a disulfide bond.

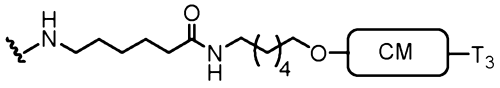
Embodiment 1788. The compound of embodiment 1786 or 1787, wherein the linker does not comprise a pyrrolidine.

Embodiment 1789. The compound of any of embodiments 1786 to 1788, wherein the linker is:



.

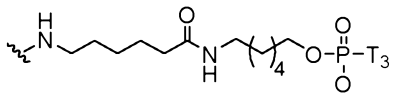
Embodiment 1790. The compound of any of embodiments 1786 to 1789, wherein T_2 has the formula:



wherein:

CM is a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1791. The compound of any of embodiments 1786 to 1790, wherein T_2 has the formula:



wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1792. The compound of any of embodiments 1786 to 1791, wherein T_2 or T_3 is a group comprising an oligomeric compound, and wherein the oligomeric compound is a modified oligonucleotide.

Embodiment 1793. The compound of embodiment 1792, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides wherein at least one nucleoside is a modified nucleoside.

Embodiment 1794. The compound of embodiment 1792 or 1793, wherein the modified oligonucleotide comprises at least one modified nucleoside selected from among: a 2'-MOE nucleoside, a 2'-OMe nucleoside, a 2'-F nucleoside, a (4'-CH_2-O-2') bicyclic nucleoside, a (4'-$(CH_2)_2$-O-2') bicyclic nucleoside, a (4'-$C(CH_3)$H-O-2') bicyclic nucleoside; and a morpholino.

Embodiment 1795. The compound of any of embodiments 1792 to 1794, wherein the modified oligonucleotide has a gapmer sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1796. The compound of embodiment 1795, wherein each 5'-region nucleoside is a modified nucleoside; each 3'-region nucleoside is a modified nucleoside; and each central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1797. The compound of any of embodiments 1795 to 1796, wherein the 5'-region consists of 2-5 linked 5'-region nucleosides; the 3'-region consists of 2-5 linked 3'-region nucleosides; and the central region consists of 8-10 central region nucleosides.

Embodiment 1798. The compound of any of embodiments 1792 to 1797, wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage.

Embodiment 1799. The compound of any of embodiments 1792 to 1798, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1800. The compound of any of embodiments 1792 to 1799, wherein each internucleoside linkage of the modified oligonucleotide is either phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

Embodiment 1801. The compound of any of embodiments 1792 to 1800, wherein the modified oligonucleotide is attached to the remainder of the compound at the 5'-end of the modified oligonucleotide.

Embodiment 1802. The compound of any of embodiments 1792 to 1800, wherein the modified oligonucleotide is attached to the remainder of the compound at the 3'-end of the modified oligonucleotide.

Embodiment 1803. The compound of any of embodiments 1792 to 1802, wherein the modified oligonucleotide is an antisense compound.

Embodiment 1804. The compound of embodiment any of embodiments 1792 to 1803, wherein the modified oligonucleotide is single-stranded.

Embodiment 1805. The compound of any of embodiments 1792 to 1803, wherein the modified oligonucleotide is double-stranded.

Embodiment 1806. The compound of any of embodiments 1792 to 1805, wherein the modified oligonucleotide activates the RISC pathway.

Embodiment 1807. The compound of any of embodiments 1792 to 1805, wherein the modified oligonucleotide is an RNase H based antisense compound.

Embodiment 1808. The compound of any of embodiments 1792 to 1805, wherein the modified oligonucleotide alters splicing of a target pre-mRNA.

Embodiment 1809. The compound of any of embodiments 1792 to 1808, wherein the modified oligonucleotide is complementary to a target nucleic acid.

Embodiment 1810. The compound of embodiment 1809, wherein the target nucleic acid is selected from among: pre-mRNA, micro-RNA, or long non-coding RNA.

Embodiment 1811. The compound of any of embodiments 1792 to 1810, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Embodiment 1812. The compound of any of embodiments 1792 to 1810, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides.

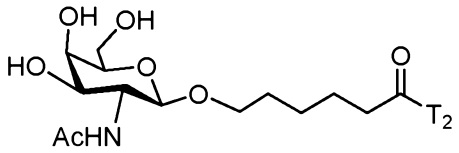
Embodiment 1813. The compound of any of embodiments 1792 to 1810, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1814. A method of administering the compound of any of embodiments 1786 to 1813 to an animal.

Embodiment 1815. A method of treating a metabolic disorder comprising administering the compound of any of embodiments 1786 to 1813 to a subject in need thereof.

Embodiment 1816. A method of treating a cardiovascular disorder comprising administering the compound of any of embodiments 1786 to 1813 to a subject in need thereof.

Embodiment 1817. A compound having the formula (XL):



(XL)

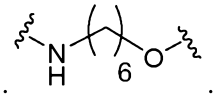
wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

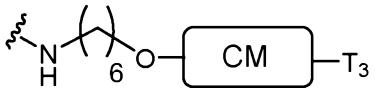
Embodiment 1818. The compound of embodiment 1817, wherein the linker comprises an amine, an amide, an ester, an ether, a pyrrolidine, PEG, a polyamide, or a disulfide bond.

Embodiment 1819. The compound of embodiment 1817 or 1818, wherein the linker does not comprise a pyrrolidine.

Embodiment 1820. The compound of any of embodiments 1817 to 1819, wherein the linker is:



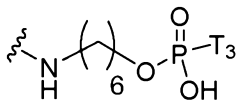
Embodiment 1821. The compound of any of embodiments 1817 to 1820, wherein T_2 has the formula:



wherein:

CM is a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1822. The compound of any of embodiments 1817 to 1821, wherein T_2 has the formula:



wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

Embodiment 1823. The compound of any of embodiments 1817 to 1822, wherein T_2 or T_3 is a group comprising an oligomeric compound, and wherein the oligomeric compound is a modified oligonucleotide.

Embodiment 1824. The compound of embodiment 1823, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides wherein at least one nucleoside is a modified nucleoside.

Embodiment 1825. The compound of embodiment 1824, wherein the modified oligonucleotide comprises at least one modified nucleoside selected from among: a 2'-MOE nucleoside, a 2'-OMe nucleoside, a 2'-F nucleoside, a (4'-CH_2-O-2') bicyclic nucleoside, a (4'-$(CH_2)_2$-O-2') bicyclic nucleoside, a (4'-$C(CH_3)$H-O-2') bicyclic nucleoside; and a morpholino.

Embodiment 1826. The compound of any of embodiments 1824 to 1825, wherein the modified oligonucleotide has a gapmer sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1827. The compound of embodiment 1826, wherein each 5'-region nucleoside is a modified nucleoside; each 3'-region nucleoside is a modified nucleoside; and each central region nucleoside is an unmodified deoxynucleoside.

Embodiment 1828. The compound of any of embodiments 1825 to 1826, wherein the 5'-region consists of 2-5 linked 5'-region nucleosides; the 3'-region consists of 2-5 linked 3'-region nucleosides; and the central region consists of 8-10 central region nucleosides.

Embodiment 1829. The compound of any of embodiments 1824 to 1828 wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage.

Embodiment 1830. The compound of any of embodiments 1824 to 1829, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1831. The compound of any of embodiments 1824 to 1830, wherein each internucleoside linkage of the modified oligonucleotide is either phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

Embodiment 1832. The compound of any of embodiments 1824 to 1831, wherein the modified oligonucleotide is attached to the remainder of the compound at the 5'-end of the modified oligonucleotide.

Embodiment 1833. The compound of any of embodiments 1824 to 1831, wherein the modified oligonucleotide is attached to the remainder of the compound at the 3'-end of the modified oligonucleotide.

Embodiment 1834. The compound of any of embodiments 1824 to 1833, wherein the modified oligonucleotide is an antisense oligonucleotide.

Embodiment 1835. The compound of embodiment any of embodiments 1824 to 1834, wherein the modified oligonucleotide is single-stranded.

Embodiment 1836. The compound of any of embodiments 1824 to 1834, wherein the modified oligonucleotide is double-stranded.

Embodiment 1837. The compound of any of embodiments 1824 to 1836, wherein the modified oligonucleotide activates the RISC pathway.

Embodiment 1838. The compound of any of embodiments 1824 to 1836, wherein the modified oligonucleotide is an RNase H based antisense compound.

Embodiment 1839. The compound of any of embodiments 1824 to 1836, wherein the modified oligonucleotide alters splicing of a target pre-mRNA.

Embodiment 1840. The compound of any of embodiments 1824 to 1839, wherein the modified oligonucleotide is complementary to a target nucleic acid.

Embodiment 1841. The compound of embodiment 1840, wherein the target nucleic acid is selected from among: pre-mRNA, micro-RNA, or long non-coding RNA.

Embodiment 1842. The compound of any of embodiments 1824 to 1841, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

Embodiment 1843. The compound of any of embodiments 1824 to 1841, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides.

Embodiment 1844. The compound of any of embodiments 1824 to 1841, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1845. A method of administering the compound of any of embodiments 1817 to 1844 to an animal.

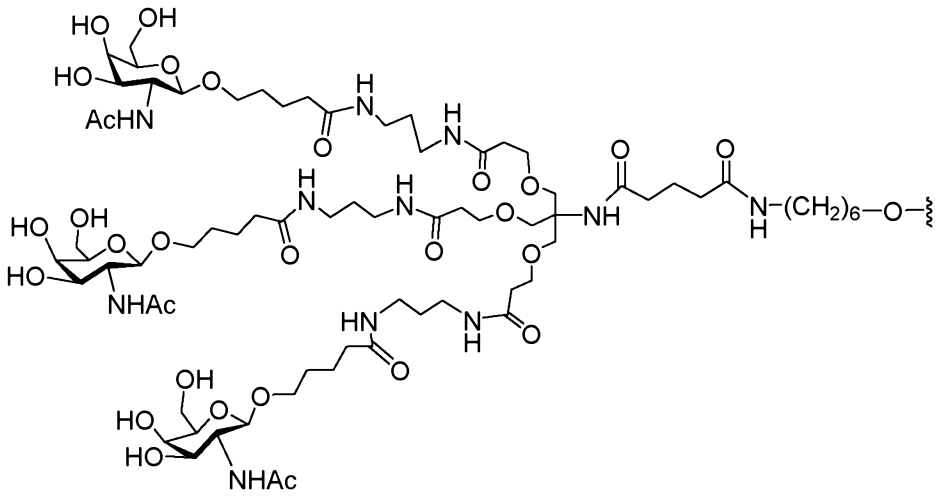
Embodiment 1846. A method of treating a metabolic disorder comprising administering the compound of any of embodiments 1817 to 1844 to a subject in need thereof.

Embodiment 1847. A method of treating a cardiovascular disorder comprising administering the compound of any of embodiments 1817 to 1844 to a subject in need thereof.

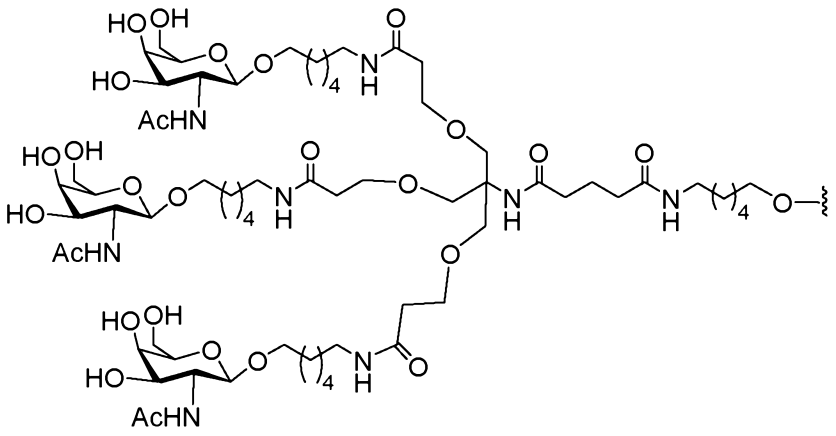
Embodiment 1848. A method comprising administering a conjugated antisense compound to an animal, wherein the conjugated antisense compound comprises a modified oligonucleotide having a gapmer sugar motif and a conjugate comprising a GalNAc.

Embodiment 1849. A method of reducing the amount or activity of a target nucleic acid in a cell in an animal comprising administering to the animal a conjugated antisense compound comprising a modified oligonucleotide and a conjugate, wherein the modified oligonucleotide has a gapmer sugar motif and the conjugate comprises a GalNAc; and thereby reducing the amount or activity of the target nucleic acid in the cell in the animal.

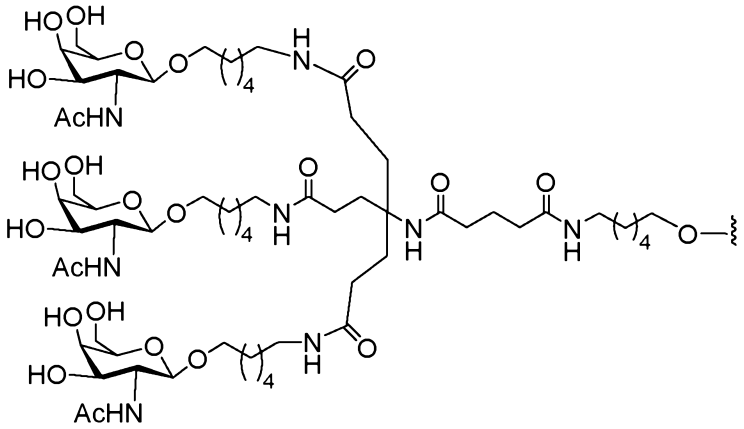
Embodiment 1850. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



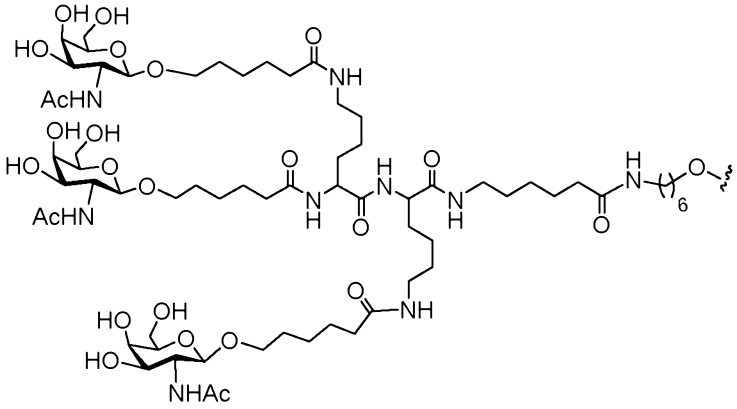
Embodiment 1851. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



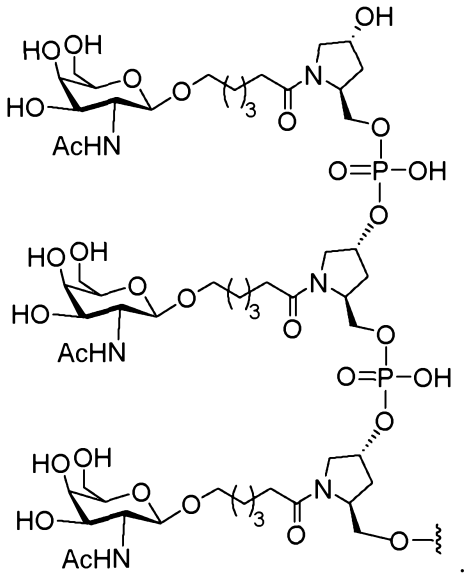
Embodiment 1852. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



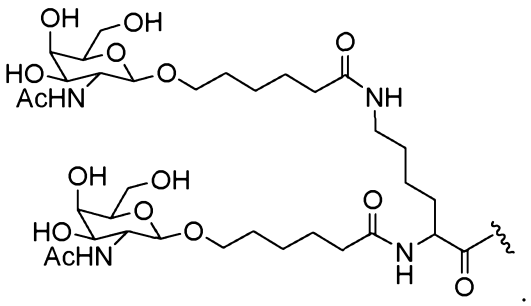
Embodiment 1853. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



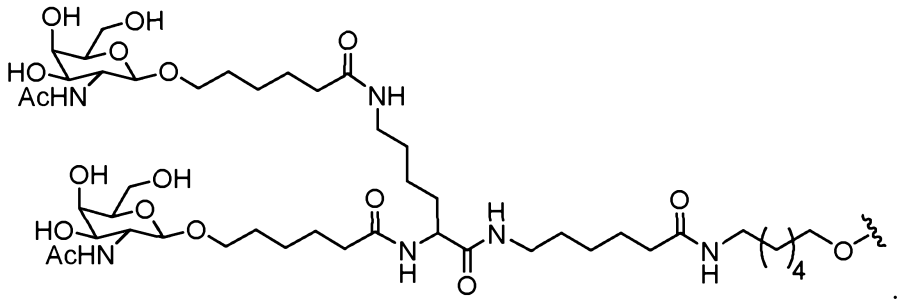
Embodiment 1854. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



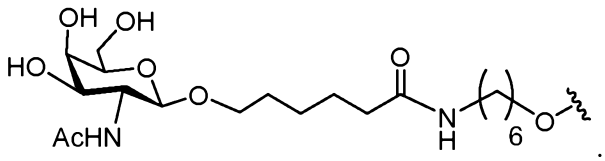
Embodiment 1855. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



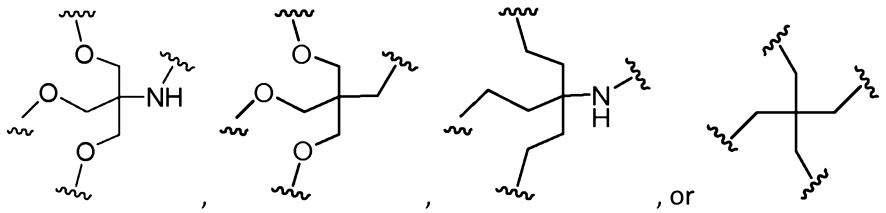
Embodiment 1856. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



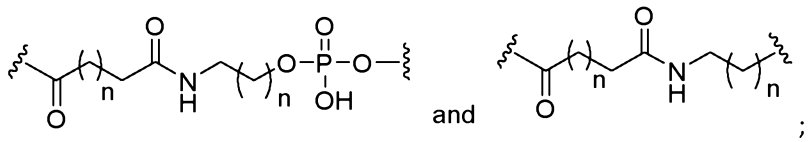
Embodiment 1857. The method of embodiment 1848 or 1849, wherein the conjugate comprises the following structure:



Embodiment 1858. The method of embodiment 1848 or 1849, wherein the conjugate has a branching group selected from the following structures:



Embodiment 1859. The method of embodiment 1848 or 1849, wherein the conjugate has a linker selected from the following structures:



wherein each n is independently selected from 0, 1, 2, 3, 4, 5, 6, or 7.

Embodiment 1860. The method of any of embodiments 1848 to 1859, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 1861. The method of embodiment 1860, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 1862. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1863. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 1864. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 1865. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 1866. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 1867. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 1868. The method of embodiment 1860 or 1861, wherein the modified oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 1869. The method of any of embodiments 1848 to 1868, wherein each internucleoside linkage of the modified oligonucleotide is selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

Embodiment 1870. The method of embodiment 1869, wherein each internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 1871. The method of any of embodiments 1848 to 1870, wherein modified oligonucleotide is at least 80% complementary to a target nucleic acid.

Embodiment 1872. The method of any of embodiments 1848 to 1870, wherein modified oligonucleotide is at least 85% complementary to a target nucleic acid.

Embodiment 1873. The method of any of embodiments 1848 to 1870, wherein modified oligonucleotide is at least 90% complementary to a target nucleic acid.

Embodiment 1874. The method of any of embodiments 1848 to 1870, wherein modified oligonucleotide is 100% complementary to a target nucleic acid.

Embodiment 1875. The method of any of embodiments 1848 to 1874, wherein the target nucleic acid is expressed in the liver.

Embodiment 1876. The method of any of embodiments 1848 to 1875, wherein the target nucleic acid is expressed in hepatocytes.

Embodiment 1877. The method of any of embodiments 1848 to 1876, wherein the target nucleic encodes a protein selected from among: Androgen Receptor, Apolipoprotein (a), Apolipoprotein B, Apolipoprotein C-III, C-Reactive Protein, eIF-4E, Factor VII, Factor XI, Glucocorticoid Receptor, Glucagon Receptor, Protein Tyrosine Phosphatase 1B, STAT3, and Transthyretin.

Embodiment 1878. A method of modulating splicing of a pre-mRNA target nucleic acid in a cell comprising contacting the cell with a conjugated antisense compound, wherein the conjugated antisense compound comprises a modified oligonucleotide and a conjugate; and wherein the conjugate comprises a GalNac; and thereby modulating splicing of the pre-mRNA target nucleic acid in the cell.

Embodiment 1879. The method of embodiment 1878, wherein the pre-mRNA target nucleic acid is expressed in a hepatocyte.

Embodiment 1880. The method of embodiment 1878 or 1879, wherein the cell is in vitro.

Embodiment 1881. The method of embodiment 1878 or 1879, wherein the cell is in vivo.

Embodiment 1882. The method of embodiment 1878 or 1879, wherein the cell is in an animal.

Embodiment 1883. The method of any of embodiments 1878 to 1882, wherein the modified oligonucleotide comprises at least one modified nucleoside.

Embodiment 1884. The method of embodiment 1883, wherein the modified oligonucleotide comprises at least one nucleoside comprising a 2'-$O(CH_2)_2OCH_3$ modification.

Embodiment 1885. The method of embodiment 1883 or 1884, wherein the modified oligonucleotide comprises at least on nucleoside comprising a 2'-OCH_3 modification.

Embodiment 1886. The method of any of embodiments 1878 to 1885, wherein the modified oligonucleotide comprises at least one bicyclic nucleoside.

Embodiment 1887. The method of embodiment 1886 comprising a (4'-CH_2-O-2') BNA nucleoside.

Embodiment 1888. The method of embodiment 1886 or 1887 comprising a (4'-$(CH_2)_2$-O-2') BNA nucleoside.

Embodiment 1889. The method of embodiment any of embodiments 1886 to 1888 (4'-$C(CH_3)$H-O-2') BNA nucleoside.

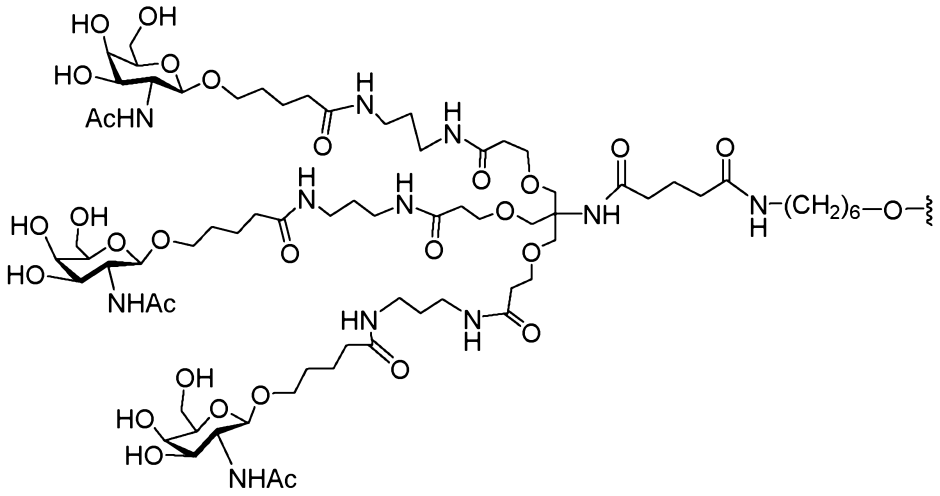
Embodiment 1890. The method of any of embodiments 1878 to 1889 wherein each nucleoside of the modified oligonucleotide is a modified nucleoside.

Embodiment 1891. The method of embodiment 1890 wherein each modified nucleoside of the modified oligonucleotide comprises the same modification.

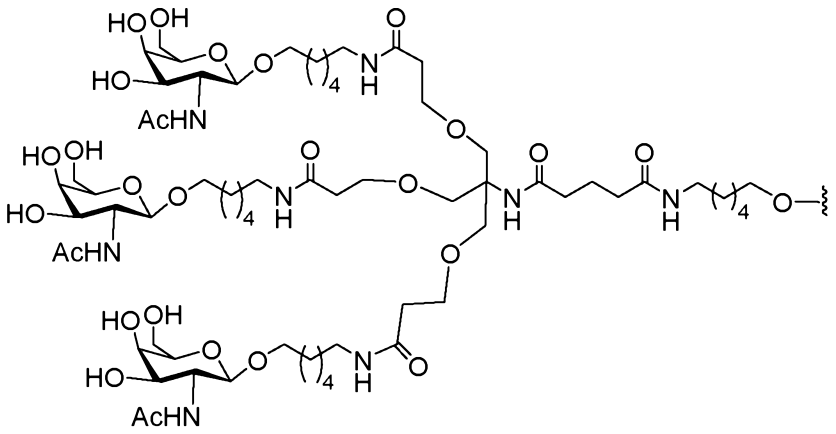
Embodiment 1892. The method of embodiment 1890 wherein at least two modified nucleosides of the modified oligonucleotide comprise modifications that are different from one another.

Embodiment 1893. The method of any of embodiments 1878 to 1889 or 1891 to 1892 wherein at least one nucleoside of the modified oligonucleotide is an unmodified deoxynucleotide.

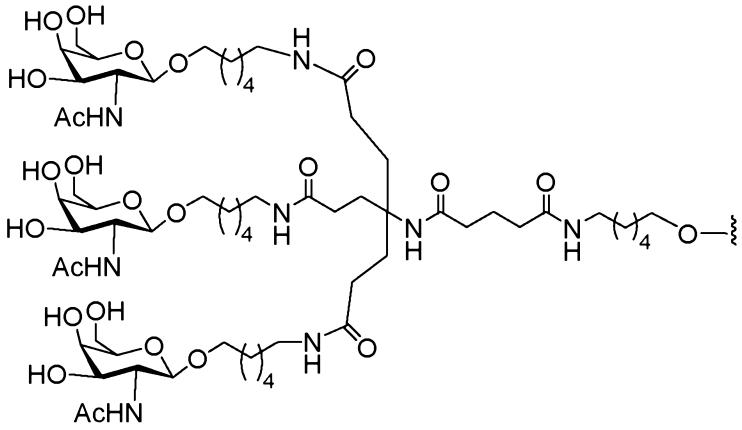
Embodiment 1894. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



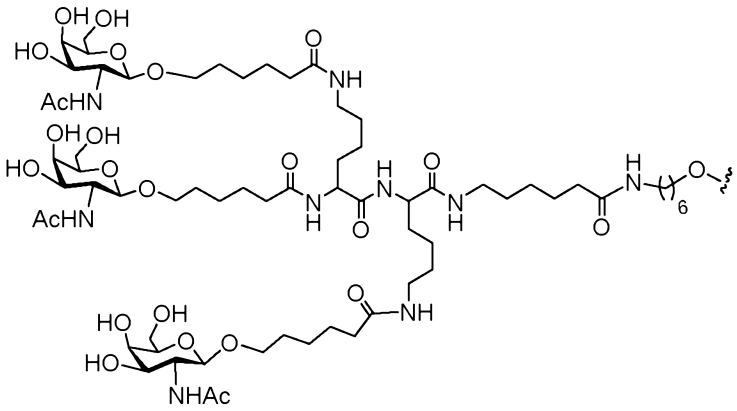
Embodiment 1895. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



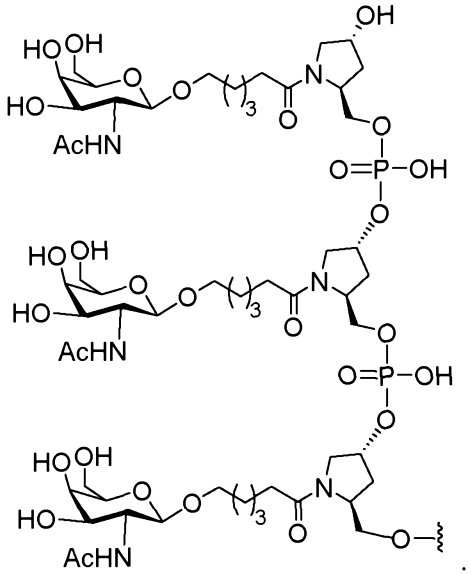
Embodiment 1896. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



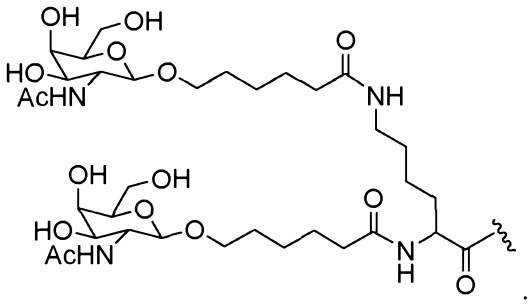
Embodiment 1897. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



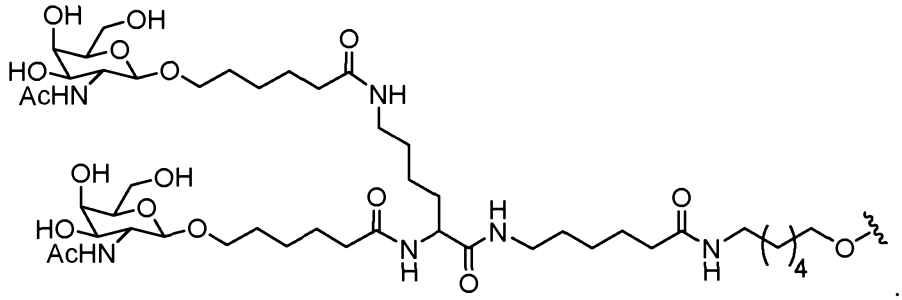
Embodiment 1898. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



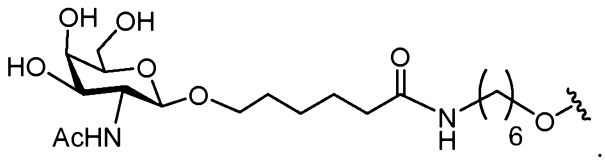
Embodiment 1899. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



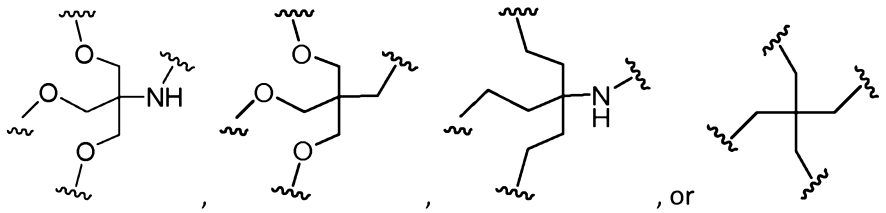
Embodiment 1900. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



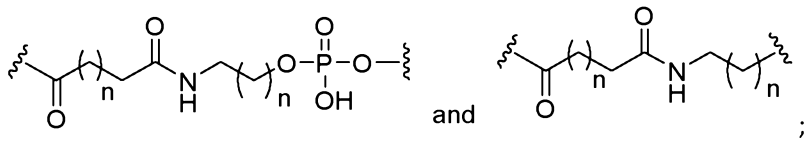
Embodiment 1901. The method of any of embodiments 1878 to 1893, wherein the conjugate comprises the following structure:



Embodiment 1902. The method of any of embodiments 1878 to 1893, wherein the conjugate has a branching group selected from the following structures:



Embodiment 1903. The method of any of embodiments 1878 to 1893, wherein the conjugate has a linker selected from the following structures:



wherein each n is independently selected from 0, 1, 2, 3, 4, 5, 6, or 7.

Embodiment 1904. The method of any of embodiments 1878 to 1903, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

Embodiment 1905. The method of embodiment 1904, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 1906. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

Embodiment 1907. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

Embodiment 1908. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

Embodiment 1909. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

Embodiment 1910. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least 5 phosphodiester internucleoside linkages.

Embodiment 1911. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least 6 phosphodiester internucleoside linkages.

Embodiment 1912. The method of embodiment 1904 or 1905, wherein the modified oligonucleotide comprises at least 7 phosphodiester internucleoside linkages.

Embodiment 1913. The method of any of embodiments 1904 or 1905, wherein each internucleoside linkage of the modified oligonucleotide is selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

Embodiment 1914. The method of embodiment 1913, wherein each internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 1915. The method of any of embodiments 1878 to 1913, wherein at least one nucleoside of the modified oligonucleotide is a morpholino nucleoside.

Embodiment 1916. The method of any of embodiments 1878 to 1913, wherein each nucleoside of the modified oligonucleotide is a morpholino nucleoside.

Embodiment 1917. A prodrug comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc and the antisense oligonucleotide is an RNAse H based antisense oligonucleotide.

Embodiment 1918. The prodrug of embodiment 1917, wherein the RNase H based antisense oligonucleotide is a gapmer.

Embodiment 1919. The prodrug of embodiment 1917 or 1918, wherein the conjugate is attached to the antisense oligonucleotide at the 5'-end of the antisense oligonucleotide.

Embodiment 1920. A prodrug comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc and the antisense oligonucleotide is an antisense oligonucleotide that alters splicing of a pre-mRNA.

Embodiment 1921. The prodrug of any of embodiments 1917 to 1920, wherein in vivo metabolism of the prodrug results in the antisense oligonucleotide lacking the conjugate.

Embodiment 1922. The prodrug of any of embodiments 1917 to 1921, wherein the prodrug is at least 5 times more potent in vivo than the antisense oligonucleotide lacking the conjugate.

Embodiment 1923. The prodrug of any of embodiments 1917 to 1921, wherein the prodrug is at least 8 times more potent in vivo than the antisense oligonucleotide lacking the conjugate.

Embodiment 1924. The prodrug of any of embodiments 1917 to 1921, wherein the prodrug is at least 10 times more potent in vivo than the antisense oligonucleotide lacking the conjugate.

Embodiment 1925. A method comprising administering the prodrug of any of embodiments 1917 to 1924 to an animal.

Embodiment 1926. A compound comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc, wherein the antisense oligonucleotide has a gapmer sugar motif, and wherein the nucleobase sequence of the antisense oligonucleotide is not 100% complementary to a target nucleic acid selected from among: mouse Raf Kinase C, mouse Fas receptor, or human Phosphatase and Tensin Homolog (PTEN).

Embodiment 1927. The compound of embodiment 1926, wherein the conjugate is attached to the 5'-end of the antisense oligonucleotide.

Embodiment 1928. The compound of any of embodiments 1926 or 1927, wherein the internucleoside linkages of the antisense oligonucleotide comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Embodiment 1929. The compound of any of embodiments 1926 to 1928, wherein the conjugate group does not comprise cholane.

Embodiment 1930. The compound of any of embodiments 1926 to 1929, wherein the branching group comprises a quaternary carbon or an amino acid.

Embodiment 1931. A compound comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc, wherein the antisense oligonucleotide has a gapmer sugar motif, and wherein the nucleobase sequence of the antisense oligonucleotide is complementary to a target nucleic acid which may be modulated for the treatment of a metabolic or cardiovascular disorder.

Embodiment 1932. The compound of embodiment 1931, wherein the conjugate is attached to the 5'-end of the antisense oligonucleotide.

Embodiment 1933. The compound of any of embodiments 1931 or 1932, wherein the internucleoside linkages of the antisense oligonucleotide comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Embodiment 1934. The compound of any of embodiments 1931 to 1933, wherein the conjugate group does not comprise cholane.

Embodiment 1935. The compound of any of embodiments 1931 to 1934, wherein the branching group comprises a quaternary carbon or an amino acid.

Embodiment 1936. A compound comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc, and wherein the antisense oligonucleotide comprises at least one phosphodiester linkage and at least one phosphorothioate linkage.

Embodiment 1937. The compound of embodiment 1936, wherein the conjugate is attached to the 5'-end of the antisense oligonucleotide.

Embodiment 1938. The compound of any of embodiments 1936 or 1937, wherein the antisense oligonucleotide has a gapmer sugar motif.

Embodiment 1939. The compound of any of embodiments 1936 to 1938, wherein the conjugate group does not comprise cholane.

Embodiment 1940. The compound of any of embodiments 1936 to 1939, wherein the branching group comprises a quaternary carbon or an amino acid.

Embodiment 1941. A compound comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc, wherein the conjugate group does not comprise cholane; and wherein the antisense oligonucleotide has a gapmer sugar motif.

Embodiment 1942. The compound of embodiment 1941, wherein the conjugate is attached to the 5'-end of the antisense oligonucleotide.

Embodiment 1943. The compound of any of embodiments 1941 or 1942, wherein the internucleoside linkages of the antisense oligonucleotide comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Embodiment 1944. The compound of any of embodiments 1941 to 1943, wherein the branching group comprises a quaternary carbon or an amino acid.

Embodiment 1945. A compound comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc, wherein the antisense oligonucleotide has a gapmer sugar motif, and wherein the branching group comprises a quaternary carbon or an amino acid.

Embodiment 1946. The compound of embodiment 1945, wherein the conjugate is attached to the 5'-end of the antisense oligonucleotide.

Embodiment 1947. The compound of any of embodiments 1945 or 1946, wherein the internucleoside linkages of the antisense oligonucleotide comprise at least one phosphodiester linkage and at least one phosphorothioate linkage.

Embodiment 1948. The compound of any of embodiments 1945 to 1957, wherein the conjugate group does not comprise cholane.

Embodiment 1949. A compound comprising an antisense oligonucleotide and a conjugate, wherein the conjugate comprises at least one GalNAc, and wherein the antisense oligonucleotide alters splicing of a pre-mRNA.

Embodiment 1950. The compound of any of embodiments 1926 to 1949, wherein the antisense oligonucleotide consists of 10 to 30 linked nucleosides.

Embodiment 1951. The compound of any of embodiments 1926 to 1949, wherein the antisense oligonucleotide consists of 18 to 22 linked nucleosides.

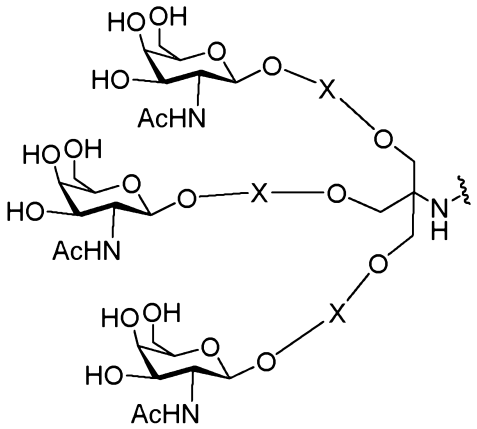
Embodiment 1952. The compound of any of embodiments 1926 to 1949, wherein the antisense oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1953. The method of any of embodiments 1926 to 1949, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides.

Embodiment 1954. The method of any of embodiments 1926 to 1949, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides.

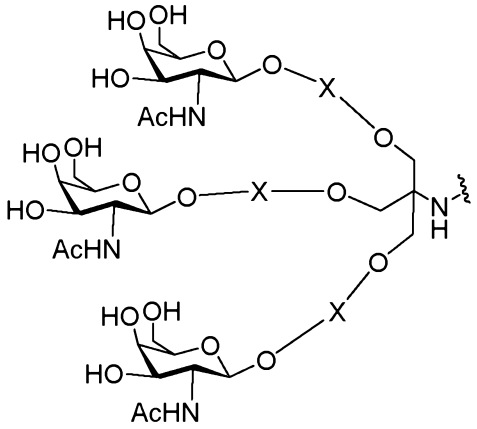
Embodiment 1955. The method of any of embodiments 1848 to 1916, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

Embodiment 1956. A compound comprising a cell-targeting moiety that has the following structure:



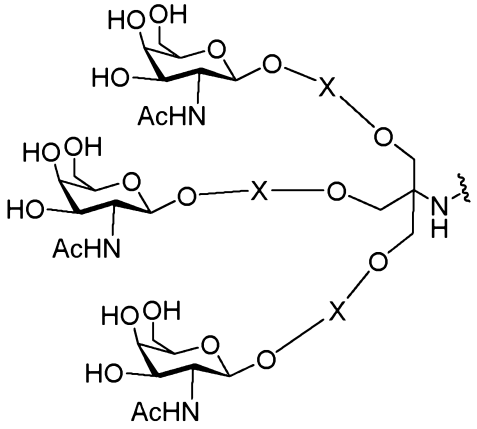
wherein X is a substituted or unsubstituted tether of six to eleven consecutively bonded atoms.

Embodiment 1957. A compound comprising a cell-targeting moiety that has the following structure:



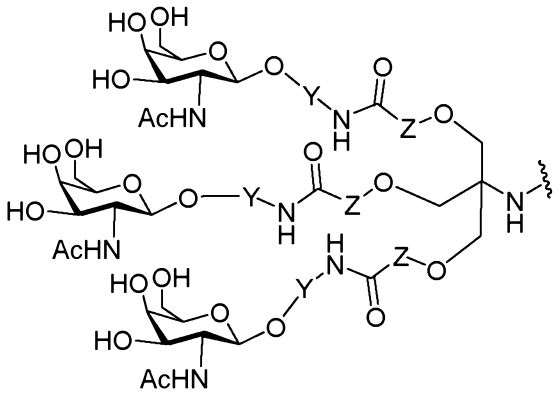
wherein X is a substituted or unsubstituted tether of ten consecutively bonded atoms.

Embodiment 1958. A compound comprising a cell-targeting moiety that has the following structure:



wherein X is a substituted or unsubstituted tether of four to eleven consecutively bonded atoms and wherein the tether comprises exactly one amide bond.

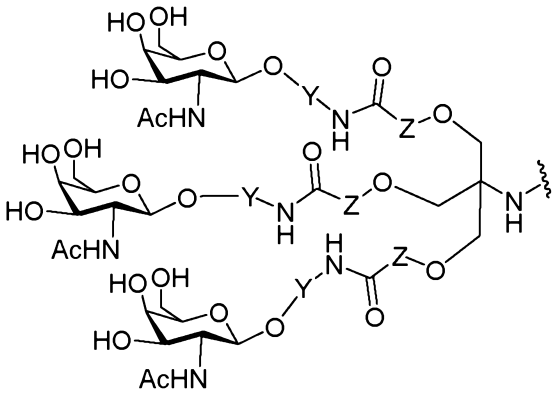
Embodiment 1959. A compound comprising a cell-targeting moiety that has the following structure:



wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a

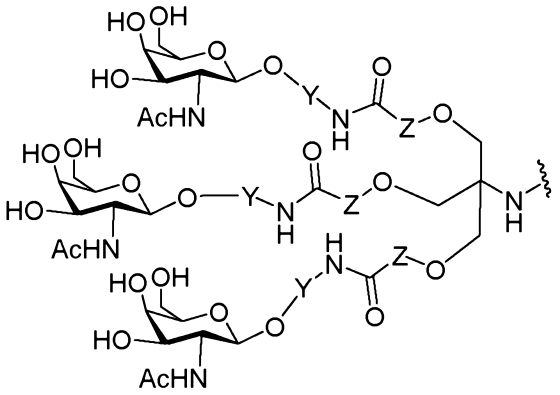
piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

Embodiment 1960. A compound comprising a cell-targeting moiety that has the following structure:



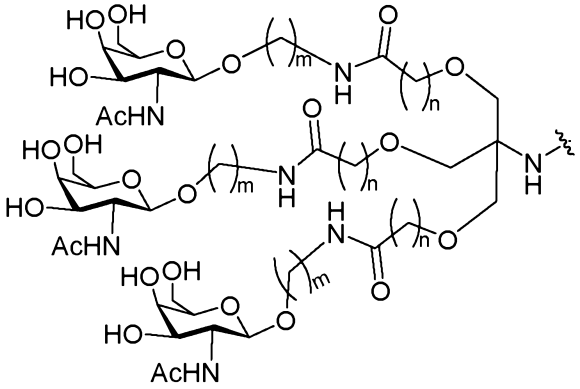
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising exactly one ether or exactly two ethers, an amide, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

Embodiment 1961. A compound comprising a cell-targeting moiety that has the following structure:



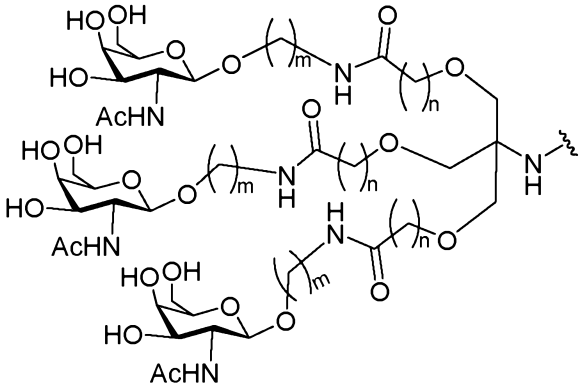
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

Embodiment 1962. A compound comprising a cell-targeting moiety that has the following structure:



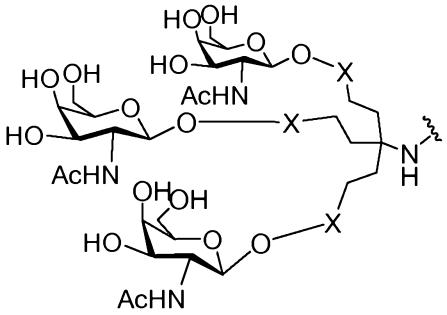
wherein m and n are independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

Embodiment 1963. A compound comprising a cell-targeting moiety that has the following structure:



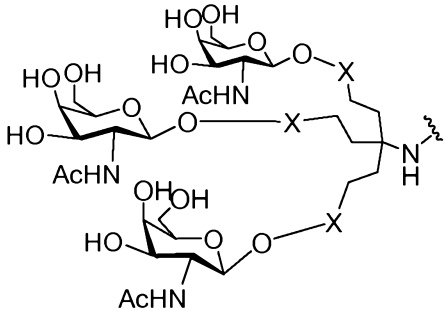
wherein m is 4, 5, 6, 7, or 8, and n is 1, 2, 3, or 4.

Embodiment 1964. A compound comprising a cell-targeting moiety that has the following structure:



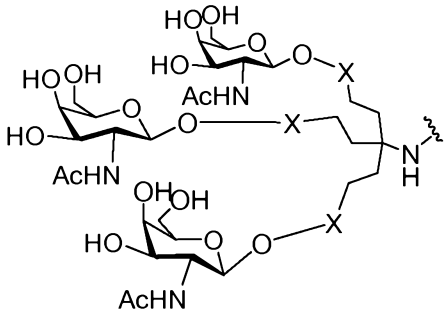
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein X does not comprise an ether group.

Embodiment 1965. A compound comprising a cell-targeting moiety that has the following structure:



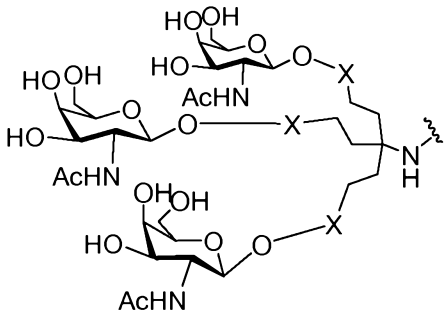
wherein X is a substituted or unsubstituted tether of eight consecutively bonded atoms, and wherein X does not comprise an ether group.

Embodiment 1966. A compound comprising a cell-targeting moiety that has the following structure:



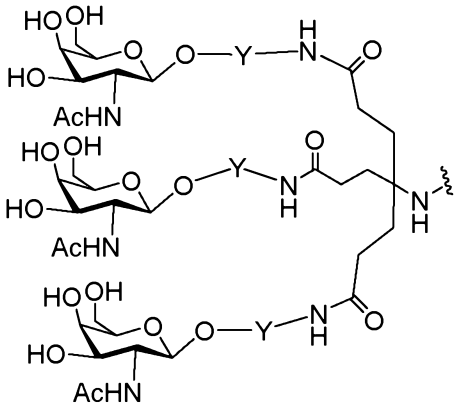
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein the tether comprises exactly one amide bond, and wherein X does not comprise an ether group.

Embodiment 1967. A compound comprising a cell-targeting moiety that has the following structure:



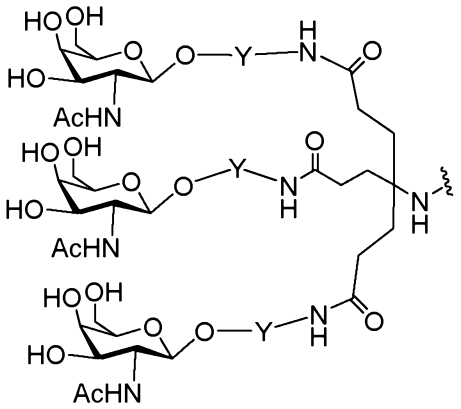
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms and wherein the tether consists of an amide bond and a substituted or unsubstituted C_2-C_{11} alkyl group.

Embodiment 1968. A compound comprising a cell-targeting moiety that has the following structure:



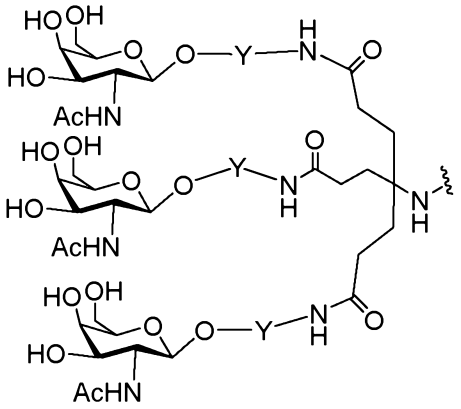
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

Embodiment 1969. A compound comprising a cell-targeting moiety that has the following structure:



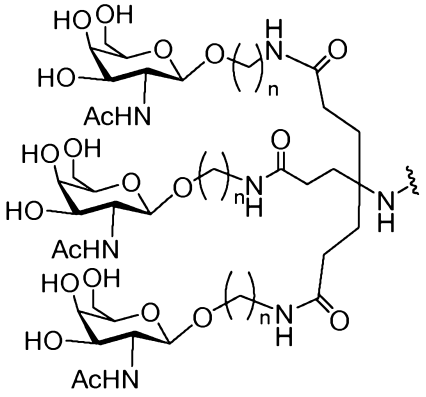
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising an ether, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

Embodiment 1970. A compound comprising a cell-targeting moiety that has the following structure:



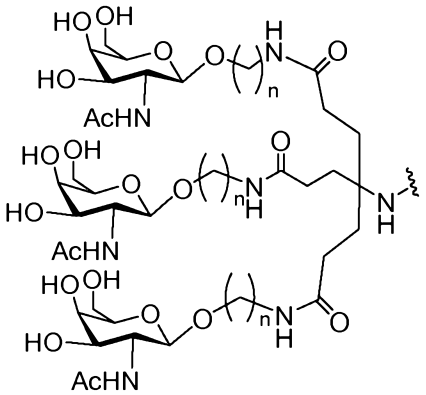
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

Embodiment 1971. A compound comprising a cell-targeting moiety that has the following structure:



Wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

Embodiment 1972. A compound comprising a cell-targeting moiety that has the following structure:



wherein n is 4, 5, 6, 7, or 8.

Embodiment 1973. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises exactly one GalNAc, and wherein the conjugate group is attached to the 5' end of the antisense oligonucleotide.

Embodiment 1974. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises exactly two GalNAc ligands, and wherein the conjugate group is attached to the 5' end of the antisense oligonucleotide.

Embodiment 1975. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises exactly one GalNAc, and wherein the conjugate group is attached to the 3' end of the antisense oligonucleotide.

Embodiment 1976. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises exactly two GalNAc ligands, and wherein the conjugate group is attached to the 3' end of the antisense oligonucleotide.

Embodiment 1977. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises 1-4 GalNAc ligands, and wherein the antisense oligonucleotide is a gapmer.

Embodiment 1978. The conjugated antisense oligonucleotide of embodiment 1977, wherein the conjugate group is attached to the 5' end of the antisense oligonucleotide.

Embodiment 1979. The conjugated antisense oligonucleotide of any of embodiments 1977-1978, wherein the conjugate group comprises a linker that does not comprise a disulfide.

Embodiment 1980. The conjugated antisense oligonucleotide of any of embodiments 1977-1979, wherein the conjugate group comprises a linker that does not comprise a thioether.

Embodiment 1981. The conjugated antisense oligonucleotide of any of embodiments 1977-1980, wherein the conjugate group comprises a linker that does not comprise a pyrrolidine.

Embodiment 1982. The conjugated antisense oligonucleotide of any of embodiments 1977-1981, wherein the conjugate group does not comprise a polycyclic moiety.

Embodiment 1983. The conjugated antisense oligonucleotide of any of embodiments 1977-1981, wherein the conjugate group comprises a branching group that does not comprise a polycyclic moiety.

Embodiment 1984. The conjugated antisense oligonucleotide of any of embodiments 1977-1983, wherein the conjugate group comprises a linker that does not comprise a lipid moiety.

Embodiment 1985. The conjugated antisense oligonucleotide of any of embodiments 1977-1984, wherein the linkage between the conjugate group and the antisense oligonucleotide is not a phosphorothioate group.

Embodiment 1986. The conjugated antisense oligonucleotide of any of embodiments 1977-1985, wherein the antisense oligonucleotide comprises at least one modified nucleoside, wherein the modified nucleoside is a 2'-O-methoxyethyl (MOE) modified nucleoside.

Embodiment 1987. The conjugated antisense oligonucleotide of any of embodiments 1977-1986, wherein the antisense oligonucleotide comprises at least one modified nucleoside, wherein the modified nucleoside is a cEt modified nucleoside.

Embodiment 1988. The conjugated antisense oligonucleotide of any of embodiments 1977-1987, wherein the antisense oligonucleotide comprises at least one phosphorothioate internucleoside linkage and at elast one phosphodiester internucleoside linkage.

Embodiment 1989. The conjugated antisense oligonucleotide of any of embodiments 1977-1987, wherein the wings of the gapmer comprise at least two different sugar modifications.

Embodiment 1990. The conjugated antisense oligonucleotide of any of embodiments 1977-1989, wherein the sequence of the antisense oligonucleotide is selected from SEQ ID NO.'s 17-159.

Embodiment 1991. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises the cell-targeting moiety of any of embodiments 1956-1972.

Embodiment 1992. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises the cell-targeting moiety of any of embodiments 1956-1972, and wherein the antisense oligonucleotide comprises a gapmer.

Embodiment 1993. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises the cell-targeting moiety of any of embodiments 1956-1972, and wherein the sugars of the antisense oligonucleotide are uniformly modified.

Embodiment 1994. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises the cell-targeting moiety of any of embodiments 1956-1972, and wherein the antisense oligonucleotide is single stranded.

Embodiment 1995. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises the cell-targeting moiety of any of embodiments 1956-1972, and wherein the antisense oligonucleotide is double stranded.

Embodiment 1996. The conjugated antisense oligonucleotide of any of embodiments 1991-1995, wherein the conjugate is attached to the 5' end of the antisense oligonucleotide.

Embodiment 1997. The conjugated antisense oligonucleotide of any of embodiments 1991-1995, wherein the conjugate is attached to the 3' end of the antisense oligonucleotide.

Embodiment 1998. A conjugated antisense oligonucleotide comprising a conjugate group and an antisense oligonucleotide, wherein the conjugate group comprises 1-4 GalNAc ligands, and wherein the sugars of the antisense oligonucleotide are uniformly modified.

In embodiments having more than one of a particular variable (e.g., more than one "m" or "n"), unless otherwise indicated, each such particular variable is selected independently. Thus, for a structure having more than one n, each n is selected independently, so they may or may not be the same as one another.

DETAILED DESCRIPTION

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.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose.

A. Definitions

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, which are hereby incorporated by reference for any purpose. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

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.

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.

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

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.

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

As used herein, “modified sugar moiety” means a substituted sugar moiety or a sugar surrogate.

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.

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.

As used herein, “MOE” means $-OCH_2CH_2OCH_3$.

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).

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.

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.

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).

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 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).

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

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.

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

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.

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.

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.

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).

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.

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

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

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

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

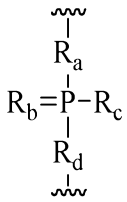
As used herein "naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

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

As used herein, "terminal internucleoside linkage" means the linkage between the last two

nucleosides of an oligonucleotide or defined region thereof.

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.

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

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

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.

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.

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

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.

As used herein, "oligomeric compound" means a polymeric structure comprising two or more sub-structures. 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.

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.

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.

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.

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.

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.

As used herein, "cleavable moiety" means a bond or group that is capable of being cleaved under physiological conditions. In certain embodiments, a cleavable moiety is cleaved inside a cell or sub-cellular compartments, such as an endosome or 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. In certain embodiments, a cleavable moiety is a phosphodiester linkage.

As used herein, "cleavable bond" means any chemical bond capable of being broken. 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.

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, which is incorporated herein by reference in its entirety, 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).

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

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

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

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, which is incorporated herein by reference in its entirety.

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.

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.

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.

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.

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.

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).

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.

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

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

As used herein, “sugar motif” means a pattern of sugar modifications in an oligonucleotide or a region thereof.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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 =O 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.

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).

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.

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 ($-C(O)N(R_{bb})(R_{cc})$ or $-N(R_{bb})C(O)R_{aa}$), 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 ($-C(=NR_{bb})N(R_{bb})(R_{cc})$ or $-N(R_{bb})C(=NR_{bb})(R_{aa})$), thiol ($-SR_{bb}$), sulfinyl ($-S(O)R_{bb}$), sulfonyl ($-S(O)_2R_{bb}$) and sulfonamidyl ($-S(O)_2N(R_{bb})(R_{cc})$ 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

B. Certain Compounds

In certain embodiments, the invention provides conjugated antisense compounds comprising antisense oligonucleoitdes and a conjugate.

a. **Certain Antisense Oligonucleotides**

In certain embodiments, the invention 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**

In certain embodiments, antisense oligonucleotide comprise one or more modification. 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. **Certain Sugar Moieties**

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.

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).

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.

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.

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-$(CH_2)_2$-O-$N(CH_3)_2$, -$O(CH_2)_2O(CH_2)_2N(CH_3)_2$, and O-$CH_2$-C(=O)-N(H)$CH_3$.

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

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-O-$N(CH_3)$-2' (*see, e.g.,* US2004/0171570, published September 2, 2004); 4'-CH_2-O-N(R)-2', and 4'-CH_2-N(R)-O-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).

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;

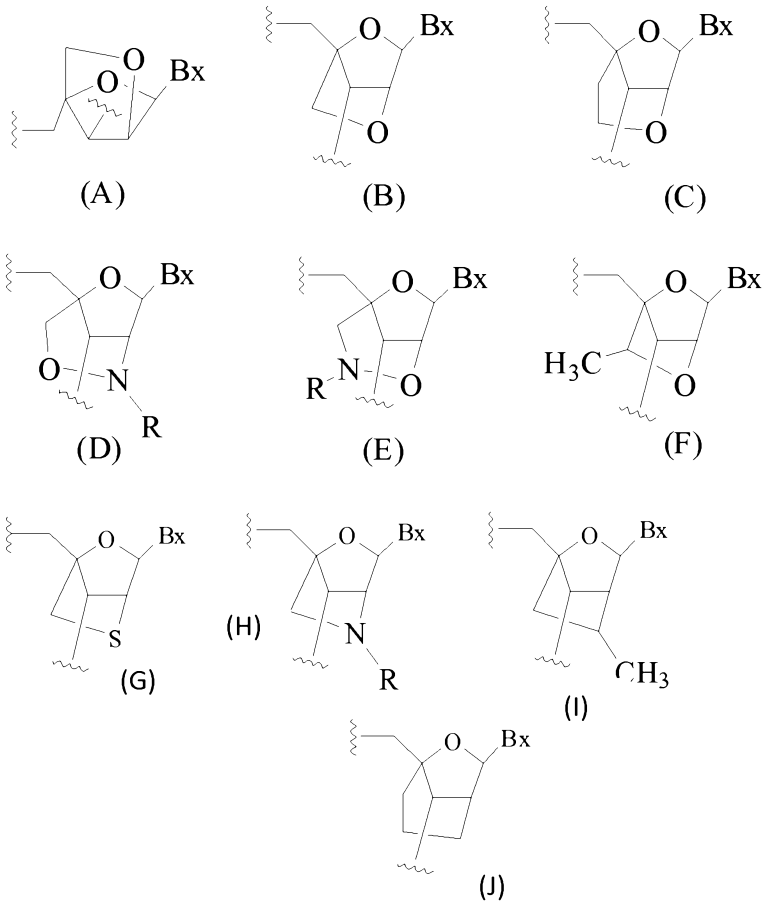
n is 1, 2, 3, or 4;

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.

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) methylene-thio (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.

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.*

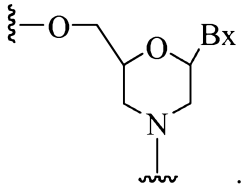
Org. Chem., 1998, *63*, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, *129(26)* 8362-8379 (Jul. 4, 2007); Elayadi *et al., Curr. Opinion Invens. Drugs,* 2001, *2*, 558-561; Braasch *et al., Chem. Biol.,* 2001, *8*, 1-7; Orum *et al., Curr. Opinion Mol. Ther.,* 2001, *3*, 239-243; U.S. Patent Nos. 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 Applications Nos. PCT/US2008/064591, PCT/US2008/066154, and PCT/US2008/068922.

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).

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 Application WO 2007/134181, published on 11/22/07, wherein LNA is substituted with, for example, a 5'-methyl or a 5'-vinyl group).

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).

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:



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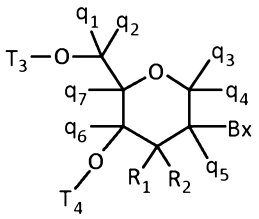
In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are refered to herein as "modifed morpholinos."

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.

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.

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).

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).

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. **Certain Nucleobase Modifications**

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.

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 O-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.

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, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

3. Certain Internucleoside Linkages

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.

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), α or β 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.

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. Certain Motifs

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. **Certain sugar motifs**

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.

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**

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.

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.

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.

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.

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.

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**

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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)**

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.

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).

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.

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.

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. Certain Internucleoside Linkage Motifs

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.

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.

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. Certain Nucleobase Modification Motifs

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.

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.

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.

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.

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**

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 $X \leq Y$. 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.

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

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.

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

i. **Certain Sequences and Targets**

In certain embodiments, the invention 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.

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.

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.

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.

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.

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.

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.

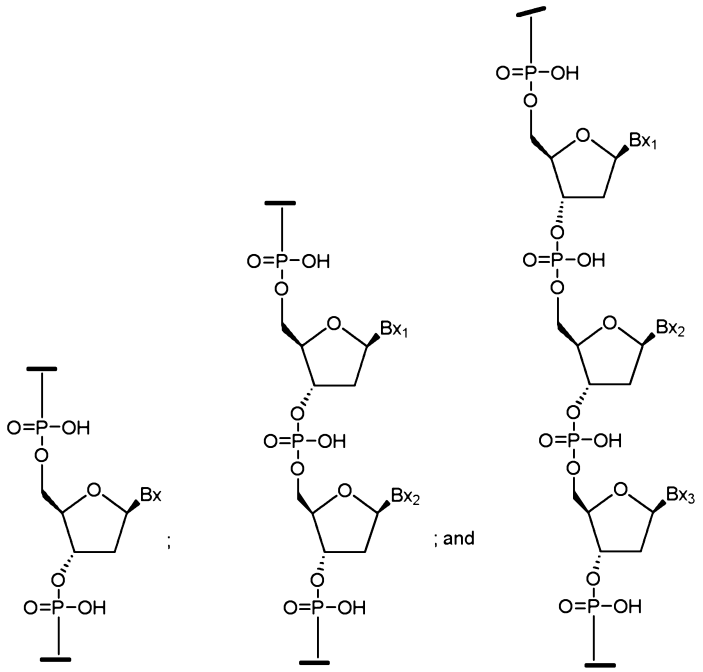
ii. **Certain Cleavable Moieties**

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.

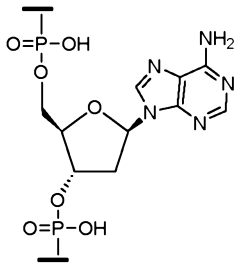
In certain embodiments, the cleavable moiety is attached to the 3' position of the antisense oligonucleotide. In certain embodiments, the cleavable moiety is attached to the 5' position of the antisense oligonucleotide. In certain embodiments, the cleavable moiety is attached to a 2' position of the 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.

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. In certain embodiments, the cleavable moiety has a structure selected from among the following:



wherein each of Bx, Bx_1, Bx_2, and Bx_3 is independently a heterocyclic base moiety. In certain embodiments, the cleavable moiety has a structure selected from among the following:



iii. Certain Linkers

In certain embodiments, the conjugate groups comprise 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. In certain embodiments, the linker is covalently bound to a cell-targeting moiety. In certain embodiments, the linker further comprises a covalent attachment to a solid support. In certain embodiments, the linker further comprises a covalent attachment to a protein binding moiety. In certain embodiments, the linker further comprises a covalent attachment to a solid support and further comprises a covalent attachment to a protein binding moiety. In certain embodiments, the linker includes multiple positions for attachment of tethered ligands. In certain embodiments, the linker includes multiple positions for attachment of tethered ligands and is not attached to a branching group. In certain embodiments, the linker further comprises one or more cleavable bond. In certain embodiments, the conjugate group does not include a linker.

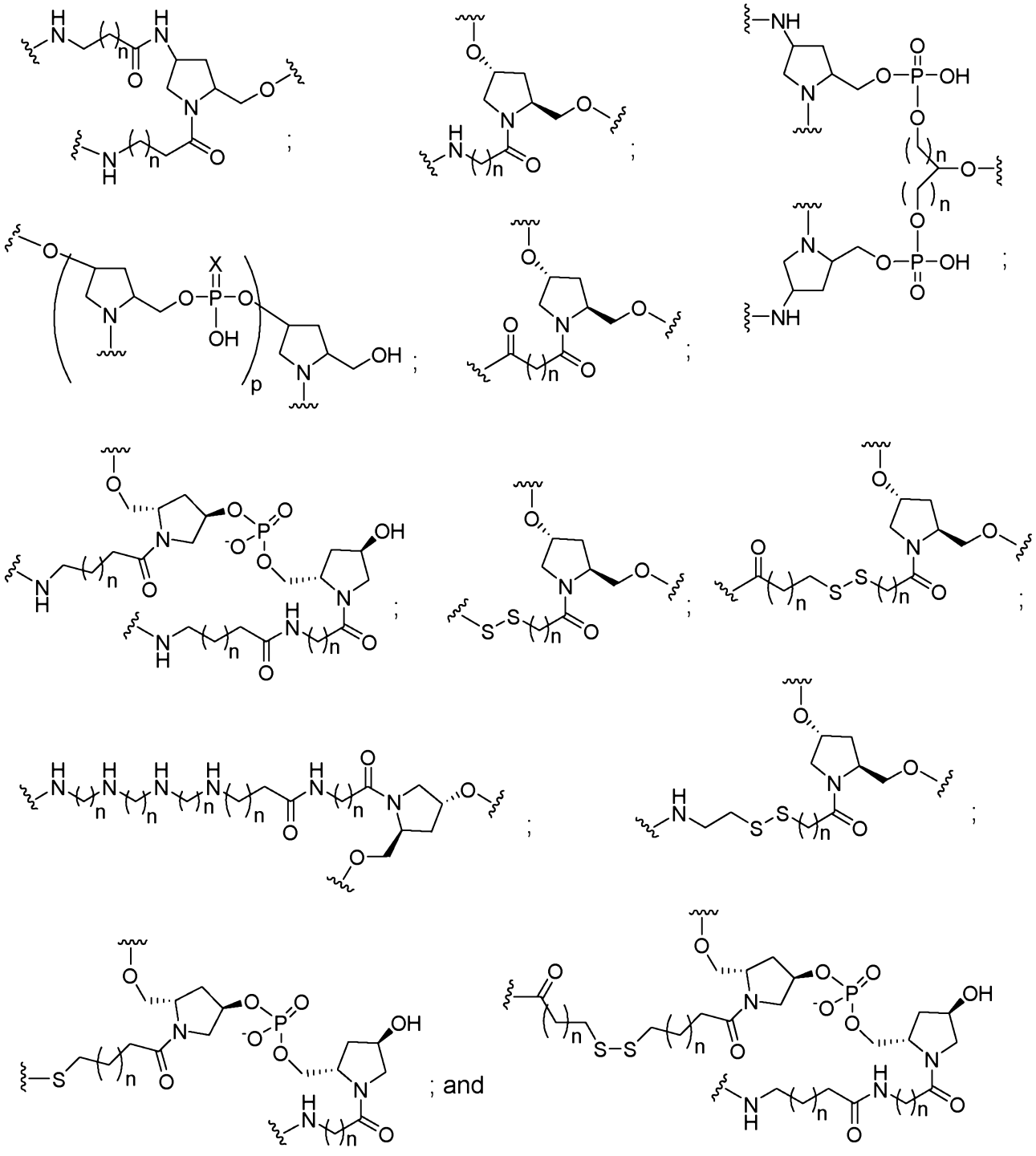
In certain embodiments, the linker includes at least a linear group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether (-S-) and hydroxylamino (-O-N(H)-) groups. In certain embodiments, the linear group comprises groups selected from alkyl, amide and ether groups. In certain embodiments, the linear group comprises groups selected from alkyl and ether groups. In certain embodiments, the linear group comprises at least one phosphorus linking group. In certain embodiments, the linear group comprises at least one phosphodiester group. In certain embodiments, the linear group includes at least one neutral linking group. 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. In certain embodiments, the linear group is covalently attached to the cell-targeting moiety, the cleavable moiety and a solid support. In certain embodiments, the linear group is covalently attached to the cell-targeting moiety, the cleavable moiety, a solid support and a protein binding moiety. In certain embodiments, the linear group includes one or more cleavable bond.

In certain embodiments, the linker includes the linear group covalently attached to a scaffold group. In certain embodiments, the scaffold includes a branched aliphatic group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain embodiments, the scaffold includes a branched aliphatic group comprising groups selected from alkyl, amide and ether groups. In certain embodiments, the scaffold includes at least one mono or polycyclic ring system. In certain embodiments, the scaffold includes at least two mono or polycyclic ring systems. In certain embodiments, the linear group is covalently attached to the scaffold group and the scaffold group is covalently attached to the cleavable moiety and the linker. In certain embodiments, the linear group is covalently attached to the scaffold group and the scaffold group is covalently attached to the cleavable moiety, the linker and a solid support. In certain embodiments, the linear group is covalently attached to the

scaffold group and the scaffold group is covalently attached to the cleavable moiety, the linker and a protein binding moiety. In certain embodiments, the linear group is covalently attached to the scaffold group and the scaffold group is covalently attached to the cleavable moiety, the linker, a protein binding moiety and a solid support. In certain embodiments, the scaffold group includes one or more cleavable bond.

In certain embodiments, the linker includes a protein binding moiety. In certain embodiments, the protein binding moiety is a lipid such as for example including but not limited to cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), a vitamin (e.g., folate, vitamin A, vitamin E, biotin, pyridoxal), a peptide, a carbohydrate (e.g., monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, e.g., sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid. In certain embodiments, the protein binding moiety is a C16 to C22 long chain saturated or unsaturated fatty acid, cholesterol, cholic acid, vitamin E, adamantane or 1-pentafluoropropyl.

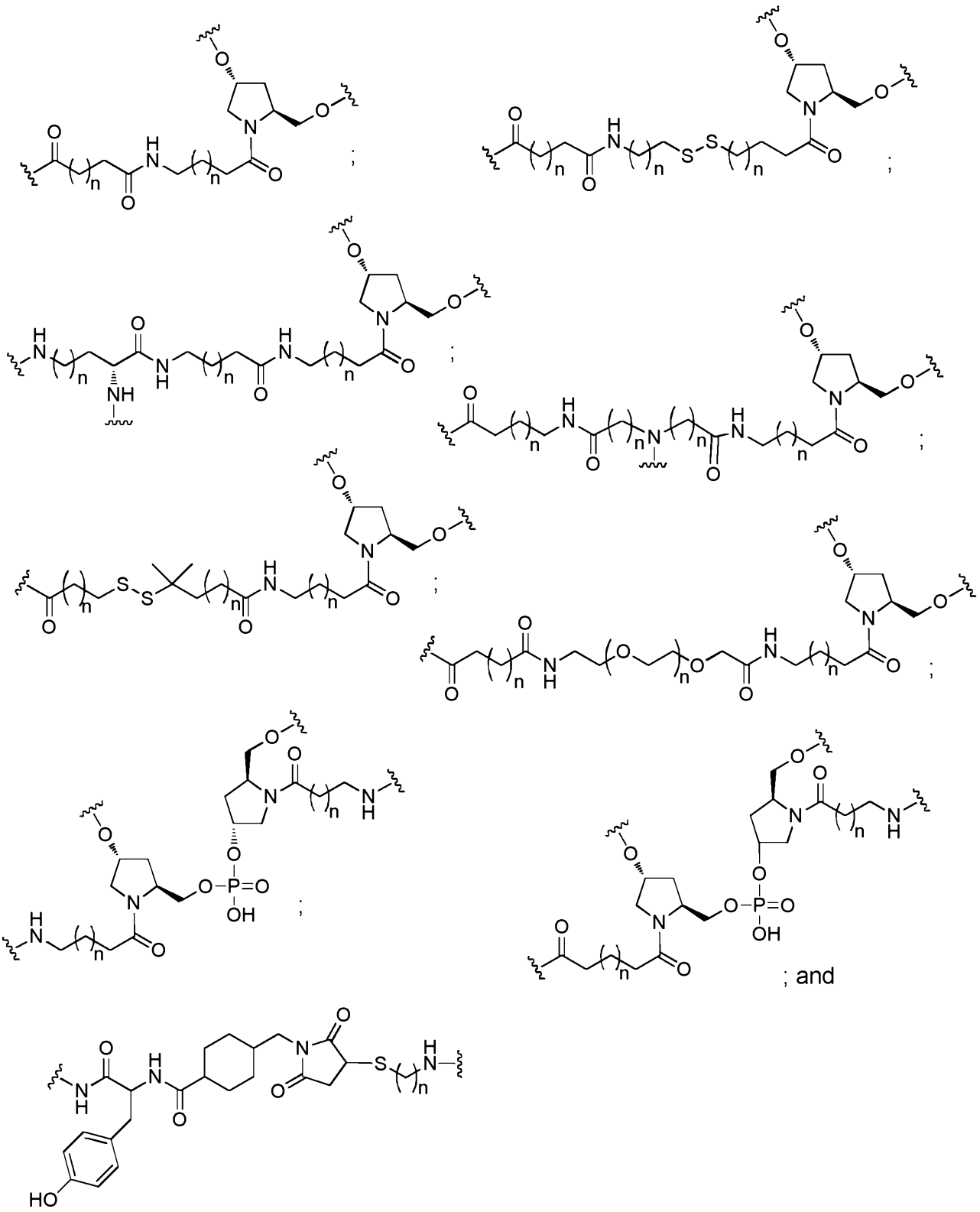
In certain embodiments, a linker has a structure selected from among:



; and

wherein each n is, independently, from 1 to 20; and p is from 1 to 6.

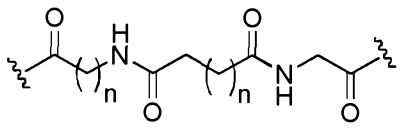
In certain embodiments, a linker has a structure selected from among:



; and

wherein each n is, independently, from 1 to 20.

In certain embodiments, a linker has a structure selected from among: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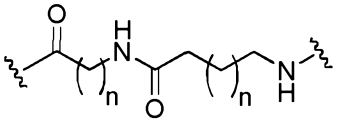
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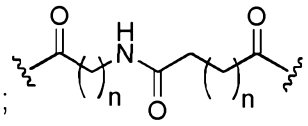
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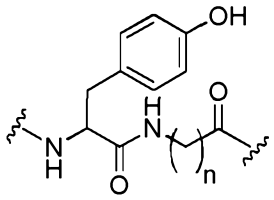
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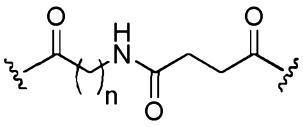
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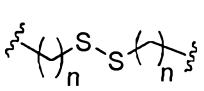
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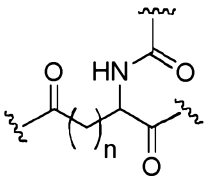
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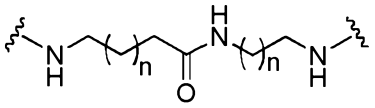
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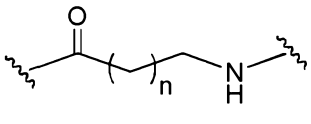
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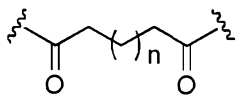
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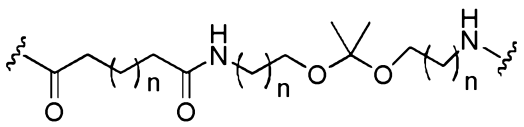
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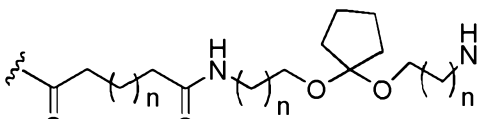
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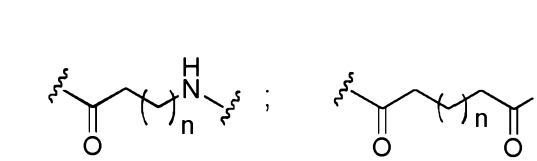
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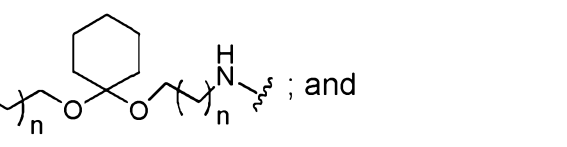
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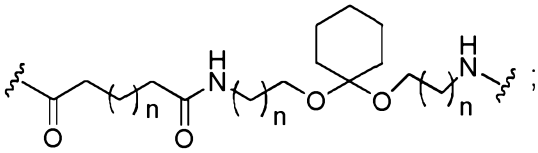
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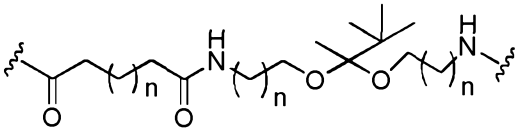
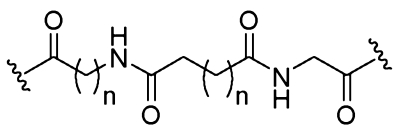
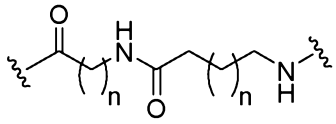
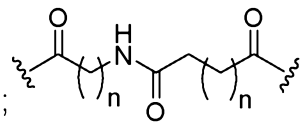
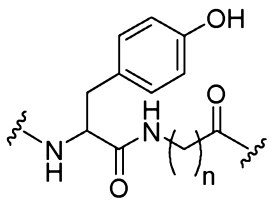


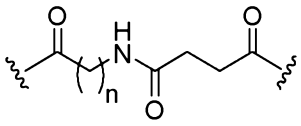
wherein n is from 1 to 20.

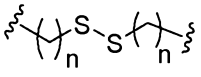


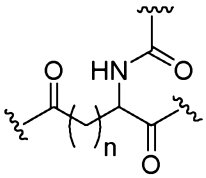


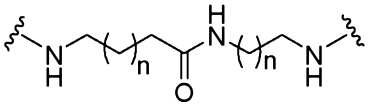


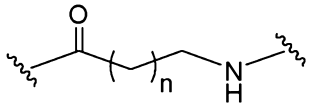


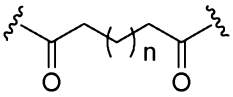


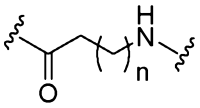


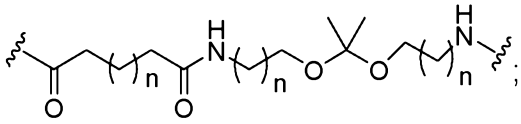


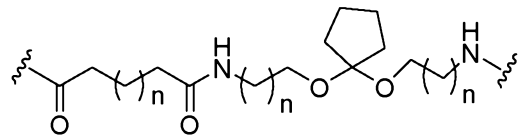


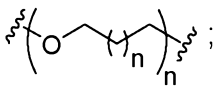


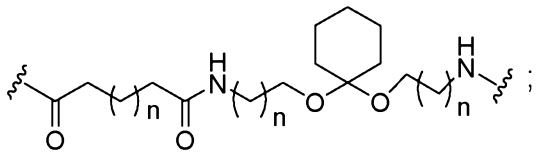


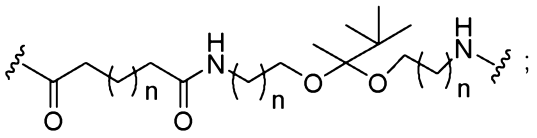


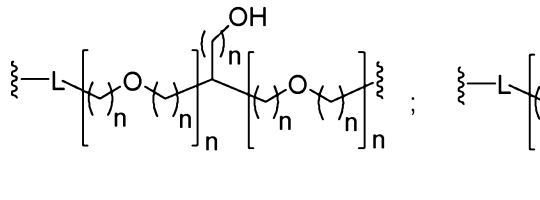


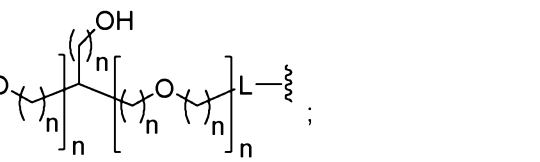


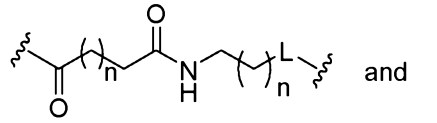


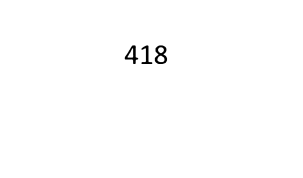












In certain embodiments, a linker has a structure selected from among:

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and

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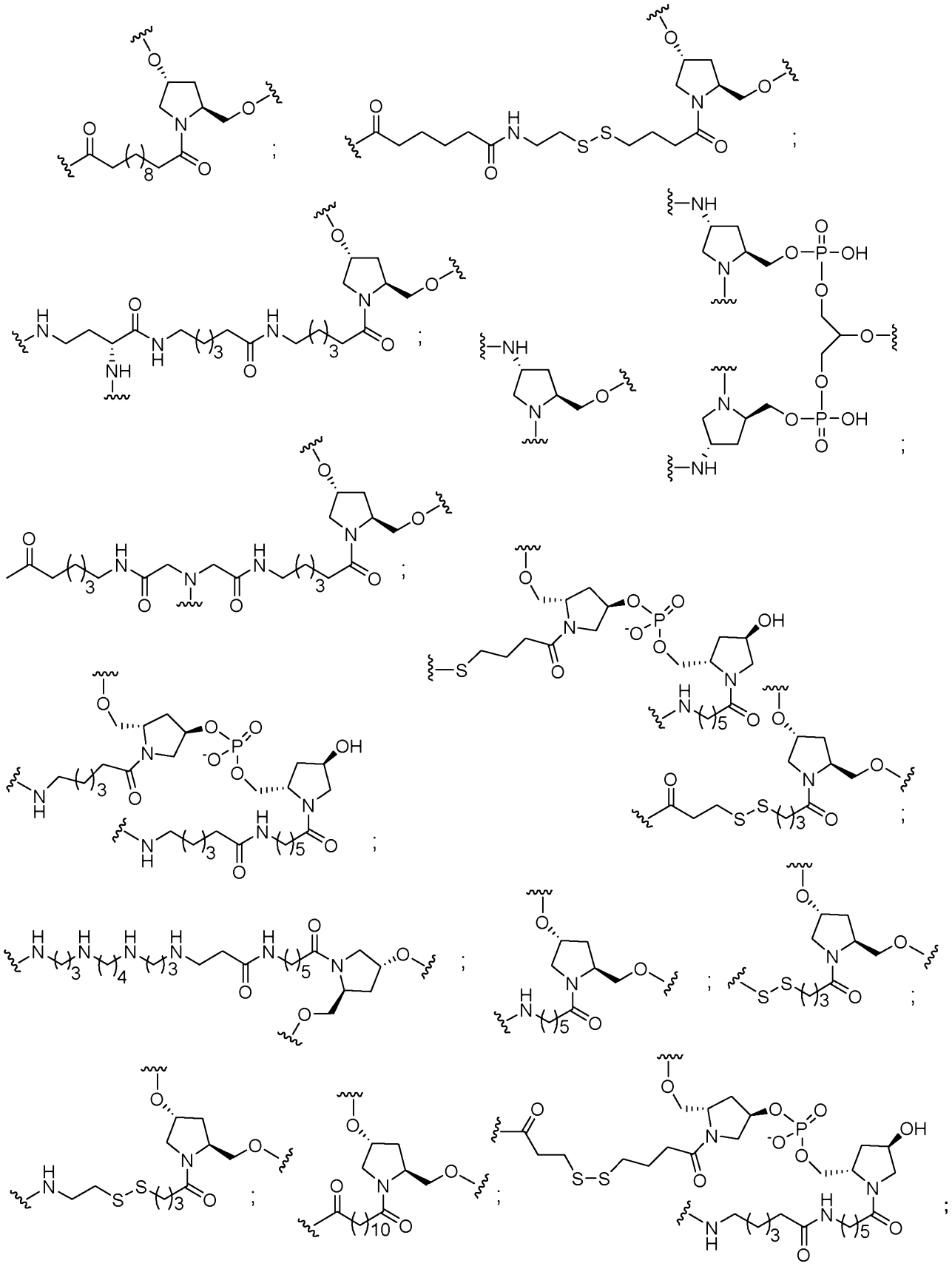
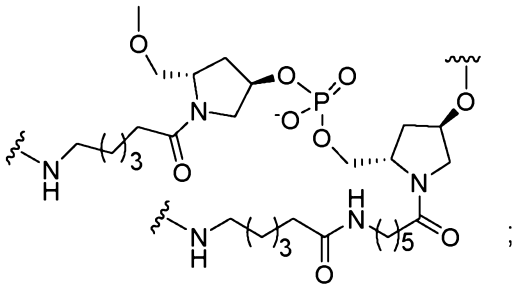
wherein each L is, independently, a phosphorus linking group or a neutral linking group; and each n is, independently, from 1 to 20.

In certain embodiments, a linker has a structure selected from among:

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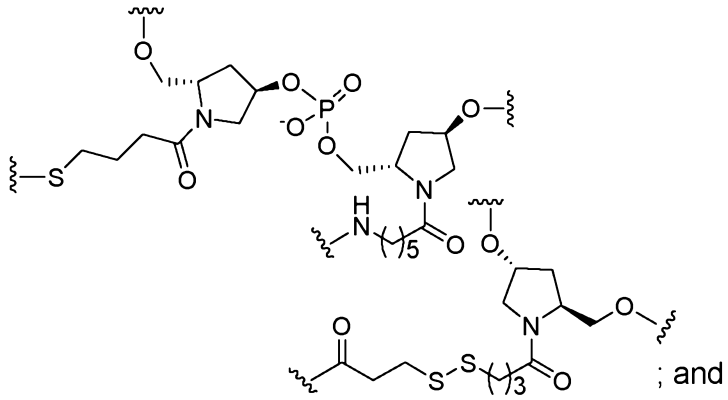
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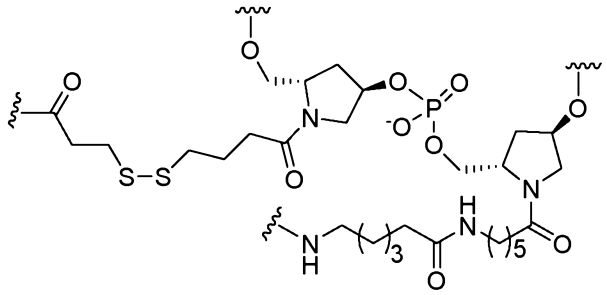
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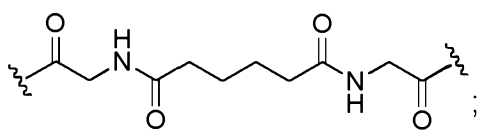
In certain embodiments, a linker has a structure selected from among: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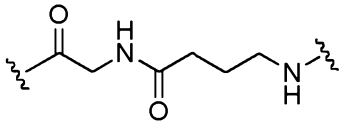
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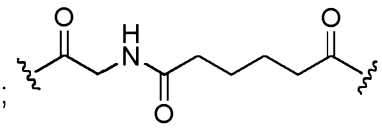
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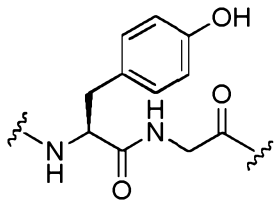
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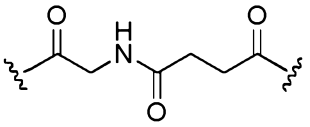
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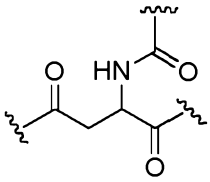
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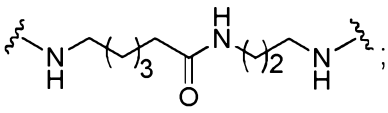
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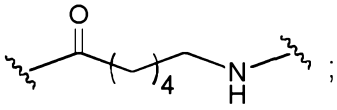
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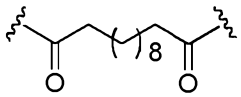
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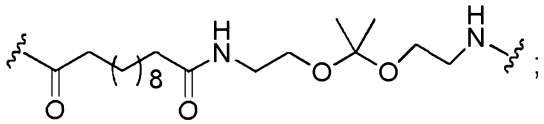
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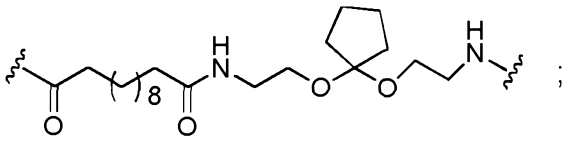
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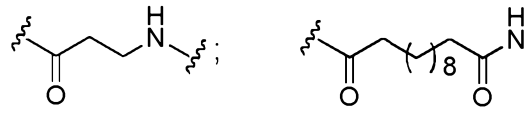
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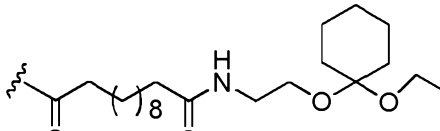
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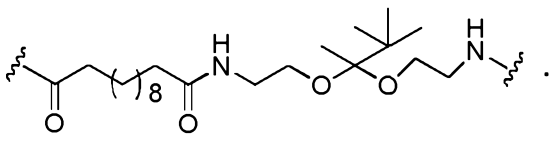
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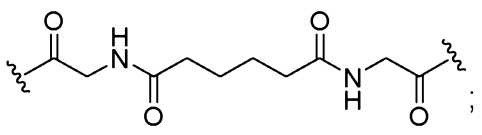
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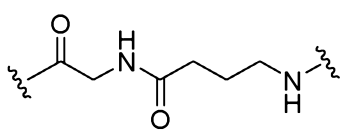
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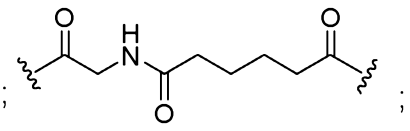
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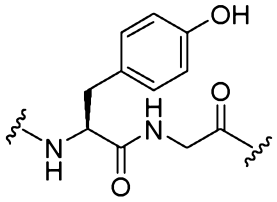
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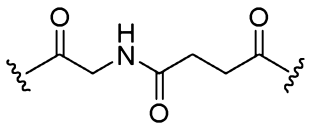
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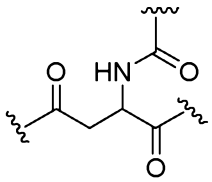
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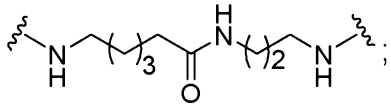
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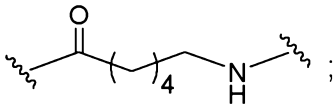
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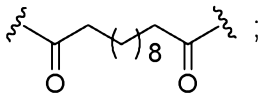
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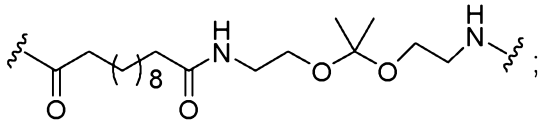
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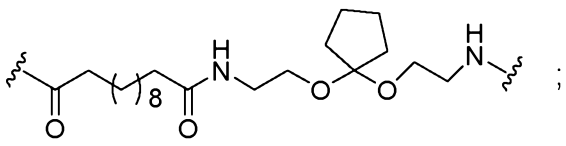
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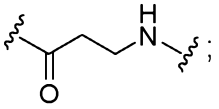
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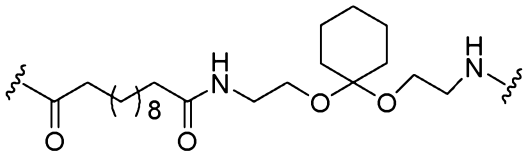

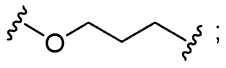
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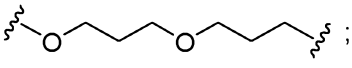
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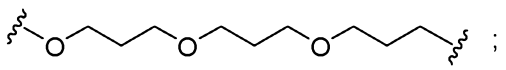
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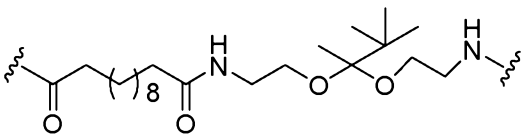
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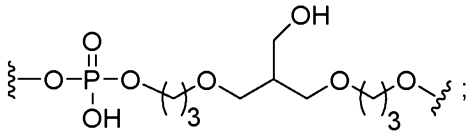
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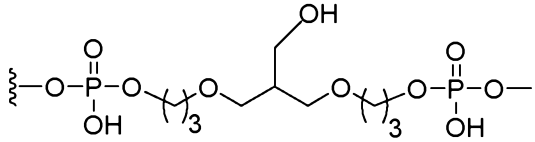
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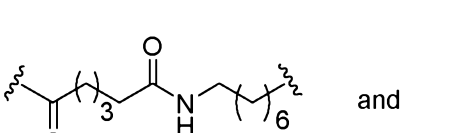
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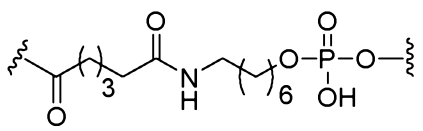
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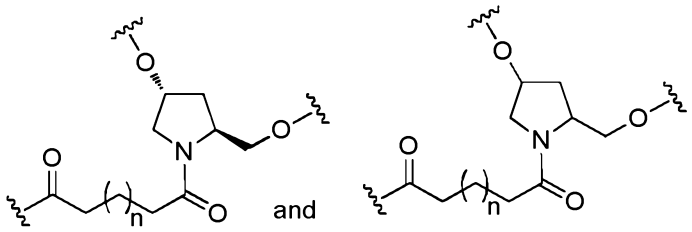
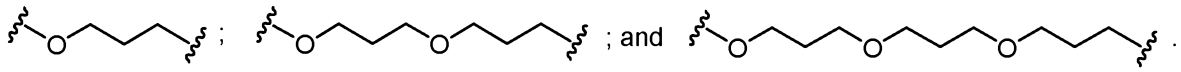
In certain embodiments, a linker has a structure selected from among:

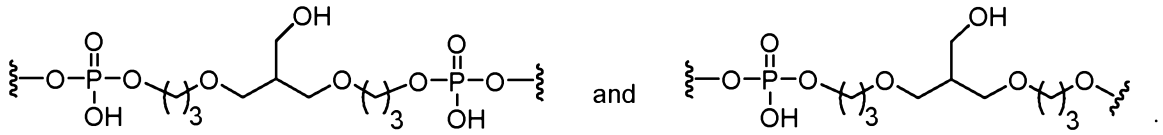


wherein n is from 1 to 20.

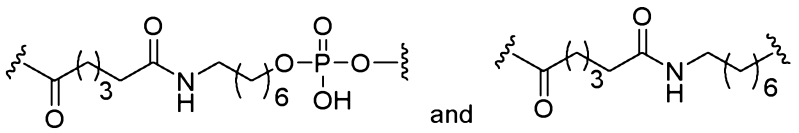
In certain embodiments, a linker has a structure selected from among:



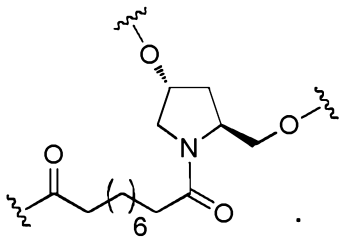
In certain embodiments, a linker has a structure selected from among:



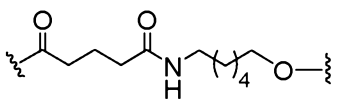
In certain embodiments, a linker has a structure selected from among:



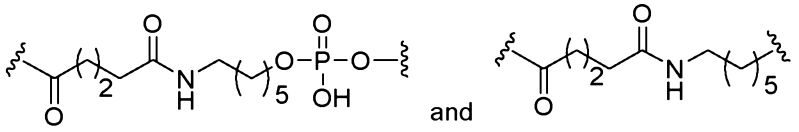
In certain embodiments, the conjugate linker has the structure:



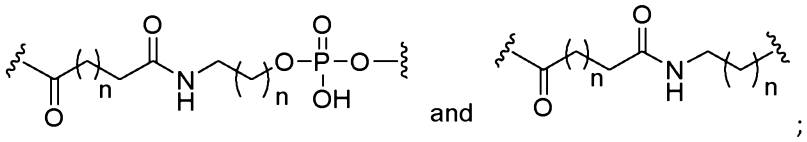
In certain embodiments, the conjugate linker has the structure:



In certain embodiments, a linker has a structure selected from among:



In certain embodiments, a linker has a structure selected from among:



wherein each n is independently, 0, 1, 2, 3, 4, 5, 6, or 7.

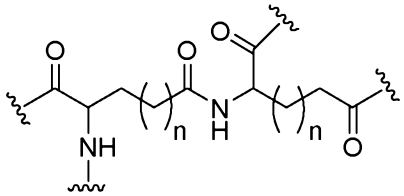
iv. **Certain Cell-Targeting Moieties**

In certain embodiments, conjugate groups comprise cell-targeting moieties. Certain such cell-targeting moieties increase cellular uptake of antisense compounds. In certain embodiments, cell-targeting moieties comprise a branching group, one or more tether, and one or more ligand. In certain embodiments, cell-targeting moieties comprise a branching group, one or more tether, one or more ligand and one or more cleavable bond.

1. **Certain Branching Groups**

In certain embodiments, the conjugate groups comprise a targeting moiety comprising a branching group and at least two tethered ligands. In certain embodiments, the branching group attaches the conjugate linker. In certain embodiments, the branching group attaches the cleavable moiety. In certain embodiments, the branching group attaches the antisense oligonucleotide. In certain embodiments, the branching group is covalently attached to the linker and each of the tethered ligands. In certain embodiments, the branching group comprises a branched aliphatic group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain embodiments, the branching group comprises groups selected from alkyl, amide and ether groups. In certain embodiments, the branching group comprises groups selected from alkyl and ether groups. In certain embodiments, the branching group comprises a mono or polycyclic ring system. In certain embodiments, the branching group comprises one or more cleavable bond. In certain embodiments, the conjugate group does not include a branching group.

In certain embodiments, a branching group has a structure selected from among: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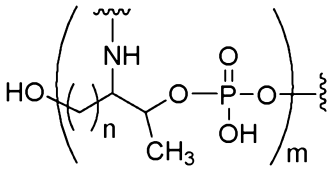
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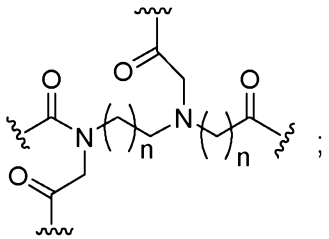
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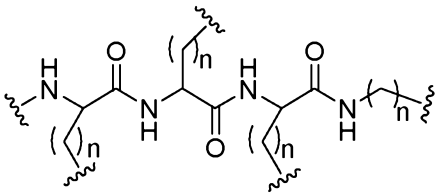
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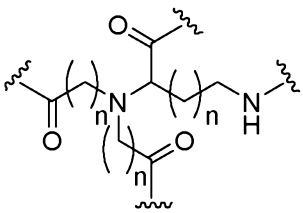
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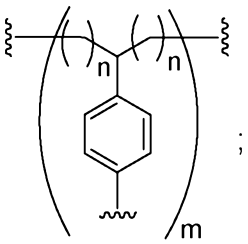
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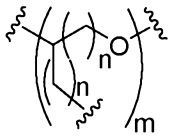
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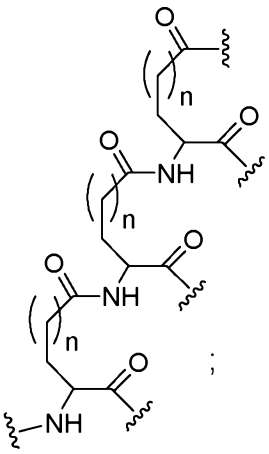
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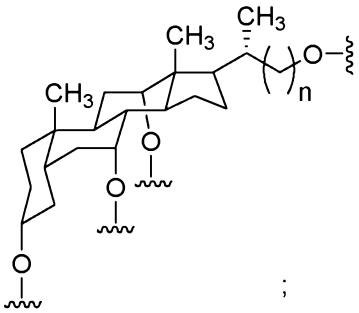
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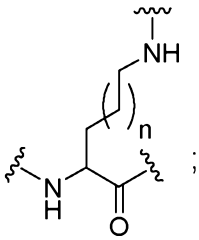
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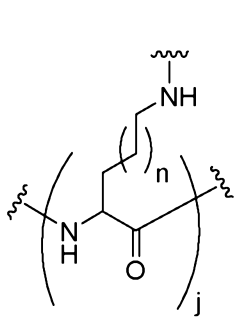
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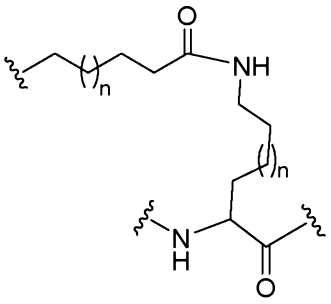
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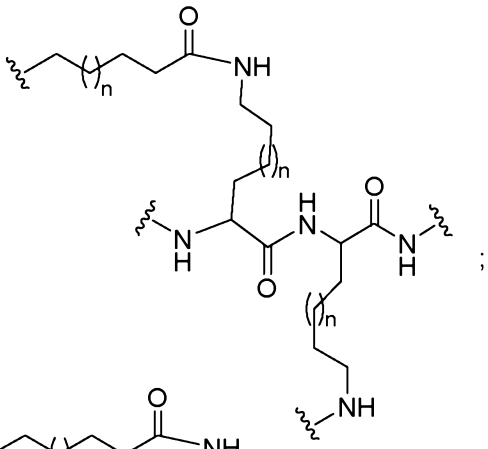
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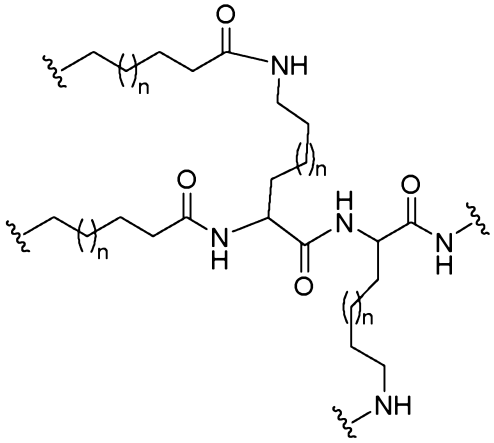
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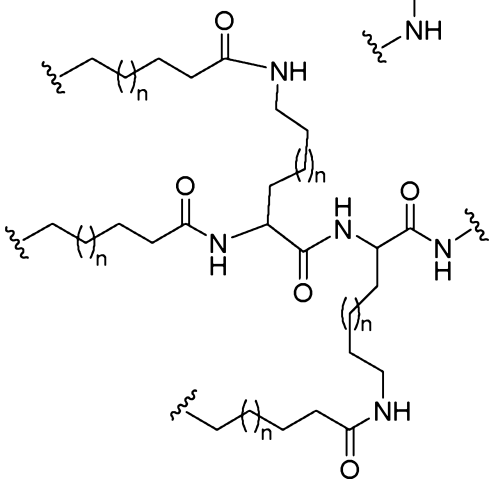
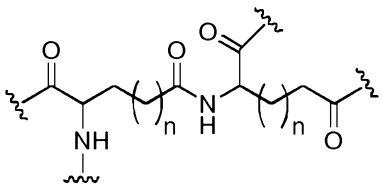

.

wherein each n is, independently, from 1 to 20;

j is from 1 to 3; and

m is from 2 to 6.

In certain embodiments, a branching group has a structure selected from among: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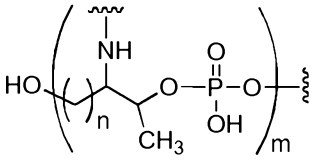
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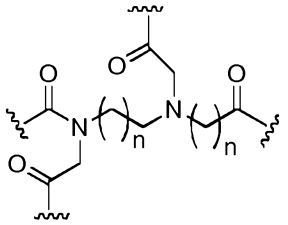
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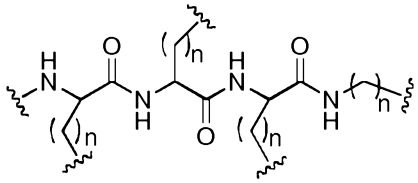
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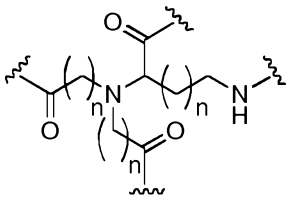
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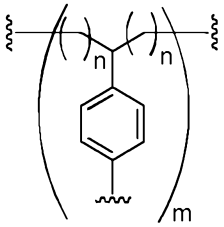
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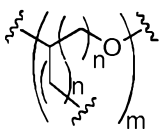
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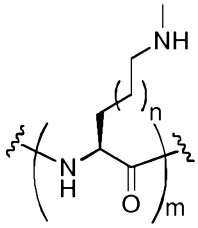
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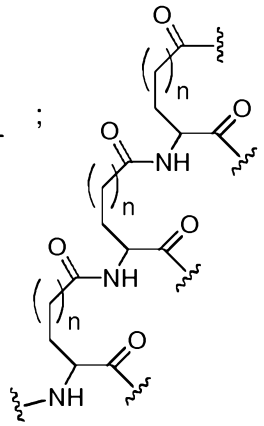
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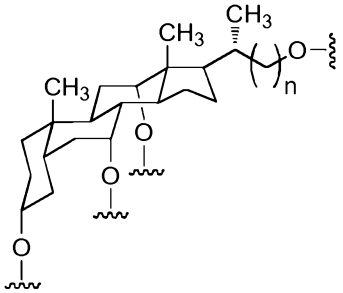
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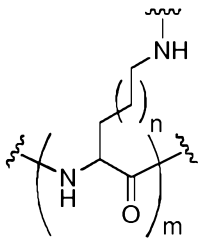
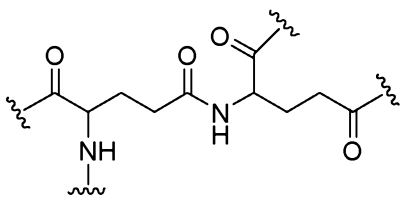


wherein each n is, independently, from 1 to 20; and

m is from 2 to 6.

In certain embodiments, a branching group has a structure selected from among: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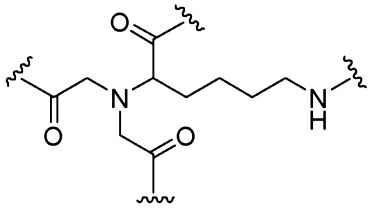
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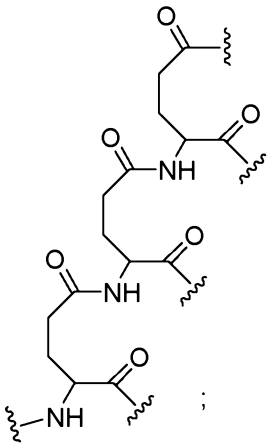
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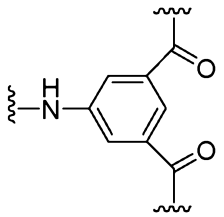
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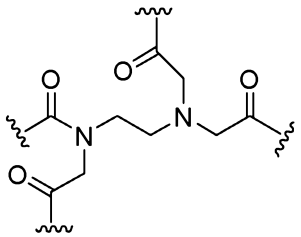
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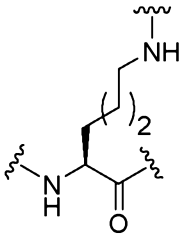
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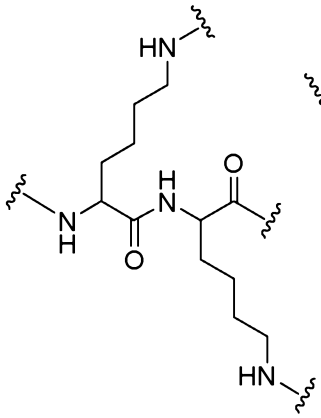
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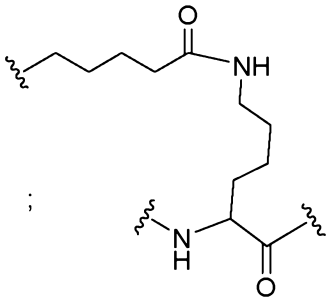
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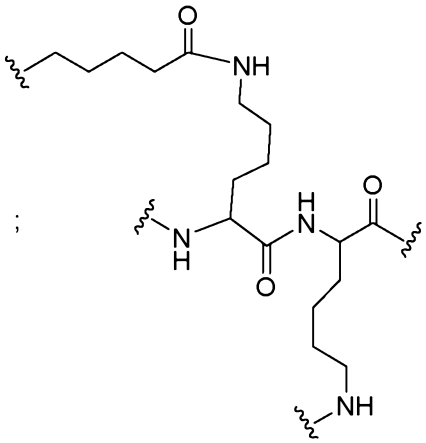
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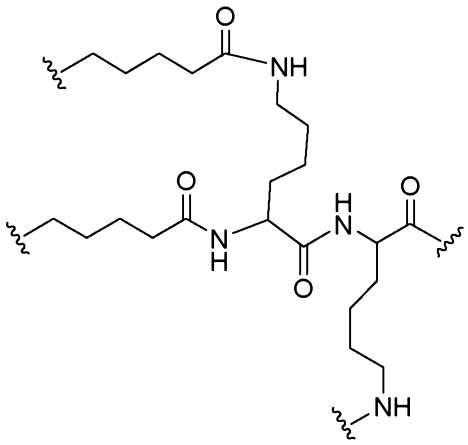
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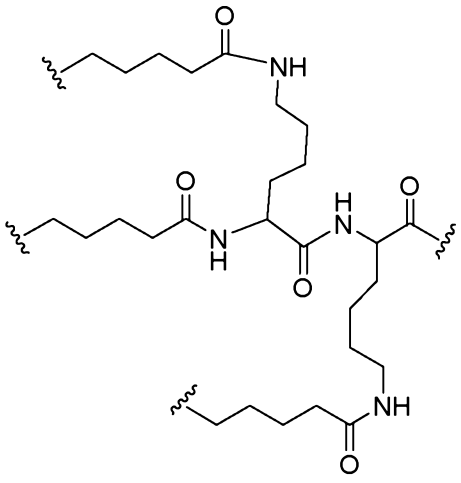
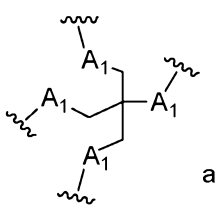
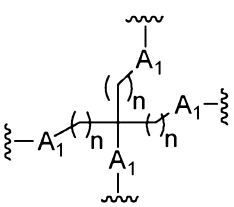

.

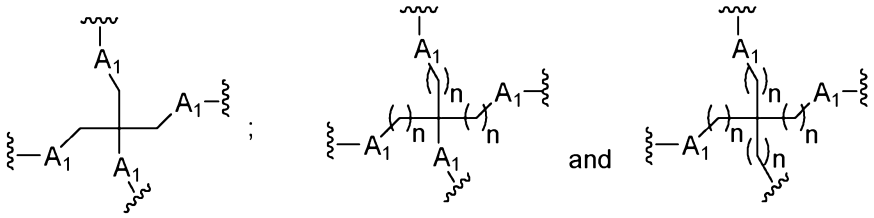
In certain embodiments, a branching group has a structure selected from among:


and


wherein each A_1 is independently, O, S, C=O or NH; and

each n is, independently, from 1 to 20.

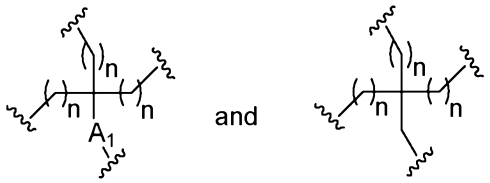
In certain embodiments, a branching group has a structure selected from among:



wherein each A_1 is independently, O, S, C=O or NH; and

each n is, independently, from 1 to 20.

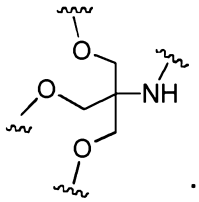
In certain embodiments, a branching group has a structure selected from among:



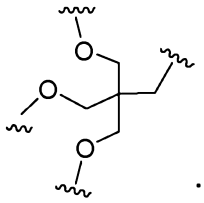
wherein A_1 is O, S, C=O or NH; and

each n is, independently, from 1 to 20.

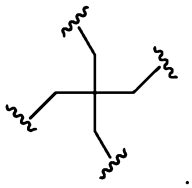
In certain embodiments, a branching group has a structure selected from among:



In certain embodiments, a branching group has a structure selected from among:



In certain embodiments, a branching group has a structure selected from among:



2. Certain Tethers

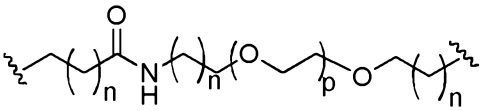
In certain embodiments, conjugate groups comprise one or more tethers covalently attached to the branching group. In certain embodiments, conjugate groups comprise one or more tethers covalently attached to the linking group. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether, thioether, disulfide, amide and polyethylene glycol groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, substituted alkyl, ether, thioether, disulfide, amide, phosphodiester and polyethylene glycol groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether and amide groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, substituted alkyl, phosphodiester, ether and amide groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl and phosphodiester in any combination. In certain embodiments, each tether comprises at least one phosphorus linking group or neutral linking group.

In certain embodiments, the tether includes one or more cleavable bond. In certain embodiments, the tether is attached to the branching group through either an amide or an ether group. In certain embodiments, the tether is attached to the branching group through a phosphodiester group. In certain embodiments, the tether is attached to the branching group through a phosphorus linking group or neutral linking group. In certain embodiments, the tether is attached to the branching group through an ether group. In certain embodiments, the tether is attached to the ligand through either an amide or an ether group. In certain embodiments, the tether is attached to the ligand through an ether group. In certain embodiments, the tether is attached to the ligand through either an amide or an ether group. In certain embodiments, the tether is attached to the ligand through an ether group.

In certain embodiments, each tether comprises from about 8 to about 20 atoms in chain length between the ligand and the branching group. In certain embodiments, each tether group comprises from

about 10 to about 18 atoms in chain length between the ligand and the branching group. In certain embodiments, each tether group comprises about 13 atoms in chain length.

In certain embodiments, a tether has a structure selected from among: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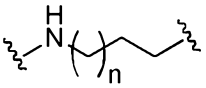
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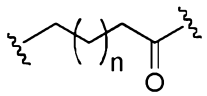
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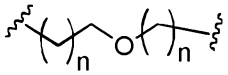
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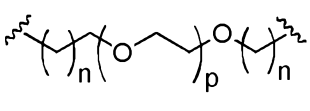
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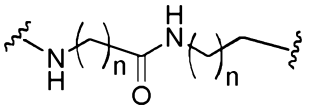
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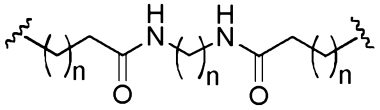
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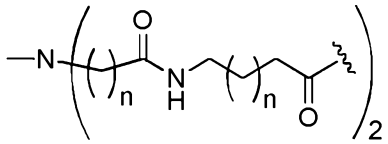
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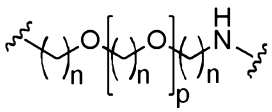
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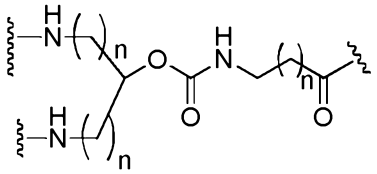
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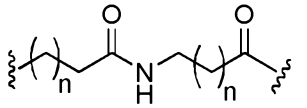
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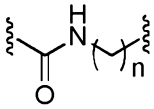
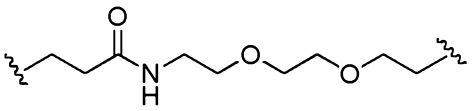
; and


wherein each n is, independently, from 1 to 20; and
each p is from 1 to about 6.

In certain embodiments, a tether has a structure selected from among: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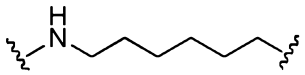
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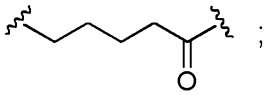
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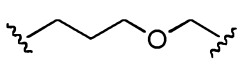
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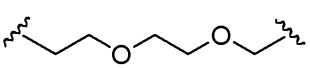
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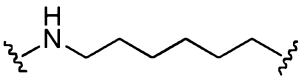
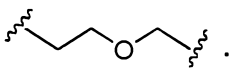
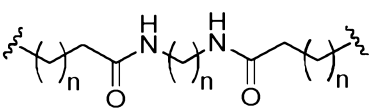
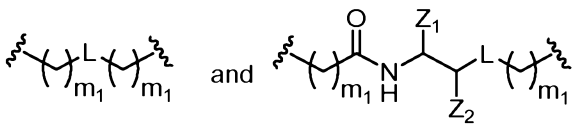

; and

.

In certain embodiments, a tether has a structure selected from among:



wherein each n is, independently, from 1 to 20.

In certain embodiments, a tether has a structure selected from among:



wherein L is either a phosphorus linking group or a neutral linking group;

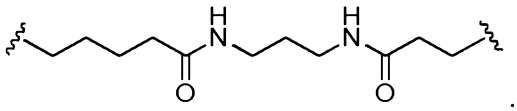
Z_1 is C(=O)O-R_2;

Z_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky;

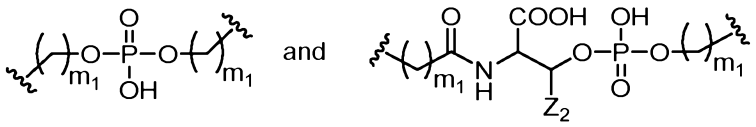
R_2 is H, C_1-C_6 alkyl or substituted C_1-C_6 alky; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

In certain embodiments, a tether has a structure selected from among:



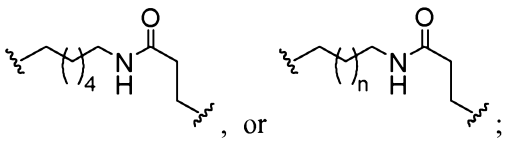
In certain embodiments, a tether has a structure selected from among:



wherein Z_2 is H or CH_3; and

each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

In certain embodiments, a tether has a structure selected from among:



; wherein each n is independently, 0, 1, 2, 3, 4, 5, 6, or 7.

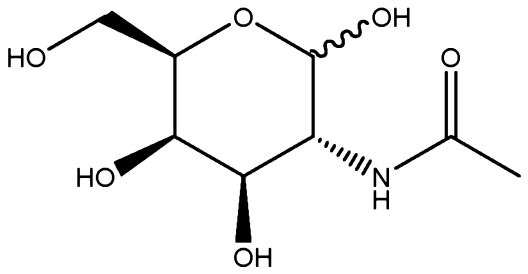
In certain embodiments, a tether comprises a phosphorus linking group. In certain embodiments, a tether does not comprise any amide bonds. In certain embodiments, a tether comprises a phosphorus linking group and does not comprise any amide bonds.

3. Certain Ligands

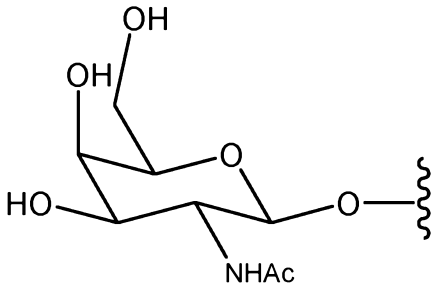
In certain embodiments, the present disclosure provides ligands wherein each ligand is covalently attached to a tether. In certain embodiments, each ligand is selected to have an affinity for at least one type of receptor on a target cell. In certain embodiments, ligands are selected that have an affinity 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, each ligand is a carbohydrate. In certain embodiments, each ligand is, independently selected from galactose, N-acetyl galactoseamine, mannose, glucose, glucosamone and fucose. In certain embodiments, each ligand is N-acetyl galactoseamine (GalNAc). In certain embodiments, the targeting moiety comprises 2 to 6 ligands. In certain embodiments, the targeting moiety comprises 3 ligands. In certain embodiments, the targeting moiety comprises 3 N-acetyl galactoseamine ligands.

In certain embodiments, the ligand is a carbohydrate, carbohydrate derivative, modified carbohydrate, multivalent carbohydrate cluster, polysaccharide, modified polysaccharide, or polysaccharide derivative. In certain embodiments, the ligand is an amino sugar or a thio sugar. For example, amino sugars may be selected from any number of compounds known in the art, for example glucosamine, sialic acid, α-D-galactosamine, N-Acetylgalactosamine, 2-acetamido-2-deoxy-D-galactopyranose (GalNAc), 2-Amino-3-*O*-[(*R*)-1-carboxyethyl]-2-deoxy-β-D-glucopyranose (β-muramic acid), 2-Deoxy-2-methylamino-L-glucopyranose, 4,6-Dideoxy-4-formamido-2,3-di-*O*-methyl-D-mannopyranose, 2-Deoxy-2-sulfoamino-D-glucopyranose and *N*-sulfo-D-glucosamine, and *N*-Glycoloyl-α-neuraminic acid. For example, thio sugars may be selected from the group consisting of 5-Thio-β-D-glucopyranose, Methyl 2,3,4-tri-*O*-acetyl-1-thio-6-*O*-trityl-α-D-glucopyranoside, 4-Thio-β-D-galactopyranose, and ethyl 3,4,6,7-tetra-*O*-acetyl-2-deoxy-1,5-dithio-α-D-*gluco*-heptopyranoside.

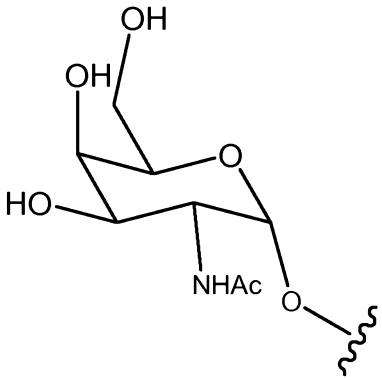
In certain embodiments, "GalNac" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose, commonly referred to in the literature as N-acetyl galactosamine. In certain embodiments, "N-acetyl galactosamine" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose. In certain embodiments, "GalNac" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose. In certain embodiments, "GalNac" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose, which includes both the β-form: 2-(Acetylamino)-2-deoxy-β-D-galactopyranose and α-form: 2-(Acetylamino)-2-deoxy-D-galactopyranose. In certain embodiments, both the β-form: 2-(Acetylamino)-2-deoxy-β-D-galactopyranose and α-form: 2-(Acetylamino)-2-deoxy-D-galactopyranose may be used interchangeably. Accordingly, in structures in which one form is depicted, these structures are intended to include the other form as well. For example, where the structure for an α-form: 2-(Acetylamino)-2-deoxy-D-galactopyranose is shown, this structure is intended to include the other form as well. In certain embodiments, In certain preferred embodiments, the β-form 2-(Acetylamino)-2-deoxy-D-galactopyranose is the preferred embodiment.



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

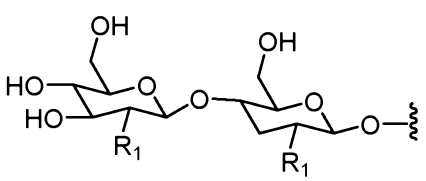


2-(Acetylamino)-2-deoxy-β-D-galactopyranose

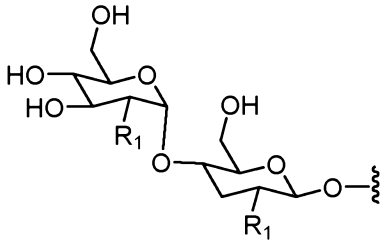


2-(Acetylamino)-2-deoxy-α-D-galactopyranose

In certain embodiments one or more ligand has a structure selected from among:

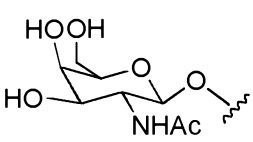


and



wherein each R_1 is selected from OH and NHCOOH.

In certain embodiments one or more ligand has a structure selected from among: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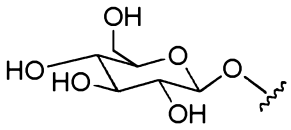
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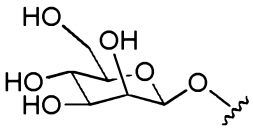
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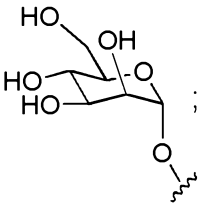
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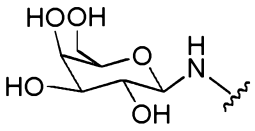
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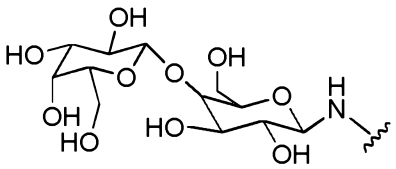
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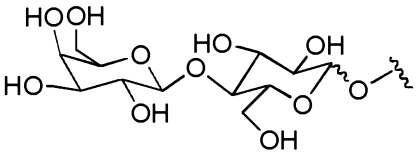
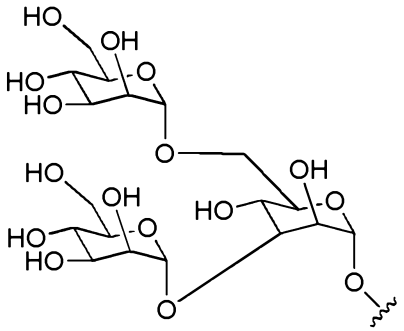
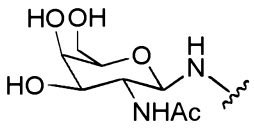
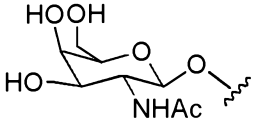

; and

.

In certain embodiments one or more ligand has a structure selected from among:

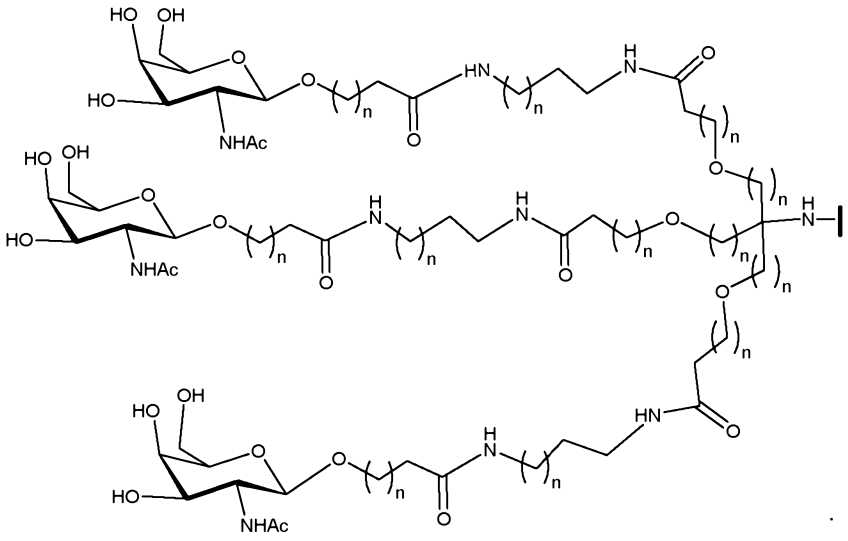

.

In certain embodiments one or more ligand has a structure selected from among:


.

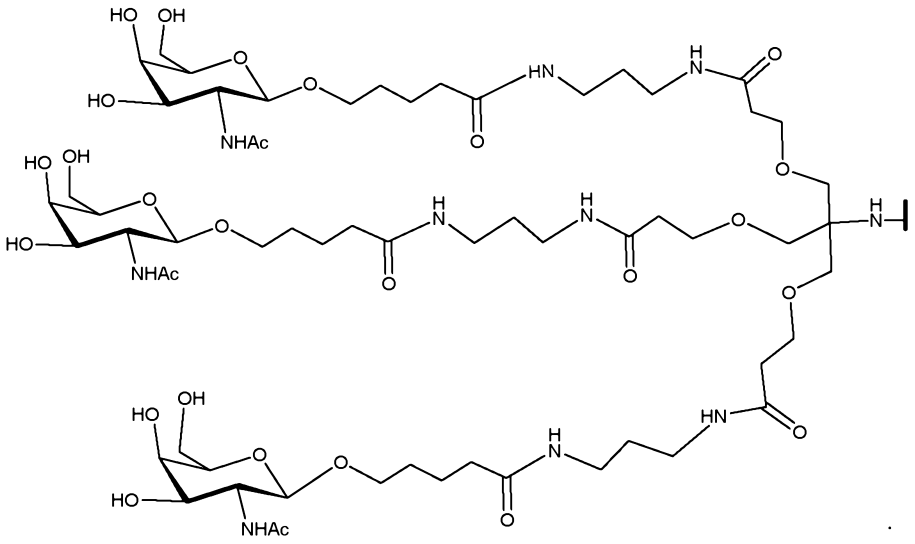
i. **Certain Conjugates**

In certain embodiments, conjugate groups comprise the structural features above. In certain such embodiments, conjugate groups have the following structure:

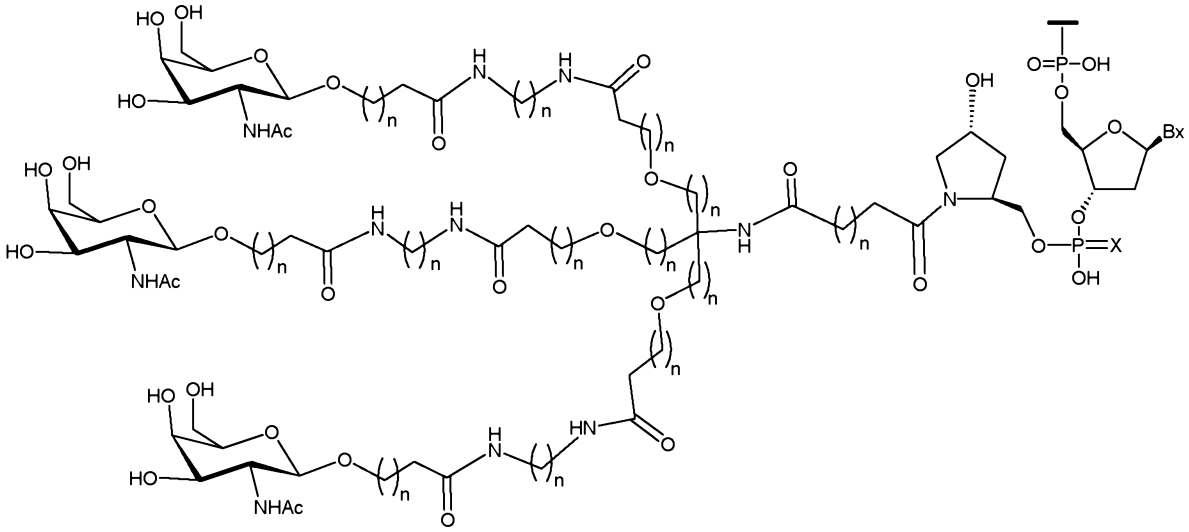


wherein each n is, independently, from 1 to 20.

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



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



wherein each n is, independently, from 1 to 20;

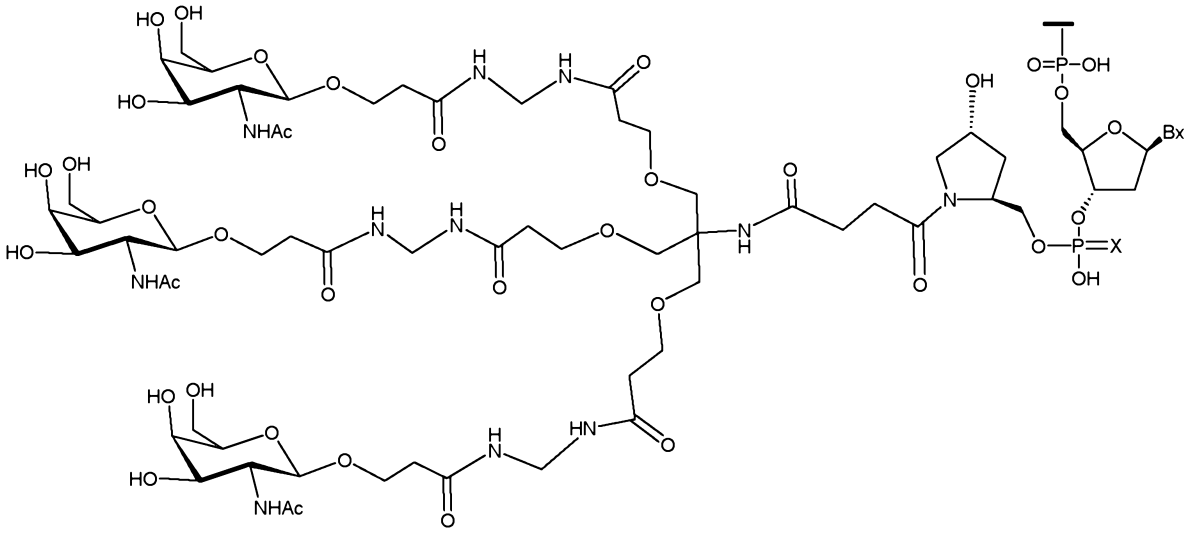
Z is H or a linked solid support;

Q is an antisense compound;

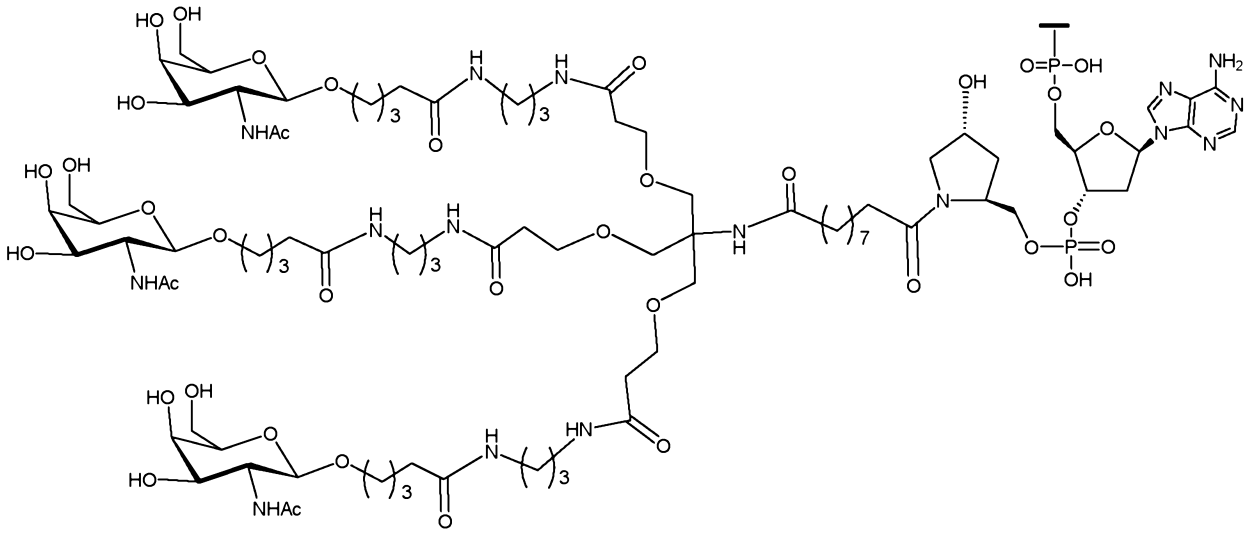
X is O or S; and

Bx is a heterocyclic base moiety.

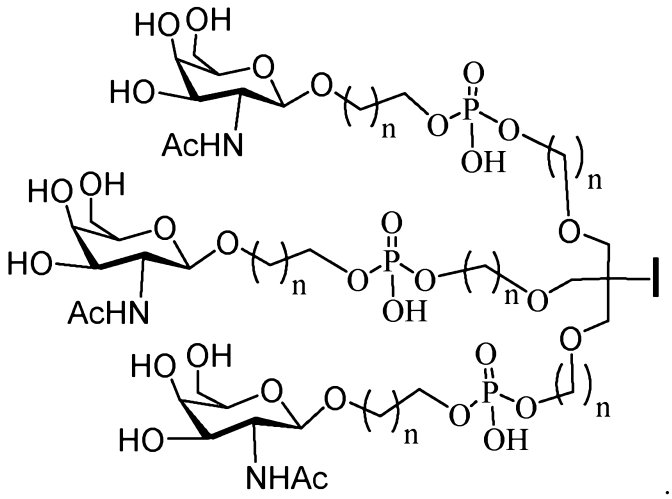
In certain such embodiments, conjugate groups have the following structure:



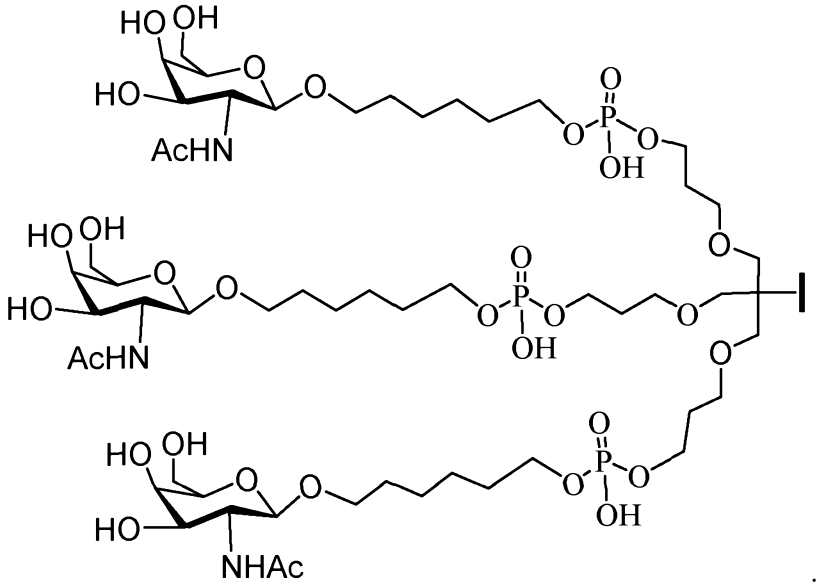
In certain such embodiments, conjugate groups have the following structure:



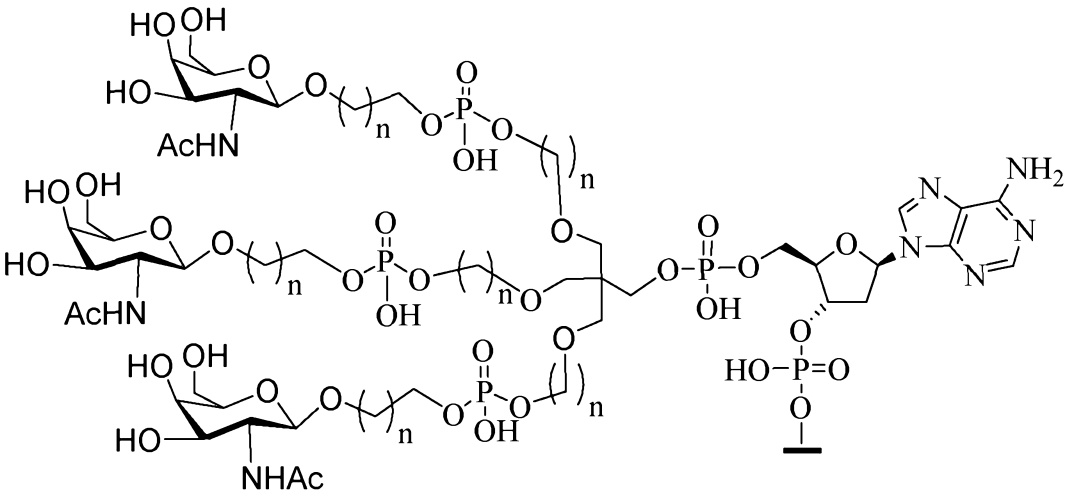
In certain such embodiments, conjugate groups have the following structure:



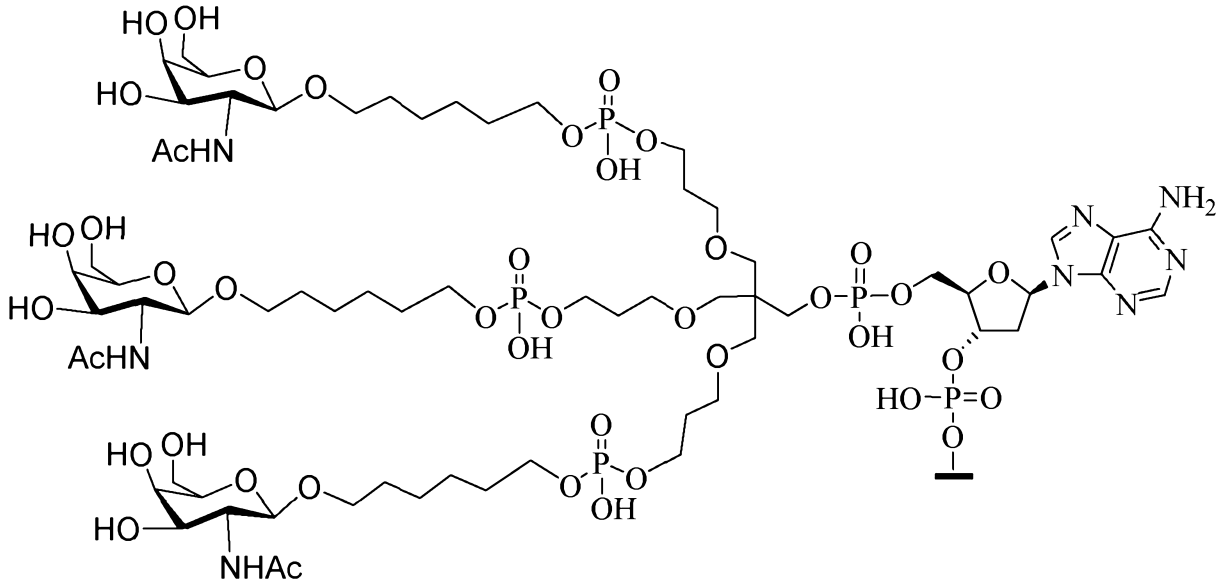
In certain such embodiments, conjugate groups have the following structure:



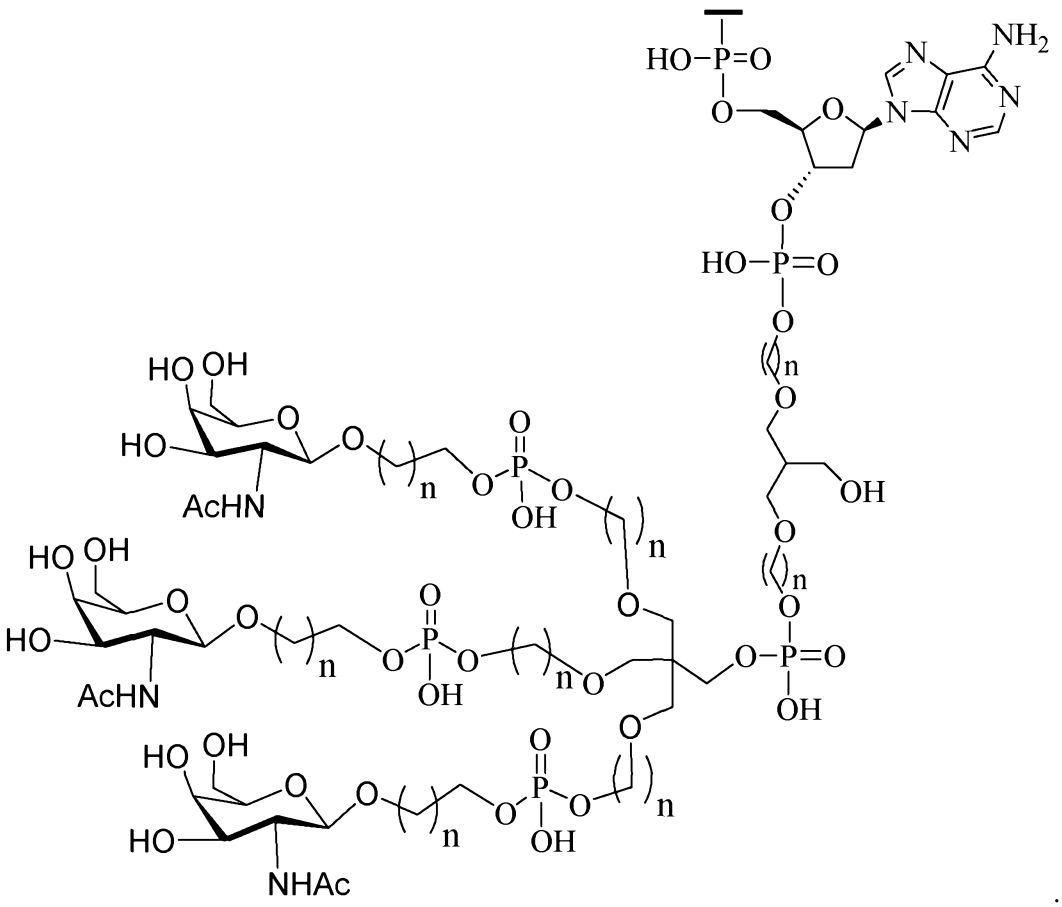
In certain such embodiments, conjugate groups have the following structure:



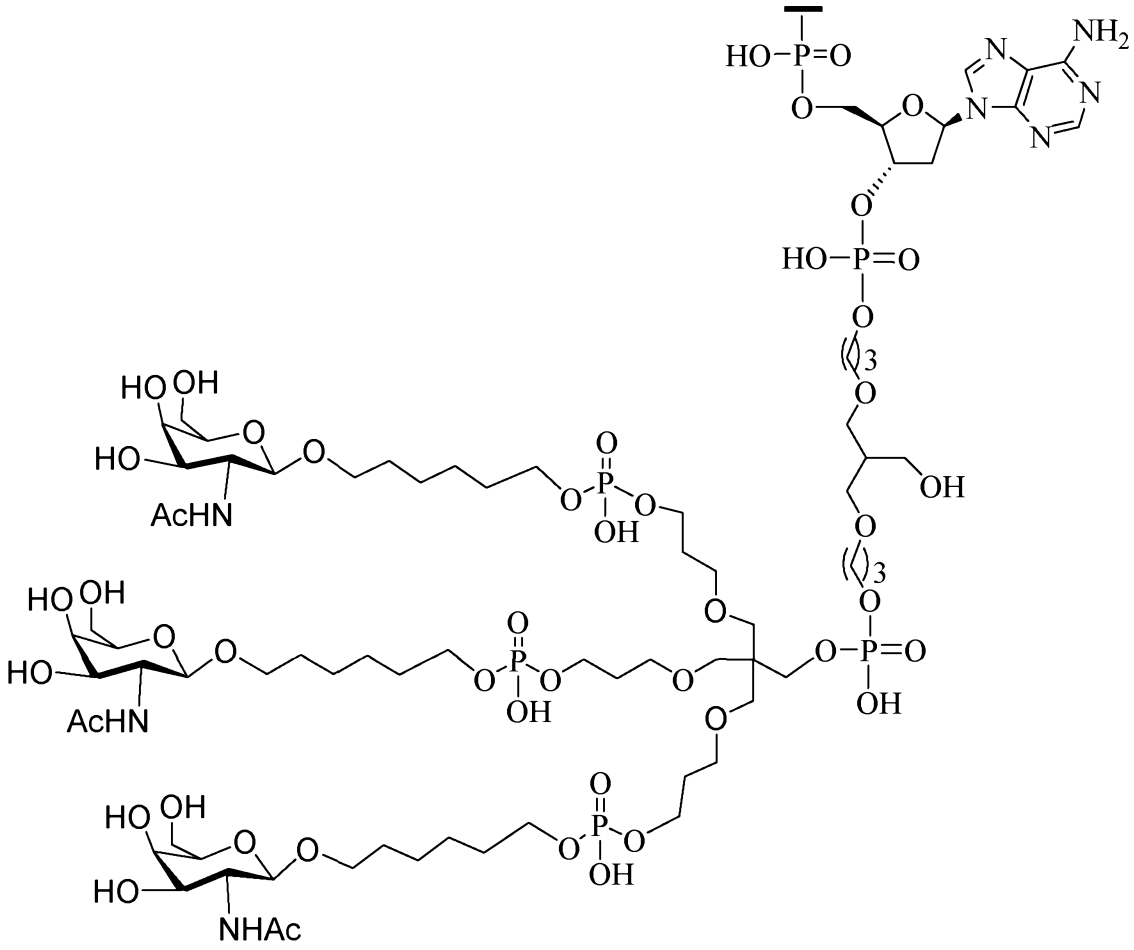
In certain such embodiments, conjugate groups have the following structure:



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

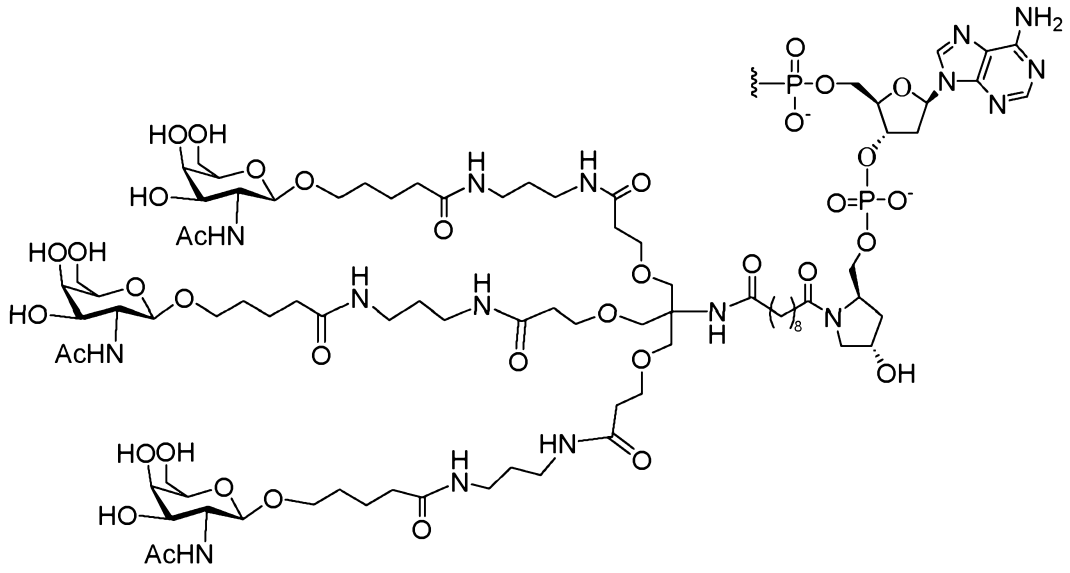


In certain such embodiments, conjugate groups have the following structure:

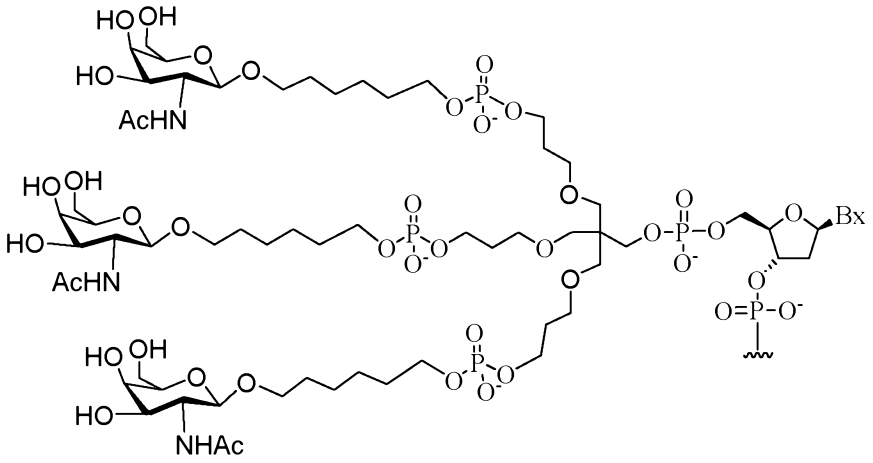


In certain embodiments, conjugates do not comprise a pyrrolidine.

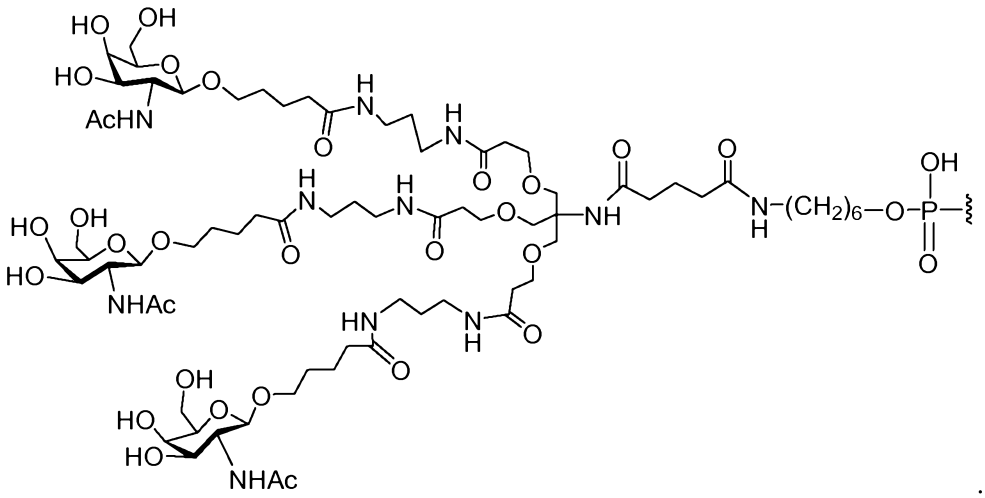
In certain such embodiments, conjugate groups have the following structure:



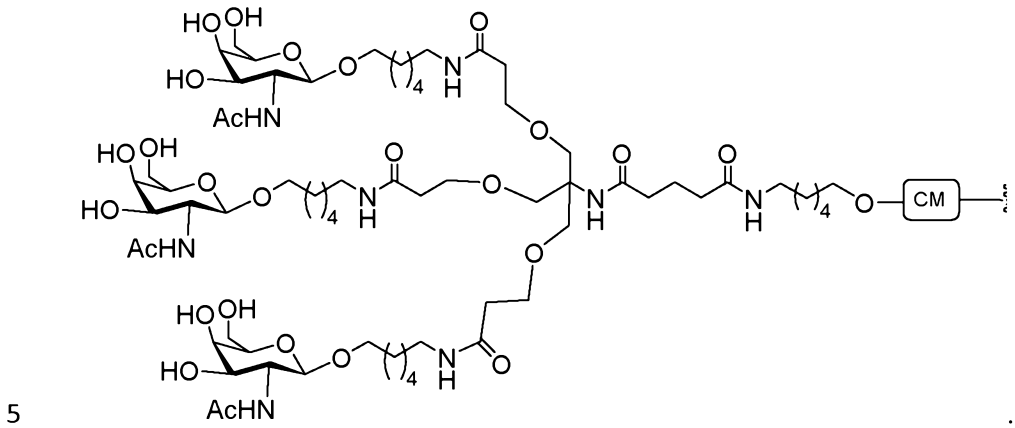
In certain such embodiments, conjugate groups have the following structure:



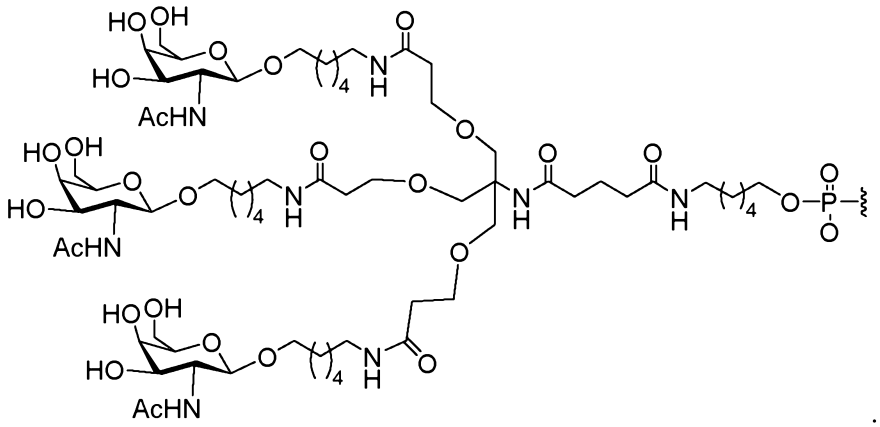
In certain such embodiments, conjugate groups have the following structure:



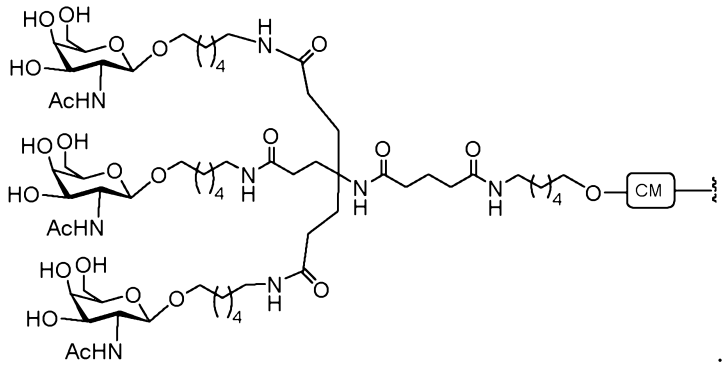
In certain such embodiments, conjugate groups have the following structure:



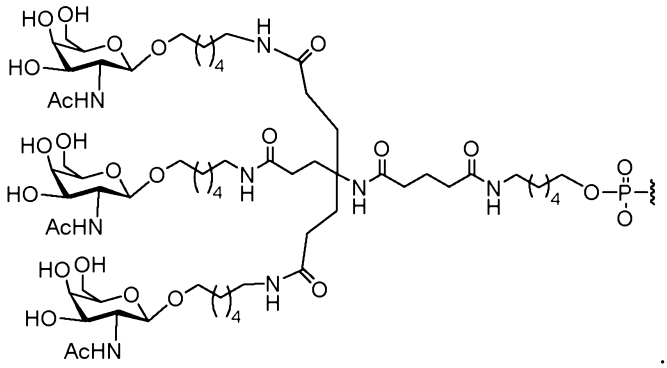
In certain such embodiments, conjugate groups have the following structure:



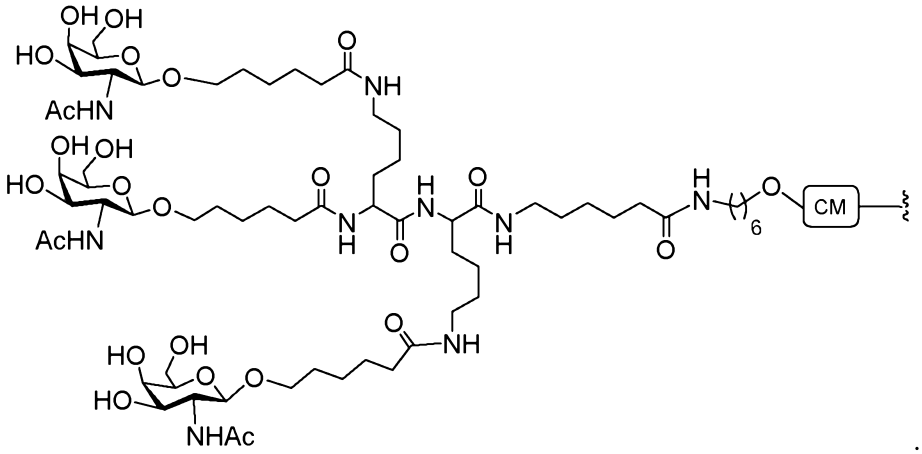
In certain such embodiments, conjugate groups have the following structure:



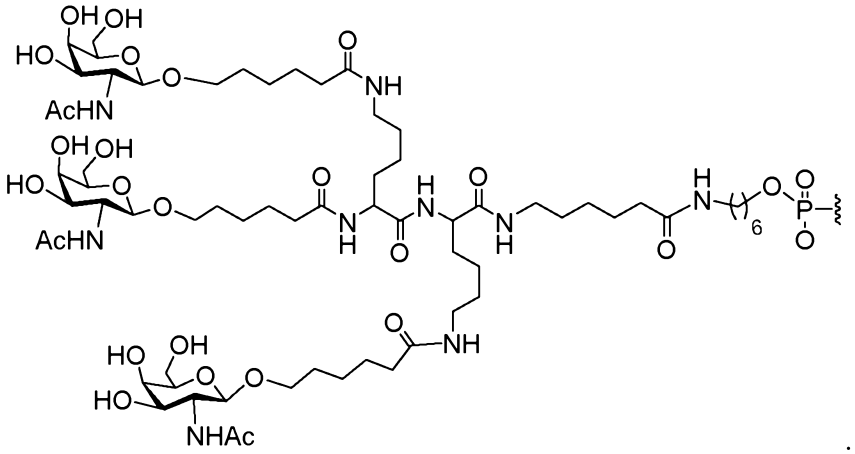
In certain such embodiments, conjugate groups have the following structure:



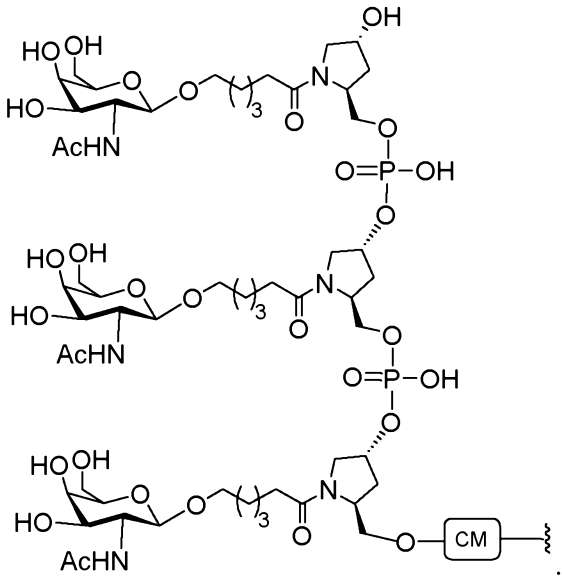
In certain such embodiments, conjugate groups have the following structure:



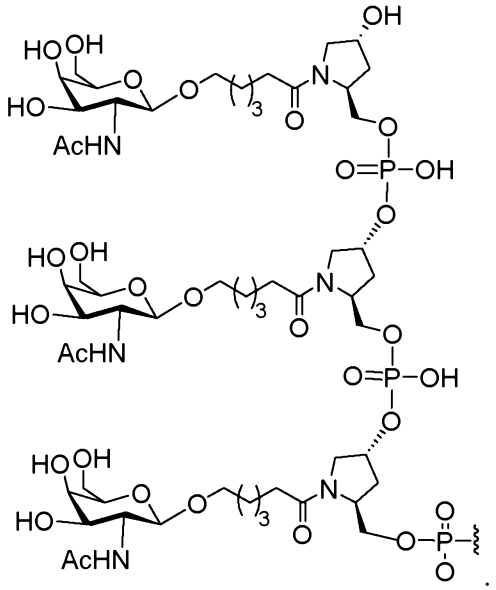
In certain such embodiments, conjugate groups have the following structure:



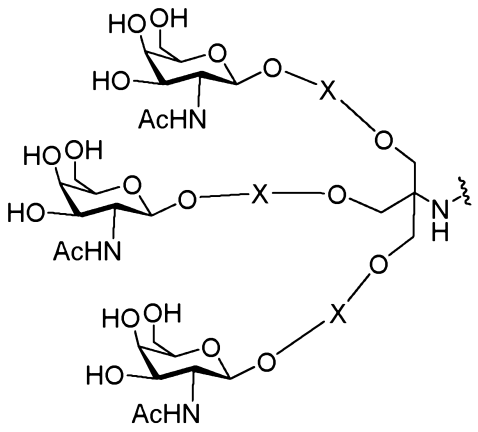
In certain such embodiments, conjugate groups have the following structure:



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

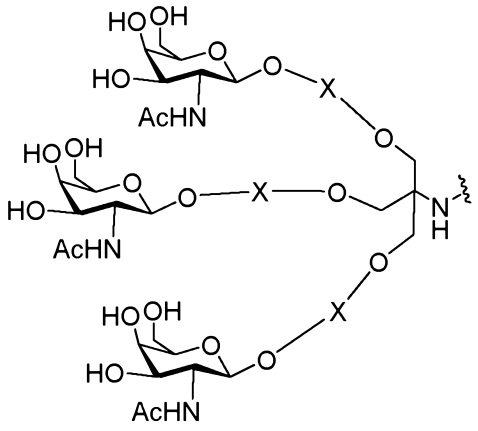


In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



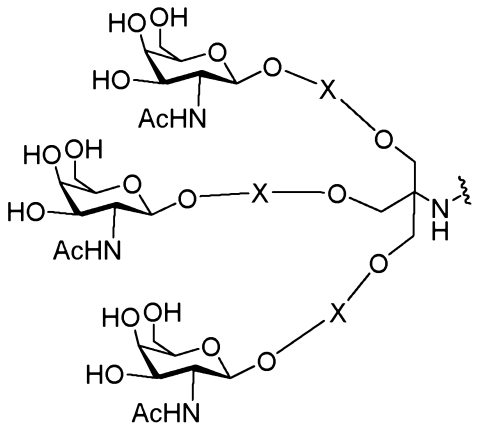
wherein X is a substituted or unsubstituted tether of six to eleven consecutively bonded atoms.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



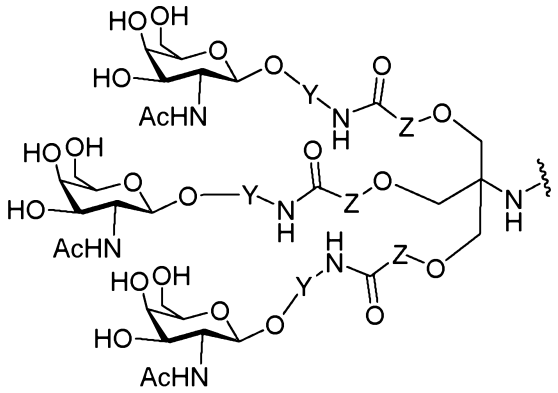
wherein X is a substituted or unsubstituted tether of ten consecutively bonded atoms.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



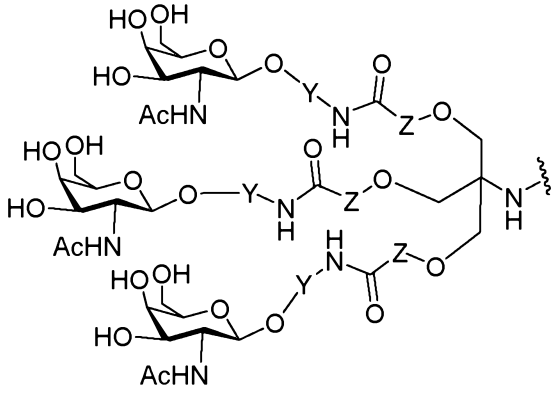
wherein X is a substituted or unsubstituted tether of four to eleven consecutively bonded atoms and wherein the tether comprises exactly one amide bond.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



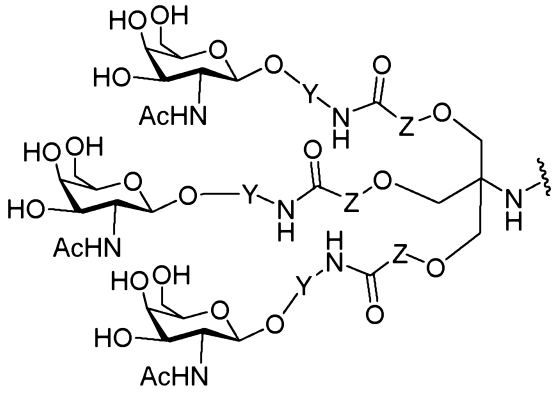
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



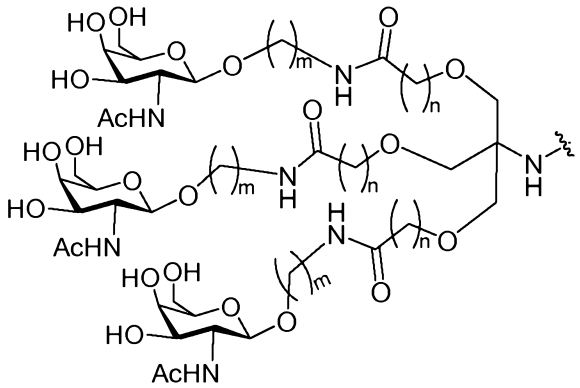
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising exactly one ether or exactly two ethers, an amide, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



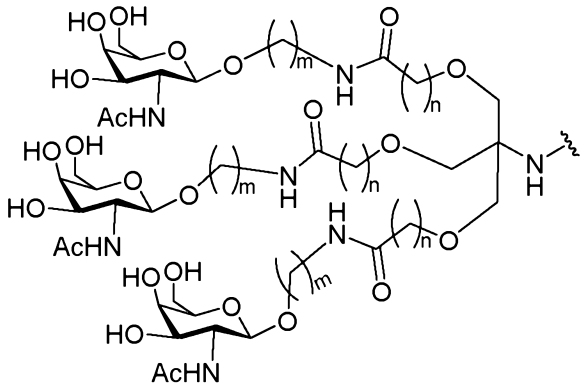
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



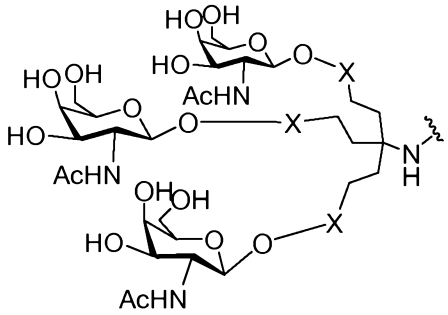
wherein m and n are independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



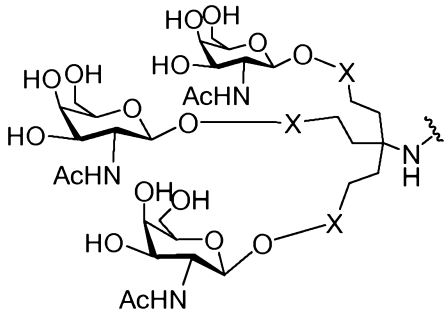
wherein m is 4, 5, 6, 7, or 8, and n is 1, 2, 3, or 4.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



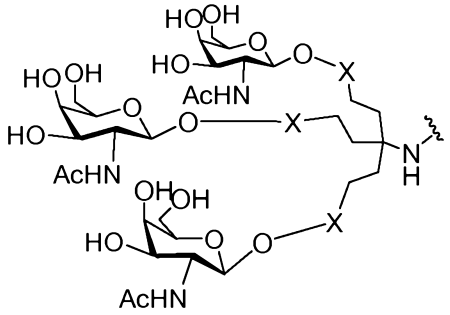
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein X does not comprise an ether group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



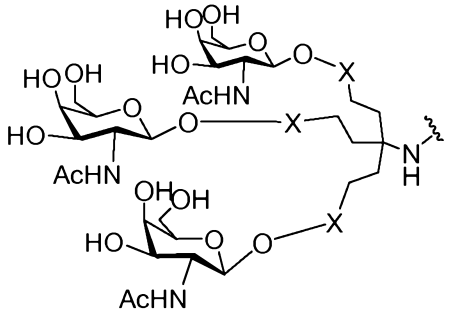
wherein X is a substituted or unsubstituted tether of eight consecutively bonded atoms, and wherein X does not comprise an ether group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



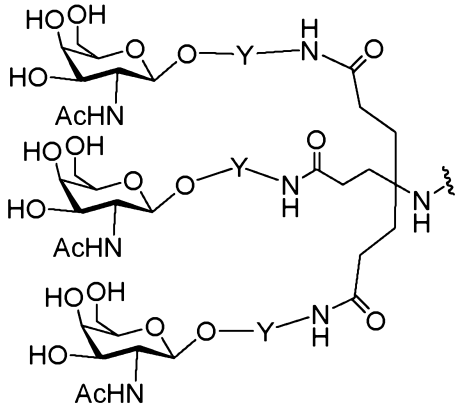
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein the tether comprises exactly one amide bond, and wherein X does not comprise an ether group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



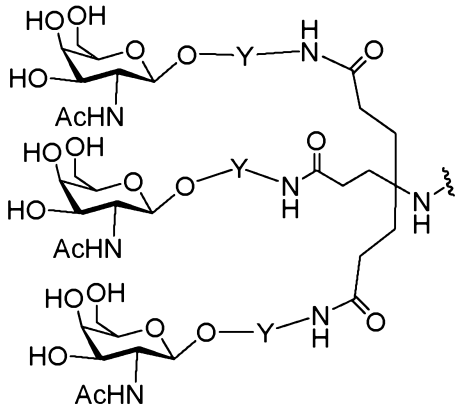
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms and wherein the tether consists of an amide bond and a substituted or unsubstituted C_2-C_{11} alkyl group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



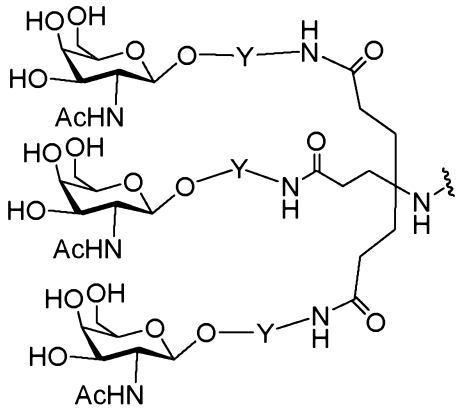
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



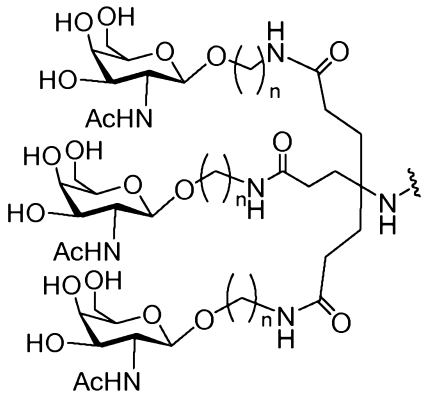
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising an ether, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



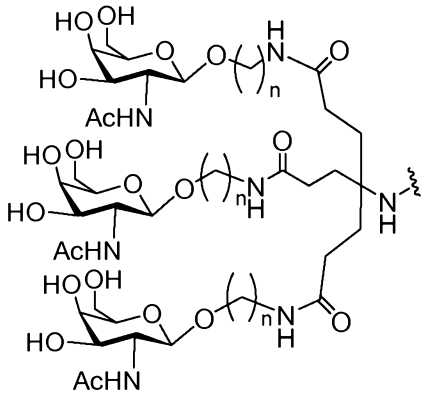
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



Wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

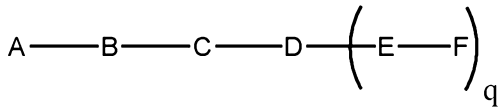
In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



wherein n is 4, 5, 6, 7, or 8.

b.Certain conjugated antisense compounds

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, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

C is the conjugate linker

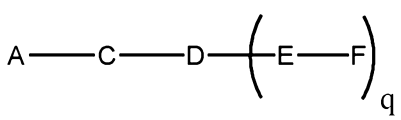
D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

In certain embodiments, a conjugated antisense compound has the following structure:



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.

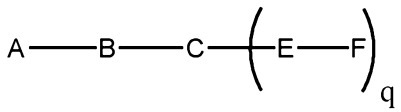
In certain such embodiments, the conjugate linker comprises at least one cleavable bond.

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

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

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, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

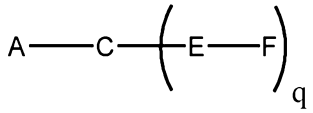
C is the conjugate linker

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

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, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

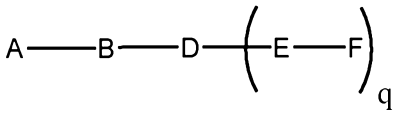
C is the conjugate linker

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

In certain embodiments, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

B is the cleavable moiety

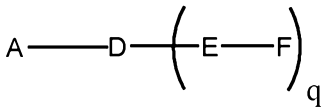
D is the branching group

each E is a tether;

each F is a ligand; and

q is an integer between 1 and 5.

In certain embodiments, a conjugated antisense compound has the following structure:



wherein

A is the antisense oligonucleotide;

D is the branching group

each E is a tether;

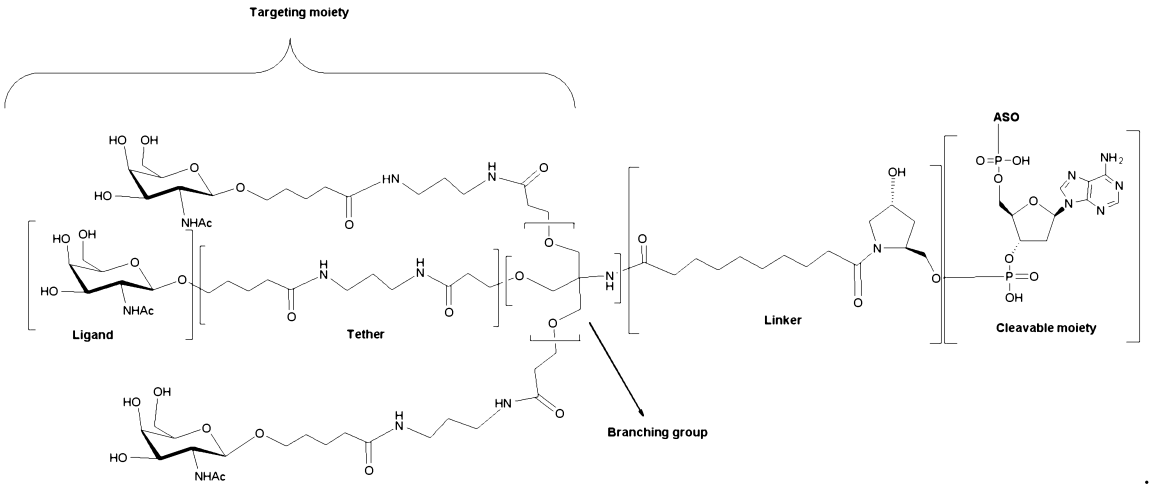
each F is a ligand; and

q is an integer between 1 and 5.

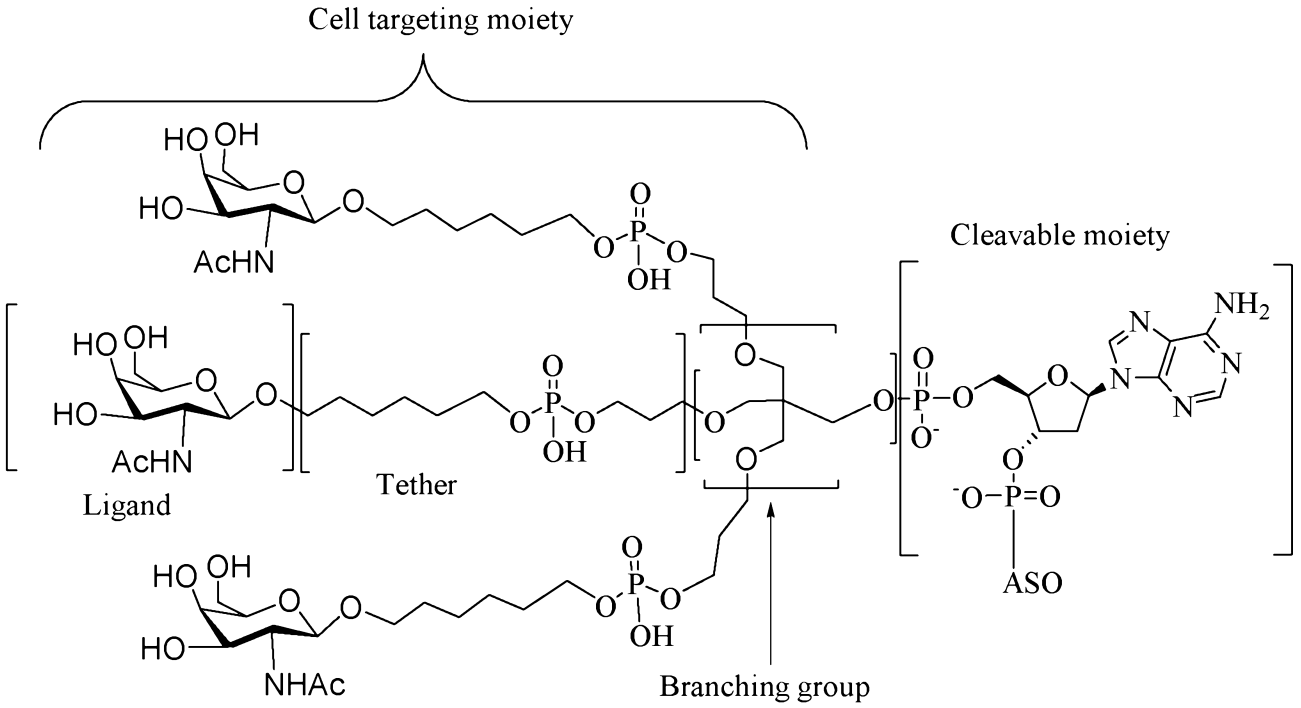
In certain such embodiments, the conjugate linker comprises at least one cleavable bond.

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

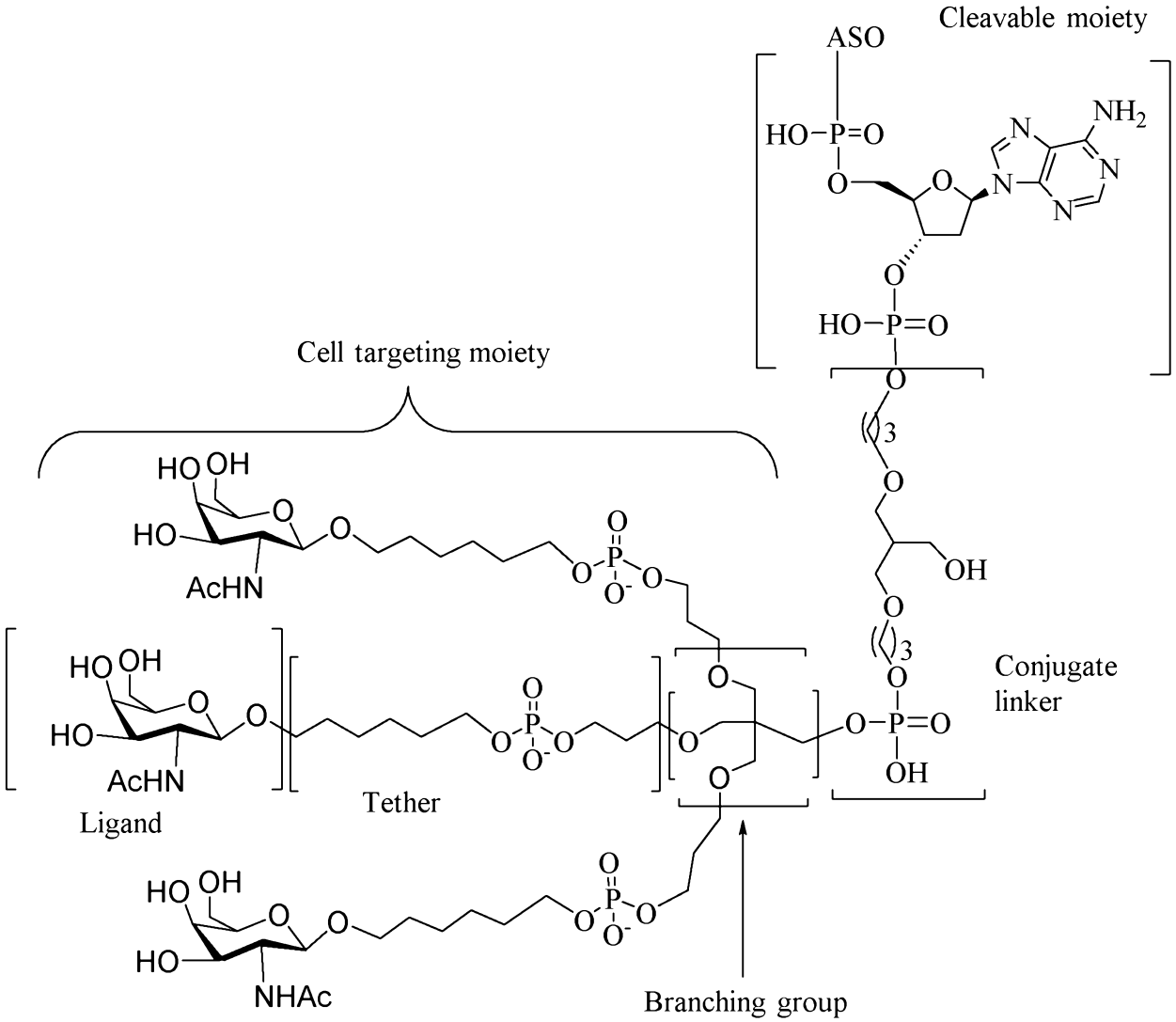
In certain embodiments, a conjugated antisense compound has a structure selected from among the following:



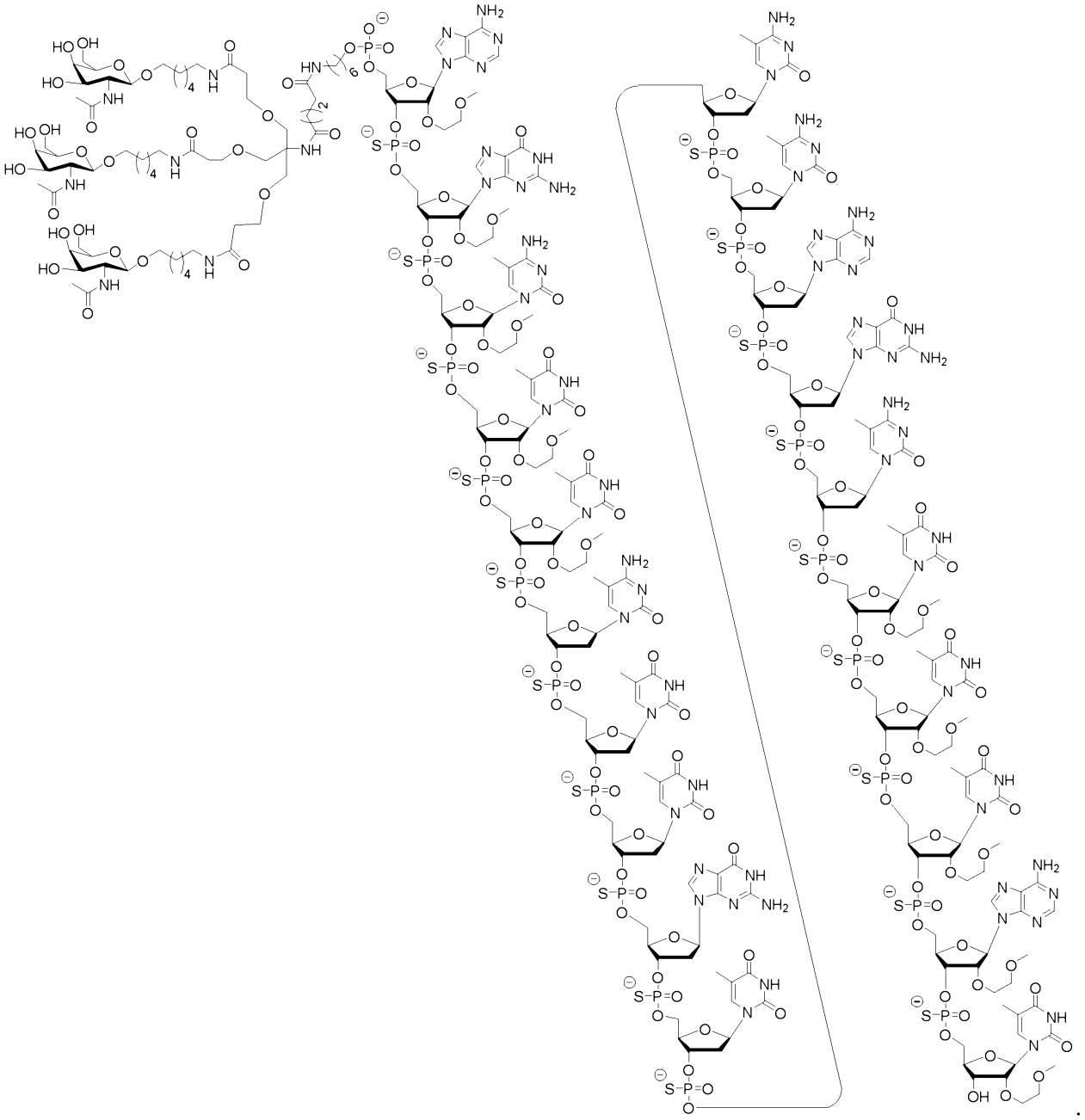
In certain embodiments, a conjugated antisense compound has a structure selected from among the following:



In certain embodiments, a conjugated antisense compound has a structure selected from among the following:



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



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, each of which is incorporated by reference herein in its entirety.

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, each of which is incorporated by reference herein in its entirety.

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; each of which is incorporated by reference in its entirety.

C. Certain Uses and Features

In certain embodiments, conjugated antisense compounds exhibit potent target 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 provided 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 invention.

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 embodiments, 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.

Productive and non-productive uptake of oligonucleotides has been 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.

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.

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 administered at doses lower than would be necessary for unconjugated antisense oligonucleotides.

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 internucleoside linkages and more phosphodiester internucleoside linkages accumulate less in the liver and more in the kidney. When treating diseases in the liver, this is undesirable 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.

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.

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.

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 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.

In certain embodiments, conjugated antisense compounds accumulate more in the liver and less in the kidney than unconjugated counterparts, even when some of the phosphorothioate 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 unconjugated counterparts, even when some of the phosphorothioate 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 embodiments, 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.

In certain embodiments, the inclusion of some phosphorothioate linkages remains desirable. For example, the terminal linkages are vulnerable to exonucleases 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 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 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 type where the modified nucleoside is at the 5' side of the linkage are sufficiently resistant to nuclease digestion, that the linkage can be phosphodiester.

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

In certain embodiments, antisense compounds comprising one or more conjugate 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 desirable. Typically, oligonucleotides 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 desired 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. Neither 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 reactions. 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).

In certain embodiments, conjugated antisense compounds are administered to a subject. In such embodiments, antisense compounds comprising one or more conjugate 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 release the active oligonucleotide. 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). This conjugated 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

In certain embodiments, oligomeric compounds of the present invention 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 of the present invention may be microRNA mimics, which typically bind to multiple targets.

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.

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.

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.

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.

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.

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.

D. **Target Nucleic Acids, Regions and Segments**

In certain embodiments, conjugated antisense compounds target any nucleic acid. In certain embodiments, the target nucleic acid encodes a target protein that is clinically relevant. In such embodiments, modulation of the target nucleic acid results in clinical benefit. Certain target nucleic acids include, but are not limited to, the target nucleic acids illustrated in Table 1.

Table 1: Certain Target Nucleic Acids

Target	Species	GENBANK® Accession Number	SEQ ID NO
Androgen Receptor (AR)	Human	NT_011669.17 truncated from nucleobases 5079000 to 5270000	1
Apolipoprotein (a) (Apo(a))	Human	NM_005577.2	2
Apolipoprotein B (ApoB)	Human	NM_000384.1	3
Apolipoprotein C-III (ApoCIII)	Human	NT_033899.8 truncated from nucleobases 20262640 to 20266603	4

Apolipoprotein C-III (ApoCIII)	Human	NM_000040.1	5
C-Reactive Protein (CRP)	Human	M11725.1	6
eIF4E	Human	M15353.1	7
Factor VII	Human	NT_027140.6 truncated from nucleobases 1255000 to 1273000	8
Factor XI	Human	NM_000128.3	9
Glucocorticoid Receptor (GCCR)	Human	the complement NT_029289.10 truncated from nucleobases 3818000 to 3980000	10
Glucagon Receptor (GCGR)	Human	NW_926918.1 truncated from nucleobases 16865000 to 16885000	11
HBV	Human	U95551.1	12
Protein Tyrosine Phosphatase 1B (PTP1B)	Human	NM_002827.2	13
Protein Tyrosine Phosphatase 1B (PTP1B)	Human	NT_011362.9 truncated from nucleobases 14178000 to 14256000	14
STAT3	Human	NM_139276.2	15
Transthyretin (TTR)	Human	NM_000371.3	16

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.

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.

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.

In certain embodiments, antisense compounds targeted to the nucleic acids listed in Table 1 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.

In certain embodiments, antisense compounds targeted to the nucleic acids listed in Table 1 can be conjugated as described herein.

1. Androgen Receptor (AR)

AR is a transcription factor implicated as a driver of prostate cancer. AR is activated by binding to its hormone ligands: androgen, testosterone, and/or DHT. Androgen deprivation therapy, also known as "chemical castration," is a first-line treatment strategy against hormone-sensitive, androgen-dependent prostate cancer that reduces circulating androgen levels and thereby inhibits AR activity. However, androgen deprivation therapy frequently leads to the emergence and growth of "castration-resistant" advanced prostate cancer, in which AR signaling is reactivated independent of ligand binding. The mechanisms underlying castration resistance in advanced prostate cancer remain unclear.

Certain Conjugated Antisense Compounds Targeted to an AR Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to an AR nucleic acid having the sequence of GENBANK® Accession No. NT_011669.17 nucleobases 5079000 to 5270000, incorporated herein as SEQ ID NO: 1. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 1.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 1 comprises an at least 8 consecutive nucleobase sequence selected from the nucleobase sequence of any of SEQ ID NOs: 17-24. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 1 comprises a nucleobase sequence selected from the nucleobase sequence of any of SEQ ID NOs: 17-24. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 2: Antisense Compounds Targeted to AR SEQ ID NO: 1

ISIS No	Target Start Site	Sequence	Motif	SEQ ID NO
560131	58721 58751	TTGATTTAATGGTTGC	kkkddddddddkkke	17
569213	58720 58750	TGATTTAATGGTTGCA	kkkddddddddkkke	18
569216	58720 58750	TGATTTAATGGTTGCA	ekkkddddddddkkke	18
569221	58720 58750	TGATTTAATGGTTGCA	eekkkddddddddkkk	18
569236	58720 58750	TGATTTAATGGTTGCA	ekkkddddddddkkkee	18
579671	58721 58751	TTGATTTAATGGTTGC	ekkekkddddddddkkk	17
586124	58719	GATTTAATGGTTGCAA	kkkddddddddddkkk	19
583918	5052	AGTCGCGACTCTGGTA	kkkddddddddddkkk	20
584149	8638	GTCAATATCAAAGCAC	kkkddddddddddkkk	21
584163	11197	GAACATTATTAGGCTA	kkkddddddddddkkk	22
584269	40615	CCTTATGGATGCTGCT	kkkddddddddddkkk	23
584468	115272	CATTGTACTATGCCAG	kkkddddddddddkkk	24

AR Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an AR nucleic acid for modulating the expression of AR in a subject. In certain embodiments, the expression of AR is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an AR nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has prostate cancer, such as castration-resistant prostate cancer. In certain embodiments, the subject has prostate cancer resistant to a diarylhydantoin Androgen Receptor (AR) inhibitor, such as MDV3100, which is also known as Enzalutamide. MDV3100 or Enzalutamide is an experimental androgen receptor antagonist drug developed by Medivation for the treatment of castration-resistant prostate cancer. In certain embodiments, the subject has breast cancer. In certain aspects, the subject's breast cancer can have one or more of the following characteristics: Androgen Receptor positive, dependent on androgen for growth, Estrogen Receptor (ER) negative, independent of estrogen for growth, Progesterone Receptor (PR) negative, independent of progesterone for growth, or Her2/neu negative. In certain aspects, the breast cancer or breast cancer cell is apocrine.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an AR nucleic acid in the preparation of a medicament.

2. Apolipoprotein (a) (Apo(a))

One Apo(a) protein is linked via a disulfide bond to a single 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 US 61/651,539, herein incorporated by reference in its entirety. An antisense oligonucleotide targeting Apo(a), ISIS-APOA_{Rx}, is currently in a Phase I clinical trial to study its safety profile.

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

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: 2. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 2.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 2 comprises an at least 8 consecutive nucleobase sequence selected from the nucleobase sequence of any of SEQ ID NOs: 25-30. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 2 comprises a nucleobase sequence selected from the nucleobase sequence of any of SEQ ID NOs: 25-30. In certain

embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 3: Antisense Compounds targeted to Apo(a) SEQ ID NO: 2

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
494372	3901	TGCTCCGTTGGTGCTTGTTC	eeeeeddddddddddeeeee	25
494283	584	TCTTCCTGTGACAGTGGTGG	eeeeeddddddddddeeeee	26
	926			
	1610			
	1952			
	2294			
	3320			
494284	585	TTCTTCCTGTGACAGTGGTG	eeeeeddddddddddeeeee	27
	927			
	1611			
	1953			
	2295			
	3321			
494286	587	GGTTCTTCCTGTGACAGTGG	eeeeeddddddddddeeeee	28
	929			
	1613			
	1955			
	2297			
494301	628	CGACTATGCGAGTGTGGTGT	eeeeeddddddddddeeeee	29
	970			
	1312			
	1654			
	1996			
	2338			
	2680			
	3022			
494302	629	CCGACTATGCGAGTGTGGTG	eeeeeddddddddddeeeee	30
	971			
	1313			
	1655			
	1997			
	2339			
	2681			
	3023			

Apo(a) Therapeutic Indications

In certain embodiments, the invention 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.

In certain embodiments, the invention provides 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 subject has a cardiovascular and/or metabolic disease, disorder or condition. In certain embodiments, the subject has hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, and/or non-alcoholic fatty liver disease.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an Apo(a) nucleic acid in the preparation of a medicament.

3. Apolipoprotein B (ApoB)

ApoB (also known as apolipoprotein B-100; ApoB-100, apolipoprotein B-48; ApoB-48 and Ag(x) antigen), is a large glycoprotein that serves an indispensable role in the assembly and secretion of lipids and in the transport and receptor-mediated uptake and delivery of distinct classes of lipoproteins. ApoB performs a variety of activities, from the absorption and processing of dietary lipids to the regulation of circulating lipoprotein levels (Davidson and Shelness, *Annu. Rev. Nutr.,* 2000, *20*, 169-193). This latter property underlies its relevance in terms of atherosclerosis susceptibility, which is highly correlated with the ambient concentration of ApoB-containing lipoproteins (Davidson and Shelness, Annu. Rev. Nutr., 2000, 20, 169-193). ApoB-100 is the major protein component of LDL-C and contains the domain required for interaction of this lipoprotein species with the LDL receptor. Elevated levels of LDL-C are a risk factor for cardiovascular disease, including atherosclerosis. Antisense compounds targeting ApoB have been previously disclosed in WO2004/044181, herein incorporated by reference in its entirety. An antisense oligonucleotide targeting ApoB, KYNAMRO™, has been approved by the U.S. Food and Drug Administration (FDA) as an adjunct treatment to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), ApoB, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH). However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to an ApoB Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to an ApoB nucleic acid having the sequence of GENBANK® Accession No. NM_000384.1, incorporated herein as SEQ ID NO: 3. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 3.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 3 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NO: 31. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 3 comprises a nucleobase sequence of SEQ ID NO: 31. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 4: Antisense Compounds targeted to ApoB SEQ ID NO: 3

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
301012	3249	GCCTCAGTCTGCTTCGCACC	eeeeeddddddddddeeeee	31

ApoB Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an ApoB nucleic acid for modulating the expression of ApoB in a subject. In certain embodiments, the expression of ApoB is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an ApoB nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a cardiovascular and/or metabolic disease, disorder or condition. In certain embodiments, the subject has hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, and/or non-alcoholic fatty liver disease.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an ApoB nucleic acid in the preparation of a medicament.

4. Apolipoprotein C-III (ApoCIII)

ApoCIII is a constituent of HDL and of triglyceride (TG)-rich lipoproteins. Elevated ApoCIII levels are associated with elevated TG levels and diseases such as cardiovascular disease, metabolic syndrome, obesity and diabetes. Elevated TG levels are associated with pancreatitis. ApoCIII slows clearance of TG-rich lipoproteins by inhibiting lipolysis through inhibition of lipoprotein lipase (LPL) and through interfering with lipoprotein binding to cell-surface glycosaminoglycan matrix. Antisense compounds targeting ApoCIII have been previously disclosed in WO2004/093783 and WO2012/149495, each herein incorporated by reference in its entirety. Currently, an antisense oligonucleotide targeting ApoCIII, ISIS-APOCIII$_{Rx}$, is in Phase II clinical trials to assess its effectiveness in the treatment of diabetes or hypertriglyceridemia. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to an ApoCIII Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to an ApoCIII nucleic acid having the sequence of GENBANK® Accession No. NT_033899.8 truncated from nucleobases 20262640 to 20266603, 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 SEQ ID NO: 4. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

In certain embodiments, conjugated antisense compounds are targeted to an ApoCIII nucleic acid having the sequence of GENBANK® Accession No. NM_000040.1, incorporated herein as SEQ ID NO: 5. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 5. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 5 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NO: 32. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 5 comprises a nucleobase sequence of SEQ ID NO: 32. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 5: Antisense Compounds targeted to ApoCIII SEQ ID NO: 5

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO

304801	508	AGCTTCTTGTCCAGCTTTAT	eeeeeddddddddddeeeee	32
647535	508	AGCTTCTTGTCCAGCTTTAT	eeeeeddddddddddeeeeeod	32
616468	508	AGCTTCTTGTCCAGCTTTAT	eeeeeddddddddddeeeee	32
647536	508	AGCTTCTTGTCCAGCTTTAT	eeoeoeoeoddddddddddeoe oeeeod	32

ApoCIII Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an ApoCIII nucleic acid for modulating the expression of ApoCIII in a subject. In certain embodiments, the expression of ApoCIII is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an ApoCIII nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a cardiovascular and/or metabolic disease, disorder or condition. In certain embodiments, the subject has hypertriglyceridemia, non-familial hypertriglyceridemia, familial hypertriglyceridemia, heterozygous familial hypertriglyceridemia, homozygous familial hypertriglyceridemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, pancreatitis and/or non-alcoholic fatty liver disease.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an ApoCIII nucleic acid in the preparation of a medicament.

5. C-Reactive Protein (CRP)

CRP (also known as PTX1) is an essential human acute-phase reactant produced in the liver in response to a variety of inflammatory cytokines. The protein, first identified in 1930, is highly conserved and considered to be an early indicator of infectious or inflammatory conditions. Plasma CRP levels increase 1,000-fold in response to infection, ischemia, trauma, burns, and inflammatory conditions. In clinical trials where patients receive lipid-lowering therapy, such as statin therapy, it has been demonstrated that patients having reductions in both LDL-C and CRP have a reduced risk of future coronary events relative to patients experiencing only reductions in LDL-C. Antisense compounds targeting CRP have been previously disclosed in WO2003/010284 and WO2005/005599, each herein incorporated by reference in its entirety. An antisense oligonucleotide targeting CRP, ISIS-CRP_{Rx}, is currently in Phase 2 clinical trials to study its effectiveness in

treating subjects with rheumatoid arthritis and paroxysmal atrial fibrillation. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a CRP Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a CRP nucleic acid having the sequence of GENBANK® Accession No. M11725.1, incorporated herein as SEQ ID NO: 6. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 6.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 6 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NO: 33. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 6 comprises a nucleobase sequence of SEQ ID NO: 33. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 6: Antisense Compounds targeted to CRP SEQ ID NO: 6

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
329993	1378	AGCATAGTTAACGAGCTCCC	eeeeeddddddddddeeeee	33

CRP Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a CRP nucleic acid for modulating the expression of CRP in a subject. In certain embodiments, the expression of CRP is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a CRP nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a cardiovascular and/or metabolic disease, disorder or condition. In certain embodiments, the subject has hypercholesterolemia, non-familial hypercholesterolemia, familial hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease. In certain embodiments, the individual has paroxysmal atrial fibrillation, acute coronary syndrome, vascular injury, arterial occlusion, unstable angina, post peripheral vascular disease, post myocardial infarction (MI), thrombosis, deep vein thrombus, end-stage renal disease (ESRD), chronic renal

failure, complement activation, congestive heart failure, or systemic vasculitis. In certain embodiments, the individual has had a stroke. In certain embodiments, the individual has undergone a procedure selected from elective stent placement, angioplasty, post percutaneous transluminal angioplasty (PTCA), cardiac transplantation, renal dialysis or cardiopulmonary bypass. In certain embodiments, the individual has an inflammatory disease. In certain such embodiments, the inflammatory disease is selected from inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, or osteoarthritis.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a CRP nucleic acid in the preparation of a medicament.

6. eIF4E

Overexpression of eIF4E has been reported in many human cancers and cancer-derived cell lines and also leads to oncogenic transformation of cells and invasive/metastatic phenotype in animal models. Unlike non-transformed, cultured cells, transformed cell lines express eIF4E independently of the presence of serum growth factors (Rosenwald, Cancer Lett., 1995, 98, 77-82). Excess eIF4E leads to aberrant growth and neoplastic morphology in HeLa cells and also causes tumorigenic transformation in NIH 3T3 and Rat2 fibroblasts, as judged by anchorage-independent growth, formation of transformed foci in culture and tumor formation in nude mice (De Benedetti et al., Proc. Natl. Acad. Sci. U S A, 1990, 87, 8212-8216; and Lazaris-Karatzas et al., Nature, 1990, 345, 544-547).

eIF4E is found elevated in several human cancers, including but not limited to non-Hodgkin's lymphomas, colon adenomas and carcinomas and larynx, head and neck, prostate, breast and bladder cancers (Crew et al., Br. J. Cancer, 2000, 82, 161-166; Graff et al., Clin. Exp. Metastasis, 2003, 20, 265-273; Haydon et al., Cancer, 2000, 88, 2803-2810; Kerekatte et al., Int. J. Cancer, 1995, 64, 27-31; Rosenwald et al., Oncogene, 1999, 18, 2507-2517; Wang et al., Am. J. Pathol., 1999, 155, 247-255). Upregulation of eIF4E is an early event in colon carcinogenesis, and is frequently accompanied by an increase in cyclin D1 levels (Rosenwald et al., Oncogene, 1999, 18, 2507-2517). Antisense compounds targeting eIF4E have been previously disclosed in WO2005/028628, herein incorporated by reference in its entirety. An antisense oligonucleotide targeting eIF4E, ISIS-eIF4E$_{Rx}$, is currently in Phase 1/2 clinical trials to study its effectiveness in treating subjects with cancer.

Certain Conjugated Antisense Compounds Targeted to an eIF4E Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to an eIF4E nucleic acid having the sequence of GENBANK® Accession No. M15353.1, incorporated herein as SEQ ID NO: 7. In

certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 7.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 7 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NO: 34. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 7 comprises a nucleobase sequence of SEQ ID NO: 34. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 7: Antisense Compounds targeted to eIF4E SEQ ID NO: 7

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
183750	1285	TGTCATATTCCTGGATCCTT	eeeeeddddddddddeeeee	34

eIF4E Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an eIF4E nucleic acid for modulating the expression of eIF4E in a subject. In certain embodiments, the expression of eIF4E is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an eIF4E nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has cancer. In certain aspects, the cancer is prostate cancer.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to an eIF4E nucleic acid in the preparation of a medicament.

7. Factor VII

Coagulation Factor VII (also known as serum prothrombin conversion accelerator) is a key component of the tissue factor coagulation pathway. Clinicians have linked elevated levels of Factor VII activity with poor prognosis in several thrombotic diseases, such as heart attacks, and with cancer-associated thrombosis, which is the second leading cause of death in cancer patients. In preclinical studies, antisense inhibition of Factor VII rapidly reduced Factor VII activity by more than 90 percent in three days with no observed increase in bleeding, which is a common side effect of currently available anti-thrombotic drugs. Antisense compounds targeting Factor VII have been previously disclosed in WO2009/061851, WO2012/174154, and PCT Application no. PCT/US2013/025381, each herein incorporated by reference in

its entirety. Clinical studies are planned to assess ISIS-FVII$_{Rx}$ in acute clinical settings, such as following surgery, to prevent patients from developing harmful blood clots. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a Factor VII Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a Factor VII nucleic acid having the sequence of GENBANK® Accession No. NT_027140.6 truncated from nucleobases 1255000 to 1273000), incorporated herein as SEQ ID NO: 8. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 8 is at least 90%, at least 95% or 100% complementary to SEQ ID NO: 8.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 8 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 35-43. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 8 comprises a nucleobase sequence of SEQ ID NOs: 35-43. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 8: Antisense Compounds targeted to Factor VII SEQ ID NO: 8

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
540175	2592	GGACACCCACGCCCCC	eekddddddddddkke	35
	2626			
	2660			
	2796			
	2966			
	3000			
	3034			
	3068			
	3153			
	3170			
	3272			
	3374			
	3578			
	3851			
	3953			
	4124			
	4260			
	4311			
	4447			
	4532			
490279	1387	CCCTCCTGTGCCTGGATGCT	eeeeeddddddddddeeeee	36
473589	15128	GCTAAACAACCGCCTT	kdkdkddddddddddee	37
407935	15191	ATGCATGGTGATGCTTCTGA	eeeeeddddddddddeeeee	38
529804	15192	CATGGTGATGCTTCTG	kddddddddddkekee	39

534796	15131	AGAGCTAAACAACCGC	Ekkddddddddddkke	40
540162	2565	ACTCCCGGGACACCCA	eekddddddddddkke	41
	2633			
	2667			
	2735			
	2803			
	2837			
	2905			
	3007			
	3041			
	3075			
	3092			
	3279			
	3381			
	3483			
	3603			
	3722			
	3756			
	3858			
	3892			
	3960			
	4046			
	4131			
	4165			
	4318			
	4454			
540182	2692	ACACCCTCGCCTCCGG	eekddddddddddkke	42
	2760			
	2862			
	2930			
	3117			
	3338			
	3440			
	3508			
	3542			
	3628			
	3662			
	3781			
	3815			
	3917			
	4190			
	4224			
	4377			
	4411			
540191	3109	GCCTCCGGAACACCCA	eekddddddddddkke	43
	3194			
	3330			
	3432			
	3500			
	3534			
	3620			

	3654			
	3773			
	4182			
	4216			
	4369			
	4403			

Factor VII Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a Factor VII nucleic acid for modulating the expression of Factor VII in a subject. In certain embodiments, the expression of Factor VII is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a Factor VII nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has or is at risk of developing a thromboembolic condition, such as, heart attack, stroke, deep vein thrombosis, or pulmonary embolism. In certain embodiments, the subject is at risk of developing a thromboemoblic condition and/or otherwise in need of anticoagulant therapy. Examples of such subjects include those undergoing major orthopedic surgery and patients in need of chronic anticoagulant treatment. In certain embodiments, the subject has or is at risk of developing an inflammatory disease, disorder or condition. In certain embodiments, the subject has or is at risk of developing allergic diseases (e.g., allergic rhinitis, chronic rhinosinusitis), autimmune diseases (e.g, multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), cardiovascular diseases, colitis, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type1, 2, 3 or 4 hypersensitivity), infectious diseases (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease) and pancreatitis.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a Factor VII nucleic acid in the preparation of a medicament.

8. Factor XI

Coagulation factor XI (also known as plasma thromboplastin antecedent) is an important member of the coagulation pathway. High levels of Factor XI increase the risk of thrombosis, a process involving aberrant blood clot formation responsible for most heart attacks and strokes. Elevated levels of Factor XI also increase the risk of venous thrombosis, a common problem after surgery, particularly major orthopedic

procedures, such as knee or hip replacement. People who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleeding risk. Antisense compounds targeting Factor XI have been previously disclosed in WO2010/045509 and WO2010/121074, each herein incorporated by reference in its entirety. Currently, an antisense oligonucleotide targeting Factor XI, ISIS-FXI_{Rx}, is in Phase 2 clinical studies to assess the effectiveness of ISIS-FXI_{Rx} in reducing the number of thrombotic events in patients following total knee arthroplasty without increasing bleeding. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a Factor XI Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a Factor XI nucleic acid having the sequence of GENBANK® Accession No. NM_000128.3, incorporated herein as SEQ ID NO: 9. In certain such embodiments, a conjugated antisense compound is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 9.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 9 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 44-48. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 9 comprises a nucleobase sequence of SEQ ID NOs: 44-48. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 9: Antisense Compounds targeted to Factor XI SEQ ID NO: 9

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
416858	1288	ACGGCATTGGTGCACAGTTT	eeeeddddddddddeeeee	44
416838	1022	GCAACCGGGATGATGAGTGC	eeeeddddddddddeeeee	45
416850	1278	TGCACAGTTTCTGGCAGGCC	eeeeddddddddddeeeee	46
416864	1296	GGCAGCGGACGGCATTGGTG	eeeeddddddddddeeeee	47
417002	1280	GGTGCACAGTTTCTGGCAGG	eedddddddddddddeeeee	48

Factor XI Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a Factor XI nucleic acid for modulating the expression of Factor XI in a subject. In certain embodiments, the expression of Factor XI is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a Factor XI nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has or is at risk of developing a thromboembolic condition, such as, heart attack, stroke, deep vein thrombosis, or pulmonary embolism. In certain embodiments, the subject is at risk of developing a thromboemoblic condition and/or otherwise in need of anticoagulant therapy. Examples of such subjects include those undergoing major orthopedic surgery and patients in need of chronic anticoagulant treatment. In certain embodiments, the subject has or is at risk of developing an inflammatory disease, disorder or condition. In certain embodiments, the subject has or is at risk of developing allergic diseases (e.g., allergic rhinitis, chronic rhinosinusitis), autimmune diseases (e.g, multiple sclerosis, arthritis, scleroderma, psoriasis, celiac disease), cardiovascular diseases, colitis, diabetes (e.g., type 1 insulin-dependent diabetes mellitus), hypersensitivities (e.g., Type1, 2, 3 or 4 hypersensitivity), infectious diseases (e.g., viral infection, mycobacterial infection, helminth infection), posterior uveitis, airway hyperresponsiveness, asthma, atopic dermatitis, colitis, endometriosis, thyroid disease (e.g., Graves' disease) and pancreatitis.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a Factor XI nucleic acid in the preparation of a medicament.

9. Glucocorticoid Receptor (GCCR)

Complementary DNA clones encoding the human glucocorticoid receptor (also known as nuclear receptor subfamily 3, group C, member 1; NR3C1; GCCR; GCR; GRL; Glucocorticoid receptor, lymphocyte) were first isolated in 1985 (Hollenberg et al., *Nature,* **1985**, *318*, 635-641; Weinberger et al., *Science,* **1985**, *228*, 740-742). The gene is located on human chromosome 5q11-q13 and consists of 9 exons (Encio and Detera-Wadleigh, *J Biol Chem,* **1991**, *266*, 7182-7188; Gehring et al., *Proc Natl Acad Sci U S A,* **1985**, *82*, 3751-3755).

The human glucocorticoid receptor is comprised of three major domains, the N-terminal activation domain, the central DNA-binding domain and the C-terminal ligand-binding domain (Giguere et al., *Cell,* **1986**, *46*, 645-652). In the absence of ligand, the glucocorticoid receptor forms a large heteromeric complex with several other proteins, from which it dissociates upon ligand binding.

In the liver, glucocorticoid agonists increase hepatic glucose production by activating the glucocorticoid receptor, which subsequently leads to increased expression of the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. Through gluconeogenesis, glucose is formed through non-hexose precursors, such as lactate, pyruvate and alanine (Link, Curr Opin Investig Drugs, 2003, 4, 421-429).

Antisense compounds targeting GCCR have been previously disclosed in WO2007/035759, WO2005/071080, and PCT application no. PCT/US2012/061984, each herein incorporated by reference in its entirety. An antisense oligonucleotide targeting GCCR, ISIS-GCCR$_{Rx}$, recently completed a Phase I clinical study with positive results. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a GCCR Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a GCCR nucleic acid having the sequence of the complement of GENBANK Accession No. NT_029289.10 truncated from nucleobases 3818000 to 3980000, incorporated herein as SEQ ID NO: 10. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 10 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 10.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 10 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 49-59. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 10 comprises a nucleobase sequence of SEQ ID NOs: 49-59. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 10: Antisense Compounds targeted to GCCR SEQ ID NO: 10

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
426115	65940	GCAGCCATGGTGATCAGGAG	eeeeeddddddddddeeeee	49
420470	57825	GGTAGAAATATAGTTGTTCC	eeeeeddddddddddeeeee	50
420476	59956	TTCATGTGTCTGCATCATGT	eeeeeddddddddddeeeee	51
426130	63677	GCATCCAGCGAGCACCAAAG	eeeeeddddddddddeeeee	52
426183	65938	AGCCATGGTGATCAGGAGGC	eeeddddddddddddddeee	53
426261	65938	AGCCATGGTGATCAGGAGGC	eeddddddddddddddeeeee	53
426262	65939	CAGCCATGGTGATCAGGAGG	eeddddddddddddddeeeee	54
426168	76224	GTCTGGATTACAGCATAAAC	eeeeeddddddddddeeeee	55
426246	76225	GGTCTGGATTACAGCATAAA	eeeddddddddddddddeee	56
426172	76229	CCTTGGTCTGGATTACAGCA	eeeeeddddddddddeeeee	57
426325	76229	CCTTGGTCTGGATTACAGCA	eeddddddddddddddeeeee	58
426267	95513	GTGCTTGTCCAGGATGATGC	eeddddddddddddddeeeee	59

GCCR Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a GCCR nucleic acid for modulating the expression of GCCR in a subject. In certain embodiments, the expression of GCCR is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a GCCR nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has metabolic related diseases, including metabolic syndrome, diabetes mellitus, insulin resistance, diabetic dyslipidemia, hypertriglyceridemia, obesity and weight gain.

Diabetes mellitus is characterized by numerous physical and physiological symptoms. Any symptom known to one of skill in the art to be associated with Type 2 diabetes can be ameliorated or otherwise modulated as set forth above in the methods described above. In certain embodiments, the symptom is a physical symptom selected from the group consisting of increased glucose levels, increased weight gain, frequent urination, unusual thirst, extreme hunger, extreme fatigue, blurred vision, frequent infections, tingling or numbness at the extremities, dry and itchy skin, weight loss, slow-healing sores, and swollen gums. In certain embodiments, the symptom is a physiological symptom selected from the group consisting of increased insulin resistance, increased glucose levels, increased fat mass, decreased metabolic rate, decreased glucose clearance, decreased glucose tolerance, decreased insulin sensitivity, decreased hepatic insulin sensitivity, increased adipose tissue size and weight, increased body fat, and increased body weight.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a GCCR nucleic acid in the preparation of a medicament.

10. Glucagon Receptor (GCGR)

Diabetes is a chronic metabolic disorder characterized by impaired insulin secretion and/or action. In type 2 diabetes (T2DM), insulin resistance leads to an inability of insulin to control the activity of gluconeogenic enzymes, and many subjects also exhibit inappropriate levels of circulating glucagon in the fasting and postprandial state. Glucagon is secreted from the α-cells of the pancreatic islets and regulates glucose homeostasis through modulation of hepatic glucose production (Quesada et al., J. Endocrinol. 2008. 199: 5-19).Glucagon exerts its action on target tissues via the activation of its receptor, GCGR. The glucagon receptor is a 62 kDa protein that is a member of the class B G-protein coupled family of receptors (Brubaker et al., Recept. Channels. 2002. 8: 179-88). GCGR activation leads to signal transduction by G proteins ($G_s\alpha$ and G_q), whereby $G_s\alpha$ activates adenylate cyclase, which causes cAMP production, resulting in an increase in levels of protein kinase A. GCGR signaling in the liver results in increased hepatic glucose production by

induction of glycogenolysis and gluconeogenesis along with inhibition of glycogenesis (Jiang and Zhang. Am. J. Physiol. Endocrinol. Metab. 2003. 284: E671-E678). GCGR is also expressed in extrahepatic tissues, which includes heart, intestinal smooth muscle, kidney, brain, and adipose tissue (Hansen et al., Peptides. 1995. 16: 1163-1166).

Antisense compounds targeting GCGR have been previously disclosed in WO2004/096996, WO2004/096016, WO2007/035771, and WO2013/043817, each herein incorporated by reference in its entirety. An antisense oligonucleotide targeting GCGR, ISIS-$GCGR_{Rx}$, recently completed a Phase I clinical study with positive results. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a GCGR Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a GCGR nucleic acid having the sequence of GENBANK® Accession No NW_926918.1 truncated from nucleobases 16865000 to 16885000, incorporated herein as SEQ ID NO: 11. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 11 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 11.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 11 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 60-67. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 11 comprises a nucleobase sequence of SEQ ID NOs: 60-67. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 11: Antisense Compounds targeted to GCGR SEQ ID NO: 11

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
449884	7270	GGTTCCCGAGGTGCCCA	eeeddddddddddeeee	60
	7295			
	7319			
	7344			
	7368			
	7392			
	7416			
	7440			

398471	8133	TCCACAGGCCACAGGTGGGC	eeeeeddddddddddeeeee	61
436140	15743	CTCTTTATTGTTGGAGGACA	eeeeeddddddddddeeeee	62
448766	9804	GCAAGGCTCGGTTGGGCTTC	eeeeeddddddddddeeeee	63
459014	10718	GGGCAATGCAGTCCTGG	eeeddddddddddeeee	64
459032	7783	GAAGGTGACACCAGCCT	eeeddddddddddeeee	65
459040	8144	GCTCAGCATCCACAGGC	eeeddddddddddeeee	66
459157	7267	GGGTTCCCGAGGTGCCCAATG	eeeeeddddddddddeeeeee	67
	7292			
	7316			
	7341			
	7365			
	7389			
	7437			

GCGR Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a GCGR nucleic acid for modulating the expression of GCGR in a subject. In certain embodiments, the expression of GCGR is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a GCGR nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has metabolic related diseases, including metabolic syndrome, diabetes mellitus, insulin resistance, diabetic dyslipidemia, hypertriglyceridemia, obesity and weight gain.

Diabetes mellitus is characterized by numerous physical and physiological signs and/or symptoms. Any symptom known to one of skill in the art to be associated with Type 2 diabetes can be ameliorated or otherwise modulated as set forth above in the methods described above. In certain embodiments, the symptom or sign is a physical symptom or sign ssuch as increased glucose levels, increased weight gain, frequent urination, unusual thirst, extreme hunger, extreme fatigue, blurred vision, frequent infections, tingling or numbness at the extremities, dry and itchy skin, weight loss, slow-healing sores, and swollen gums. In certain embodiments, the symptom or sign is a physiological symptom or sign selected from the group consisting of increased insulin resistance, increased glucose levels, increased fat mass, decreased metabolic rate, decreased glucose clearance, decreased glucose tolerance, decreased insulin sensitivity, decreased hepatic insulin sensitivity, increased adipose tissue size and weight, increased body fat, and increased body weight.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a GCGR nucleic acid in the preparation of a medicament.

11. Hepatitis B (HBV)

Hepatitis B is a viral disease transmitted parenterally by contaminated material such as blood and blood products, contaminated needles, sexually and vertically from infected or carrier mothers to their offspring. It is estimated by the World Health Organization that more than 2 billion people have been infected worldwide, with about 4 million acute cases per year, 1 million deaths per year, and 350-400 million chronic carriers (World Health Organization: Geographic Prevalence of Hepatitis B Prevalence, 2004. http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm).

The virus, HBV, is a double-stranded hepatotropic virus which infects only humans and non-human primates. Viral replication takes place predominantly in the liver and, to a lesser extent, in the kidneys, pancreas, bone marrow and spleen (Hepatitis B virus biology. Microbiol Mol Biol Rev. 64: 2000; 51-68.). Viral and immune markers are detectable in blood and characteristic antigen-antibody patterns evolve over time. The first detectable viral marker is HBsAg, followed by hepatitis B e antigen (HBeAg) and HBV DNA. Titers may be high during the incubation period, but HBV DNA and HBeAg levels begin to fall at the onset of illness and may be undetectable at the time of peak clinical illness (Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med.. 350: 2004; 1118-1129). HBeAg is a viral marker detectable in blood and correlates with active viral replication, and therefore high viral load and infectivity (Hepatitis B e antigen—the dangerous end game of hepatitis B. N Engl J Med. 347: 2002; 208-210). The presence of anti-HBsAb and anti-HBcAb (IgG) indicates recovery and immunity in a previously infected individual.

Currently the recommended therapies for chronic HBV infection by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) include interferon alpha (INFα), pegylated interferon alpha-2a (Peg-IFN2a), entecavir, and tenofovir. The nucleoside and nucleobase therapies, entecavir and tenofovir, are successful at reducing viral load, but the rates of HBeAg seroconversion and HBsAg loss are even lower than those obtained using IFNα therapy. Other similar therapies, including lamivudine (3TC), telbivudine (LdT), and adefovir are also used, but for nucleoside/nucleobase therapies in general, the emergence of resistance limits therapeutic efficacy.

Thus, there is a need in the art to discover and develop new anti-viral therapies. Additionally, there is a need for new anti-HBV therapies capable of increasing HBeAg and HBsAg seroconversion rates. Recent clinical research has found a correlation between seroconversion and reductions in HBeAg (Fried et al (2008)

Hepatology 47:428) and reductions in HBsAg (Moucari et al (2009) Hepatology 49:1151). Reductions in antigen levels may have allowed immunological control of HBV infection because high levels of antigens are thought to induce immunological tolerance. Current nucleoside therapies for HBV are capable of dramatic reductions in serum levels of HBV but have little impact on HBeAg and HBsAg levels.

Antisense compounds targeting HBV have been previously disclosed in WO2011/047312, WO2012/145674, and WO2012/145697, each herein incorporated by reference in its entirety. Clinical studies are planned to assess the effect of antisense compounds targeting HBV in patients. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a HBV Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a HBV nucleic acid having the sequence of GENBANK® Accession No. U95551.1, incorporated herein as SEQ ID NO: 12. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 12 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 12.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 12 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NO: 68. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 12 comprises a nucleobase sequence of SEQ ID NO: 68. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 12: Antisense Compounds targeted to HBV SEQ ID NO: 12

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
505358	1583	GCAGAGGTGAAGCGAAGTGC	eeeeeddddddddddeeeee	68

HBV Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a HBV nucleic acid for modulating the expression of HBV in a subject. In certain embodiments, the expression of HBV is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a HBV nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a HBV-related condition. In certain embodiments, the HBV-related condition

includes, but is not limited to, chronic HBV infection, inflammation, fibrosis, cirrhosis, liver cancer, serum hepatitis, jaundice, liver cancer, liver inflammation, liver fibrosis, liver cirrhosis, liver failure, diffuse hepatocellular inflammatory disease, hemophagocytic syndrome, serum hepatitis, and HBV viremia. In certain embodiments, the HBV-related condition may have which may include any or all of the following: flu-like illness, weakness, aches, headache, fever, loss of appetite, diarrhea, jaundice, nausea and vomiting, pain over the liver area of the body, clay- or grey-colored stool, itching all over, and dark-colored urine, when coupled with a positive test for presence of a hepatitis B virus, a hepatitis B viral antigen, or a positive test for the presence of an antibody specific for a hepatitis B viral antigen. In certain embodiments, the subject is at risk for an HBV-related condition. This includes subjects having one or more risk factors for developing an HBV-related condition, including sexual exposure to an individual infected with Hepatitis B virus, living in the same house as an individual with a lifelong hepatitis B virus infection, exposure to human blood infected with the hepatitis B virus, injection of illicit drugs, being a person who has hemophilia, and visiting an area where hepatitis B is common. In certain embodiments, the subject has been identified as in need of treatment for an HBV-related condition.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a HBV nucleic acid in the preparation of a medicament.

12. Protein tyrosine phosphatase 1B (PTP1B)

PTP1B is a member of a family of PTPs (Barford, et al., Science 1994. 263: 1397-1404) and is a cytosolic enzyme (Neel and Tonks, Curr. Opin. Cell Biol. 1997. 9: 193-204). PTP1B is expressed ubiquitously including tissues that are key regulators of insulin metabolism such as liver, muscle and fat (Goldstein, Receptor 1993. 3: 1-15), where it is the main PTP enzyme.

PTP1B is considered to be a negative regulator of insulin signaling. PTP1B interacts with and dephosphorylates the insulin receptor, thus attenuating and potentially terminating the insulin signalling transduction (Goldstein et al., J. Biol. Chem. 2000. 275: 4383-4389). The physiological role of PTP1B in insulin signalling has been demonstrated in knockout mice models. Mice lacking the PTP1B gene were protected against insulin resistance and obesity (Elchebly et al., Science 1999. 283: 1544-1548). PTP1B-deficient mice had low adiposity, increased basal metabolic rate as well as total energy expenditure and were protected from diet-induced obesity. Insulin-stimulated glucose uptake was elevated in skeletal muscle, whereas adipose tissue was unaffected providing evidence that increased insulin sensitivity in PTP1B-deficient mice was tissue-specific (Klaman et al., Mol. Cell. Biol. 2000. 20: 5479-5489). These mice were phenotypically normal and were also resistant to diet-induced obesity, insulin resistance and had significantly

lower triglyceride levels on a high-fat diet. Therefore, inhibition of PTP1B in patients suffering from Type II diabetes, metabolic syndrome, diabetic dyslipidemia, or related metabolic diseases would be beneficial.

Antisense compounds targeting PTP1B have been previously disclosed in WO2001/053528, WO2002/092772, WO2004/071407, WO2006/044531, WO2012/142458, WO2006/044531, and WO2012/142458, each herein incorporated by reference in its entirety. An antisense oligonucleotide targeting PTP1B, ISIS-PTP1B$_{Rx}$, recently completed a Phase I clinical study with positive results. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a PTP1B Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a PTP1B nucleic acid having the sequence of GENBANK® Accession No. NM_002827.2, incorporated herein as SEQ ID NO: 13 or GENBANK Accession NT_011362.9 truncated from nucleobases 14178000 to 14256000, incorporated herein as SEQ ID NO: 14. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 13 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 13.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 13 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 69-72. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 13 comprises a nucleobase sequence of SEQ ID NOs: 69-72. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 13: Conjugated Antisense Compounds targeted to PTP1B SEQ ID NO: 13

ISIS No	Target Start Site on mRNA	Sequence (5'-3')	Chemistry	SEQ ID NO
404173	3290	AATGGTTTATTCCATGGCCA	eeeeeddddddddddeeeee	69
409826	3287	GGTTTATTCCATGGCCATTG	eeeeeddddddddddeeeee	70
142082	3291	AAATGGTTTATTCCATGGCC	eeeeeddddddddddeeeee	71
446431	3292	AATGGTTTATTCCATGGC	eeeeddddddddddeeee	72

PTP1B Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a PTP1B nucleic acid for modulating the expression of PTP1B in a subject. In certain embodiments, the expression of PTP1B is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a PTP1B nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has metabolic related diseases, including metabolic syndrome, diabetes mellitus, insulin resistance, diabetic dyslipidemia, hypertriglyceridemia, obesity and weight gain.

Diabetes mellitus is characterized by numerous physical and physiological symptoms. Any symptom known to one of skill in the art to be associated with Type 2 diabetes can be ameliorated or otherwise modulated as set forth above in the methods described above. In certain embodiments, the symptom is a physical symptom selected from the group consisting of increased glucose levels, increased weight gain, frequent urination, unusual thirst, extreme hunger, extreme fatigue, blurred vision, frequent infections, tingling or numbness at the extremities, dry and itchy skin, weight loss, slow-healing sores, and swollen gums. In certain embodiments, the symptom is a physiological symptom selected from the group consisting of increased insulin resistance, increased fat mass, decreased metabolic rate, decreased glucose clearance, decreased glucose tolerance, decreased insulin sensitivity, decreased hepatic insulin sensitivity, increased adipose tissue size and weight, increased body fat, and increased body weight.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a PTP1B nucleic acid in the preparation of a medicament.

13. STAT3

The STAT (signal transducers and activators of transcription) family of proteins comprises DNA-binding proteins that play a dual role in signal transduction and activation of transcription. Presently, there are six distinct members of the STAT family (STAT1, STAT2, STAT3, STAT4, STAT5, and STAT6) and several isoforms (STAT1α, STAT1β, STAT3 α and STAT3β). The activities of the STATs are modulated by various cytokines and mitogenic stimuli. Binding of a cytokine to its receptor results in the activation of Janus protein tyrosine kinases (JAKs) associated with these receptors. This phosphorylates STAT, resulting in translocation to the nucleus and transcriptional activation of STAT responsive genes. Phosphorylation on a specific tyrosine residue on the STATs results in their activation, resulting in the formation of homodimers and/or heterodimers of STAT which bind to specific gene promoter sequences. Events mediated by cytokines through STAT activation include cell proliferation and differentiation and prevention of apoptosis.

The specificity of STAT activation is due to specific cytokines, i.e., each STAT is responsive to a small number of specific cytokines. Other non-cytokine signaling molecules, such as growth factors, have also been found to activate STATs. Binding of these factors to a cell surface receptor associated with protein tyrosine kinase also results in phosphorylation of STAT.

STAT3 (also acute phase response factor (APRF)), in particular, has been found to be responsive to interleukin-6 (IL-6) as well as epidermal growth factor (EGF) (Darnell, Jr., J.E., et al., Science, 1994, 264, 1415-1421). In addition, STAT3 has been found to have an important role in signal transduction by interferons (Yang, C.-H., et al., Proc. Natl. Acad. Sci. USA, 1998, 95, 5568-5572). Evidence exists suggesting that STAT3 may be regulated by the MAPK pathway. ERK2 induces serine phosphorylation and also associates with STAT3 (Jain, N., et al., Oncogene, 1998, 17, 3157-3167).

STAT3 is expressed in most cell types (Zhong, Z., et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 4806-4810). It induces the expression of genes involved in response to tissue injury and inflammation. STAT3 has also been shown to prevent apoptosis through the expression of bcl-2 (Fukada, T., et al., Immunity, 1996, 5, 449-460).

Recently, STAT3 was detected in the mitochondria of transformed cells, and was shown to facilitate glycolytic and oxidative phosphorylation activities similar to that of cancer cells (Gough, D.J., et al., Science, 2009, 324, 1713-1716). The inhibition of STAT3 in the mitochondria impaired malignant transformation by activated Ras. The data confirms a Ras-mediated transformation function for STAT3 in the mitochondria in addition to its nuclear roles.

Aberrant expression of or constitutive expression of STAT3 is associated with a number of disease processes.

Antisense compounds targeting STAT3 have been previously disclosed in WO2012/135736 and WO2005/083124, each herein incorporated by reference in its entirety. An antisense oligonucleotide targeting STAT3, ISIS-STAT3$_{Rx}$, is currently in Phase 1/2 clinical trials to study its effectiveness in treating subjects with cancer. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a STAT3 Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a STAT3 nucleic acid having the sequence of GENBANK® Accession No. NM_139276.2, incorporated herein as SEQ ID NO: 15. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 15 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 15.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 15 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NO: 73. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 15 comprises a nucleobase sequence of SEQ ID NO: 73. In

certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 14: Antisense Compounds targeted to STAT3 SEQ ID NO: 15

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
481464	3016	CTATTTGGATGTCAGC	kkkddddddddddkkk	73

STAT3 Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a STAT3 nucleic acid for modulating the expression of STAT3 in a subject. In certain embodiments, the expression of STAT3 is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a STAT3 nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a hyperproliferative disease, disorder or condition. In certain embodiments such hyperproliferative disease, disorder, and condition include cancer as well as associated malignancies and metastases. In certain embodiments, such cancers include lung cancer, including non small cell lung cancer (NSCLC), pancreatic cancer, colorectal cancer, multiple myeloma, hepatocellular carcinoma (HCC), glioblastoma, ovarian cancer, osteosarcoma, head and neck cancer, breast cancer, epidermoid carcinomas, intestinal adenomas, prostate cancer, and gastric cancer.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a STAT3 nucleic acid in the preparation of a medicament.

14. Transthyretin (TTR)

TTR (also known as prealbumin, hyperthytoxinemia, dysprealbuminemic, thyroxine; senile systemic amyloidosis, amyloid polyneuropathy, amyloidosis I, PALB; dystransthyretinemic, HST2651; TBPA; dysprealbuminemic euthyroidal hyperthyroxinemia) is a serum/plasma and cerebrospinal fluid protein responsible for the transport of thyroxine and retinol (Sakaki et al, Mol Biol Med. 1989, 6:161-8). Structurally, TTR is a homotetramer; point mutations and misfolding of the protein leads to deposition of amyloid fibrils and is associated with disorders, such as senile systemic amyloidosis (SSA), familial amyloid polyneuropathy (FAP), and familial amyloid cardiopathy (FAC).

TTR is synthesized primarily by the liver and the choroid plexus of the brain and, to a lesser degree, by the retina in humans (Palha, *Clin Chem Lab Med,* 2002, *40*, 1292-1300). Transthyretin that is synthesized

in the liver is secreted into the blood, whereas transthyretin originating in the choroid plexus is destined for the CSF. In the choroid plexus, transthyretin synthesis represents about 20% of total local protein synthesis and as much as 25% of the total CSF protein (Dickson et al., *J Biol Chem,* 1986, *261*, 3475-3478).

With the availability of genetic and immunohistochemical diagnostic tests, patients with TTR amyloidosis have been found in many nations worldwide. Recent studies indicate that TTR amyloidosis is not a rare endemic disease as previously thought, and may affect as much as 25% of the elderly population (Tanskanen et al, Ann Med. 2008;40(3):232-9).

At the biochemical level, TTR was identified as the major protein component in the amyloid deposits of FAP patients (Costa et al, *Proc. Natl. Acad. Sci. USA* 1978, **75**:4499–4503) and later, a substitution of methionine for valine at position 30 of the protein was found to be the most common molecular defect causing the disease (Saraiva et al, *J. Clin. Invest.* 1984, **74**: 104–119). In FAP, widespread systemic extracellular deposition of TTR aggregates and amyloid fibrils occurs throughout the connective tissue, particularly in the peripheral nervous system (Sousa and Saraiva, *Prog. Neurobiol.* 2003, **71**: 385–400). Following TTR deposition, axonal degeneration occurs, starting in the unmyelinated and myelinated fibers of low diameter, and ultimately leading to neuronal loss at ganglionic sites.

Antisense compounds targeting TTR have been previously disclosed in US2005/0244869, WO2010/017509, and WO2011/139917, each herein incorporated by reference in its entirety. An antisense oligonucleotide targeting TTR, ISIS-TTR_{Rx}, is currently in Phase 2/3 clinical trials to study its effectiveness in treating subjects with Familial Amyloid Polyneuropathy. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a TTR Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a TTR nucleic acid having the sequence of GENBANK® Accession No. NM_000371.3, incorporated herein as SEQ ID NO: 16. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 16 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 16.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 16 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 74-81. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 16 comprises a nucleobase sequence of SEQ ID NO: 74-81. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 15: Antisense Compounds targeted to TTR SEQ ID NO: 16

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
420915	508	TCTTGGTTACATGAAATCCC	eeeeeddddddddddeeeee	74
304299	507	CTTGGTTACATGAAATCCCA	eeeeeddddddddddeeeee	75
420921	515	GGAATACTCTTGGTTACATG	eeeeeddddddddddeeeee	76
420922	516	TGGAATACTCTTGGTTACAT	eeeeeddddddddddeeeee	77
420950	580	TTTTATTGTCTCTGCCTGGA	eeeeeddddddddddeeeee	78
420955	585	GAATGTTTTATTGTCTCTGC	eeeeeddddddddddeeeee	79
420957	587	AGGAATGTTTTATTGTCTCT	eeeeeddddddddddeeeee	80
420959	589	ACAGGAATGTTTTATTGTCT	eeeeeddddddddddeeeee	81

TTR Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a TTR nucleic acid for modulating the expression of TTR in a subject. In certain embodiments, the expression of TTR is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a TTR nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a transthyretin related disease, disorder or condition, or symptom thereof. In certain embodiments, the transthyretin related disease, disorder or condition is transthyretin amyloidosis. "Transthyretin-related amyloidosis" or "transthyretin amyloidosis" or "Transthyretin amyloid disease", as used herein, is any pathology or disease associated with dysfunction or dysregulation of transthyretin that result in formation of transthyretin-containing amyloid fibrils. Transthyretin amyloidosis includes, but is not limited to, hereditary TTR amyloidosis, leptomeningeal amyloidosis, familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy, familial oculoleptomeningeal amyloidosis, senile cardiac amyloidosis, or senile systemic amyloidosis.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a TTR nucleic acid in the preparation of a medicament.

15. PCSK9

PCSK9 (also known as Proprotein convertase subtilisin kexin 9) is a member of the subtilisin serine protease family. The other eight mammalian subtilisin proteases, PCSK1-PCSK8 (also called PC1/3, PC2, furin, PC4, PC5/6, PACE4, PC7, and S1P/SKI-1) are proprotein convertases that process a wide variety of proteins in the secretory pathway and play roles in diverse biological processes (Bergeron, F. (2000) J. Mol.

Endocrinol. 24, 1-22, Gensberg, K., (1998) Semin. Cell Dev. Biol. 9, 11-17, Seidah, N. G. (1999) Brain Res. 848, 45-62, Taylor, N. A., (2003) FASEB J. 17, 1215-1227, and Zhou, A., (1999) J. Biol. Chem. 274, 20745-20748). PCSK9 has been proposed to play a role in cholesterol metabolism. PCSK9 mRNA expression is down-regulated by dietary cholesterol feeding in mice (Maxwell, K. N., (2003) J. Lipid Res. 44, 2109-2119), up-regulated by statins in HepG2 cells (Dubuc, G., (2004) Arterioscler. Thromb. Vasc. Biol. 24, 1454-1459), and up-regulated in sterol regulatory element binding protein (SREBP) transgenic mice (Horton, J. D., (2003) Proc. Natl. Acad. Sci. USA 100, 12027-12032), similar to the cholesterol biosynthetic enzymes and the low-density lipoprotein receptor (LDLR). Furthermore, PCSK9 missense mutations have been found to be associated with a form of autosomal dominant hypercholesterolemia (Hchola3) (Abifadel, M., et al. (2003) Nat. Genet. 34, 154-156, Timms, K. M., (2004) Hum. Genet. 114, 349-353, Leren, T. P. (2004) Clin. Genet. 65, 419-422). PCSK9 may also play a role in determining LDL cholesterol levels in the general population, because single-nucleotide polymorphisms (SNPs) have been associated with cholesterol levels in a Japanese population (Shioji, K., (2004) J. Hum. Genet. 49, 109-114).

Antisense compounds targeting PCSK9 have been previously disclosed in U.S. Patents 8,084,437; 8,093,222; 8,664,190; and International applications WO 2008/066776 and WO 2009/148605. However, there is still a need to provide patients with additional and more potent treatment options.

Certain Conjugated Antisense Compounds Targeted to a PCSK9 Nucleic Acid

In certain embodiments, conjugated antisense compounds are targeted to a PCSK9 nucleic acid having the sequence of GENBANK® Accession, incorporated herein as SEQ ID NO: 160. In certain such embodiments, a conjugated antisense compound targeted to SEQ ID NO: 160 is at least 90%, at least 95%, or 100% complementary to SEQ ID NO: 160.

In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 160 comprises an at least 8 consecutive nucleobase sequence of SEQ ID NOs: 156-159. In certain embodiments, a conjugated antisense compound targeted to SEQ ID NO: 160 comprises a nucleobase sequence of SEQ ID NO: 156-159. In certain embodiments, such conjugated antisense compounds comprise a conjugate comprising 1-3 GalNAc ligands. In certain embodments, such antisense compounds comprise a conjugate disclosed herein.

Table 15: Antisense Compounds targeted to PCSK9 SEQ ID NO: 156

ISIS No	Target Start Site	Sequence (5'-3')	Motif	SEQ ID NO
405879	1073	CCTTGGCCACGCCGGCATCC	eeeeeddddddddddeeeee	156

431131	1015	GTCACACTTGCTGGCCTGTC	eeeeeddddddddddeeeee	157
405995	2001	TGGCAGTGGACACGGGTCCC	eeeeeddddddddddeeeee	158
480604	3381	ACTCACCGAGCTTCCTGGTC	eeeeeddddddddddeeeee	159

PCSK9 Therapeutic Indications

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a PCSK9 nucleic acid for modulating the expression of PCSK9 in a subject. In certain embodiments, the expression of PCSK9 is reduced.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a PCSK9 nucleic acid in a pharmaceutical composition for treating a subject. In certain embodiments, the subject has a PCSK9 related disease, disorder or condition, or symptom thereof. In certain embodiments, the PCSK9 related disease, disorder or condition is a metabolic or cardiovascular disease.

In certain embodiments, the invention provides methods for using a conjugated antisense compound targeted to a PCSK9 nucleic acid in the preparation of a medicament.

E. Certain Nucleic Acid GalNAc Conjugates

In certain embodiments, conjugated antisense compounds comprise antisense compounds having the nucleobase sequence of the antisense compounds in Table 16 below attached to a GalNAc conjugate. In certain embodiments, conjugated antisense compounds comprise antisense compounds having the nucleobase sequence and chemical modifications of the antisense compounds in Table 16 below attached to a GalNAc conjugate. All internucleoside linkages are phosphorothioate internucleoside linkages unless otherwise indicated. A subscript "l" indicates an LNA bicyclic nucleoside. A subscript "d" indicates a 2'-deoxy nucleoside. A subscript "e" indicates a 2'-MOE modified nucleoside. A subscript "v" indicates a 2-amino-2'-deoxyadenosine.

Table 16

Sequence 5' to 3'	Target	Motif	Chemistry	Internucleoside Linkages	SEQ ID NO.
$T_lG_lG_lC_dA_dA_dG_dC_dA_dT_dC_dC_dT_lG_lT_lA_d$	HIF-1α	3-9-3-1	LNA/deoxy	phosphorothioate	82
$C_lT_lC_lA_lA_dT_dC_dC_dA_dT_dG_dG_dC_lA_lG_lC_d$	Survivin	4-8-3-1	LNA/deoxy	phosphorothioate	83
$A_lC_lC_lA_dA_dG_dT_dT_dT_dC_dT_dT_dC_dA_lG_lC_l$	Androgen Receptor	3-10-3	LNA/deoxy	phosphorothioate	84

$G_lC_lA_dT_dT_dG_dG_dT_dA_dT_dT_lC_lA_l$	ApoB	2-8-3	LNA/deoxy	phosphorothioate	85
$T_lT_lC_lA_lG_lC_dA_dT_dT_dG_dG_dT_dA_dT_dT_d$ $C_lA_lG_lT_lG_l$	ApoB	5-10-5	LNA/deoxy	phosphorothioate	86
$C_lA_lG_lC_dA_dT_dT_dG_dG_dT_dA_dT_dT_lC_lA_l$ G_d	ApoB	3-10-3	LNA/deoxy	phosphorothioate	87
$C_lA_lG_lC_dA_dT_dT_dG_dG_dT_dA_dT_dT_lC_lA_l$	ApoB	3-9-3	LNA/deoxy	phosphorothioate	88
$A_lG_lC_lA_dT_dT_dG_dG_dT_dA_dT_dT_lC_lA_l$	ApoB	3-8-3	LNA/deoxy	phosphorothioate	89
$G_lC_lA_dT_dT_dG_dG_dT_dA_dT_dT_lC_l$	ApoB	2-8-2	LNA/deoxy	phosphorothioate	90
$T_lG_lC_lT_dA_dC_dA_dA_dA_dA_dC_dC_lC_lA_l$	PCSK9	3-8-3	LNA/deoxy	phosphorothioate	135
$C_lcC_dA_lT_dT_dG_lT_lC_dA_dC_lA_dC_lT_dC_lC_l$	miR-122		LNA/deoxy	phosphorothioate	136
CGGCATGTCTATTTTGTA	TGF-β2			phosphorothioate	91
GGCTAAATCGCTCCACCAAG	RRM2			phosphorothioate	92
CTCTAGCGTCTTAAAGCCGA	RRM1			phosphorothioate	93
GCTGCATGATCTCCTTGGCG	AKT-1			phosphorothioate	94
ACGTTGAGGGGCATCGTCGC	c-Myc			Morpholino	95
CGGTTAGAAGACTCATCTTT	Influenza PB1-AUG			Morpholino	137
CTCCAACATCAAGGAAGATG GCATTTCTAG	dystrophin			Morpholino	138
GAATATTAACANACTGACAA GTC	Marburg virus NP			Morpholino	139
CGTTGATANTTCTGCCATNCT	Marburg virus VP24			Morpholino	140
GCCATGGTTTTTTCTCAGG	Ebola virus VP24			Morpholino	141
CCTGCCCTTTGTTCTAGTTG	Ebola virus VP35			Morpholino	142
$GGGTCTGCA_vGCGGGA_vTGGT$	CCR3 & CSF2RB			phosphorothioate	96
$GTTA_vCTA_vCTTCCA_vCCTGCC$ TG	CCR3 & CSF2RB			phosphorothioate	97
TATCCGGAGGGCTCGCCATG CTGCT	IRS-1			phosphorothioate	98
GTCGCCCCTTCTCCCCGCAGC	Smad7			phosphorothioate	143
GGACCCTCCTCCGGAGCC	IGF-1R			phosphorothioate	144
ACCAGGCGTCTCGTGGGGCA CAT	Ki-67			phosphorothioate	145
TCTCCCAGCGTGCGCCAT	BCL-2			phosphorothioate	146
GTGCTCCATTGATGC	c-Raf			phosphate	147
$T_eC_eC_eC_eG_eC_eCTGTGACAT_eG_eC_e$ $A_eT_eT_e$	c-Raf	6-8-6	MOE/deoxy		99
$C_eA_eG_eC_eAGCAGAGTCTTCAT_e$ $C_eA_eT_e$	Clusterin	4-13-4	MOE/deoxy		100
$G_eG_eG_eA_eC_dG_dC_dG_dG_dC_dG_dC_dT_dC_d$ $G_dG_dT_eC_eA_eT_e$	HSPB1	4-12-4	MOE/deoxy		101
$C_eC_eA_eC_eA_eA_dG_dC_dT_dG_dT_dC_dC_dA_d$ $G_dT_eC_eT_eA_eA_e$	CTGF	5-10-5	MOE/deoxy		102
$C_eC_eG_eC_dA_dG_dC_dC_dA_dT_dG_dC_dG_eC_e$ $T_eC_eT_eT_eG_eG_e$	CD49d / VLA-4	3-9-8	MOE/deoxy		103
$T_eC_eA_eG_eG_eG_dC_dA_dT_dT_dC_dT_dT_dT_d$ $C_dC_eA_eT_eT_eC_e$	GHR	5-10-5	MOE/deoxy		148
$C_eG_eA_eA_eG_eG_dA_dA_dA_dC_dA_dA_dT_dA$	IGF-1R	5-10-5	MOE/deoxy		149

$_dC_dT_eC_eC_eG_eA_e$					
$G_eA_eC_eA_eG_eC_dA_dG_dC_dC_dG_dC_dA_dG_dC_dA_eG_eA_eA_eA_e$	hepcidin	5-10-5	MOE/deoxy		150
$T_eG_eG_eA_eA_eA_dG_dG_dC_dT_dT_dA_dT_dA_dC_dC_eC_eC_eT_eC_e$	IL-4Rα1	5-10-5	MOE/deoxy		151
TCAAGGAAGATGGCATTTCT	dystrophin		2'-O-Methyl	phosphorothioate	152
GUGGCUAACAGAAGCU	dystrophin		2'-O-Methyl	phosphorothioate	153
UUUGCCGCUGCCCAAUGCCAUCCUG	dystrophin		2'-O-Methyl	phosphorothioate	154
$G_mC_mG_mU_mG_dC_dC_dT_dC_dC_dT_dC_dA_dC_dU_mG_mG_mC_m$	Protein kinase A	4-10-4	2'-O-Methyl/deoxy	phosphorothioate	155

Additional Sequences and Oligonucleotides suitable for conjugateion with any conjugate herein

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to eukaryotic Initiation Factor 4E (eIF4E) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to dIF4E are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to dIF4E are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to eIF4E suitable for conjugation include but are not limited to those disclosed in US 7,425,544, which is incorporated by reference in its entirety herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 18-122 disclosed in US 7,425,544 and a conjugate group described herein. In certain embodiments, a compound comprises an antisense strand having a nucleobase sequence of any of SEQ ID NOs: 212-459 disclosed in US 7,425,544 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Signal Transducer and Activator of Transcription 3 (STAT3) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to STAT3 are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to STAT3 are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to STAT3 suitable for conjugation include but are not limited to those disclosed in WO 2012/135736, WO 2005/083124, and US 6,727,064; which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 9-426, 430-442, 445-464, 471-498, 500-1034, 1036-1512, and 1541-2757 disclosed in WO 2012/135736 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: 2-81, 108-150, and 159-381 disclosed in WO 2005/083124

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: 2-81 and 108-150 disclosed in US 6,727,064 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to glucocorticoid receptor (GCCR) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to GCCR are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to GCCR are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to GCCR suitable for conjugation include but are not limited to those disclosed in WO 2005/071080, WO 2007/035759, and WO 2007/136988; which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 30-216, and 306-310 disclosed in WO 2005/071080 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: 26-113 disclosed in WO 2007/035759 and a conjugate group disclosed herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 413-485 disclosed in WO 2007/136988 and a conjugate group disclosed herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to glucagon receptor (GCGR) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to GCGR are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to GCGR are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to GCGR suitable for conjugation include but are not limited to those disclosed in US 7,750,142; US 7,399,853; WO 2007/035771; and WO 2007/134014; which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs: 20-399 disclosed in US 7,750,142 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: 20-399 disclosed in US 7,399,853 and a conjugate group described herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of SEQ ID NO: 2 disclosed in WO 2007/035771 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: 486-680 disclosed in WO 2007/134014 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Protein Tyrosine Phosphatase 1B (PTP1B) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to PTP1B are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to PT1B are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to PTP1B suitable for conjugation include but are not limited to those disclosed in US 7,563,884 and WO 2007/131237, which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 17-96 and 244-389 disclosed in US 7,563,884 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 886-1552 disclosed in WO 2007/131237 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Fibroblast Growth Factor Receptor 4 (FGFR4) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to FGFR4 are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to FGFR4 are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to FGFR4 suitable for conjugation include but are not limited to those disclosed in WO 2009/046141, which is incorporated by reference in its entirety herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 21-24, 28, 29, 36, 38, 39, 43, 48, 51, 54-56, 58-60, 64-66, and 92-166 disclosed in WO 2009/046141 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to alpha-1-antitrypsin (A1AT) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to A1AT are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to A1AT are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to A1AT suitable for conjugation include but are not limited to those disclosed in WO 2013/142514, which is incorporated by reference in its entirety herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 20-41 disclosed in WO 2013/142514 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Factor VII known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to Factor VII are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense

oligonucleotides targeted to Factor VII are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to Factor VII suitable for conjugation include but are not limited to those disclosed in WO 2013/119979 and WO 2009/061851, which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 21-659 disclosed in WO 2013/119979 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 4-159 and 168-611 disclosed in WO 2009/061851 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Factor XI known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to Factor XI are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to Factor XI are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to Factor XI suitable for conjugation include but are not limited to those disclosed in WO 2010/045509 and WO 2010/121074, which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 15-270 disclosed in WO 2010/045509 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 15-270 disclosed in WO 2010/121074 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Hepatitis B Virus (HBV) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to HBV are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to HBV are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to HBV suitable for conjugation include but are not limited to those disclosed in WO 2012/145697 and WO 2012/145697, which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 5-310, 321-802, 804-1272, 1288-1350, 1364-1372, 1375, 1376, and 1379 disclosed in WO 2012/145697 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 14-22 disclosed in WO 2011/047312 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to transthyretin (TTR) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to TTR are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to TTR are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to TTR suitable for conjugation include but are not limited to those disclosed in WO 2011/139917 and US 8,101,743, which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 8-160, 170-177 disclosed in WO 2011/139917 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 12-89 disclosed in US 8,101,743 and a conjugate group described herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence complementary to a preferred target segment of any of SEQ ID NOs 90-133 disclosed in US 8,101,743 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to apolipoprotein(a) (apo(a)) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to apo(a) are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to apo(a) are RNase H based antisense compounds. 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; which are incorporated by reference in their entireties herein. 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. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Apolipoprotein B (ApoB) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to ApoB are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to ApoB are RNase H based antisense compounds.

Examples of antisense oligonucleotides targeted to ApoB suitable for conjugation include but are not limited to those disclosed in US Patent Application Publication Nos. US 2010/0331390, US 2009/0306180, and US 2005/0009088; which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of SEQ ID NO: 20 disclosed in US 2010/0331390 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 16-213 disclosed in US 2009/0306180 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 17-70, 124-317, 319-333, 335-502, 504-804, and 864-887 disclosed in US 2005/0009088 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to Apolipoprotein C-III (ApoC-III) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to ApoC-III are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to ApoC-III are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to ApoC-III suitable for conjugation include but are not limited to those disclosed in US Patent Application Publication No. US 2013/0317085, which is incorporated by reference in its entirety herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 19-96 and 209-221 disclosed in US 2013/0317085 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to proprotein convertase subtilisin/kexin type 9 (PCSK9) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to PCSK9 are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to PCSK9 are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to PCSK9 suitable for conjugation include but are not limited to those disclosed in US 8,143,230 and US 8,664,190; which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 329-403 disclosed in US 8,143,230 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 4-455 and 458-461 disclosed in US 8,664,190 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

In certain embodiments, a compound comprises an antisense oligonucleotide targeted to C-reactive protein (CRP) known in the art and a conjugate group described herein. In certain embodiments, antisense oligonucleotides targeted to CRP are RNAi (siRNA or ssRNA) compounds. In certain embodiments, antisense oligonucleotides targeted to CRP are RNase H based antisense compounds. Examples of antisense oligonucleotides targeted to CRP suitable for conjugation include but are not limited to those disclosed in WO 2003/010284, WO 2005/005599, and WO 2007/143317; which are incorporated by reference in their entireties herein. In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs 10-63 disclosed in WO 2003/010284 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 19-72, 76-259, and 598-613 disclosed in WO 2005/005599 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 409-412 disclosed in WO 2007/143317 and a conjugate group described herein. The nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein.

F. Certain Pharmaceutical Compositions

In certain embodiments, the present disclosure provides pharmaceutical compositions comprising one or more antisense compound. 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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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).

Nonlimiting disclosure and incorporation by reference

While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references, GenBank accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

Certain compounds, compositions, and methods herein are described as "comprising exactly" or "comprises exactly" a particular number of a particular element or feature. Such descriptions are used to indicate that while the compound, composition, or method may comprise additional other elements, the number of the particular element or feature is the identified number. For example, "a conjugate comprising exactly one GalNAc" is a conjugate that contains one and only one GalNAc, though it may contain other elements in addition to the one GalNAc.

Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH for the natural 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) for natural uracil of RNA).

Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligonucleotide having the nucleobase sequence "ATCGATCG" encompasses any oligonucleotides having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and oligonucleotides having other modified bases, such as "AT^{me}CGAUCG," wherein ^{me}C indicates a cytosine base comprising a methyl group at the 5-position.

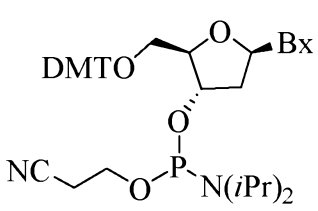
EXAMPLES

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.

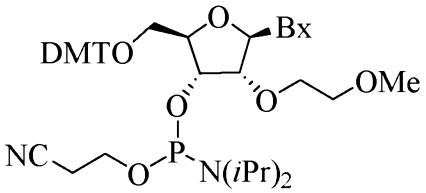
EXAMPLES

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.

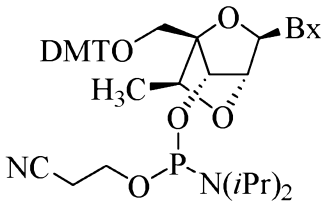
Example 1: General Method for the Preparation of Phosphoramidites, Compounds 1, 1a and 2



1



1a

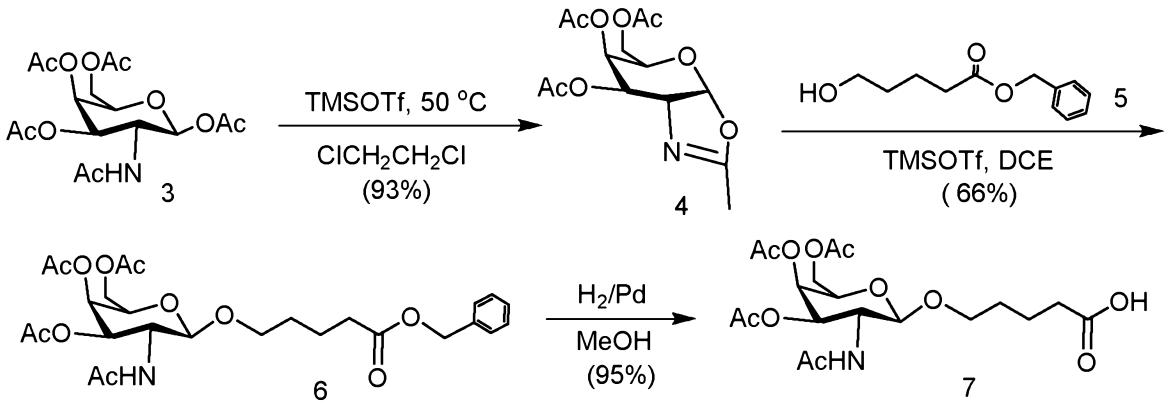


2

Bx is a heterocyclic base;

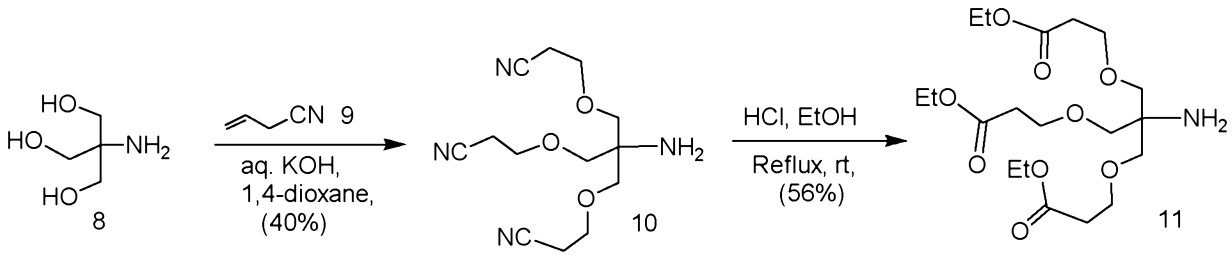
Compounds 1, 1a and 2 were prepared as per the procedures well known in the art as described in the specification herein (see Seth et al., Bioorg. Med. Chem., 2011, 21(4), 1122-1125, J. Org. Chem., 2010, 75(5), 1569-1581, Nucleic Acids Symposium Series, 2008, 52(1), 553-554); and also see published PCT 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



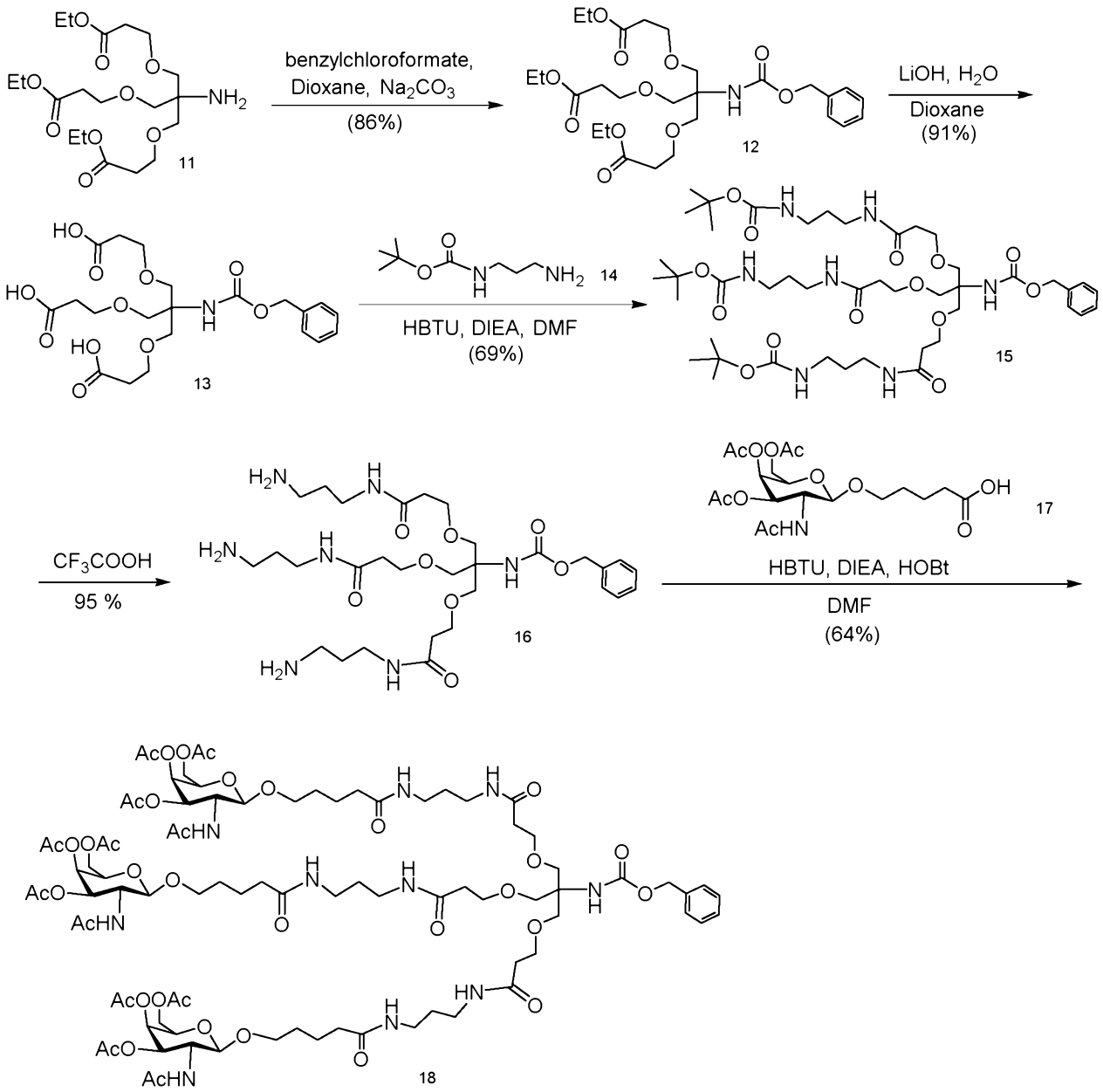
Compounds 3 (2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-Dgalactopyranose or galactosamine pentaacetate) is commercially available. Compound 5 was prepared according to published procedures (Weber *et al., J. Med. Chem.*, 1991, *34*, 2692).

Example 3: Preparation of Compound 11



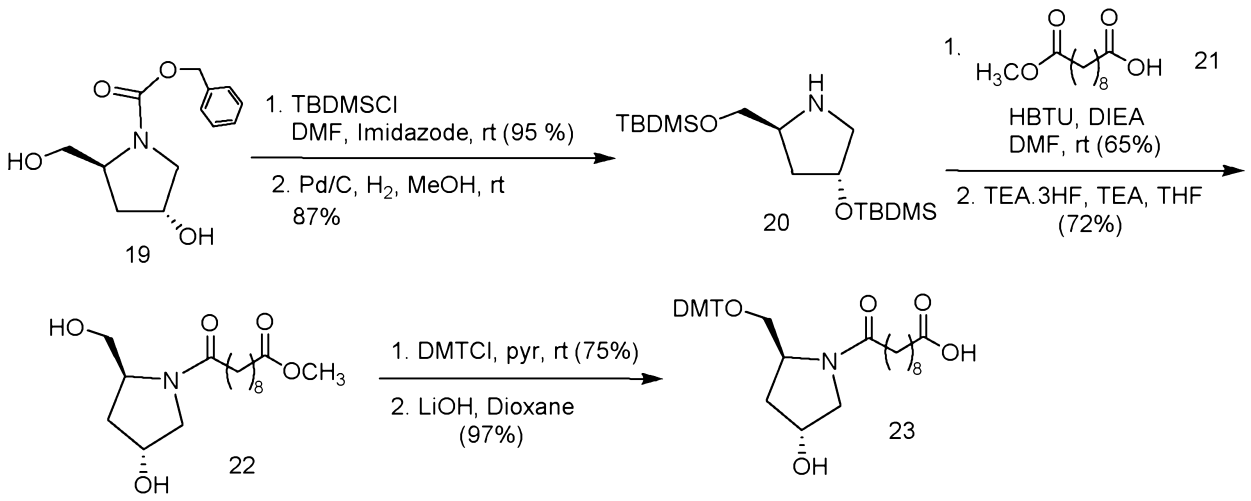
Compounds 8 and 9 are commercially available.

Example 4: Preparation of Compound 18



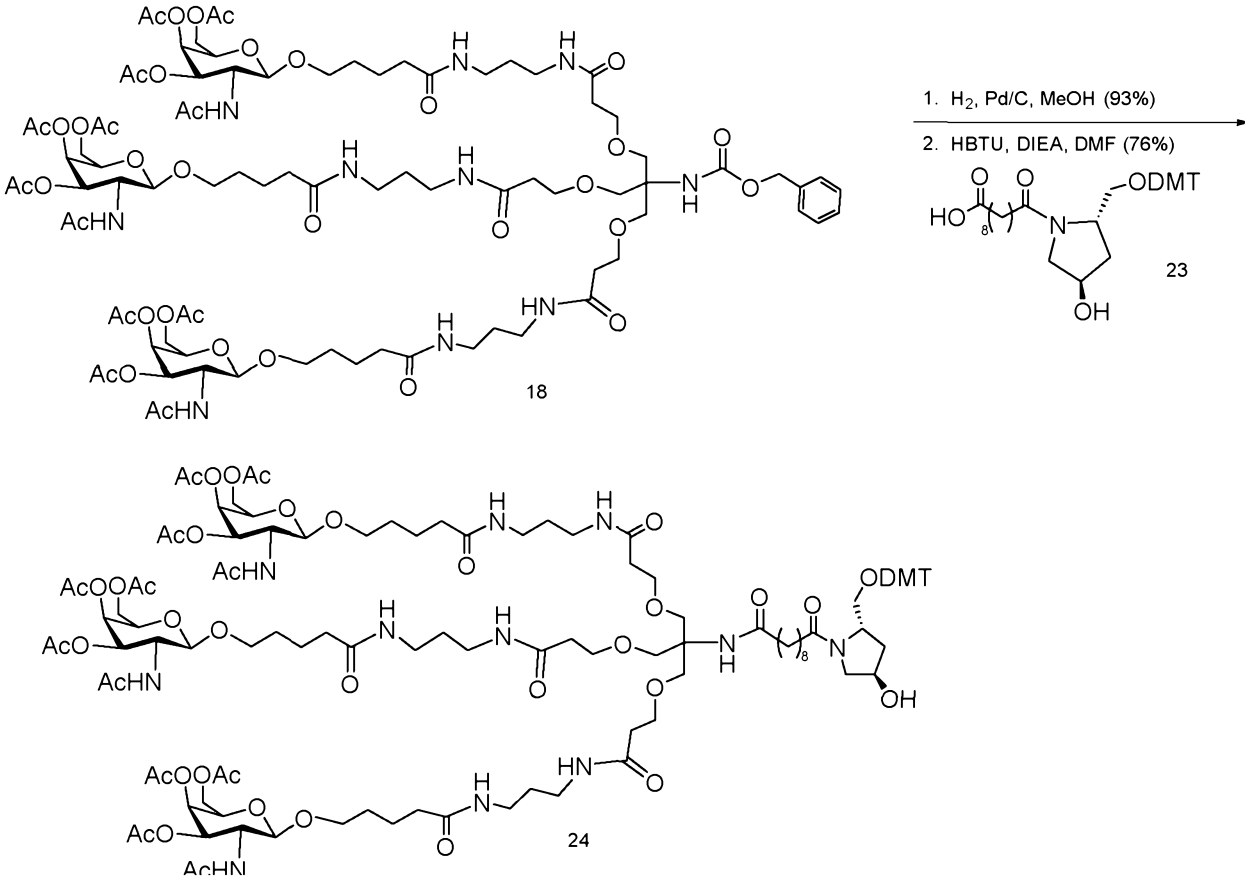
Compound 11 was prepared as per the procedures illustrated in Example 3. Compound 14 is commercially available. Compound 17 was prepared using similar procedures reported by Rensen *et al., J. Med. Chem.,* 2004, *47,* 5798-5808.

Example 5: Preparation of Compound 23



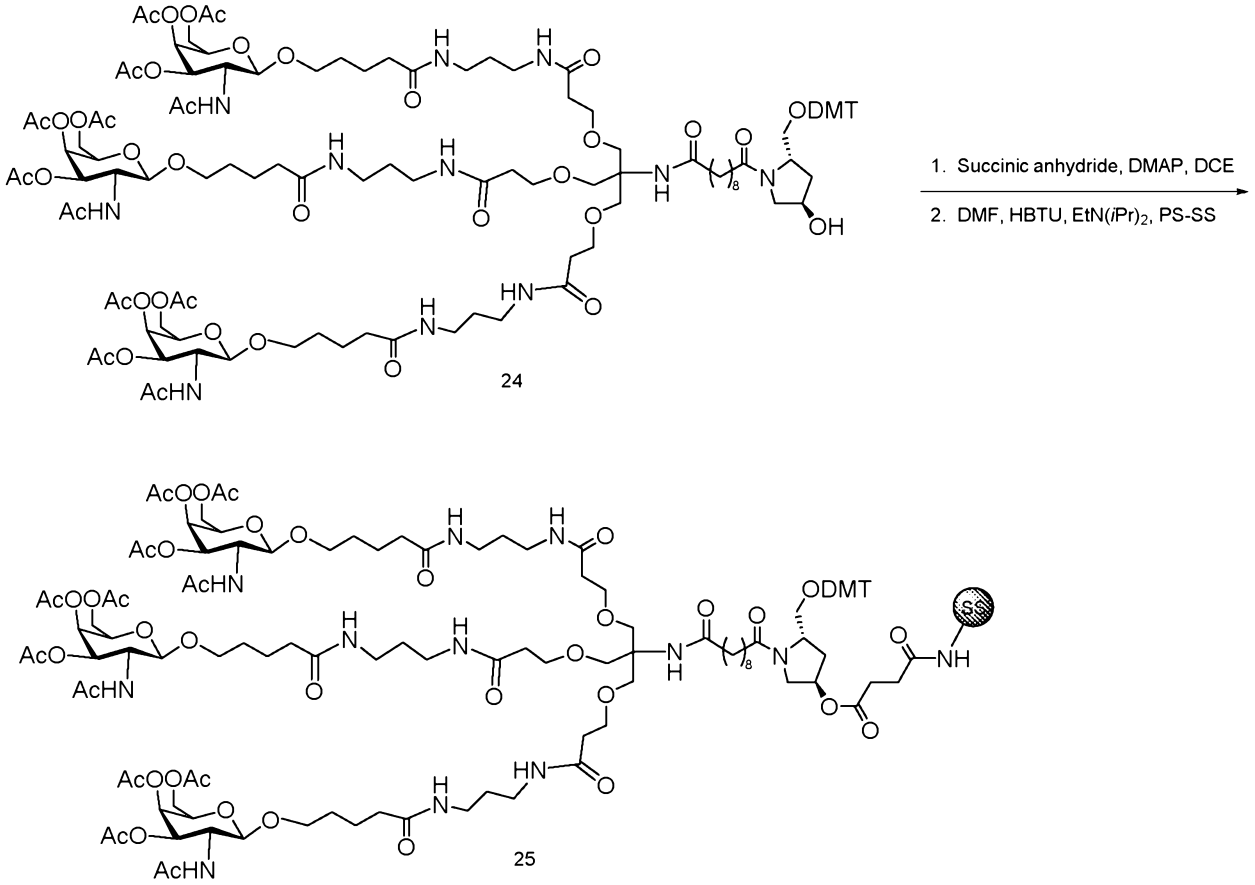
Compounds 19 and 21 are commercially available.

Example 6: Preparation of Compound 24



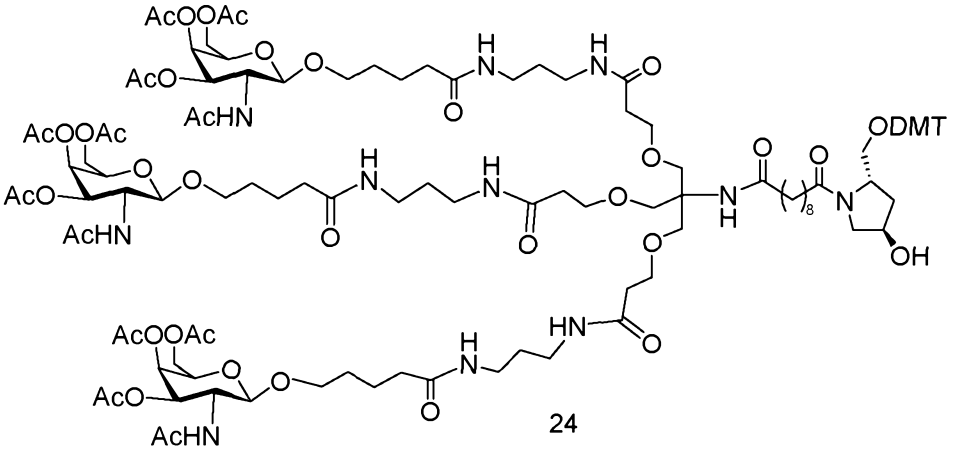
Compounds 18 and 23 were prepared as per the procedures illustrated in Examples 4 and 5.

Example 7: Preparation of Compound 25

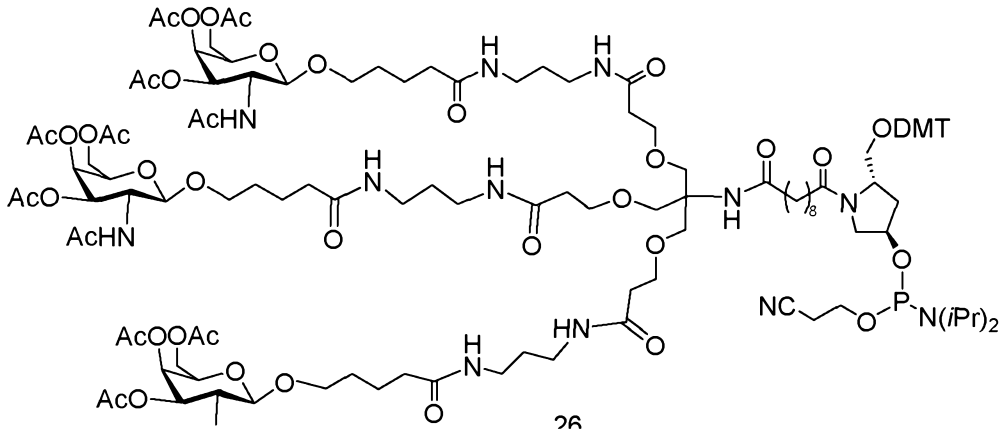


Compound 24 was prepared as per the procedures illustrated in Example 6.

Example 8: Preparation of Compound 26



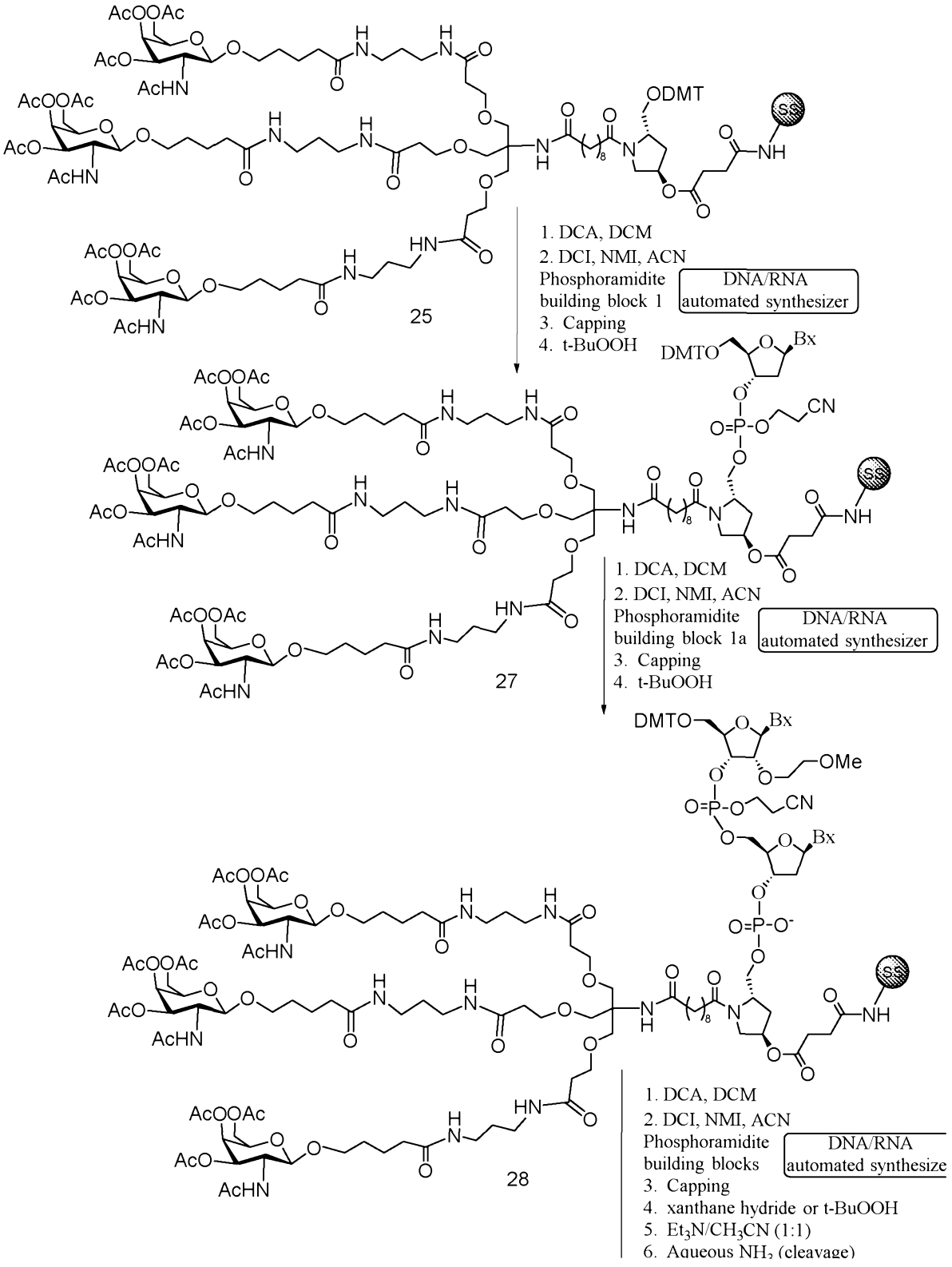
Phosphitylation

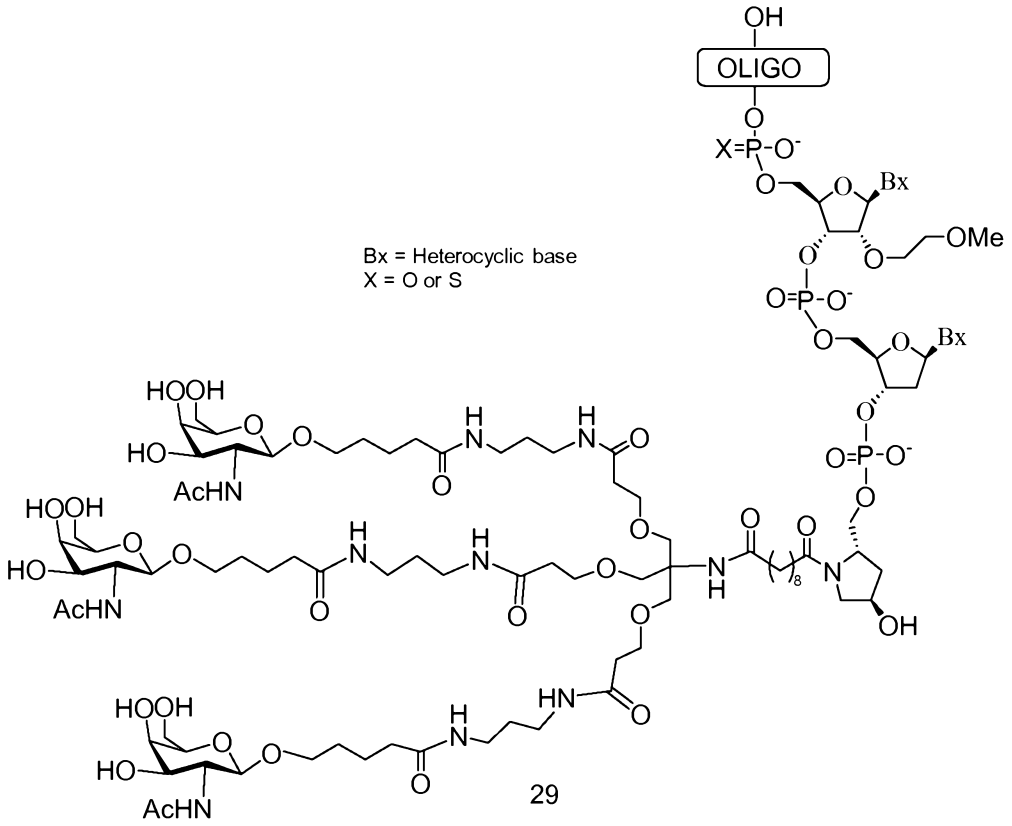


Compound 24 is prepared as per the procedures illustrated in Example 6.

5

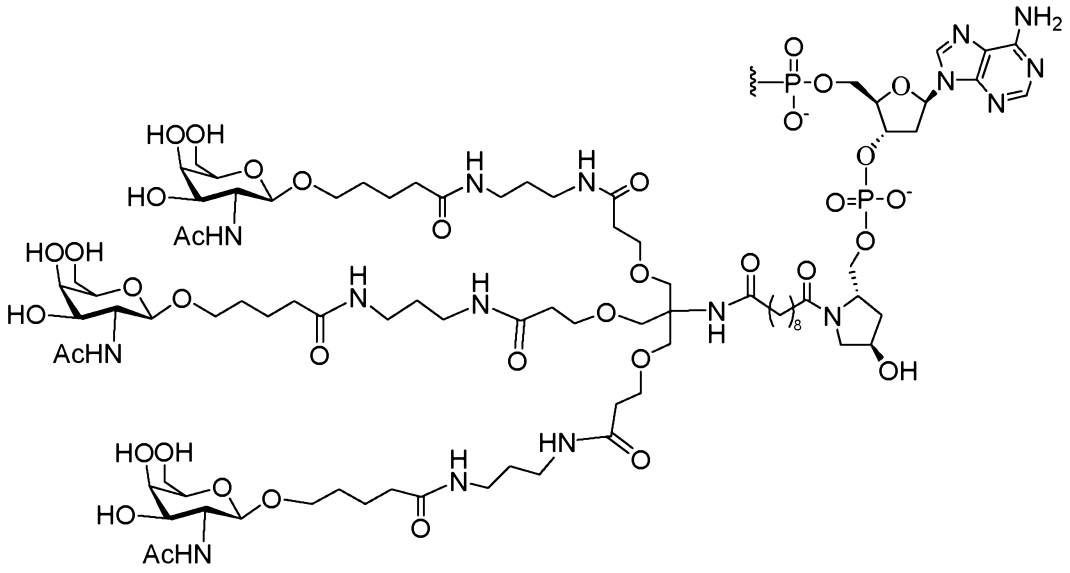
Example 9: General preparation of conjugated ASOs comprising GalNAc$_3$-1 at the 3' terminus, Compound 29



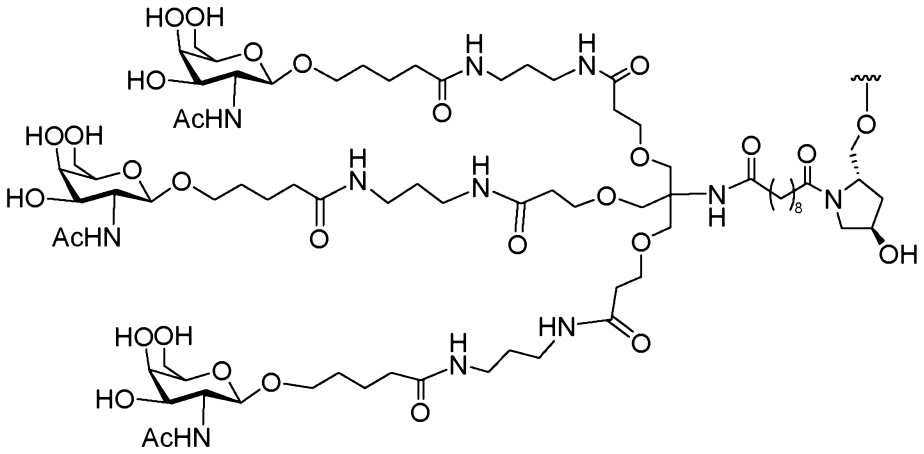


29

Wherein the protected **GalNAc$_3$-1** has the structure:

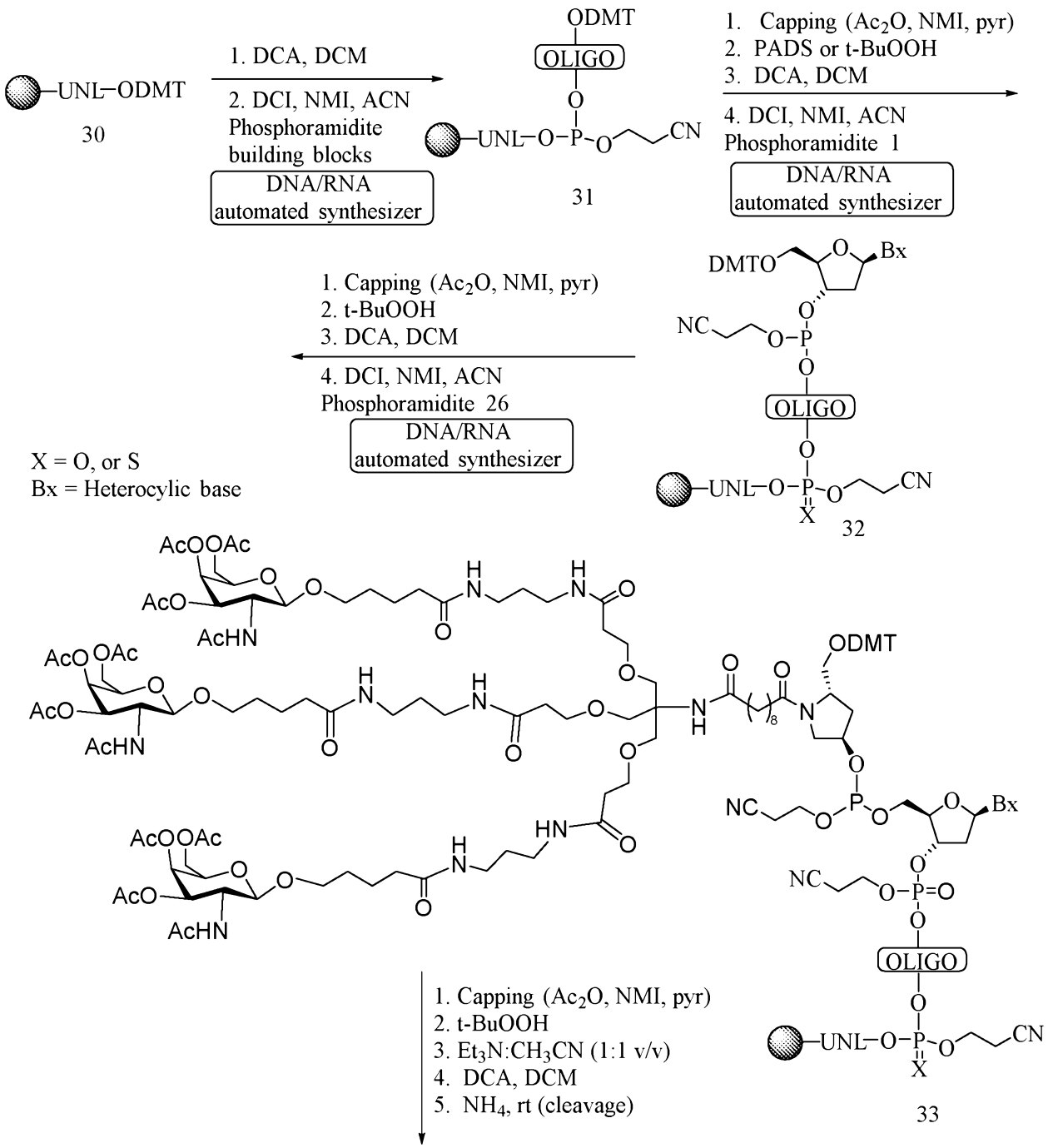


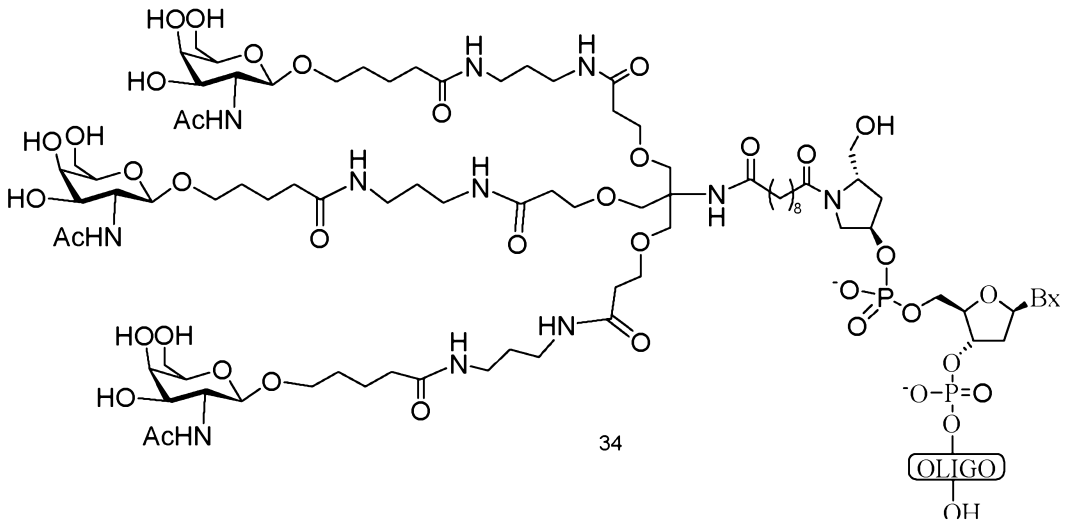
The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-1 (GalNAc$_3$-1$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-1$_a$ has the formula:



The solid support bound protected **GalNAc$_3$-1**, Compound 25, was prepared as per the procedures illustrated in Example 7. Oligomeric Compound 29 comprising **GalNAc$_3$-1** at the 3' terminus was prepared using standard procedures in automated DNA/RNA synthesis (see Dupouy *et al., Angew. Chem. Int. Ed.,* 2006, *45,* 3623-3627). Phosphoramidite building blocks, Compounds 1 and 1a were prepared as per the procedures illustrated in Example 1. The phosphoramidites illustrated are meant to be representative and not intended to be limiting as other phosphoramidite building blocks can be used to prepare oligomeric compounds having a predetermined sequence and composition. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare gapped oligomeric compounds as described herein. Such gapped oligomeric compounds can have predetermined composition and base sequence as dictated by any given target.

Example 10: General preparation conjugated ASOs comprising GalNAc$_3$-1 at the 5' terminus, Compound 34

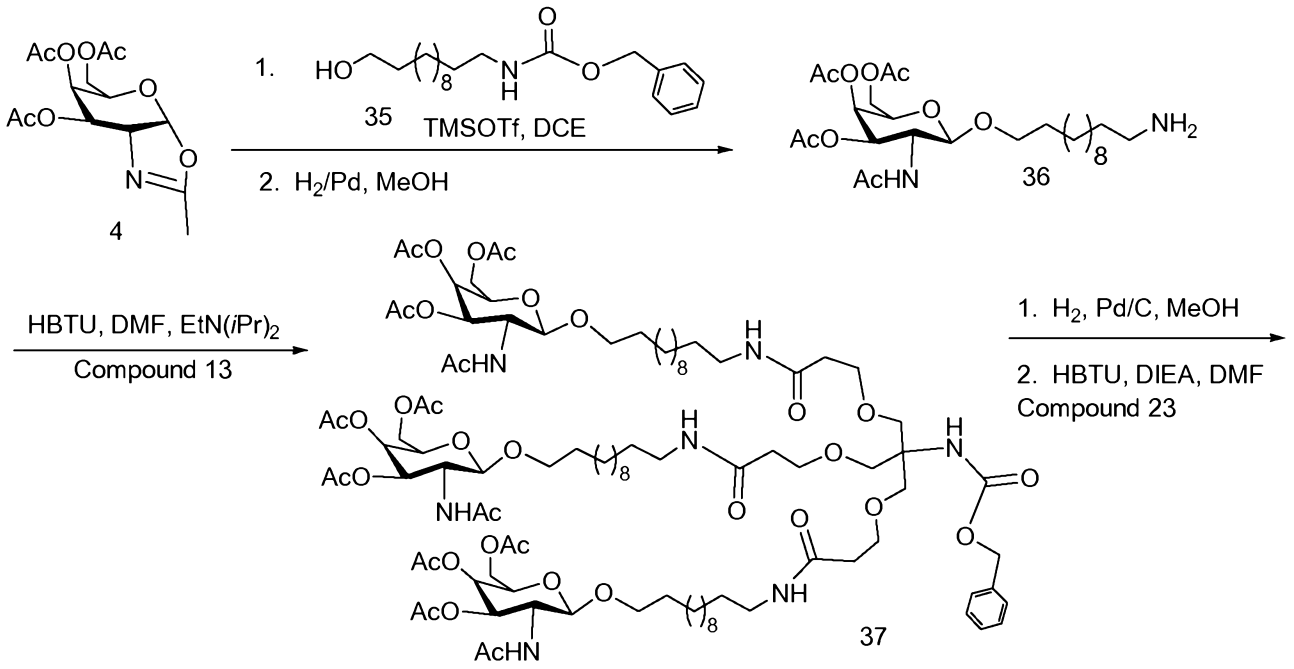


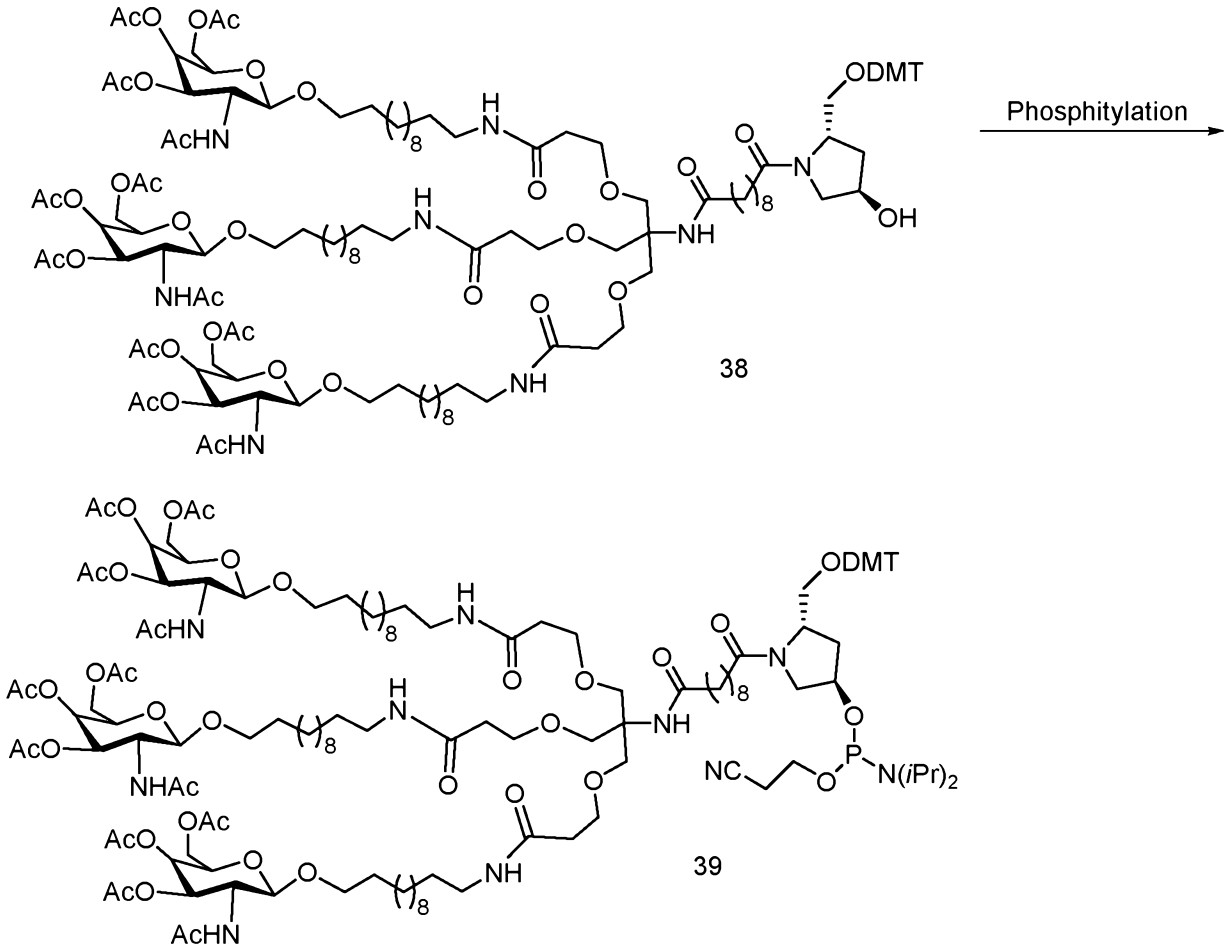


34

The Unylinker™ 30 is commercially available. Oligomeric Compound 34 comprising a **GalNAc$_3$-1** cluster at the 5' terminus is prepared using standard procedures in automated DNA/RNA synthesis (see Dupouy *et al., Angew. Chem. Int. Ed.,* 2006, *45,* 3623-3627). Phosphoramidite building blocks, Compounds 1 and 1a were prepared as per the procedures illustrated in Example 1. The phosphoramidites illustrated are meant to be representative and not intended to be limiting as other phosphoramidite building blocks can be used to prepare an oligomeric compound having a predetermined sequence and composition. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare gapped oligomeric compounds as described herein. Such gapped oligomeric compounds can have predetermined composition and base sequence as dictated by any given target.

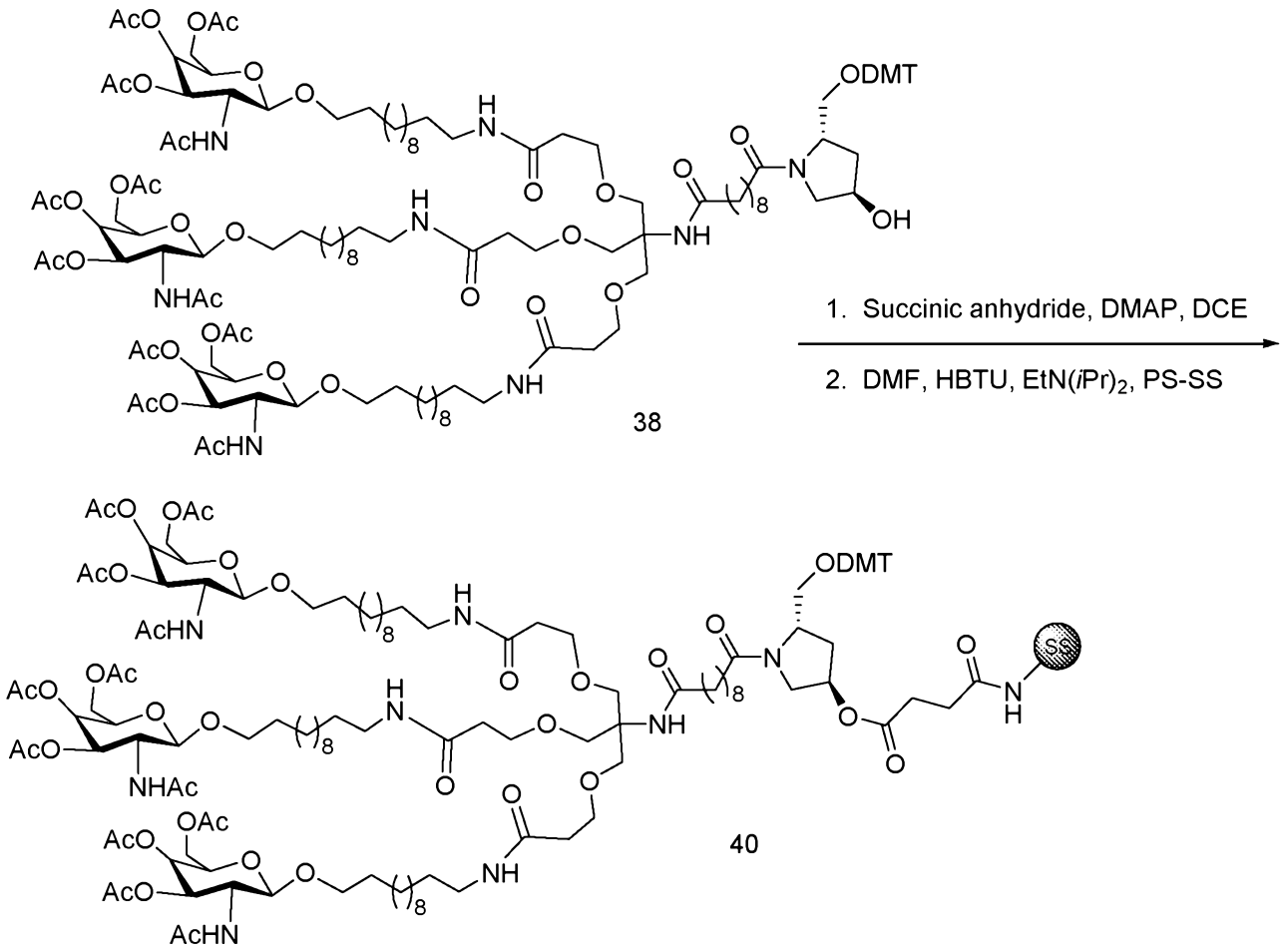
Example 11: Preparation of Compound 39





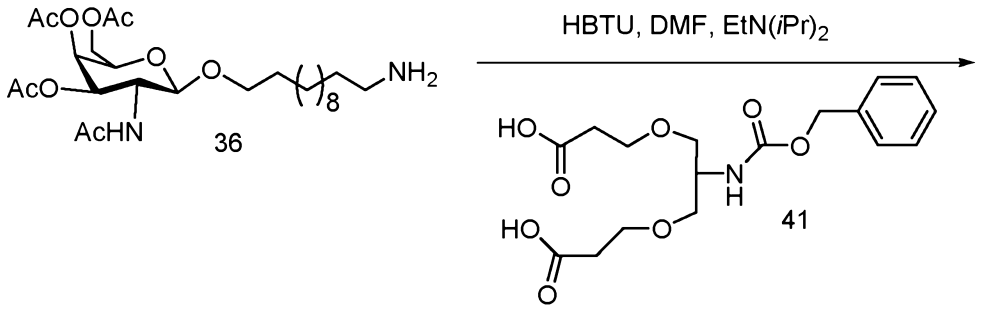
Compounds 4, 13 and 23 were prepared as per the procedures illustrated in Examples 2, 4, and 5. Compound 35 is prepared using similar procedures published in Rouchaud *et al., Eur. J. Org. Chem.,* 2011, *12*, 2346-2353.

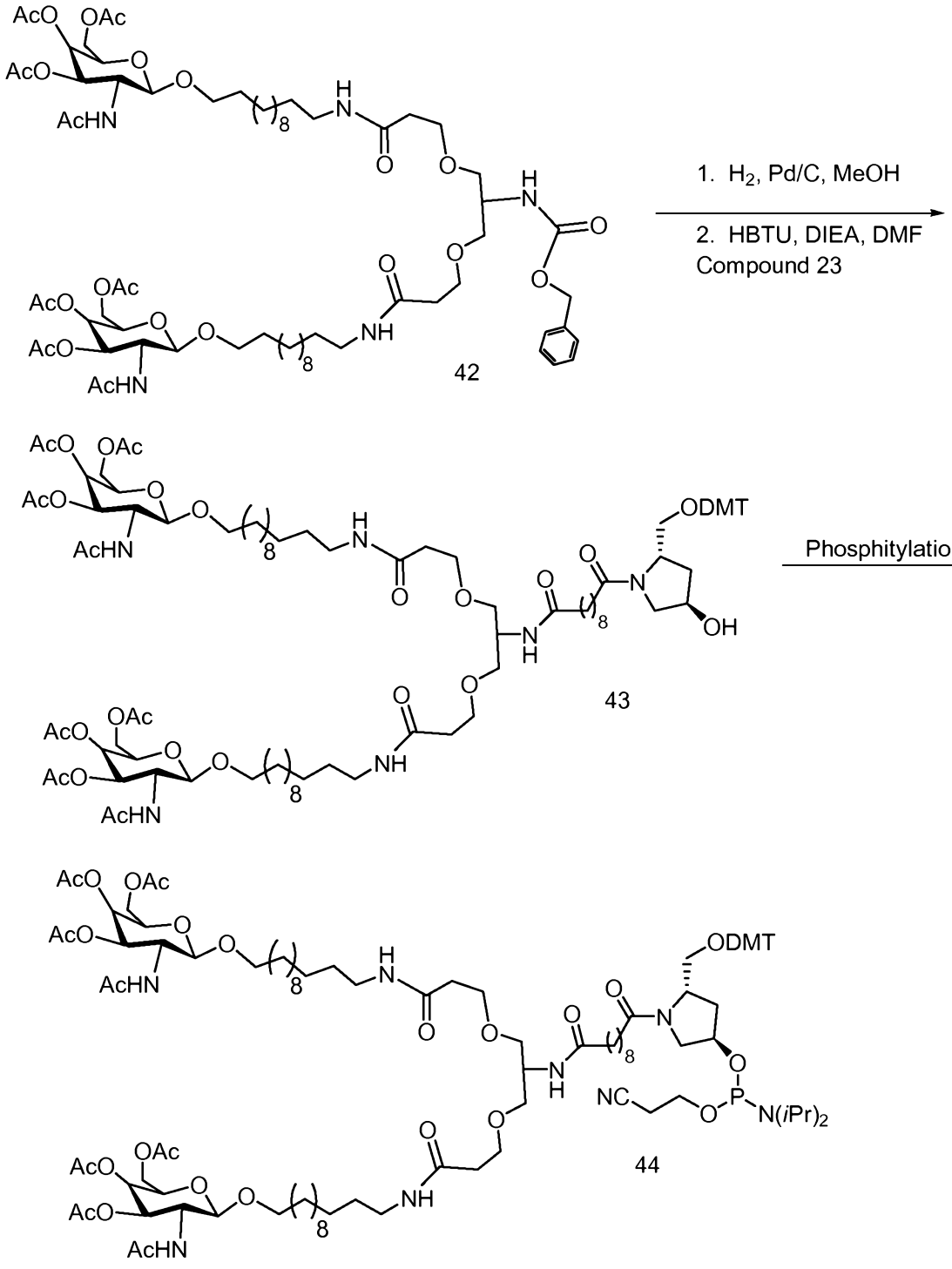
Example 12: Preparation of Compound 40



Compound 38 is prepared as per the procedures illustrated in Example 11.

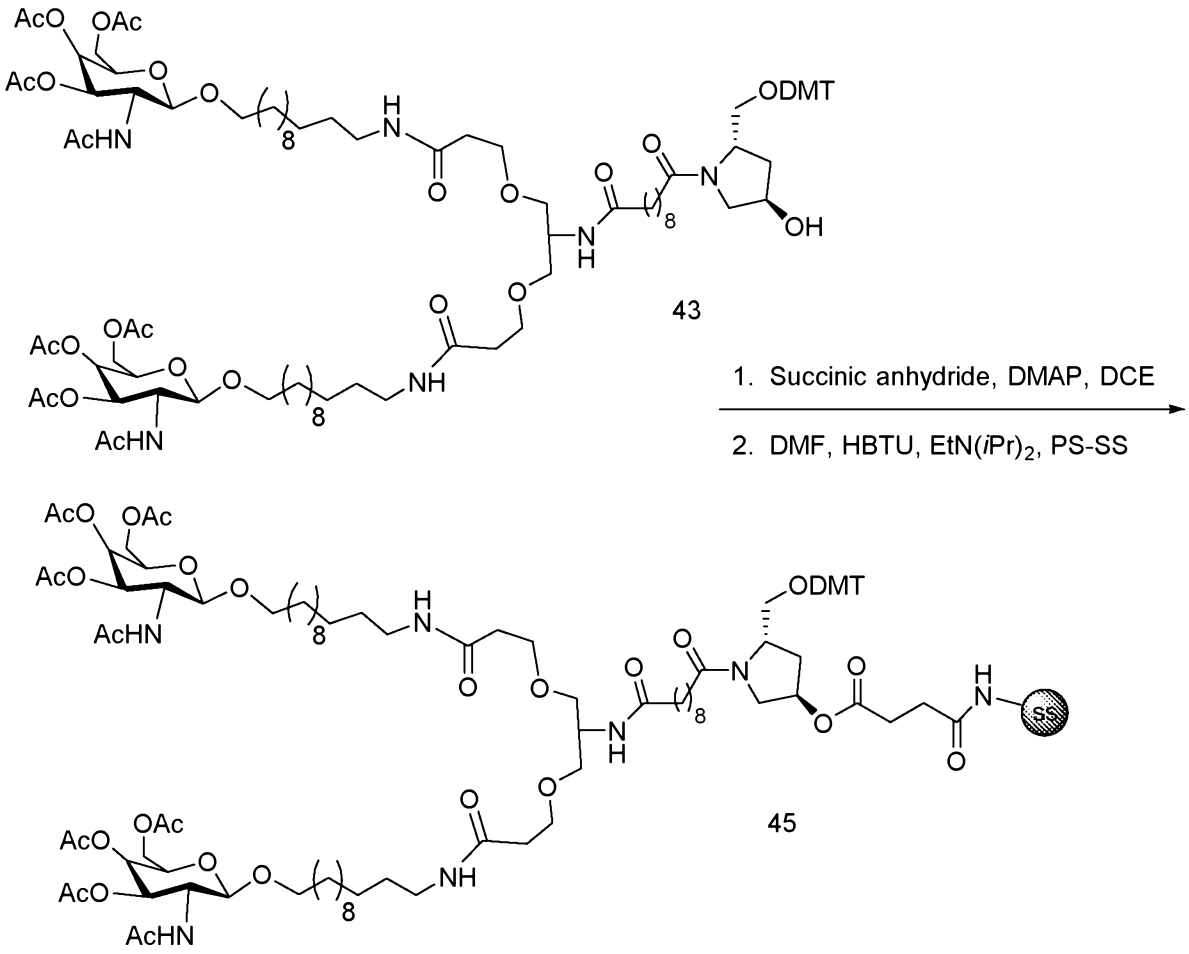
Example 13: Preparation of Compound 44





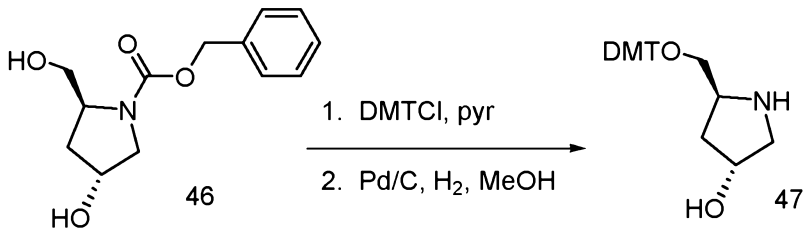
Compounds 23 and 36 are prepared as per the procedures illustrated in Examples 5 and 11. Compound 41 is prepared using similar procedures published in WO 2009082607.

Example 14: Preparation of Compound 45



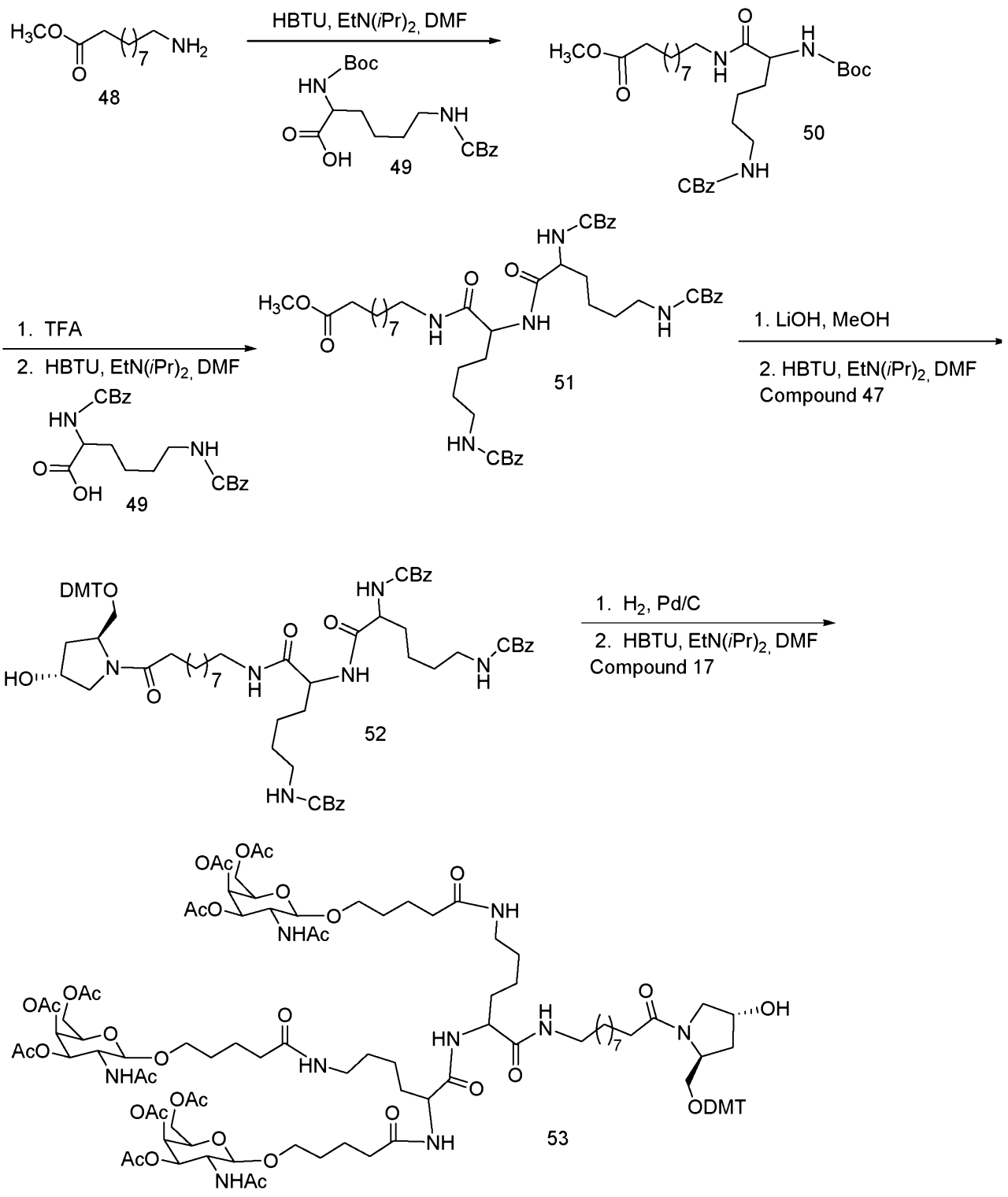
Compound 43 is prepared as per the procedures illustrated in Example 13.

Example 15: Preparation of Compound 47



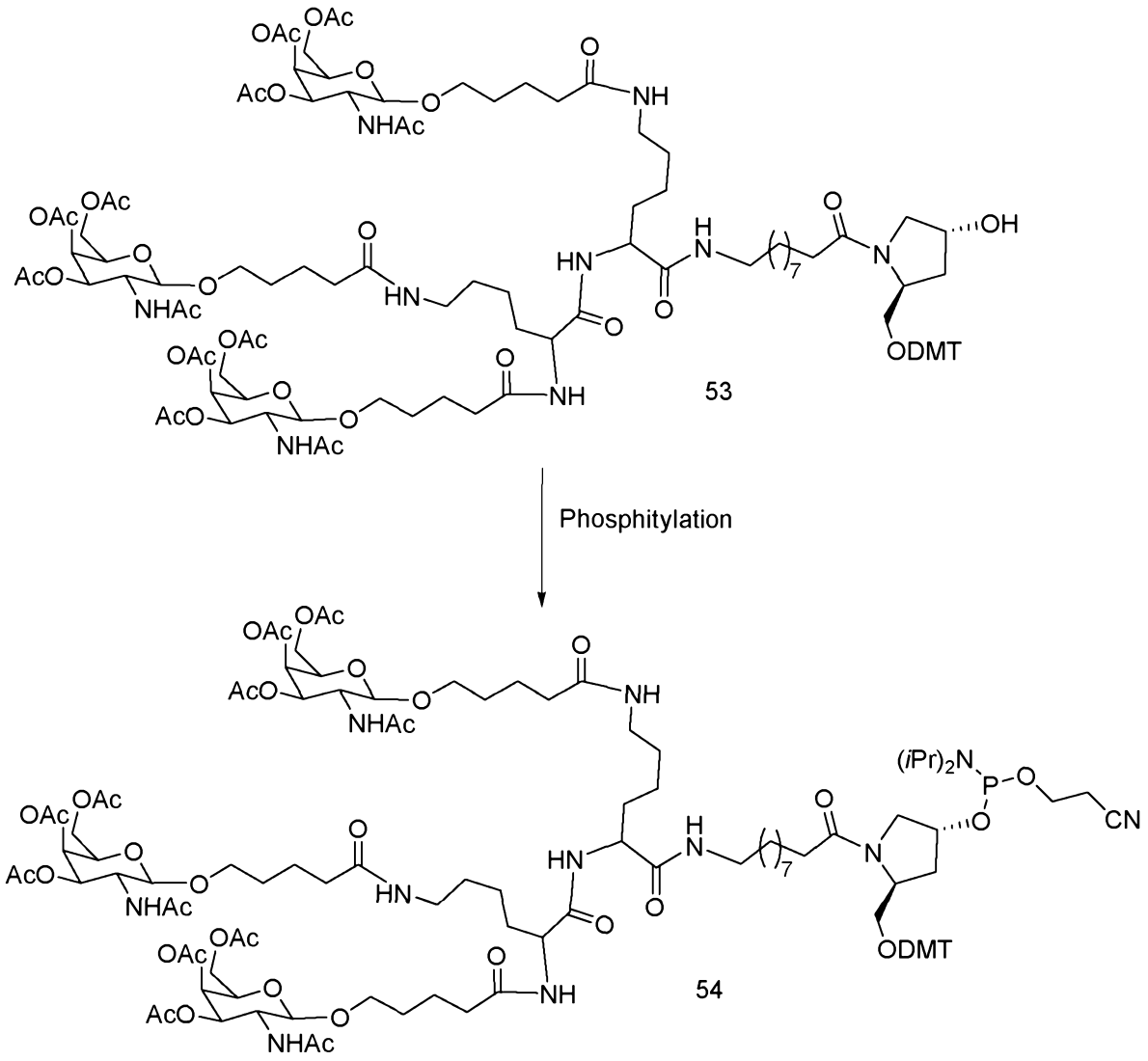
Compound 46 is commercially available.

Example 16: Preparation of Compound 53



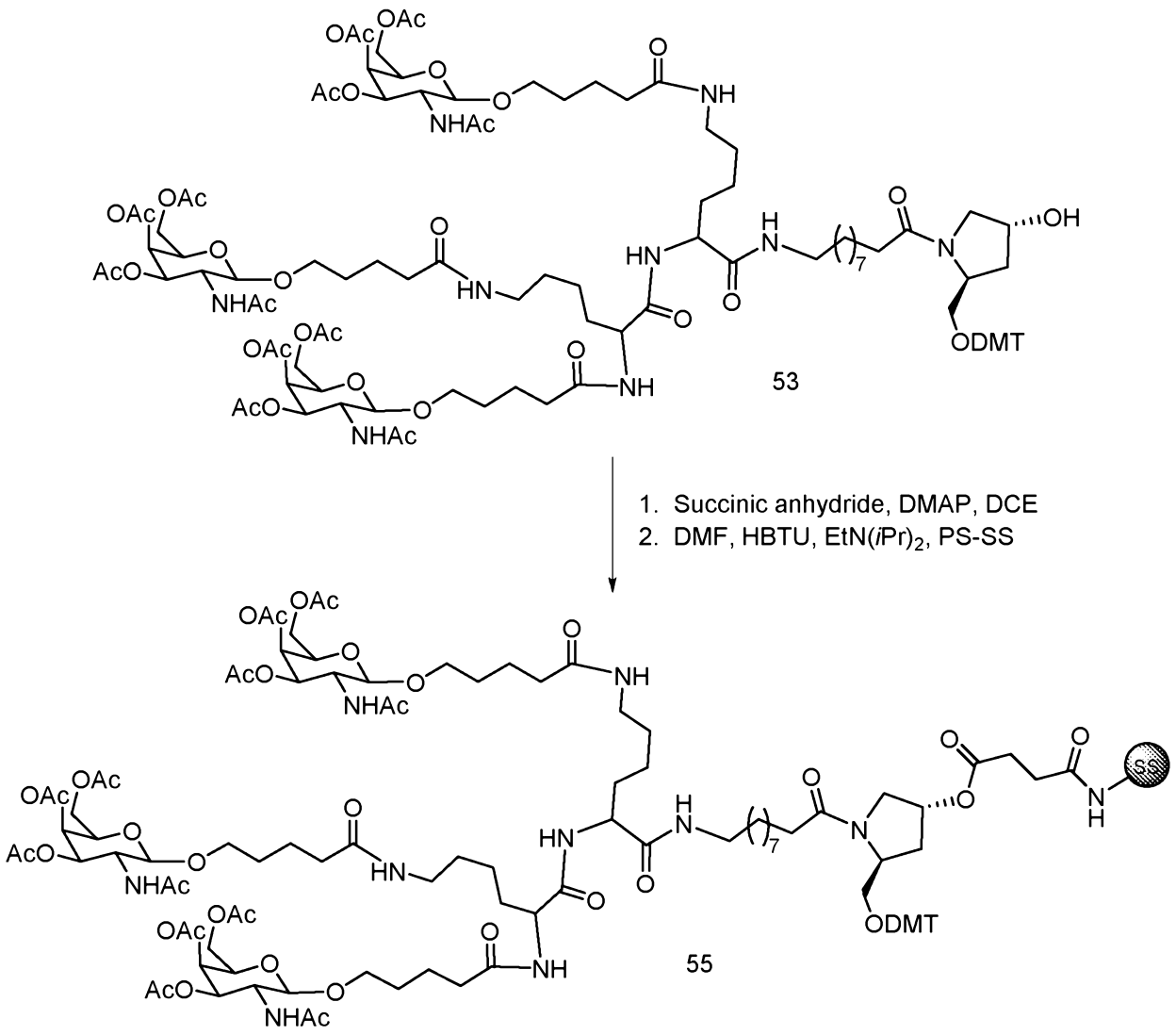
Compounds 48 and 49 are commercially available. Compounds 17 and 47 are prepared as per the procedures illustrated in Examples 4 and 15.

Example 17: Preparation of Compound 54



Compound 53 is prepared as per the procedures illustrated in Example 16.

Example 18: Preparation of Compound 55



Compound 53 is prepared as per the procedures illustrated in Example 16.

Example 19: General method for the preparation of conjugated ASOs comprising GalNAc$_3$-1 at the 3' position via solid phase techniques (preparation of ISIS 647535, 647536 and 651900)

Unless otherwise stated, all reagents and solutions used for the synthesis of oligomeric compounds are purchased from commercial sources. Standard phosphoramidite building blocks and solid support are used for incorporation nucleoside residues which include for example T, A, G, and ^{m}C residues. A 0.1 M solution of phosphoramidite in anhydrous acetonitrile was used for β-D-2'-deoxyribonucleoside and 2'-MOE.

The ASO syntheses were performed on ABI 394 synthesizer (1-2 µmol scale) or on GE Healthcare Bioscience ÄKTA oligopilot synthesizer (40-200 µmol scale) by the phosphoramidite coupling method on an **GalNAc$_3$-1** loaded VIMAD solid support (110 µmol/g, Guzaev *et al.*, 2003) packed in the column. For the coupling step, the phosphoramidites were delivered 4 fold excess over the loading on the solid support and

phosphoramidite condensation was carried out for 10 min. All other steps followed standard protocols supplied by the manufacturer. A solution of 6% dichloroacetic acid in toluene was used for removing dimethoxytrityl (DMT) group from 5'-hydroxyl group of the nucleotide. 4,5-Dicyanoimidazole (0.7 M) in anhydrous CH_3CN was used as activator during coupling step. Phosphorothioate linkages were introduced by sulfurization with 0.1 M solution of xanthane hydride in 1:1 pyridine/CH_3CN for a contact time of 3 minutes. A solution of 20% *tert*-butylhydroperoxide in CH_3CN containing 6% water was used as an oxidizing agent to provide phosphodiester internucleoside linkages with a contact time of 12 minutes.

After the desired sequence was assembled, the cyanoethyl phosphate protecting groups were deprotected using a 1:1 (v/v) mixture of triethylamine and acetonitrile with a contact time of 45 minutes. The solid-support bound ASOs were suspended in aqueous ammonia (28-30 wt %) and heated at 55 °C for 6 h.

The unbound ASOs were then filtered and the ammonia was boiled off. The residue was purified by high pressure liquid chromatography on a strong anion exchange column (GE Healthcare Bioscience, Source 30Q, 30 μm, 2.54 x 8 cm, A = 100 mM ammonium acetate in 30% aqueous CH_3CN, B = 1.5 M NaBr in A, 0-40% of B in 60 min, flow 14 mL min-1, λ = 260 nm). The residue was desalted by HPLC on a reverse phase column to yield the desired ASOs in an isolated yield of 15-30% based on the initial loading on the solid support. The ASOs were characterized by ion-pair-HPLC coupled MS analysis with Agilent 1100 MSD system.

Antisense oligonucleotides not comprising a conjugate were synthesized using standard oligonucleotide synthesis procedures well known in the art.

Using these methods, three separate antisense compounds targeting ApoC III were prepared. As summarized in Table 17, below, each of the three antisense compounds targeting ApoC III had the same nucleobase sequence; ISIS 304801 is a 5-10-5 MOE gapmer having all phosphorothioate linkages; ISIS 647535 is the same as ISIS 304801, except that it had a **GalNAc$_3$-1** conjugated at its 3'end; and ISIS 647536 is the same as ISIS 647535 except that certain internucleoside linkages of that compound are phosphodiester linkages. As further summarized in Table 17, two separate antisense compounds targeting SRB-1 were synthesized. ISIS 440762 was a 2-10-2 cEt gapmer with all phosphorothioate internucleoside linkages; ISIS 651900 is the same as ISIS 440762, except that it included a **GalNAc$_3$-1** at its 3'-end.

Table 17

Modified ASO targeting ApoC III and SRB-1

ASO	Sequence (5' to 3')	Target	CalCd Mass	Observed Mass	SEQ ID No.
ISIS 304801	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	ApoC III	7165.4	7164.4	32
ISIS 647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{eo}\mathbf{A_{do}}$'-**GalNAc$_3-1_a$**	ApoC III	9239.5	9237.8	111
ISIS 647536	$A_{es}G_{eo}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{eo}T_{eo}T_{es}A_{es}T_{eo}\mathbf{A_{do}}$'-**GalNAc$_3-1_a$**	ApoC III	9142.9	9140.8	111

ISIS 440762	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	SRB-1	4647.0	4646.4	104
ISIS 651900	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	SRB-1	6721.1	6719.4	112

Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "k" indicates 6'-*(S)*-CH_3 bicyclic nucleoside (e.g. cEt); "s" indicates phosphorothioate internucleoside linkages (PS); "o" indicates phosphodiester internucleoside linkages (PO); and "o'" indicates -O-P(=O)(OH)-. Superscript "m" indicates 5-methylcytosines. "**GalNAc$_3$-1**" indicates a conjugate group having the structure shown previously in Example 9. Note that **GalNAc$_3$-1** comprises a cleavable adenosine which links the ASO to remainder of the conjugate, which is designated "**GalNAc$_3$-1$_a$.**" This nomenclature is used in the above table to show the full nucleobase sequence, including the adenosine, which is part of the conjugate. Thus, in the above table, the sequences could also be listed as ending with "**GalNAc$_3$-1**" with the "**A$_{do}$**" omitted. This convention of using the subscript "a" to indicate the portion of a conjugate group lacking a cleavable nucleoside or cleavable moiety is used throughout these Examples. This portion of a conjugate group lacking the cleavable moiety is referred to herein as a "cluster" or "conjugate cluster" or "GalNAc$_3$ cluster." In certain instances it is convenient to describe a conjugate group by separately providing its cluster and its cleavable moiety.

Example 20: Dose-dependent antisense inhibition of human ApoC III in huApoC III transgenic mice

ISIS 304801 and ISIS 647535, each targeting human ApoC III and described above, were separately tested and evaluated in a dose-dependent study for their ability to inhibit human ApoC III in human ApoC III transgenic mice.

Treatment

Human ApoCIII transgenic mice were maintained on a 12-hour light/dark cycle and fed *ad libitum* Teklad lab chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. ASOs were prepared in PBS and sterilized by filtering through a 0.2 micron filter. ASOs were dissolved in 0.9% PBS for injection.

Human ApoC III transgenic mice were injected intraperitoneally once a week for two weeks with ISIS 304801 or 647535 at 0.08, 0.25. 0.75, 2.25 or 6.75 μmol/kg or with PBS as a control. Each treatment group consisted of 4 animals. Forty-eight hours after the administration of the last dose, blood was drawn from each mouse and the mice were sacrificed and tissues were collected.

ApoC III mRNA Analysis

ApoC III mRNA levels in the mice's livers were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. ApoC III 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 ApoC III

mRNA levels for each treatment group, normalized to PBS-treated control and are denoted as "% PBS". The half maximal effective dosage (ED_{50}) of each ASO is also presented in Table 18, below.

As illustrated, both antisense compounds reduced ApoC III RNA relative to the PBS control. Further, the antisense compound conjugated to **$GalNAc_3$-1** (ISIS 647535) was substantially more potent than the antisense compound lacking the **$GalNAc_3$-1** conjugate (ISIS 304801).

Table 18

Effect of ASO treatment on ApoC III mRNA levels in human ApoC III transgenic mice

ASO	Dose (µmol/kg)	% PBS	ED_{50} (µmol/kg)	3' Conjugate	Internucleoside linkage/Length	SEQ ID No.
PBS	0	100	--	-	--	
ISIS 304801	0.08	95	0.77	None	PS/20	32
	0.75	42				
	2.25	32				
	6.75	19				
ISIS 647535	0.08	50	0.074	**$GalNAc_3$-1**	PS/20	111
	0.75	15				
	2.25	17				
	6.75	8				

ApoC III Protein Analysis (Turbidometric Assay)

Plasma ApoC III protein analysis was determined using procedures reported by Graham *et al, Circulation Research,* published online before print March 29, 2013.

Approximately 100 µl of plasma isolated from mice was analyzed without dilution using an Olympus Clinical Analyzer and a commercially available turbidometric ApoC III assay (Kamiya, Cat# KAI-006, Kamiya Biomedical, Seattle, WA). The assay protocol was performed as described by the vendor.

As shown in the Table 19 below, both antisense compounds reduced ApoC III protein relative to the PBS control. Further, the antisense compound conjugated to **$GalNAc_3$-1** (ISIS 647535) was substantially more potent than the antisense compound lacking the **$GalNAc_3$-1** conjugate (ISIS 304801).

Table 19

Effect of ASO treatment on ApoC III plasma protein levels in human ApoC III transgenic mice

ASO	Dose (µmol/kg)	% PBS	ED_{50} (µmol/kg)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	100	--	--	--	
ISIS 304801	0.08	86	0.73	None	PS/20	32
	0.75	51				

	2.25	23				
	6.75	13				
ISIS 647535	0.08	72	0.19	**GalNAc$_3$-1**	PS/20	111
	0.75	14				
	2.25	12				
	6.75	11				

Plasma triglycerides and cholesterol were extracted by the method of Bligh and Dyer (Bligh, E.G. and Dyer, W.J. Can. J. Biochem. Physiol. 37: 911-917, 1959)(Bligh, E and Dyer, W, *Can J Biochem Physiol*, 37, 911-917, 1959)(Bligh, E and Dyer, W, *Can J Biochem Physiol*, 37, 911-917, 1959) and measured by using a Beckmann Coulter clinical analyzer and commercially available reagents.

The triglyceride levels were measured relative to PBS injected mice and are denoted as "% PBS". Results are presented in Table 20. As illustrated, both antisense compounds lowered triglyceride levels. Further, the antisense compound conjugated to **GalNAc$_3$-1** (ISIS 647535) was substantially more potent than the antisense compound lacking the **GalNAc$_3$-1** conjugate (ISIS 304801).

Table 20

Effect of ASO treatment on triglyceride levels in transgenic mice

ASO	Dose (µmol/kg)	% PBS	ED_{50} (µmol/kg)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	100	--	--	--	
ISIS 304801	0.08	87	0.63	None	PS/20	32
	0.75	46				
	2.25	21				
	6.75	12				
ISIS 647535	0.08	65	0.13	**GalNAc$_3$-1**	PS/20	111
	0.75	9				
	2.25	8				
	6.75	9				

Plasma samples were analyzed by HPLC to determine the amount of total cholesterol and of different fractions of cholesterol (HDL and LDL). Results are presented in Tables 21 and 22. As illustrated, both antisense compounds lowered total cholesterol levels; both lowered LDL; and both raised HDL. Further, the antisense compound conjugated to **GalNAc$_3$-1** (ISIS 647535) was substantially more potent than the antisense compound lacking the **GalNAc$_3$-1** conjugate (ISIS 304801). An increase in HDL and a decrease in LDL levels is a cardiovascular beneficial effect of antisense inhibition of ApoC III.

Table 21

Effect of ASO treatment on total cholesterol levels in transgenic mice

ASO	Dose (μmol/kg)	Total Cholesterol (mg/dL)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	257	--	--	
ISIS 304801	0.08	226	None	PS/20	32
	0.75	164			
	2.25	110			
	6.75	82			
ISIS 647535	0.08	230	**GalNAc$_3$-1**	PS/20	111
	0.75	82			
	2.25	86			
	6.75	99			

Table 22

Effect of ASO treatment on HDL and LDL cholesterol levels in transgenic mice

ASO	Dose (μmol/kg)	HDL (mg/dL)	LDL (mg/dL)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	17	28	--	--	
ISIS 304801	0.08	17	23	None	PS/20	32
	0.75	27	12			
	2.25	50	4			
	6.75	45	2			
ISIS 647535	0.08	21	21	**GalNAc$_3$-1**	PS/20	111
	0.75	44	2			
	2.25	50	2			
	6.75	58	2			

Pharmacokinetics Analysis (PK)

The PK of the ASOs was also evaluated. Liver and kidney samples were minced and extracted using standard protocols. Samples were analyzed on MSD1 utilizing IP-HPLC-MS. The tissue level (μg/g) of full-length ISIS 304801 and 647535 was measured and the results are provided in Table 23. As illustrated, liver concentrations of total full-length antisense compounds were similar for the two antisense compounds. Thus, even though the **GalNAc$_3$-1** -conjugated antisense compound is more active in the liver (as demonstrated by the RNA and protein data above), it is not present at substantially higher concentration in the liver. Indeed, the calculated EC_{50} (provided in Table 23) confirms that the observed increase in potency of the conjugated compound cannot be entirely attributed to increased accumulation. This result suggests that

the conjugate improved potency by a mechanism other than liver accumulation alone, possibly by improving the productive uptake of the antisense compound into cells.

The results also show that the concentration of **GalNAc$_3$-1** conjugated antisense compound in the kidney is lower than that of antisense compound lacking the GalNAc 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. These data suggest that **GalNAc$_3$-1** conjugation reduces kidney accumulation.

Table 23

PK analysis of ASO treatment in transgenic mice

ASO	Dose (μmol/kg)	Liver (μg/g)	Kidney (μg/g)	Liver EC_{50} (μg/g)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
ISIS 304801	0.1	5.2	2.1	53	None	PS/20	32
	0.8	62.8	119.6				
	2.3	142.3	191.5				
	6.8	202.3	337.7				
ISIS 647535	0.1	3.8	0.7	3.8	**GalNAc$_3$-1**	PS/20	111
	0.8	72.7	34.3				
	2.3	106.8	111.4				
	6.8	237.2	179.3				

Metabolites of ISIS 647535 were also identified and their masses were confirmed by high resolution mass spectrometry analysis. The cleavage sites and structures of the observed metabolites are shown below. The relative % of full length ASO was calculated using standard procedures and the results are presented in Table 23a. The major metabolite of ISIS 647535 was full-length ASO lacking the entire conjugate (i.e. ISIS 304801), which results from cleavage at cleavage site A, shown below. Further, additional metabolites resulting from other cleavage sites were also observed. These results suggest that introducing other cleavable bonds such as esters, peptides, disulfides, phosphoramidates or acyl-hydrazones between the **GalNAc$_3$-1** sugar and the ASO, which can be cleaved by enzymes inside the cell, or which may cleave in the reductive environment of the cytosol, or which are labile to the acidic pH inside endosomes and lyzosomes, can also be useful.

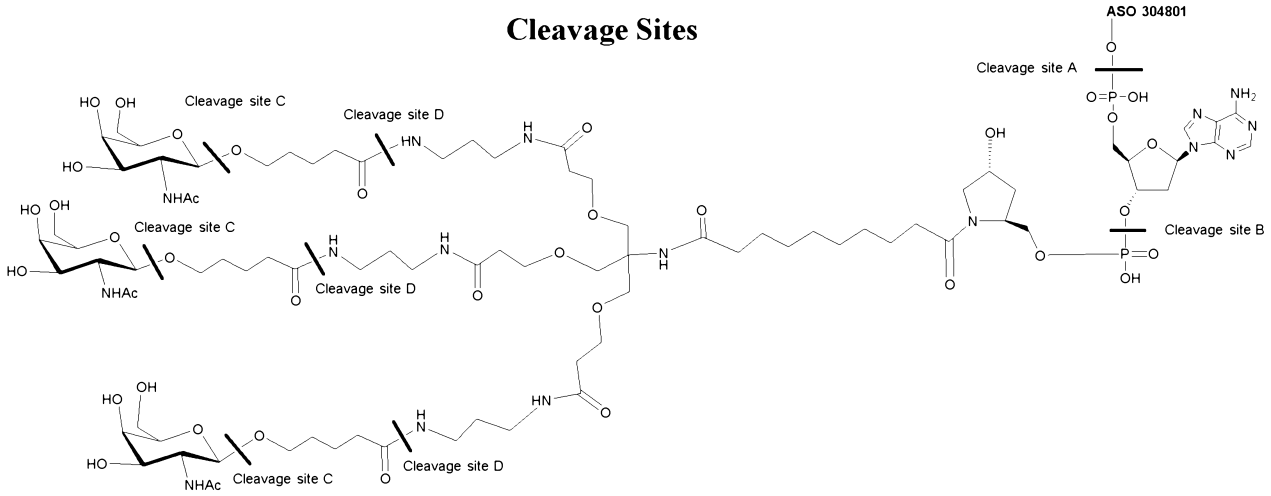
Table 23a

Observed full length metabolites of ISIS 647535

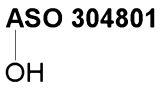
Metabolite	ASO	Cleavage site	Relative %
1	ISIS 304801	A	36.1

2	ISIS 304801 + dA	B	10.5
3	ISIS 647535 minus [3 GalNAc]	C	16.1
4	ISIS 647535 minus [3 GalNAc + 1 5-hydroxy-pentanoic acid tether]	D	17.6
5	ISIS 647535 minus [2 GalNAc + 2 5-hydroxy-pentanoic acid tether]	D	9.9
6	ISIS 647535 minus [3 GalNAc + 3 5-hydroxy-pentanoic acid tether]	D	9.8

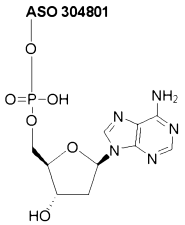
Cleavage Sites

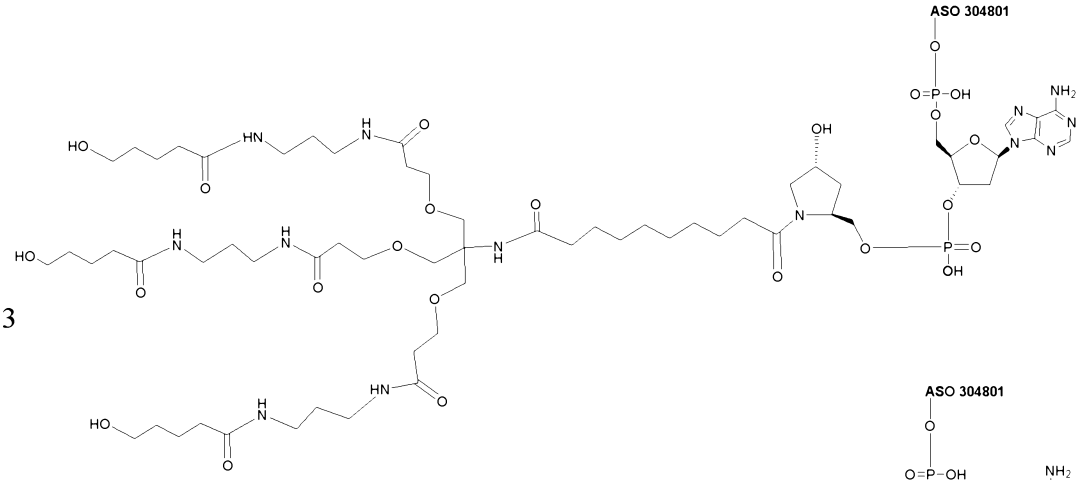


Metabolite 1

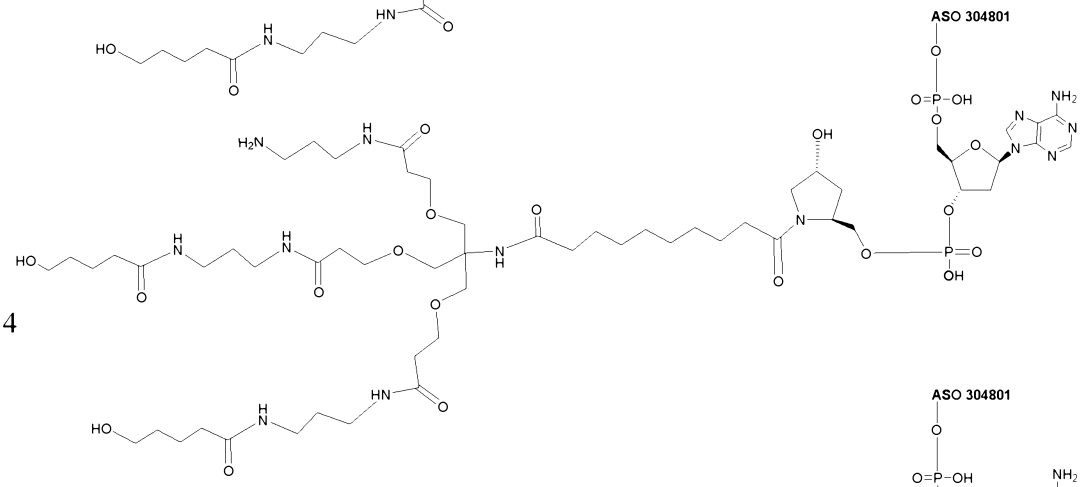


Metabolite 2

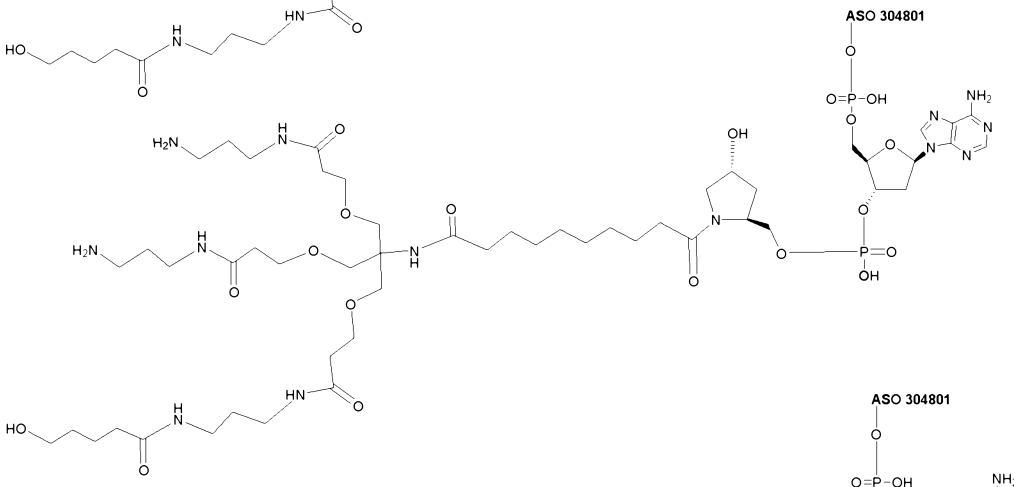




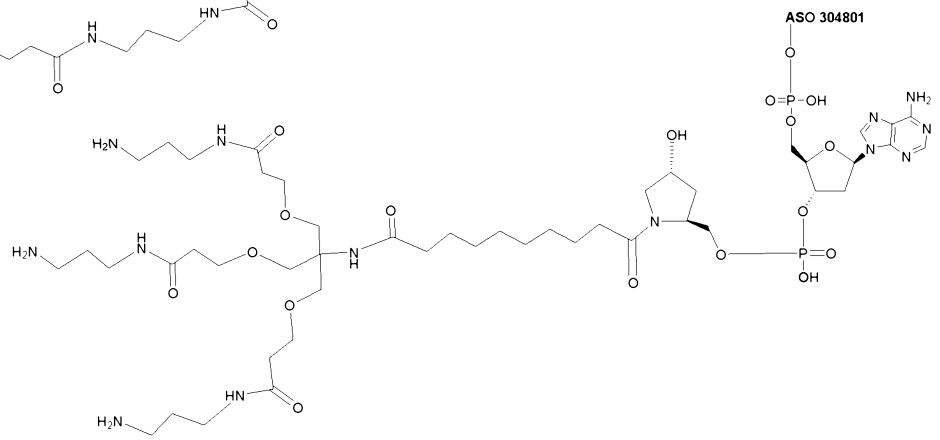
Metabolite 3



Metabolite 4



Metabolite 5



Metabolite 6

Example 21: Antisense inhibition of human ApoC III in human ApoC III transgenic mice in single administration study

ISIS 304801, 647535 and 647536 each targeting human ApoC III and described in Table 17, were further evaluated in a single administration study for their ability to inhibit human ApoC III in human ApoC III transgenic mice.

Treatment

Human ApoCIII transgenic mice were maintained on a 12-hour light/dark cycle and fed *ad libitum* Teklad lab chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. ASOs were prepared in PBS and sterilized by filtering through a 0.2 micron filter. ASOs were dissolved in 0.9% PBS for injection.

Human ApoC III transgenic mice were injected intraperitoneally once at the dosage shown below with ISIS 304801, 647535 or 647536 (described above) or with PBS treated control. The treatment group consisted of 3 animals and the control 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 last administration .

Samples were collected and analyzed to determine the ApoC III mRNA and protein levels in the liver; plasma triglycerides; and cholesterol, including HDL and LDL fractions were assessed as described above (Example 20). Data from those analyses are presented in Tables 24-28, below. Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. The ALT and AST levels showed that the antisense compounds were well tolerated at all administered doses.

These results show improvement in potency for antisense compounds comprising a **GalNAc$_3$-1** conjugate at the 3' terminus (ISIS 647535 and 647536) compared to the antisense compound lacking a **GalNAc$_3$-1** conjugate (ISIS 304801). Further, ISIS 647536, which comprises a **GalNAc$_3$-1** conjugate and some phosphodiester linkages was as potent as ISIS 647535, which comprises the same conjugate and all internucleoside linkages within the ASO are phosphorothioate.

Table 24

Effect of ASO treatment on ApoC III mRNA levels in human ApoC III transgenic mice

ASO	Dose (mg/kg)	% PBS	ED_{50} (mg/kg)	3' Conjugate	Internucleoside linkage/Length	SEQ ID No.
PBS	0	99	--	-	--	
ISIS 304801	1	104	13.2	None	PS/20	32
	3	92				
	10	71				
	30	40				
ISIS	0.3	98	1.9	**GalNAc$_3$-1**	PS/20	111

647535	1	70				
	3	33				
	10	20				
ISIS 647536	0.3	103	1.7	**GalNAc$_3$-1**	PS/PO/20	111
	1	60				
	3	31				
	10	21				

Table 25

Effect of ASO treatment on ApoC III plasma protein levels in human ApoC III transgenic mice

ASO	Dose (mg/kg)	% PBS	ED$_{50}$ (mg/kg)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	99	--	--	--	
ISIS 304801	1	104	23.2	None	PS/20	32
	3	92				
	10	71				
	30	40				
ISIS 647535	0.3	98	2.1	**GalNAc$_3$-1**	PS/20	111
	1	70				
	3	33				
	10	20				
ISIS 647536	0.3	103	1.8	**GalNAc$_3$-1**	PS/PO/20	111
	1	60				
	3	31				
	10	21				

Table 26

Effect of ASO treatment on triglyceride levels in transgenic mice

ASO	Dose (mg/kg)	% PBS	ED$_{50}$ (mg/kg)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	98	--	--	--	
ISIS 304801	1	80	29.1	None	PS/20	32
	3	92				
	10	70				
	30	47				
ISIS 647535	0.3	100	2.2	**GalNAc$_3$-1**	PS/20	111
	1	70				
	3	34				
	10	23				
ISIS	0.3	95	1.9	**GalNAc$_3$-1**	PS/PO/20	111

647536	1	66				
	3	31				
	10	23				

Table 27

Effect of ASO treatment on total cholesterol levels in transgenic mice

ASO	Dose (mg/kg)	% PBS	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	96	--	--	
ISIS 304801	1	104	None	PS/20	32
	3	96			
	10	86			
	30	72			
ISIS 647535	0.3	93	**GalNAc$_3$-1**	PS/20	111
	1	85			
	3	61			
	10	53			
ISIS 647536	0.3	115	**GalNAc$_3$-1**	PS/PO/20	111
	1	79			
	3	51			
	10	54			

Table 28

Effect of ASO treatment on HDL and LDL cholesterol levels in transgenic mice

ASO	Dose (mg/kg)	HDL % PBS	LDL % PBS	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	131	90	--	--	
ISIS 304801	1	130	72	None	PS/20	32
	3	186	79			
	10	226	63			
	30	240	46			
ISIS 647535	0.3	98	86	**GalNAc$_3$-1**	PS/20	111
	1	214	67			
	3	212	39			
	10	218	35			
ISIS 647536	0.3	143	89	**GalNAc$_3$-1**	PS/PO/20	111
	1	187	56			
	3	213	33			
	10	221	34			

These results confirm that the **GalNAc$_3$-1** conjugate improves potency of an antisense compound. The results also show equal potency of a **GalNAc$_3$-1** conjugated antisense compounds where the antisense oligonucleotides have mixed linkages (ISIS 647536 which has six phosphodiester linkages) and a full phosphorothioate version of the same antisense compound (ISIS 647535).

Phosphorothioate linkages provide several properties to antisense compounds. For example, they resist nuclease digestion and they bind proteins resulting in accumulation of compound in the liver, rather than in the kidney/urine. These are desirable properties, particularly when treating an indication in the liver. However, phosphorothioate linkages have also been associated with an inflammatory response. Accordingly, reducing the number of phosphorothioate linkages in a compound is expected to reduce the risk of inflammation, but also lower concentration of the compound in liver, increase concentration in the kidney and urine, decrease stability in the presence of nucleases, and lower overall potency. The present results show that a **GalNAc$_3$-1** conjugated antisense compound where certain phosphorothioate linkages have been replaced with phosphodiester linkages is as potent against a target in the liver as a counterpart having full phosphorothioate linkages. Such compounds are expected to be less proinflammatory (See Example 24 describing an experiment showing reduction of PS results in reduced inflammatory effect).

Example 22: Effect of GalNAc$_3$-1 conjugated modified ASO targeting SRB-1 *in vivo*

ISIS 440762 and 651900, each targeting SRB-1 and described in Table 17, were evaluated in a dose-dependent study for their ability to inhibit SRB-1 in Balb/c mice.

Treatment

Six week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 440762, 651900 or with PBS treated control. Each treatment group consisted of 4 animals. The mice were sacrificed 48 hours following the final administration to determine the SRB-1 mRNA levels in liver 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 PBS-treated control and is denoted as "% PBS".

As illustrated in Table 29, both antisense compounds lowered SRB-1 mRNA levels. Further, the antisense compound comprising the **GalNAc$_3$-1** conjugate (ISIS 651900) was substantially more potent than the antisense compound lacking the **GalNAc$_3$-1** conjugate (ISIS 440762). These results demonstrate that the potency benefit of **GalNAc$_3$-1** conjugates are observed using antisense oligonucleotides complementary to a different target and having different chemically modified nucleosides, in this instance modified nucleosides comprise constrained ethyl sugar moieties (a bicyclic sugar moiety).

Table 29

Effect of ASO treatment on SRB-1 mRNA levels in Balb/c mice

ASO	Dose (mg/kg)	Liver % PBS	ED_{50} (mg/kg)	3' Conjugate		Internucleoside linkage/Length	SEQ ID No.
PBS	0	100		-		--	
ISIS 440762	0.7	85	2.2	None		PS/14	104
	2	55					
	7	12					
	20	3					
ISIS 651900	0.07	98	0.3	**$GalNAc_3$-1**		PS/14	112
	0.2	63					
	0.7	20					
	2	6					
	7	5					

Example 23: Human Peripheral Blood Mononuclear Cells (hPBMC) Assay Protocol

The hPBMC assay was performed using BD Vautainer CPT tube method. A sample of whole blood from volunteered donors with informed consent at US HealthWorks clinic (Faraday & El Camino Real, Carlsbad) was obtained and collected in 4-15 BD Vacutainer CPT 8 ml tubes (VWR Cat.# BD362753). The approximate starting total whole blood volume in the CPT tubes for each donor was recorded using the PBMC assay data sheet.

The blood sample was remixed immediately prior to centrifugation by gently inverting tubes 8-10 times. CPT tubes were centrifuged at rt (18-25 °C) in a horizontal (swing-out) rotor for 30 min. at 1500-1800 RCF with brake off (2700 RPM Beckman Allegra 6R). The cells were retrieved from the buffy coat interface (between Ficoll and polymer gel layers); transferred to a sterile 50 ml conical tube and pooled up to 5 CPT tubes/50 ml conical tube/donor. The cells were then washed twice with PBS (Ca^{++}, Mg^{++} free; GIBCO). The tubes were topped up to 50 ml and mixed by inverting several times. The sample was then centrifuged at 330 x g for 15 minutes at rt (1215 RPM in Beckman Allegra 6R) and aspirated as much supernatant as possible without disturbing pellet. The cell pellet was dislodged by gently swirling tube and resuspended cells in RPMI+10% FBS+pen/strep (~1 ml / 10 ml starting whole blood volume). A 60 µl sample was pipette into a sample vial (Beckman Coulter) with 600 µl VersaLyse reagent (Beckman Coulter Cat# A09777) and was gently vortexed for 10-15 sec. The sample was allowed to incubate for 10 min. at rt and being mixed again before counting. The cell suspension was counted on Vicell XR cell viability analyzer (Beckman Coulter) using PBMC cell type (dilution factor of 1:11 was stored with other parameters). The live cell/ml and viability were recorded. The cell suspension was diluted to 1 x 10^7 live PBMC/ml in RPMI+ 10% FBS+pen/strep.

The cells were plated at 5 x 10^5 in 50 µl/well of 96-well tissue culture plate (Falcon Microtest). 50 µl/well of 2x concentration oligos/controls diluted in RPMI+10% FBS+pen/strep. was added according to experiment template (100 µl/well total). Plates were placed on the shaker and allowed to mix for approx. 1 min. After being incubated for 24 hrs at 37 °C; 5% CO_2, the plates were centrifuged at 400 x g for 10 minutes before removing the supernatant for MSD cytokine assay (i.e. human IL-6, IL-10, IL-8 and MCP-1).

Example 24: Evaluation of Proinflammatory Effects in hPBMC Assay for GalNAc$_3$-1 conjugated ASOs

The antisense oligonucleotides (ASOs) listed in Table 30 were evaluated for proinflammatory effect in hPBMC assay using the protocol described in Example 23. ISIS 353512 is an internal standard known to be a high responder for IL-6 release in the assay. The hPBMCs were isolated from fresh, volunteered donors and were treated with ASOs at 0, 0.0128, 0.064, 0.32, 1.6, 8, 40 and 200 µM concentrations. After a 24 hr treatment, the cytokine levels were measured.

The levels of IL-6 were used as the primary readout. The EC_{50} and E_{max} was calculated using standard procedures. Results are expressed as the average ratio of E_{max}/EC_{50} from two donors and is denoted as "E_{max}/EC_{50}." The lower ratio indicates a relative decrease in the proinflammatory response and the higher ratio indicates a relative increase in the proinflammatory response.

With regard to the test compounds, the least proinflammatory compound was the PS/PO linked ASO (ISIS 616468). The **GalNAc$_3$-1** conjugated ASO, ISIS 647535 was slightly less proinflammatory than its non-conjugated counterpart ISIS 304801. These results indicate that incorporation of some PO linkages reduces proinflammatory reaction and addition of a **GalNAc$_3$-1** conjugate does not make a compound more proinflammatory and may reduce proinflammatory response. Accordingly, one would expect that an antisense compound comprising both mixed PS/PO linkages and a **GalNAc$_3$-1** conjugate would produce lower proinflammatory responses relative to full PS linked antisense compound with or without a **GalNAc$_3$-1** conjugate. These results show that **GalNAc$_3$-1** conjugated antisense compounds, particularly those having reduced PS content are less proinflammatory.

Together, these results suggest that a **GalNAc$_3$-1** conjugated compound, particularly one with reduced PS content, can be administered at a higher dose than a counterpart full PS antisense compound lacking a **GalNAc$_3$-1** conjugate. Since half-life is not expected to be substantially different for these compounds, such higher administration would result in less frequent dosing. Indeed such administration could be even less frequent, because the **GalNAc$_3$-1** conjugated compounds are more potent (See Examples 20-22) and re-dosing is necessary once the concentration of a compound has dropped below a desired level, where such desired level is based on potency.

Table 30

Modified ASOs

ASO	Sequence (5' to 3')	Target	SEQ ID No.
ISIS 104838	$G_{es}{}^{m}C_{es}T_{es}G_{es}A_{es}T_{ds}T_{ds}A_{ds}G_{ds}A_{ds}G_{ds}$ $A_{ds}G_{ds}A_{ds}G_{ds}G_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	TNFα	105
ISIS 353512	$T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{ds}A_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}$ $G_{ds}A_{ds}G_{ds}A_{ds}{}^{m}C_{ds}{}^{m}C_{ds}T_{es}G_{es}G_{e}$	CRP	106
ISIS 304801	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	ApoC III	32
ISIS 647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	ApoC III	111
ISIS 616468	$A_{es}G_{eo}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{eo}T_{eo}T_{es}A_{es}T_{e}$	ApoC III	32

Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "k" indicates 6'-*(S)*-CH_3 bicyclic nucleoside (e.g. cEt); "s" indicates phosphorothioate internucleoside linkages (PS); "o" indicates phosphodiester internucleoside linkages (PO); and "o'" indicates -O-P(=O)(OH)-. Superscript "m" indicates 5-methylcytosines. "**$A_{do'}$-GalNAc$_3$-1$_a$**" indicates a conjugate having the structure **GalNAc$_3$-1** shown in Example 9 attached to the 3'-end of the antisense oligonucleotide, as indicated.

Table 31

Proinflammatory Effect of ASOs targeting ApoC III in hPBMC assay

ASO	EC_{50} (μM)	E_{max} (μM)	E_{max}/EC_{50}	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
ISIS 353512 (high responder)	0.01	265.9	26,590	None	PS/20	106
ISIS 304801	0.07	106.55	1,522	None	PS/20	32
ISIS 647535	0.12	138	1,150	**GalNAc$_3$-1**	PS/20	111
ISIS 616468	0.32	71.52	224	None	PS/PO/20	32

Example 25: Effect of GalNAc$_3$-1 conjugated modified ASO targeting human ApoC III *in vitro*

ISIS 304801 and 647535 described above were tested *in vitro*. Primary hepatocyte cells from transgenic mice at a density of 25,000 cells per well were treated with 0.03,0.08, 0.24, 0.74, 2.22, 6.67 and 20 μM concentrations of modified oligonucleotides. After a treatment period of approximately 16 hours, RNA

was isolated from the cells and mRNA levels were measured by quantitative real-time PCR and the hApoC III mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN.

The IC_{50} was calculated using the standard methods and the results are presented in Table 32. As illustrated, comparable potency was observed in cells treated with ISIS 647535 as compared to the control, ISIS 304801.

Table 32

Modified ASO targeting human ApoC III in primary hepatocytes

ASO	IC_{50} (μM)	3' Conjugate	Internucleoside linkage/Length	SEQ ID No.
ISIS 304801	0.44	None	PS/20	32
ISIS 647535	0.31	**$GalNAc_3$-1**	PS/20	111

In this experiment, the large potency benefits of **$GalNAc_3$-1** conjugation that are observed *in vivo* were not observed *in vitro*. Subsequent free uptake experiments in primary hepatocytes *in vitro* did show increased potency of oligonucleotides comprising various GalNAc conjugates relative to oligonucleotides that lacking the GalNAc conjugate.(see Examples 60, 82, and 92)

Example 26: Effect of PO/PS linkages on ApoC III ASO Activity

Human ApoC III transgenic mice were injected intraperitoneally once at 25 mg/kg of ISIS 304801, or ISIS 616468 (both described above) or with PBS treated control once per week for two weeks. The treatment group consisted of 3 animals and the control 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 last administration.

Samples were collected and analyzed to determine the ApoC III protein levels in the liver as described above (Example 20). Data from those analyses are presented in Table 33, below.

These results show reduction in potency for antisense compounds with PO/PS (ISIS 616468) in the wings relative to full PS (ISIS 304801).

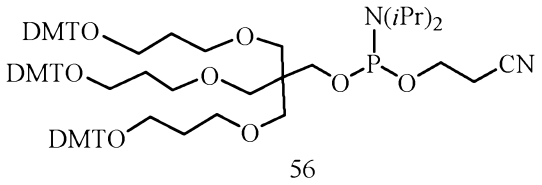
Table 33

Effect of ASO treatment on ApoC III protein levels in human ApoC III transgenic mice

ASO	Dose (mg/kg)	% PBS	3' Conjugate	Internucleoside linkage/Length	SEQ ID No.
PBS	0	99	-	--	

ISIS 304801	25 mg/kg/wk for 2 wks	24	None	Full PS	32
ISIS 616468	25 mg/kg/wk for 2 wks	40	None	14 PS/6 PO	32

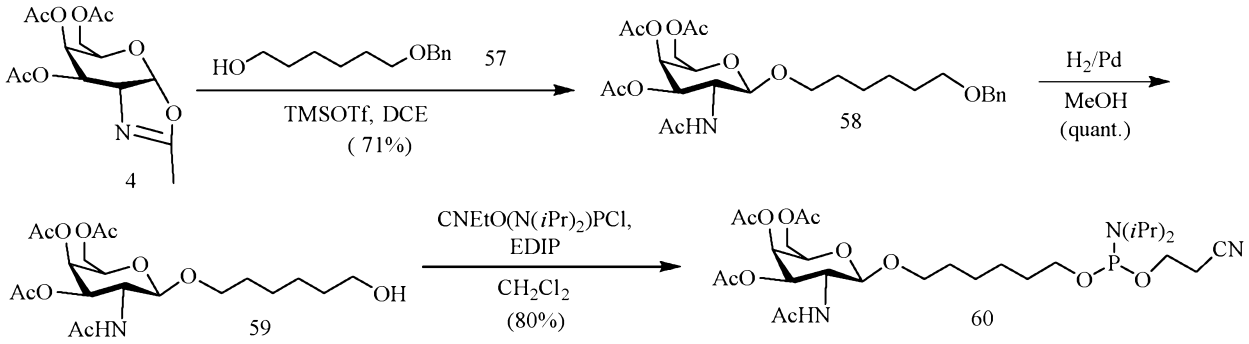
Example 27: Compound 56



56

Compound 56 is commercially available from Glen Research or may be prepared according to published procedures reported by Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

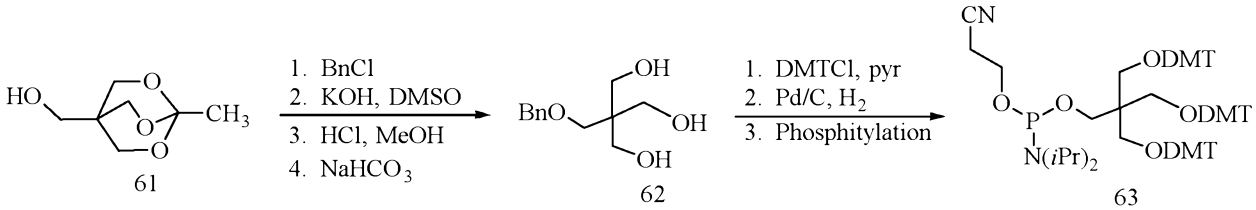
Example 28: Preparation of Compound 60



Compound 4 was prepared as per the procedures illustrated in Example 2. Compound 57 is commercially available. Compound 60 was confirmed by structural analysis.

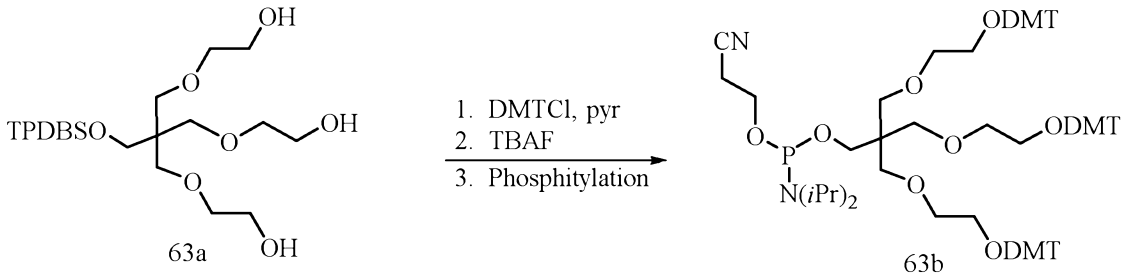
Compound 57 is meant to be representative and not intended to be limiting as other monoprotected substituted or unsubstituted alkyl diols including but not limited to those presented in the specification herein can be used to prepare phosphoramidites having a predetermined composition.

Example 29: Preparation of Compound 63



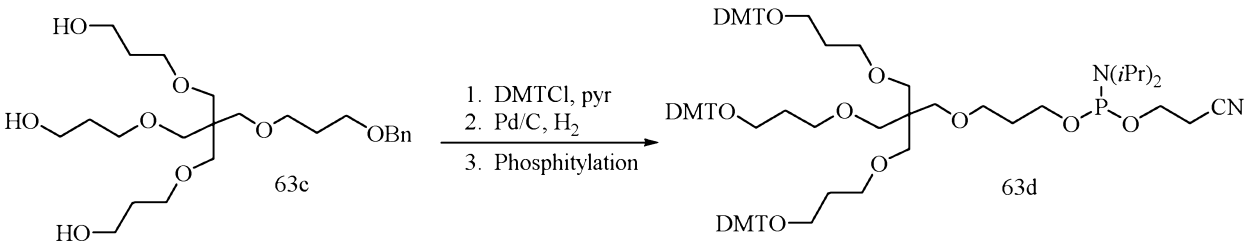
Compounds 61 and 62 are prepared using procedures similar to those reported by Tober *et al., Eur. J. Org. Chem.*, 2013, *3*, 566-577; and Jiang *et al., Tetrahedron,* 2007, *63(19),* 3982-3988.

Alternatively, Compound 63 is prepared using procedures similar to those reported in scientific and patent literature by Kim *et al., Synlett,* 2003, *12,* 1838-1840; and Kim *et al.,* published PCT International Application, WO 2004063208.**Example 30: Preparation of Compound 63b**



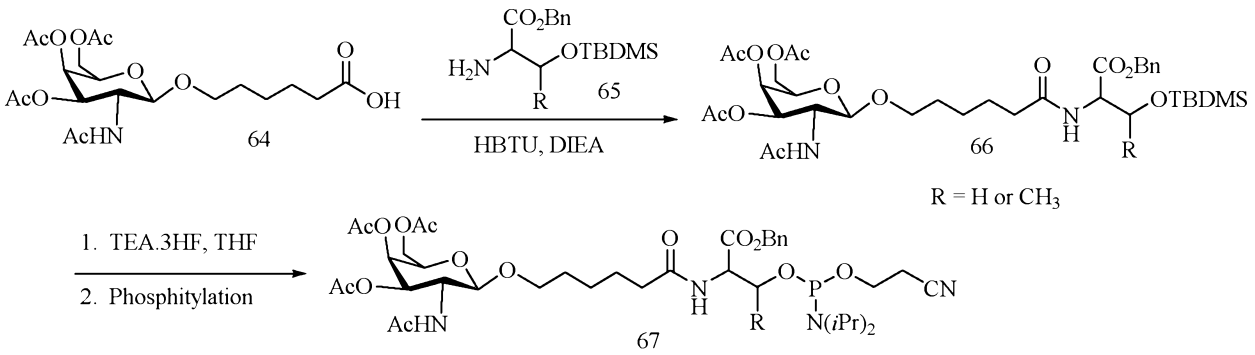
Compound 63a is prepared using procedures similar to those reported by Hanessian *et al., Canadian Journal of Chemistry,* 1996, *74(9),* 1731-1737.

Example 31: Preparation of Compound 63d



Compound 63c is prepared using procedures similar to those reported by Chen *et al., Chinese Chemical Letters,* 1998, *9(5),* 451-453.

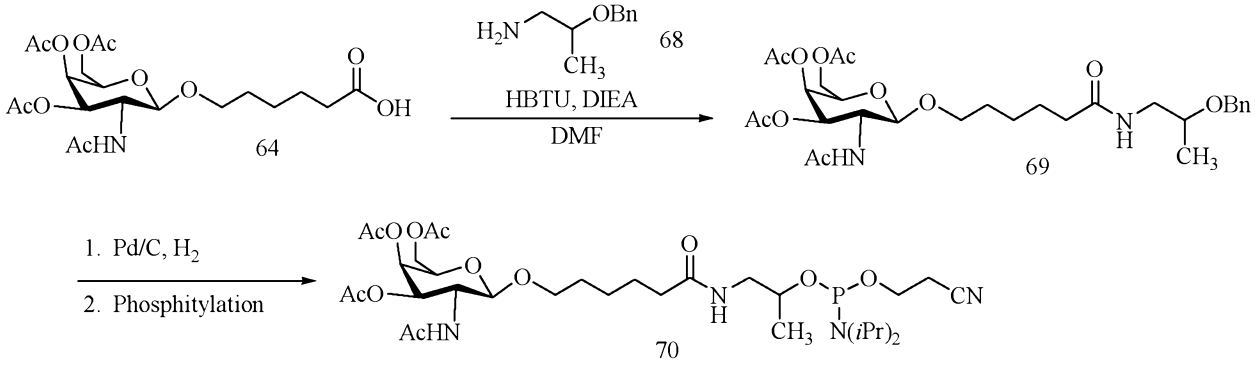
Example 32: Preparation of Compound 67



Compound 64 was prepared as per the procedures illustrated in Example 2. Compound 65 is prepared using procedures similar to those reported by Or *et al.,* published PCT International Application, WO 2009003009. The protecting groups used for Compound 65 are meant to be representative and not

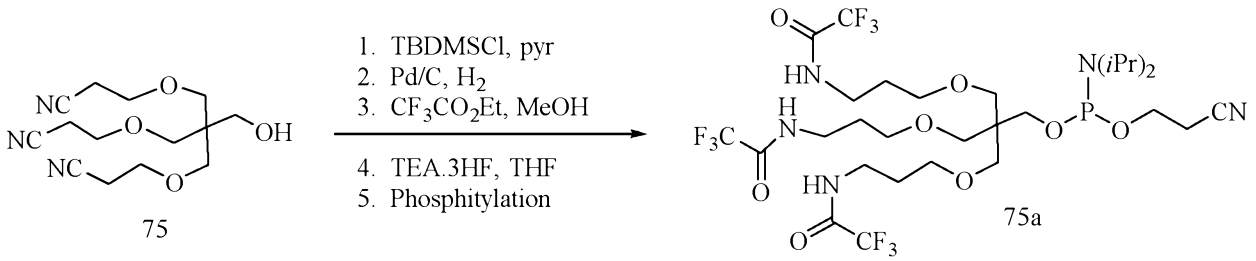
intended to be limiting as other protecting groups including but not limited to those presented in the specification herein can be used.

Example 33: Preparation of Compound 70



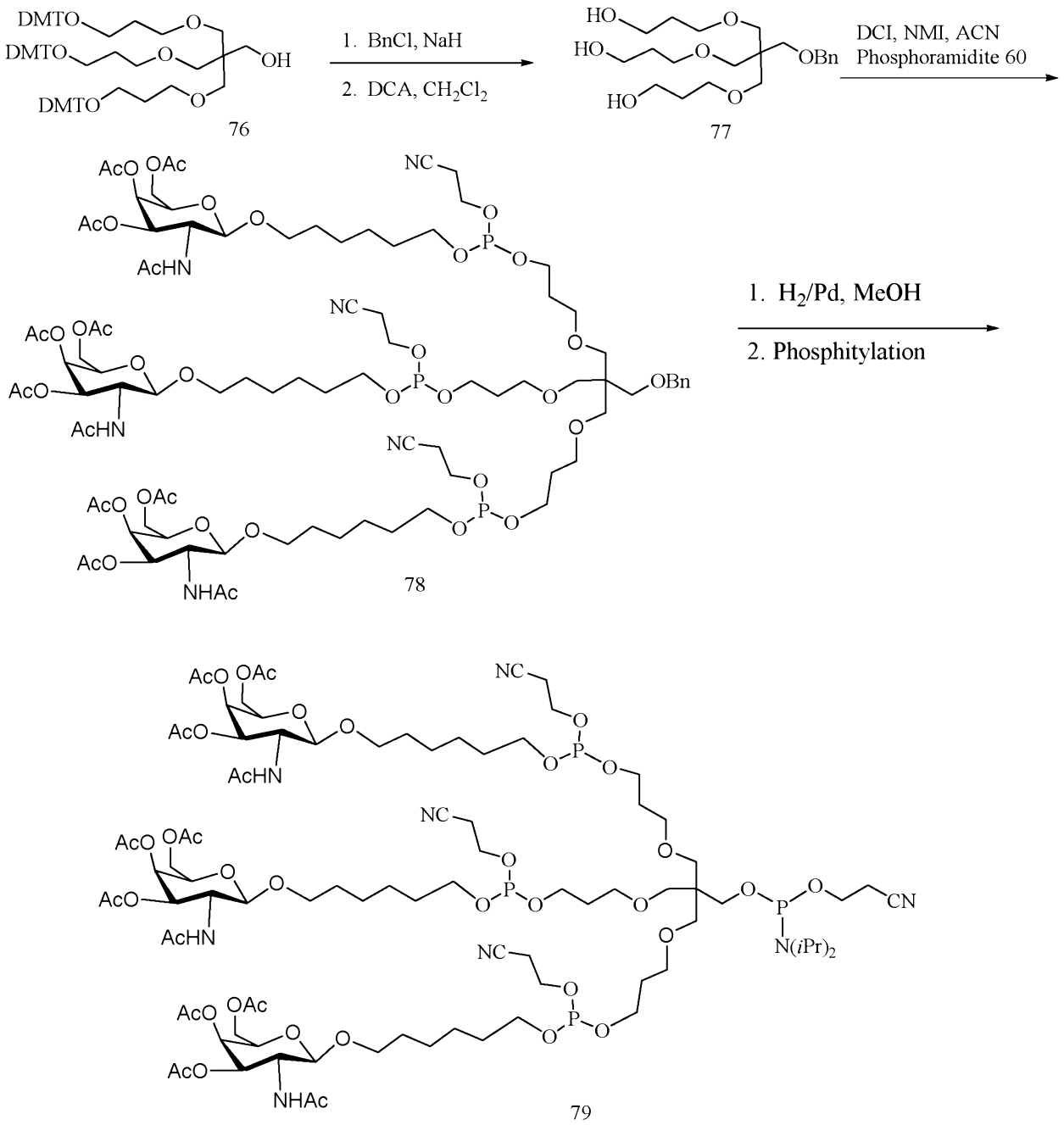
Compound 64 was prepared as per the procedures illustrated in Example 2. Compound 68 is commercially available. The protecting group used for Compound 68 is meant to be representative and not intended to be limiting as other protecting groups including but not limited to those presented in the specification herein can be used.

Example 34: Preparation of Compound 75a



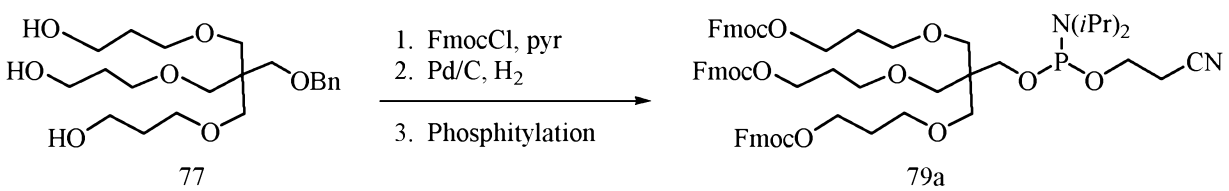
Compound 75 is prepared according to published procedures reported by Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

Example 35: Preparation of Compound 79



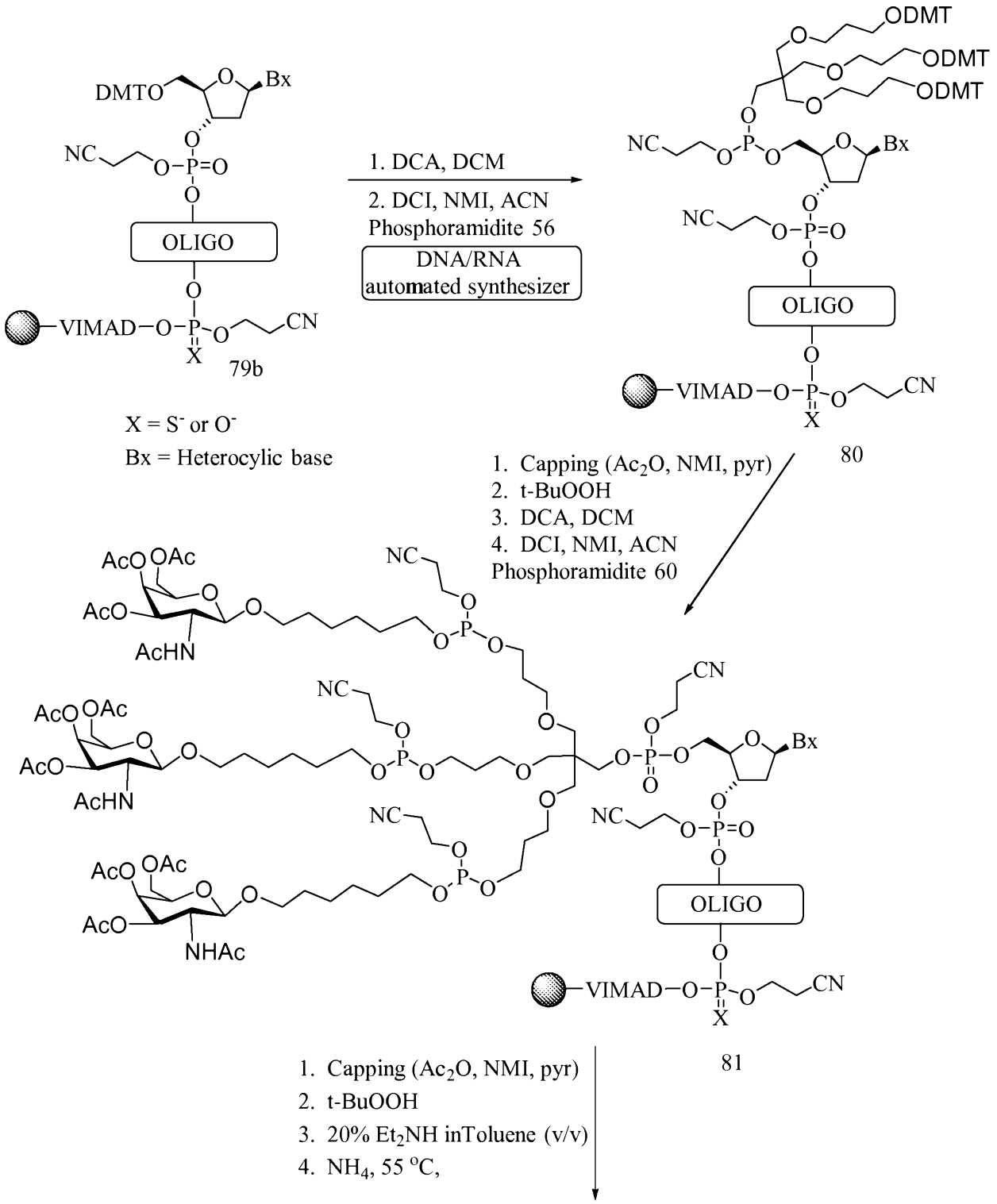
Compound 76 was prepared according to published procedures reported by Shchepinov *et al.*, *Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

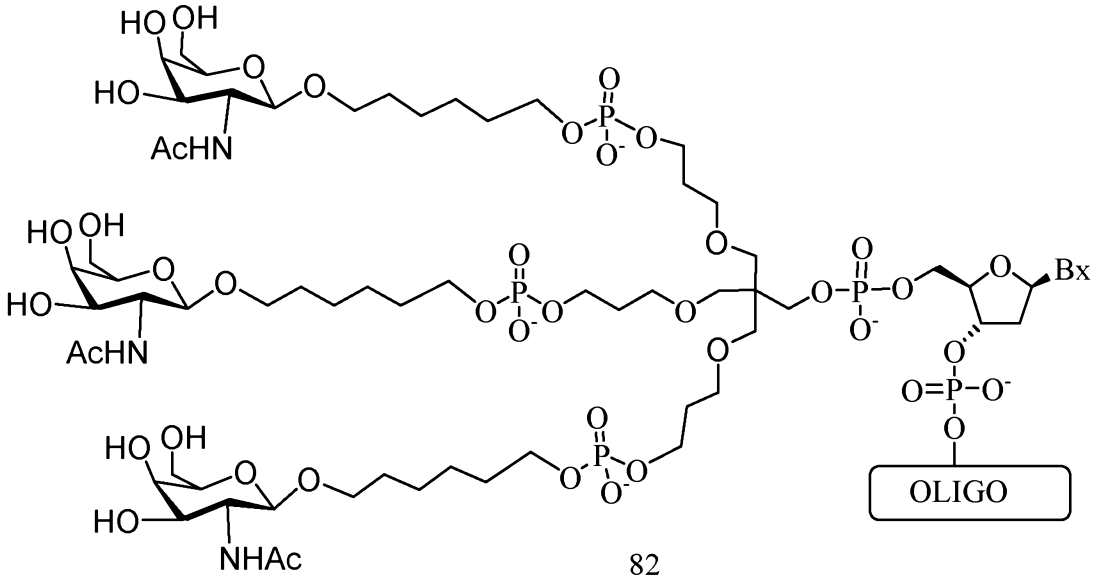
Example 36: Preparation of Compound 79a



Compound 77 is prepared as per the procedures illustrated in Example 35.

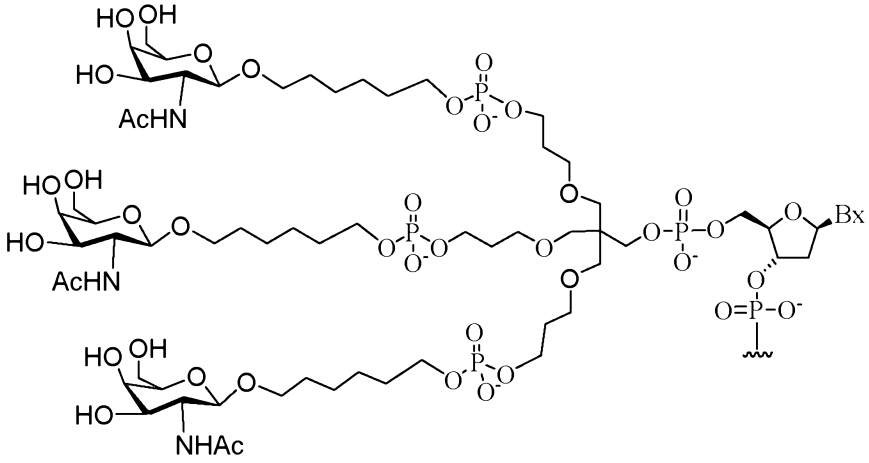
Example 37: General method for the preparation of conjugated oligomeric compound 82 comprising a phosphodiester linked GalNAc$_3$-2 conjugate at 5' terminus *via* solid support (Method I)



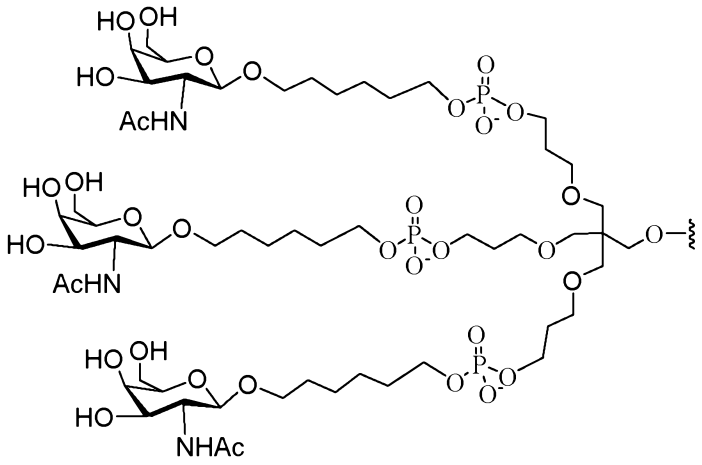


82

wherein GalNAc$_3$-2 has the structure:

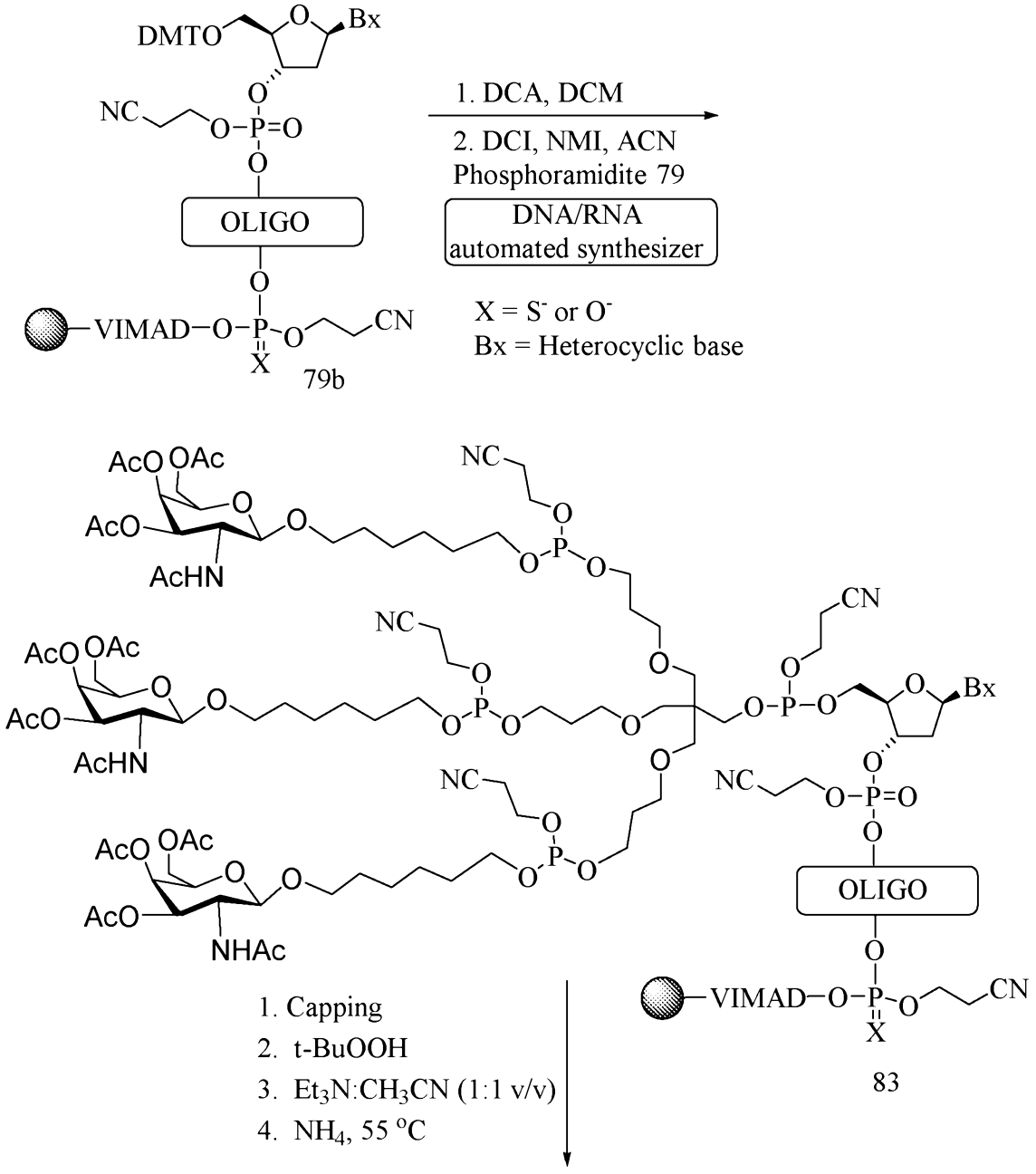


The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-2 (GalNAc$_3$-2$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-2$_a$ has the formula:



The VIMAD-bound oligomeric compound 79b was prepared using standard procedures for automated DNA/RNA synthesis (see Dupouy *et al., Angew. Chem. Int. Ed.,* 2006, *45,* 3623-3627). The phosphoramidite Compounds 56 and 60 were prepared as per the procedures illustrated in Examples 27 and 28, respectively. The phosphoramidites illustrated are meant to be representative and not intended to be limiting as other phosphoramidite building blocks including but not limited those presented in the specification herein can be used to prepare an oligomeric compound having a phosphodiester linked conjugate group at the 5' terminus. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare the oligomeric compounds as described herein having any predetermined sequence and composition.

Example 38: Alternative method for the preparation of oligomeric compound 82 comprising a phosphodiester linked GalNAc$_3$-2 conjugate at 5' terminus (Method II)

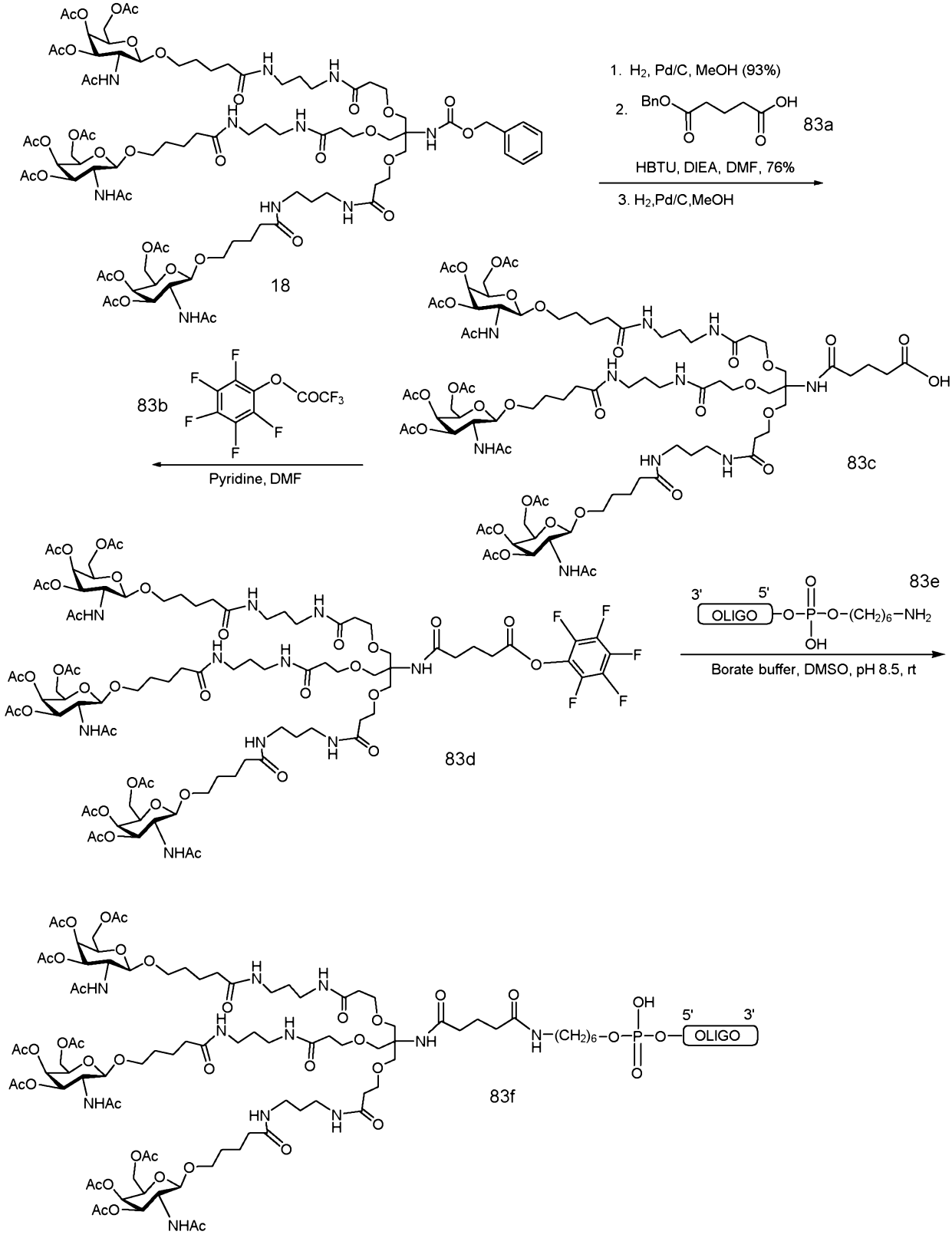


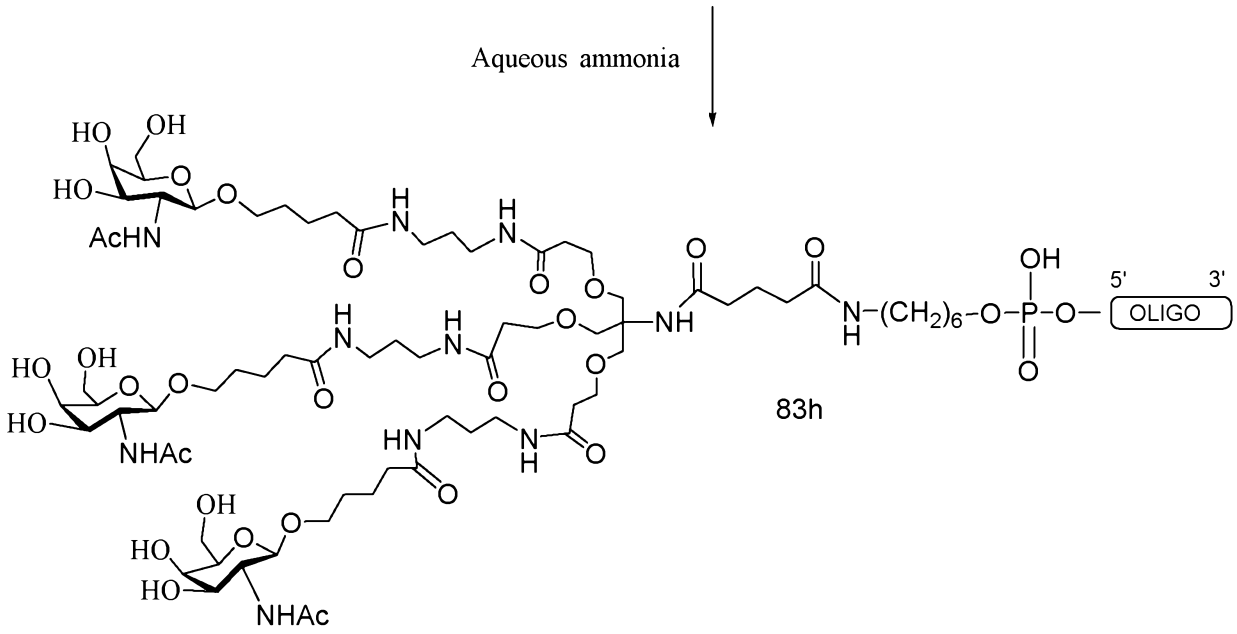
Oligomeric Compound 82

The VIMAD-bound oligomeric compound 79b was prepared using standard procedures for automated DNA/RNA synthesis (see Dupouy *et al., Angew. Chem. Int. Ed.,* 2006, *45,* 3623-3627). The GalNAc$_3$-2 cluster phosphoramidite, Compound 79 was prepared as per the procedures illustrated in Example 35. This alternative method allows a one-step installation of the phosphodiester linked GalNAc$_3$-2 conjugate to the oligomeric compound at the final step of the synthesis. The phosphoramidites illustrated are meant to

be representative and not intended to be limiting, as other phosphoramidite building blocks including but not limited to those presented in the specification herein can be used to prepare oligomeric compounds having a phosphodiester conjugate at the 5' terminus. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare the oligomeric compounds as described herein having any predetermined sequence and composition.

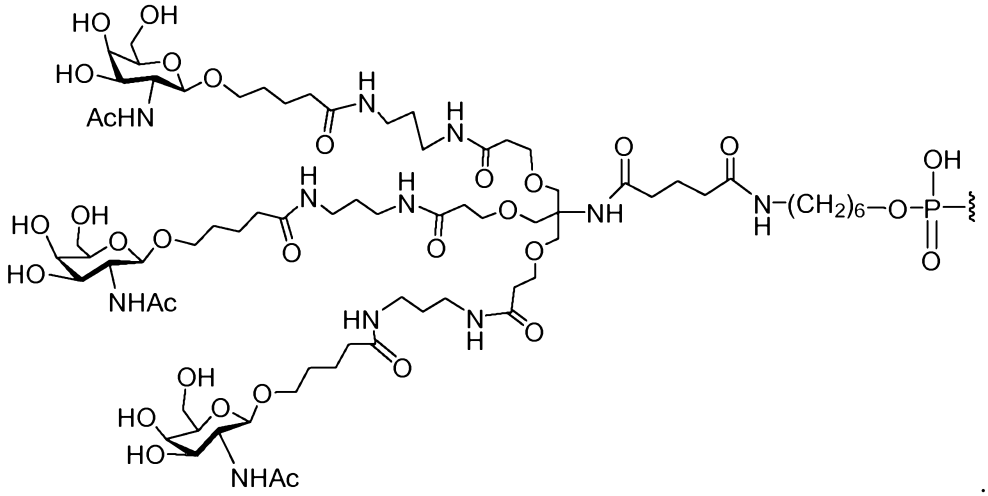
Example 39: General method for the preparation of oligomeric compound 83h comprising a $GalNAc_3$-3 Conjugate at the 5' Terminus ($GalNAc_3$-1 modified for 5' end attachment) *via* Solid Support



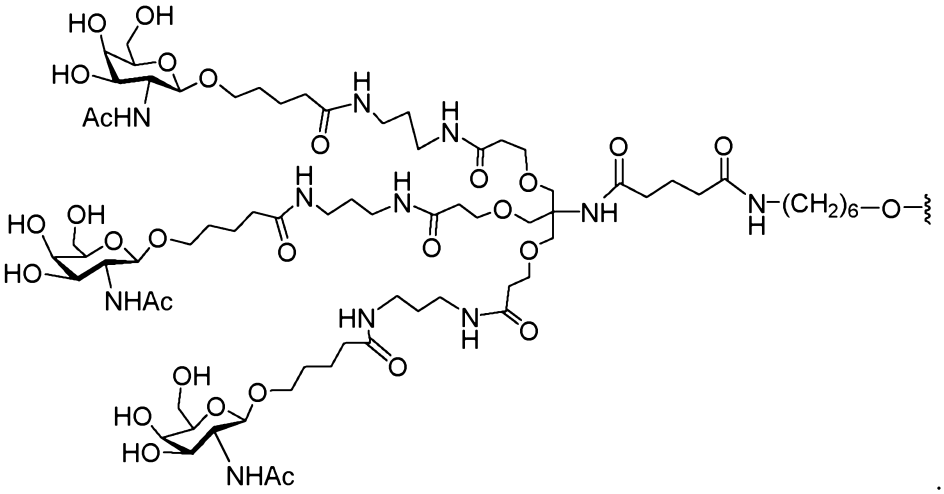


Compound 18 was prepared as per the procedures illustrated in Example 4. Compounds 83a and 83b are commercially available. Oligomeric Compound 83e comprising a phosphodiester linked hexylamine was prepared using standard oligonucleotide synthesis procedures. Treatment of the protected oligomeric compound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

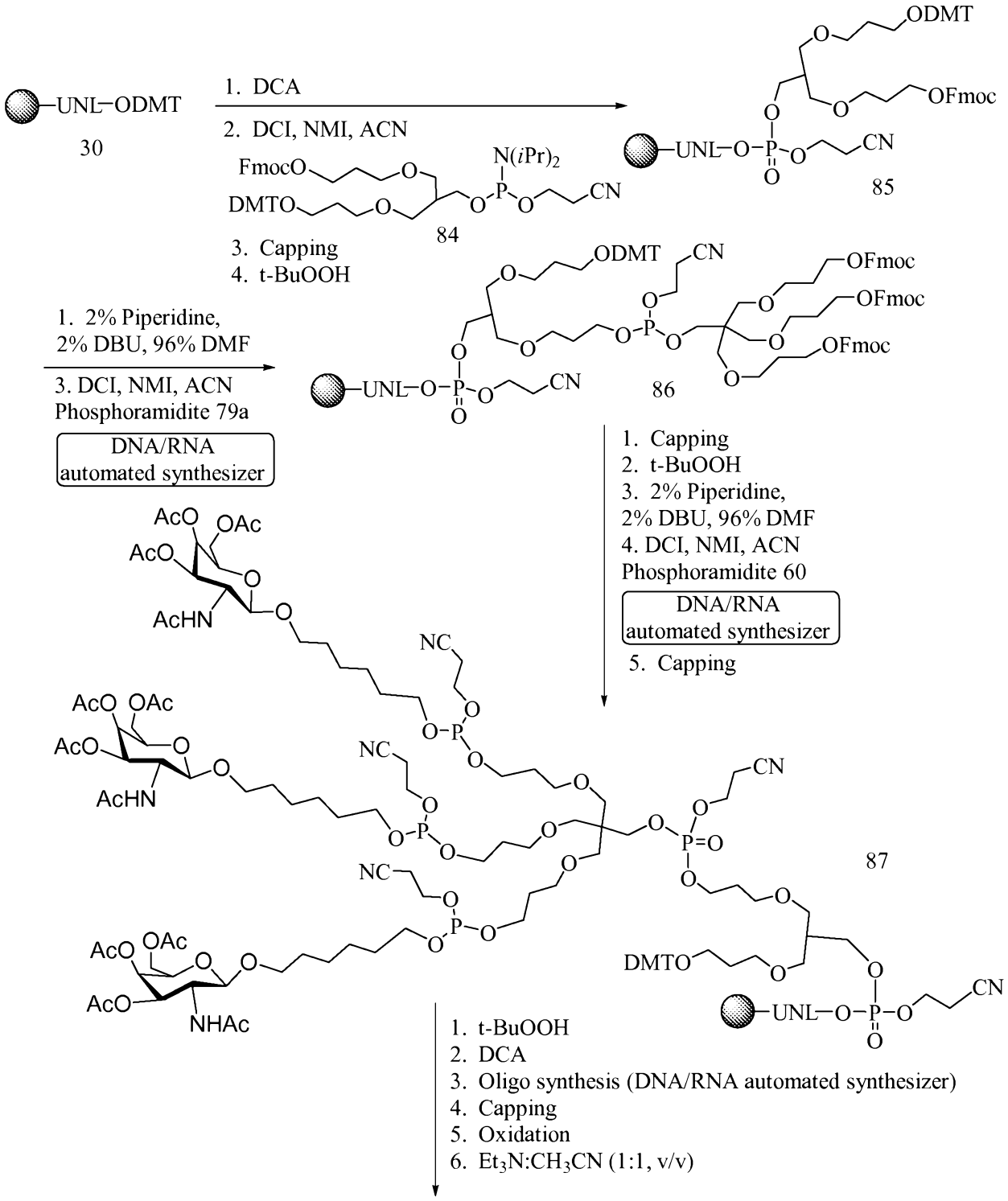
Wherein GalNAc$_3$-3 has the structure:

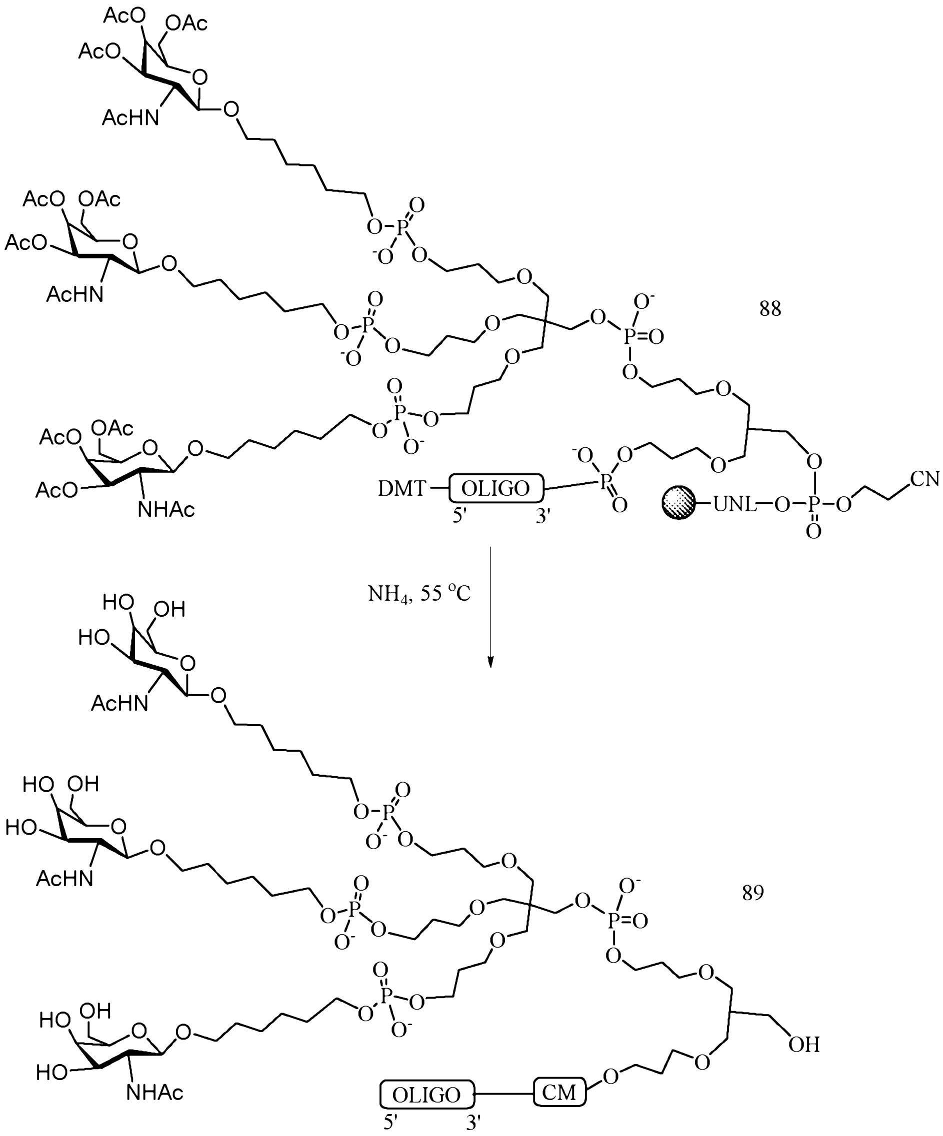


The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-3 (GalNAc$_3$-3$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-3$_a$ has the formula:

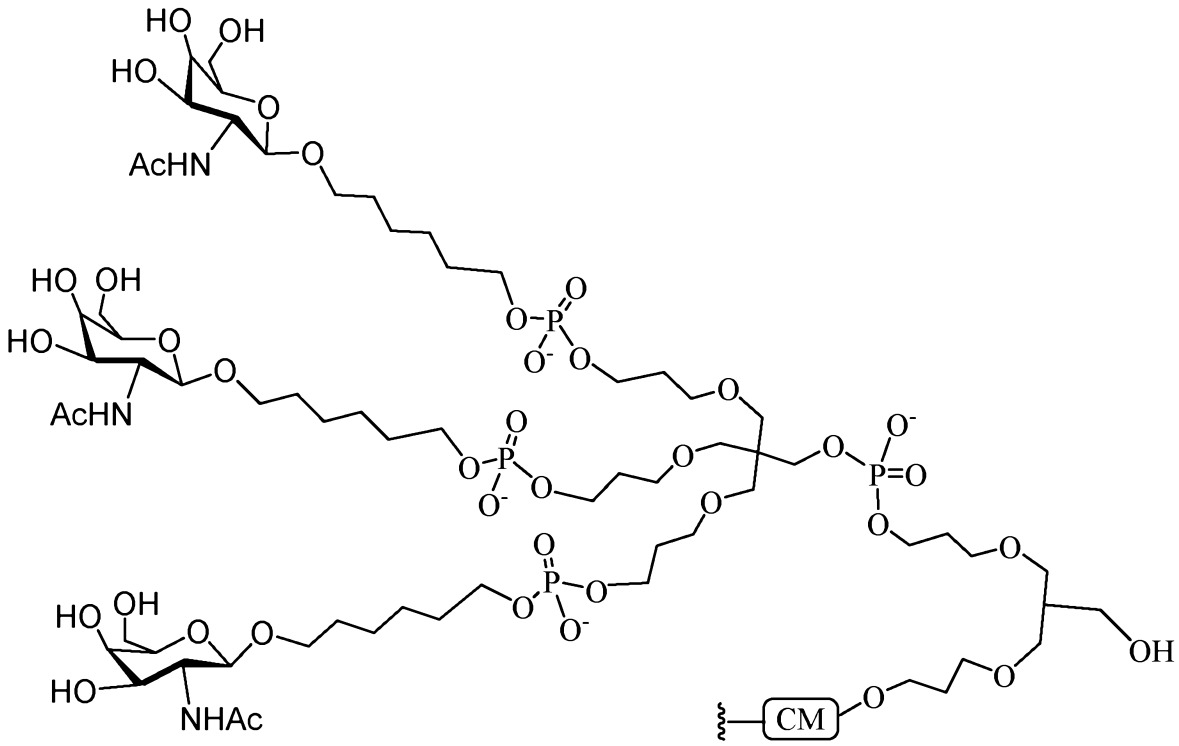


Example 40: General method for the preparation of oligomeric compound 89 comprising a phosphodiester linked GalNAc$_3$-4 conjugate at the 3' terminus *via* solid support

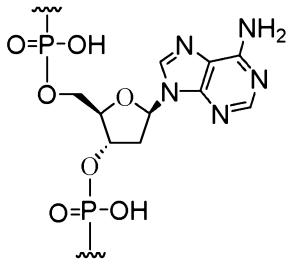



AcO
OAc
AcO
O
AcHN
O
88
DMT
OLIGO
5'
3'
UNL
CN
NHAc
NH_4, 55 °C
HO
OH
89
CM
OH

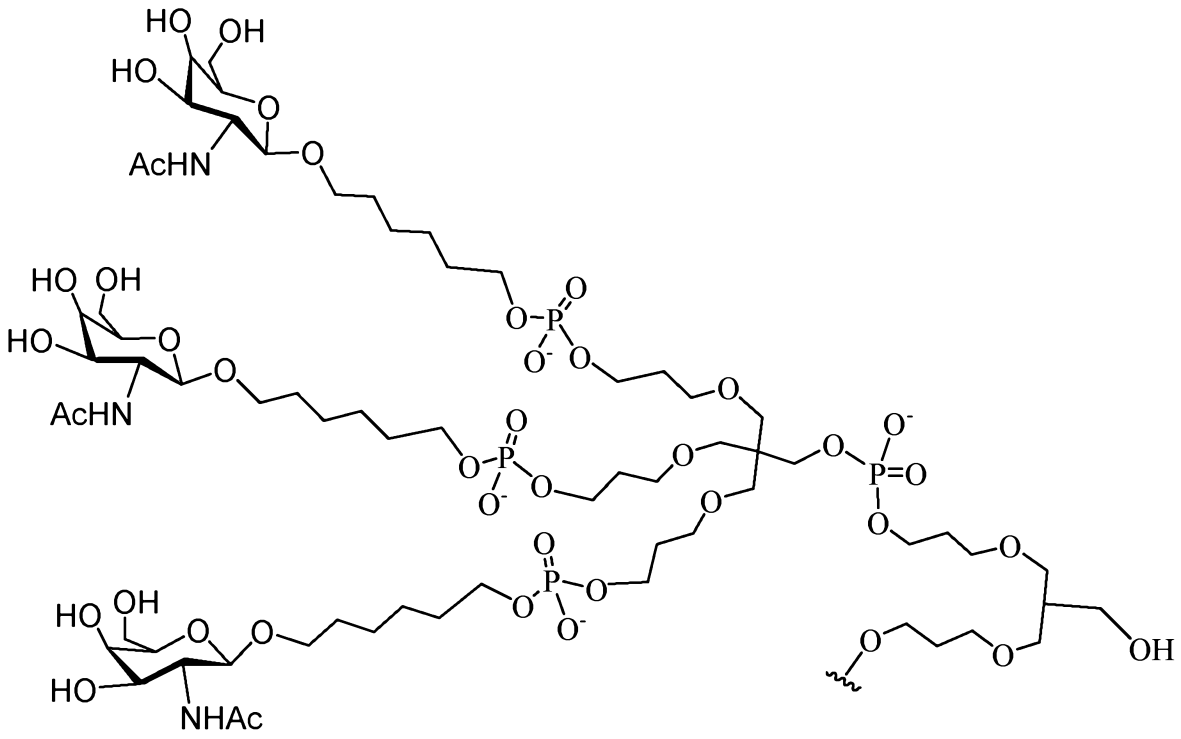
Wherein $GalNAc_3$-4 has the structure:



Wherein CM is a cleavable moiety. In certain embodiments, cleavable moiety is:



The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-4 ($GalNAc_3$-4_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein $GalNAc_3$-4_a has the formula:



The protected Unylinker functionalized solid support Compound 30 is commercially available. Compound 84 is prepared using procedures similar to those reported in the literature (*see* Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454; Shchepinov *et al., Nucleic Acids Research,* 1999, *27*, 3035-3041; and Hornet *et al., Nucleic Acids Research,* 1997, *25*, 4842-4849).

The phosphoramidite building blocks, Compounds 60 and 79a are prepared as per the procedures illustrated in Examples 28 and 36. The phosphoramidites illustrated are meant to be representative and not intended to be limiting as other phosphoramidite building blocks can be used to prepare an oligomeric compound having a phosphodiester linked conjugate at the 3' terminus with a predetermined sequence and composition. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare the oligomeric compounds as described herein having any predetermined sequence and composition.

Example 41: General method for the preparation of ASOs comprising a phosphodiester linked GalNAc$_3$-2 (see Example 37, Bx is adenine) conjugate at the 5' position *via* solid phase techniques (preparation of ISIS 661134)

Unless otherwise stated, all reagents and solutions used for the synthesis of oligomeric compounds are purchased from commercial sources. Standard phosphoramidite building blocks and solid support are used for incorporation nucleoside residues which include for example T, A, G, and ^{m}C residues. Phosphoramidite compounds 56 and 60 were used to synthesize the phosphodiester linked GalNAc$_3$-2

conjugate at the 5' terminus. A 0.1 M solution of phosphoramidite in anhydrous acetonitrile was used for β-D-2'-deoxyribonucleoside and 2'-MOE.

The ASO syntheses were performed on ABI 394 synthesizer (1-2 µmol scale) or on GE Healthcare Bioscience ÄKTA oligopilot synthesizer (40-200 µmol scale) by the phosphoramidite coupling method on VIMAD solid support (110 µmol/g, Guzaev *et al.*, 2003) packed in the column. For the coupling step, the phosphoramidites were delivered at a 4 fold excess over the initial loading of the solid support and phosphoramidite coupling was carried out for 10 min. All other steps followed standard protocols supplied by the manufacturer. A solution of 6% dichloroacetic acid in toluene was used for removing the dimethoxytrityl (DMT) groups from 5'-hydroxyl groups of the nucleotide. 4,5-Dicyanoimidazole (0.7 M) in anhydrous CH_3CN was used as activator during the coupling step. Phosphorothioate linkages were introduced by sulfurization with 0.1 M solution of xanthane hydride in 1:1 pyridine/CH_3CN for a contact time of 3 minutes. A solution of 20% *tert*-butylhydroperoxide in CH_3CN containing 6% water was used as an oxidizing agent to provide phosphodiester internucleoside linkages with a contact time of 12 minutes.

After the desired sequence was assembled, the cyanoethyl phosphate protecting groups were deprotected using a 20% diethylamine in toluene (v/v) with a contact time of 45 minutes. The solid-support bound ASOs were suspended in aqueous ammonia (28-30 wt %) and heated at 55 °C for 6 h.

The unbound ASOs were then filtered and the ammonia was boiled off. The residue was purified by high pressure liquid chromatography on a strong anion exchange column (GE Healthcare Bioscience, Source 30Q, 30 µm, 2.54 x 8 cm, A = 100 mM ammonium acetate in 30% aqueous CH_3CN, B = 1.5 M NaBr in A, 0-40% of B in 60 min, flow 14 mL min-1, λ = 260 nm). The residue was desalted by HPLC on a reverse phase column to yield the desired ASOs in an isolated yield of 15-30% based on the initial loading on the solid support. The ASOs were characterized by ion-pair-HPLC coupled MS analysis with Agilent 1100 MSD system.

Table 34

ASO comprising a phosphodiester linked $GalNAc_3$-2 conjugate at the 5' position targeting SRB-1

ISIS No.	Sequence (5' to 3')	CalCd Mass	Observed Mass	SEQ ID No.
661134	**$GalNAc_3$-2_a-$_{o'}$$A_{do}$**$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	6482.2	6481.6	114

Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "k" indicates 6'-*(S)*-CH_3 bicyclic nucleoside (e.g. cEt); "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 $GalNAc_3$-2_a is shown in Example 37.

Example 42: General method for the preparation of ASOs comprising a GalNAc$_3$-3 conjugate at the 5' position *via* solid phase techniques (preparation of ISIS 661166)

The synthesis for ISIS 661166 was performed using similar procedures as illustrated in Examples 39 and 41.

ISIS 661166 is a 5-10-5 MOE gapmer, wherein the 5' position comprises a GalNAc$_3$-3 conjugate. The ASO was characterized by ion-pair-HPLC coupled MS analysis with Agilent 1100 MSD system.

Table 34a
ASO comprising a GalNAc$_3$-3 conjugate at the 5' position via a hexylamino phosphodiester linkage targeting Malat-1

ISIS No.	Sequence (5' to 3')	Conjugate	Calcd Mass	Observed Mass	SEQ ID No.
661166	5'-**GalNAc$_3$-3$_{a-o}$**,$^{m}C_{es}G_{es}G_{es}T_{es}G_{es}$ $^{m}C_{ds}A_{ds}A_{ds}G_{ds}G_{ds}$$^{m}C_{ds}T_{ds}T_{ds}A_{ds}G_{ds}$ $G_{es}A_{es}A_{es}T_{es}T_{e}$	**5'-GalNAc$_3$-3**	8992.16	8990.51	107

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 "5'-GalNAc$_3$-3a" is shown in Example 39.

Example 43: Dose-dependent study of phosphodiester linked GalNAc$_3$-2 (see examples 37 and 41, Bx is adenine) at the 5' terminus targeting SRB-1 *in vivo*

ISIS 661134 (see Example 41) comprising a phosphodiester linked GalNAc$_3$-2 conjugate at the 5' terminus was tested in a dose-dependent study for antisense inhibition of SRB-1 in mice. Unconjugated ISIS 440762 and 651900 (GalNAc$_3$-1 conjugate at 3' terminus, see Example 9) were included in the study for comparison and are described previously in Table 17.

Treatment

Six week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 440762, 651900, 661134 or with PBS treated control. 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. 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 PBS-treated control and is denoted as "% PBS". The ED_{50}s were measured using similar methods as described previously and are presented below.

As illustrated in Table 35, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. Indeed, the antisense oligonucleotides comprising the phosphodiester linked $GalNAc_3$-2 conjugate at the 5' terminus (ISIS 661134) or the $GalNAc_3$-1 conjugate linked at the 3' terminus (ISIS 651900) showed substantial improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 440762). Further, ISIS 661134, which comprises the phosphodiester linked $GalNAc_3$-2 conjugate at the 5' terminus was equipotent compared to ISIS 651900, which comprises the $GalNAc_3$-1 conjugate at the 3' terminus.

Table 35

ASOs containing $GalNAc_3$-1 or $GalNAc_3$-2 targeting SRB-1

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA levels (% PBS)	ED_{50} (mg/kg)	Conjugate	SEQ ID No.
PBS	0	100	--	--	
440762	0.2	116	2.58	No conjugate	104
	0.7	91			
	2	69			
	7	22			
	20	5			
651900	0.07	95	0.26	**3' $GalNAc_3$-1**	112
	0.2	77			
	0.7	28			
	2	11			
	7	8			
661134	0.07	107	0.25	**5' $GalNAc_3$-2**	114
	0.2	86			
	0.7	28			
	2	10			
	7	6			

Structures for 3' $GalNAc_3$-1 and 5' $GalNAc_3$-2 were described previously in Examples 9 and 37.

Pharmacokinetics Analysis (PK)

The PK of the ASOs from the high dose group (7 mg/kg) was examined and evaluated in the same manner as illustrated in Example 20. Liver sample was minced and extracted using standard protocols. The full length metabolites of 661134 (5' $GalNAc_3$-2) and ISIS 651900 (3' $GalNAc_3$-1) were identified and their masses were confirmed by high resolution mass spectrometry analysis. The results showed that the major metabolite detected for the ASO comprising a phosphodiester linked $GalNAc_3$-2 conjugate at the 5' terminus (ISIS 661134) was ISIS 440762 (data not shown). No additional metabolites, at a detectable level, were observed. Unlike its counterpart, additional metabolites similar to those reported previously in Table 23a

were observed for the ASO having the GalNAc$_3$-1 conjugate at the 3' terminus (ISIS 651900). These results suggest that having the phosphodiester linked GalNAc$_3$-1 or GalNAc$_3$-2 conjugate may improve the PK profile of ASOs without compromising their potency.

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

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.

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	108
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	110
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	110

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

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 PBS-treated control and is denoted as "% PBS". The ED_{50}s were measured using similar methods as described previously and are reported below.

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	108
	10	52.40			
	30	24.95			
655861	0.5	81.22	2.2	Full PS with $GalNAc_3$-1 conjugate	110
	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	110
	1.5	45.78			
	5	19.70			
	15	12.90			

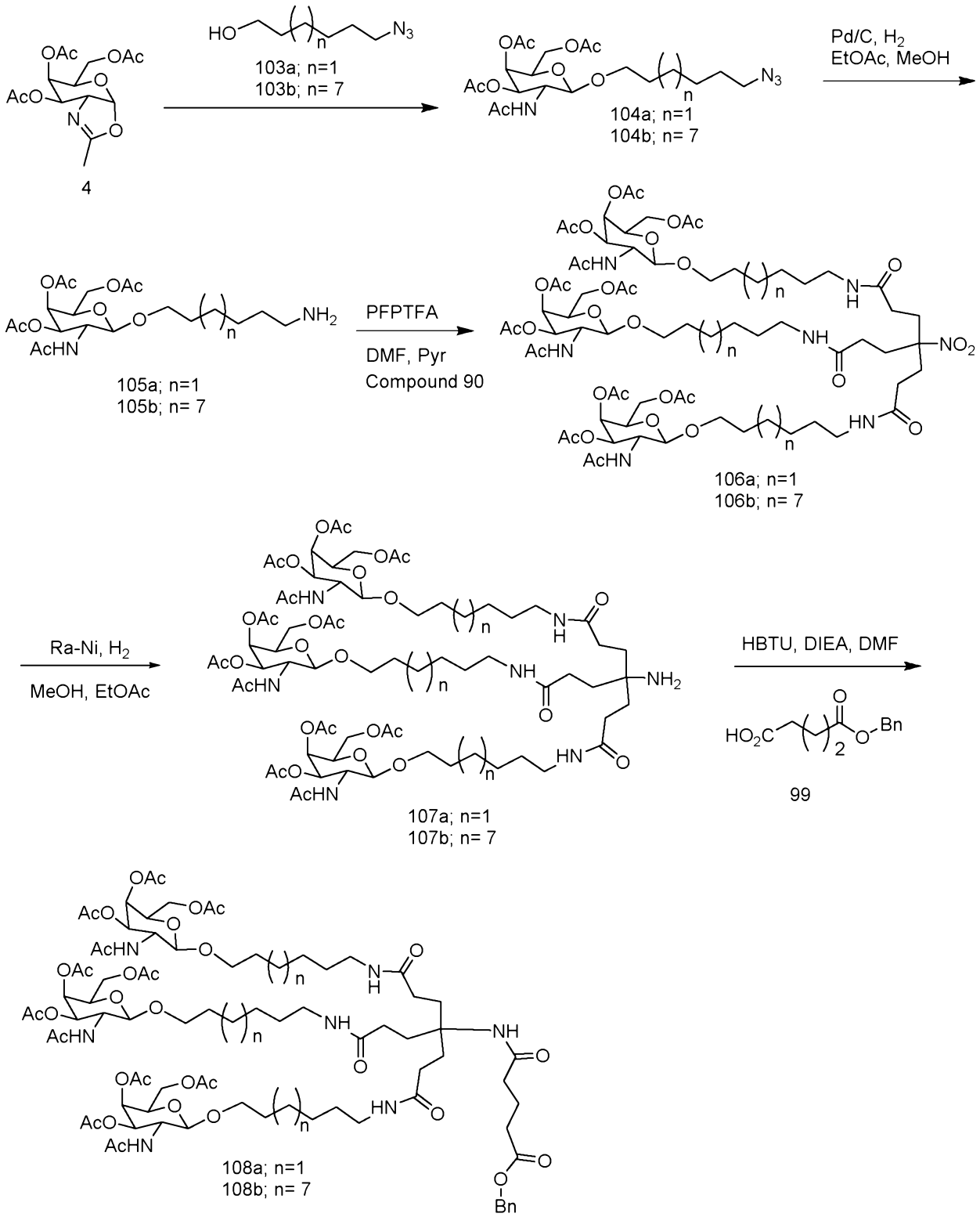
Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Organ weights were also evaluated. The results demonstrated that no elevation in transaminase levels (Table 38) or organ weights (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).

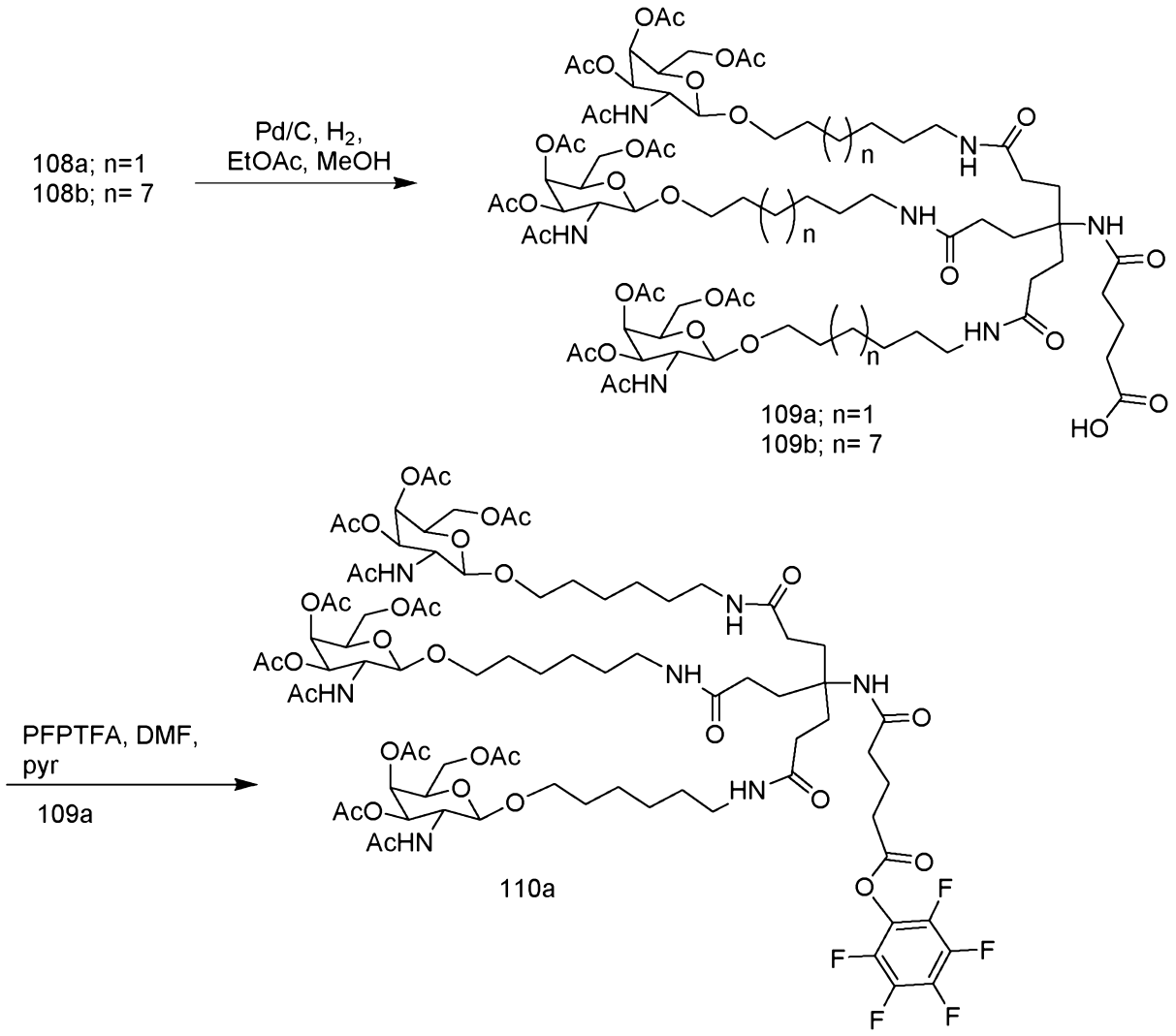
Table 38
Effect of PO/PS linkages on transaminase levels of ASOs comprising $GalNAc_3$-1 conjugate at 3' terminus targeting SRB-1

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	108
	10	27.5	79.3		
	30	27.3	97		
655861	0.5	28	55.7	Full PS with	110

	1.5	30	78	**GalNAc$_3$-1**	
	5	29	63.5		
	15	28.8	67.8		
655862	0.5	50	75.5	Mixed PS/PO with **GalNAc$_3$-1**	110
	1.5	21.7	58.5		
	5	29.3	69		
	15	22	61		

Example 45: Preparation of PFP Ester, Compound 110a





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.

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.

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.

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.

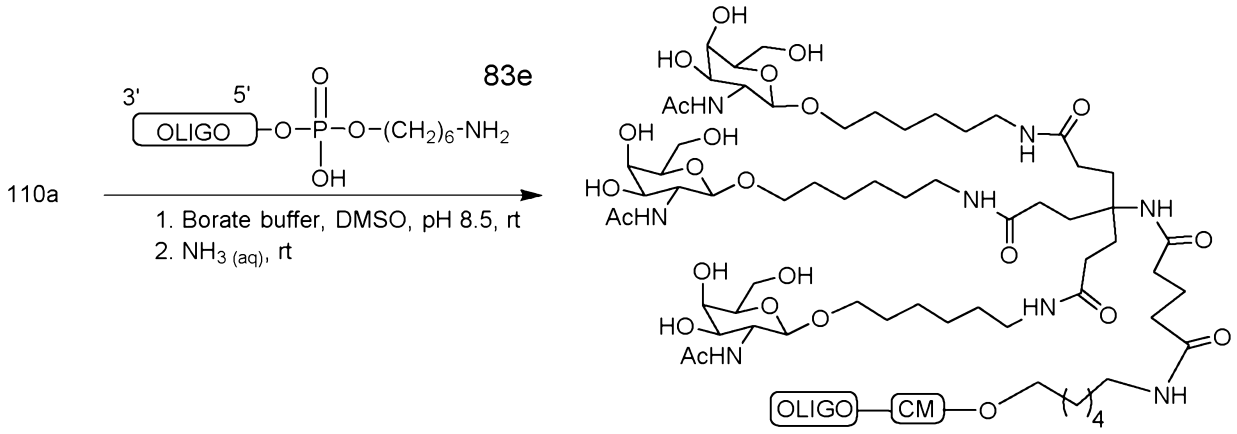
Compounds 107a and 107b were treated to the same conditions as for compounds 97a-d (Example 47), to give compounds 108a and 108b in 40-60% yield. LCMS and proton NMR was consistent with the structure.

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.

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.

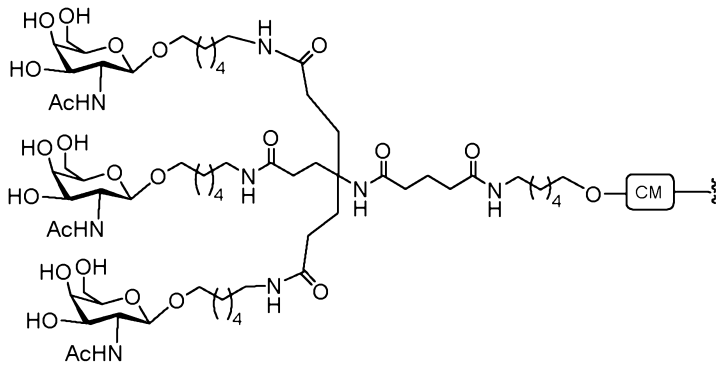
Example 46: General Procedure for Conjugation with PFP Esters (Oligonucleotide 111); Preparation of ISIS 666881 ($GalNAc_3$-10)

A 5'-hexylamino modified oligonucleotide was synthesized and purified using standard solid-phase oligonucleotide procedures. The 5'-hexylamino modified oligonucleotide was dissolved in 0.1 M sodium tetraborate, pH 8.5 (200 μL) and 3 equivalents of a selected PFP esterified $GalNAc_3$ cluster dissolved in DMSO (50 μL) was added. If the PFP ester precipitated upon addition to the ASO solution DMSO was added until all PFP ester was in solution. The reaction was complete after about 16 h of mixing at room temperature. The resulting solution was diluted with water to 12 mL and then spun down at 3000 rpm in a spin filter with a mass cut off of 3000 Da. This process was repeated twice to remove small molecule impurities. The solution was then lyophilized to dryness and redissolved in concentrated aqueous ammonia and mixed at room temperature for 2.5 h followed by concentration *in vacuo* to remove most of the ammonia. The conjugated oligonucleotide was purified and desalted by RP-HPLC and lyophilized to provide the $GalNAc_3$ conjugated oligonucleotide.



111

Oligonucleotide 111 is conjugated with $GalNAc_3$-10. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-10 ($GalNAc_3$-10_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)- as shown in the oligonucleotide (ISIS 666881) synthesized with $GalNAc_3$-10 below. The structure of $GalNAc_3$-10 ($GalNAc_3$-10_a-CM-) is shown below:



Following this general procedure ISIS 666881 was prepared. 5'-hexylamino modified oligonucleotide, ISIS 660254, was synthesized and purified using standard solid-phase oligonucleotide procedures. ISIS 660254 (40 mg, 5.2 μmol) was dissolved in 0.1 M sodium tetraborate, pH 8.5 (200 μL) and 3 equivalents PFP ester (Compound 110a) dissolved in DMSO (50 μL) was added. The PFP ester precipitated upon addition to the ASO solution requiring additional DMSO (600 μL) to fully dissolve the PFP ester. The reaction was complete after 16 h of mixing at room temperature. The solution was diluted with water to 12 mL total volume and spun down at 3000 rpm in a spin filter with a mass cut off of 3000 Da. This process was repeated twice to remove small molecule impurities. The solution was lyophilized to dryness and redissolved in concentrated aqueous ammonia with mixing at room temperature for 2.5 h followed by

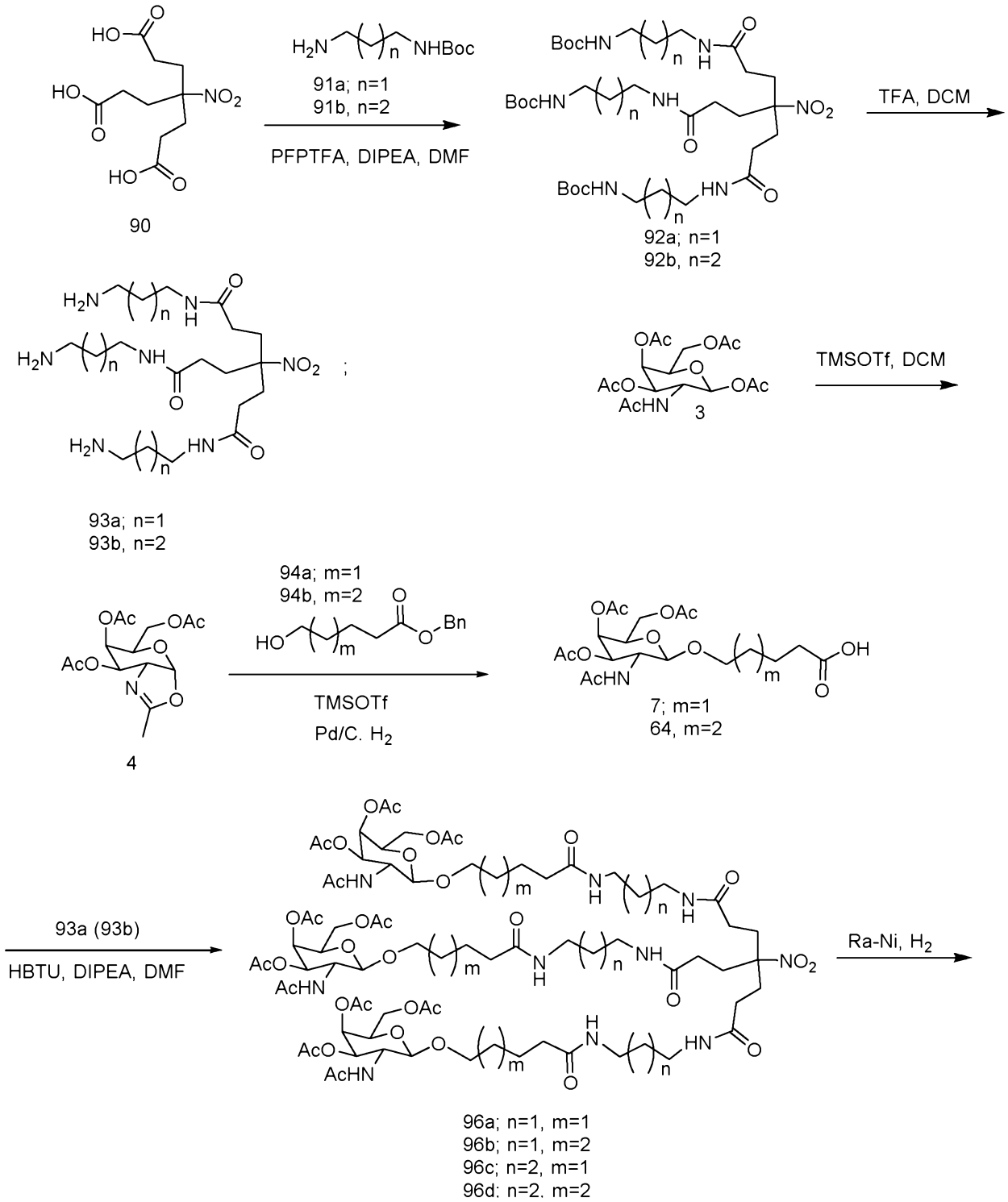
concentration *in vacuo* to remove most of the ammonia. The conjugated oligonucleotide was purified and desalted by RP-HPLC and lyophilized to give ISIS 666881 in 90% yield by weight (42 mg, 4.7 μmol).

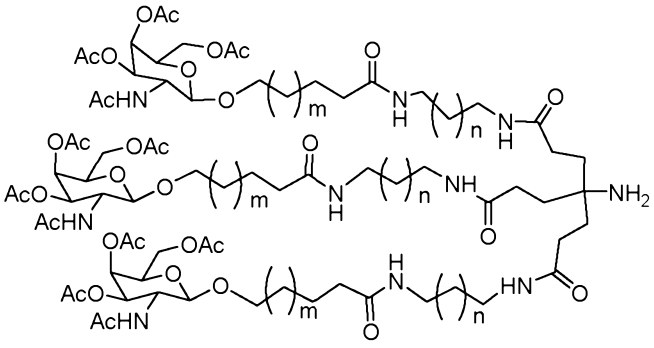
$GalNAc_3$-10 conjugated oligonucleotide

ASO	Sequence (5' to 3')	5' group	SEQ ID No.
ISIS 660254	$NH_2(CH_2)_6$-$_o$$A_{do}G_{es}{}^mC_{es}T_{es}T_{es}{}^mC_{es}A_{ds}G_{ds}T_{ds}$ $^mC_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^mC_{ds}T_{ds}T_{es}{}^mC_{es}{}^mC_{es}T_{es}T_e$	Hexylamine	109
ISIS 666881	**$GalNAc_3$-10$_a$-$_o$'A_{do}**$G_{es}{}^mC_{es}T_{es}T_{es}{}^mC_{es}A_{ds}G_{ds}T_{ds}$ $^mC_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^mC_{ds}T_{ds}T_{es}{}^mC_{es}{}^mC_{es}T_{es}T_e$	**$GalNAc_3$-10**	109

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 β-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.

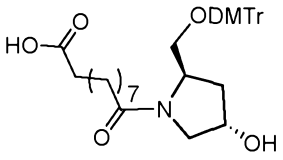
Example 47: Preparation of Oligonucleotide 102 Comprising GalNAc$_3$-8



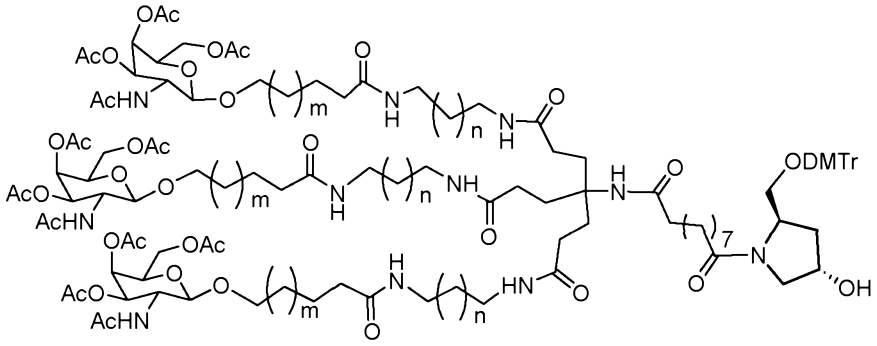


97a; n=1, m=1
97b; n=1, m=2
97c; n=2, m=1
97d; n=2, m=2

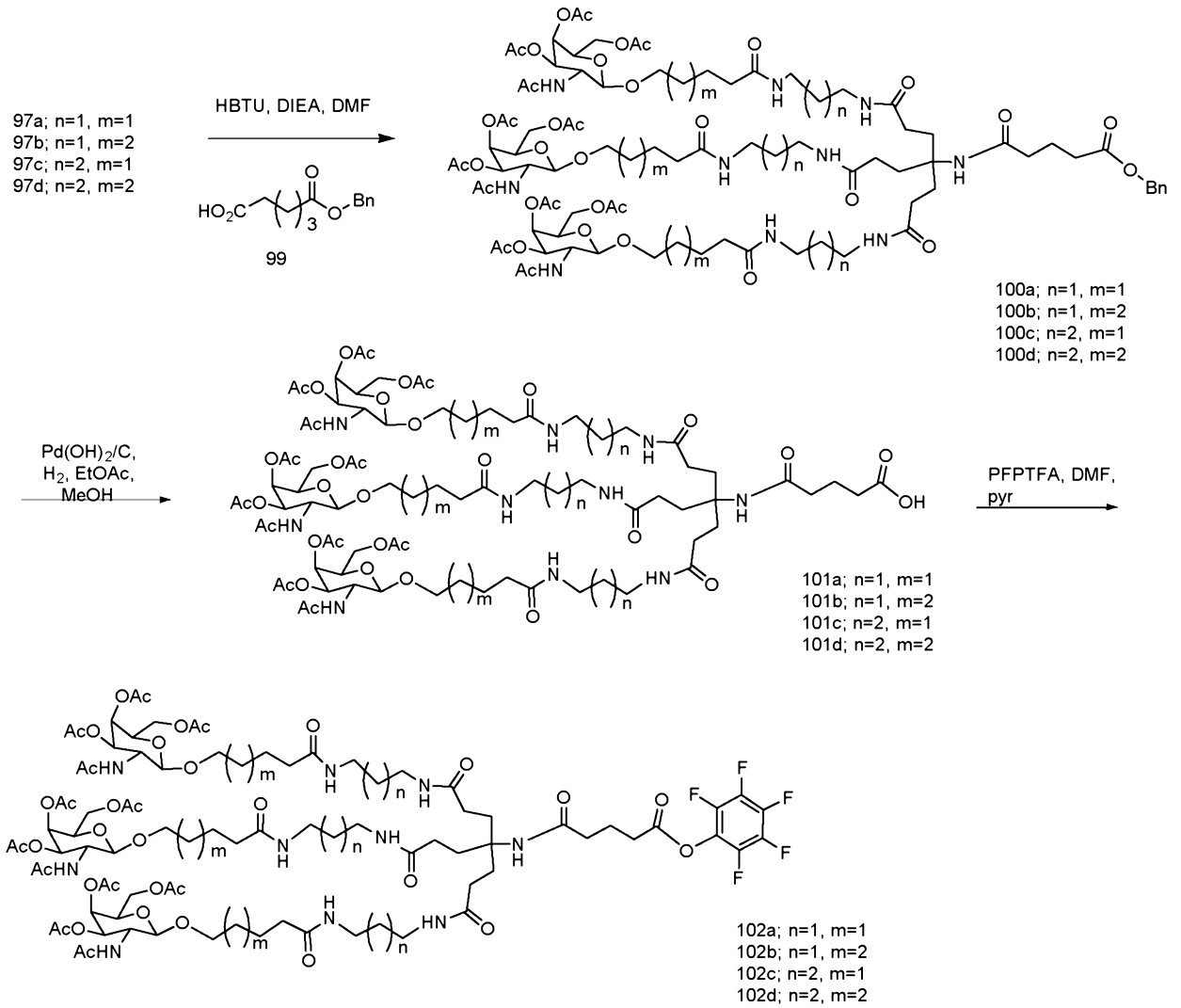
HBTU, DIEA, DMF



23



98a; n=1, m=1
98b; n=1, m=2
98c; n=2, m=1
98d; n=2, m=2



The triacid 90 (4 g, 14.43 mmol) was dissolved in DMF (120 mL) and *N*,*N*-Diisopropylethylamine (12.35 mL, 72 mmoles). Pentafluorophenyl trifluoroacetate (8.9 mL, 52 mmoles) was added dropwise, under argon, and the reaction was allowed to stir at room temperature for 30 minutes. Boc-diamine 91a or 91b (68.87 mmol) was added, along with *N*,*N*-Diisopropylethylamine (12.35 mL, 72 mmoles), and the reaction was allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->10% methanol/dichloromethane) to give compounds 92a and 92b in an approximate 80% yield. LCMS and proton NMR were consistent with the structure.

Compound 92a or 92b (6.7 mmoles) was treated with 20 mL of dichloromethane and 20 mL of trifluoroacetic acid at room temperature for 16 hours. The resultant solution was evaporated and then

dissolved in methanol and treated with DOWEX-OH resin for 30 minutes. The resultant solution was filtered and reduced to an oil under reduced pressure to give 85-90% yield of compounds 93a and 93b.

Compounds 7 or 64 (9.6 mmoles) were treated with HBTU (3.7g, 9.6 mmoles) and *N*,*N*-Diisopropylethylamine (5 mL) in DMF (20 mL) for 15 minutes. To this was added either compounds 93a or 93b (3 mmoles), and allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (5%-->20% methanol/dichloromethane) to give compounds 96a-d in 20-40% yield. LCMS and proton NMR was consistent with the structure.

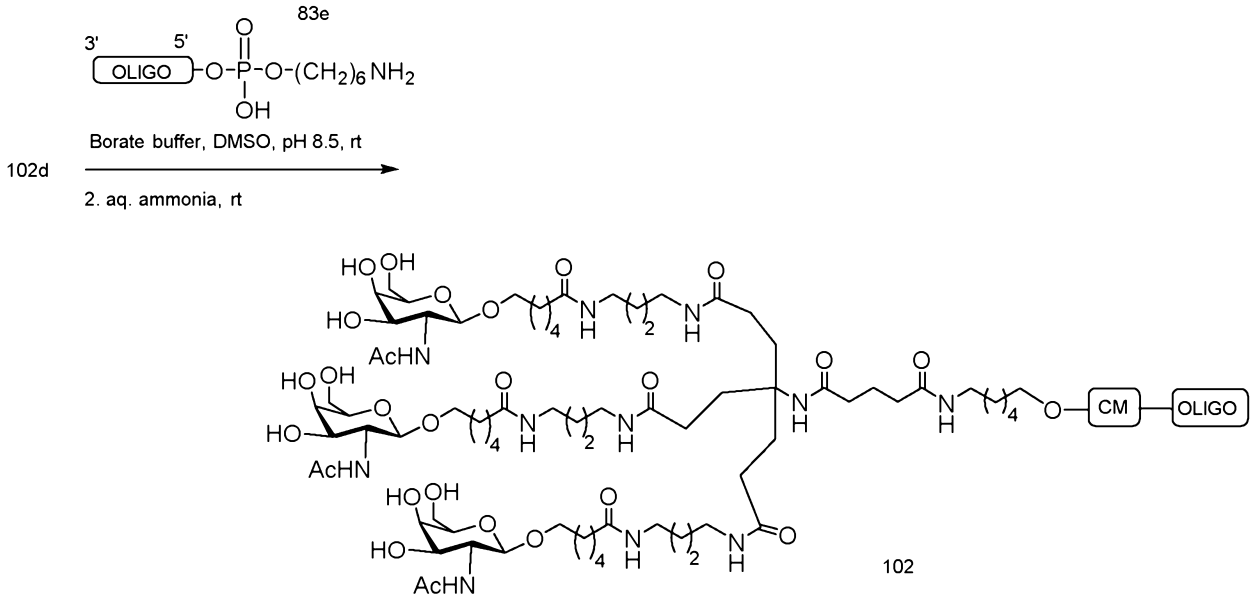
Compounds 96a-d (0.75 mmoles), individually, were hydrogenated over Raney Nickel for 3 hours in Ethanol (75 mL). At that time, the catalyst was removed by filtration thru celite, and the ethanol removed under reduced pressure to give compounds 97a-d in 80-90% yield. LCMS and proton NMR were consistent with the structure.

Compound 23 (0.32g, 0.53 mmoles) was treated with HBTU (0.2g, 0.53 mmoles) and *N*,*N*-Diisopropylethylamine (0.19 mL, 1.14 mmoles) in DMF (30mL) for 15 minutes. To this was added compounds 97a-d (0.38 mmoles), individually, and allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->20% methanol/dichloromethane) to give compounds 98a-d in 30-40% yield. LCMS and proton NMR was consistent with the structure.

Compound 99 (0.17g, 0.76 mmoles) was treated with HBTU (0.29 g, 0.76 mmoles) and *N*,*N*-Diisopropylethylamine (0.35 mL, 2.0 mmoles) in DMF (50mL) for 15 minutes. To this was added compounds 97a-d (0.51 mmoles), individually, and allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (5%-->20% methanol/ dichloromethane) to give compounds 100a-d in 40-60% yield. LCMS and proton NMR was consistent with the structure.

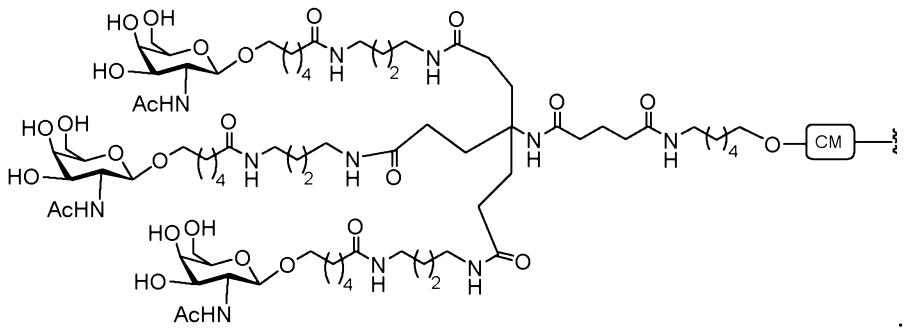
Compounds 100a-d (0.16 mmoles), individually, were hydrogenated over 10% $Pd(OH)_2/C$ for 3 hours in methanol/ethyl acetate (1:1, 50 mL). At that time, the catalyst was removed by filtration thru celite, and the organics removed under reduced pressure to give compounds 101a-d in 80-90% yield. LCMS and proton NMR was consistent with the structure.

Compounds 101a-d (0.15 mmoles), individually, were dissolved in DMF (15 mL) and pyridine (0.016 mL, 0.2 mmoles). Pentafluorophenyl trifluoroacetate (0.034 mL, 0.2 mmoles) was added dropwise, under argon, and the reaction was allowed to stir at room temperature for 30 minutes. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->5% methanol/dichloromethane) to give compounds 102a-d in an approximate 80% yield. LCMS and proton NMR were consistent with the structure.

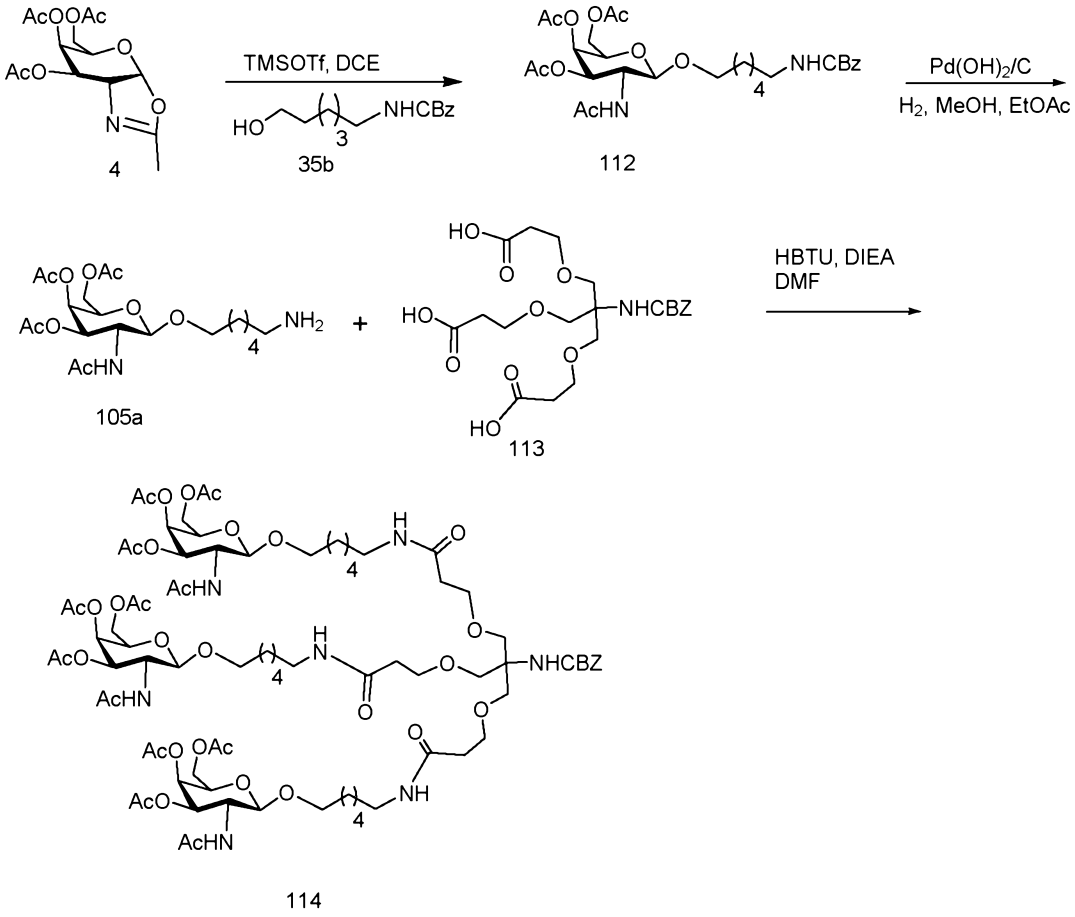


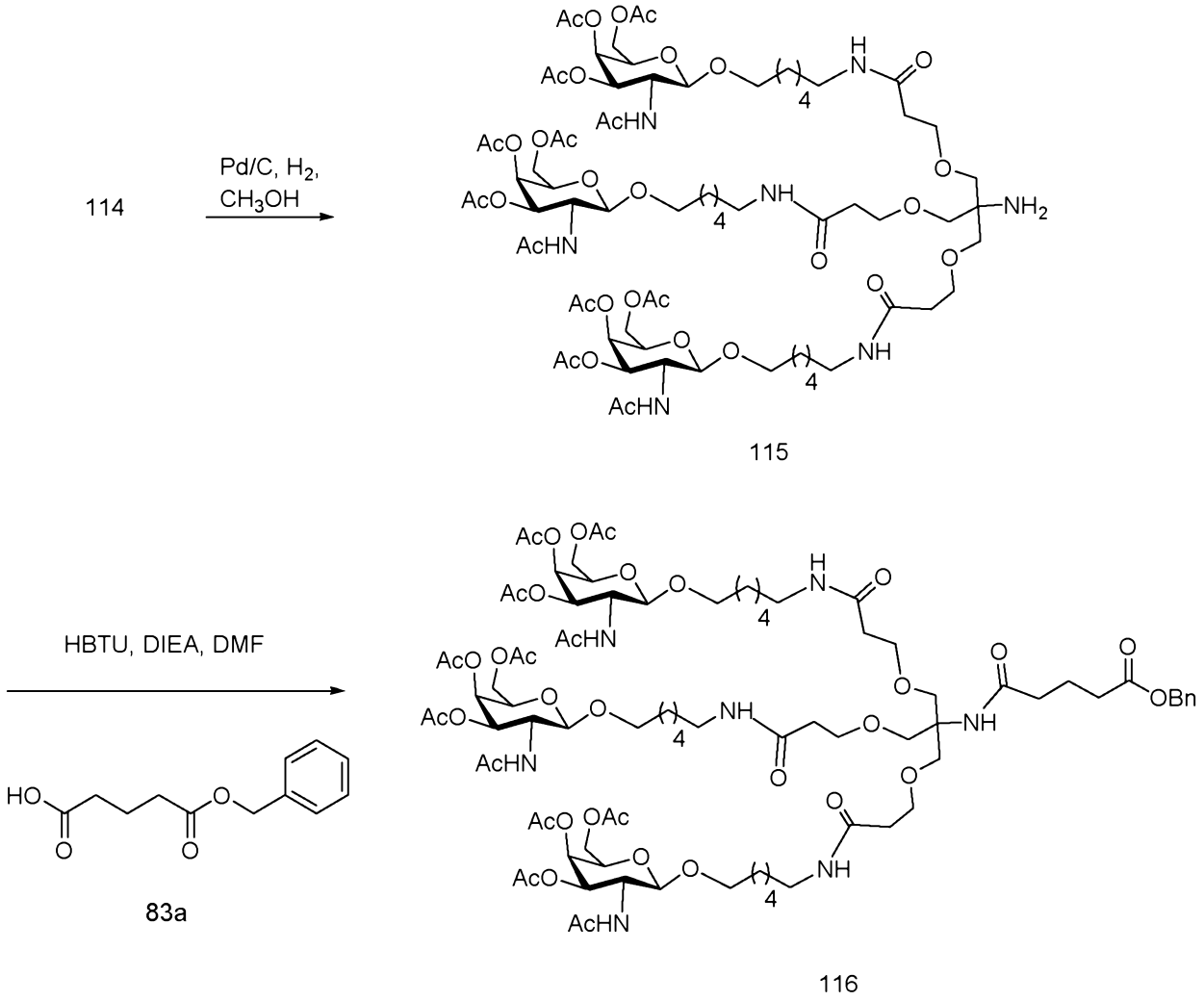
Oligomeric Compound 102, comprising a $GalNAc_3$-8 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-8 ($GalNAc_3$-8_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In a preferred embodiment, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-.

The structure of $GalNAc_3$-8 ($GalNAc_3$-8_a-CM-) is shown below:



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





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

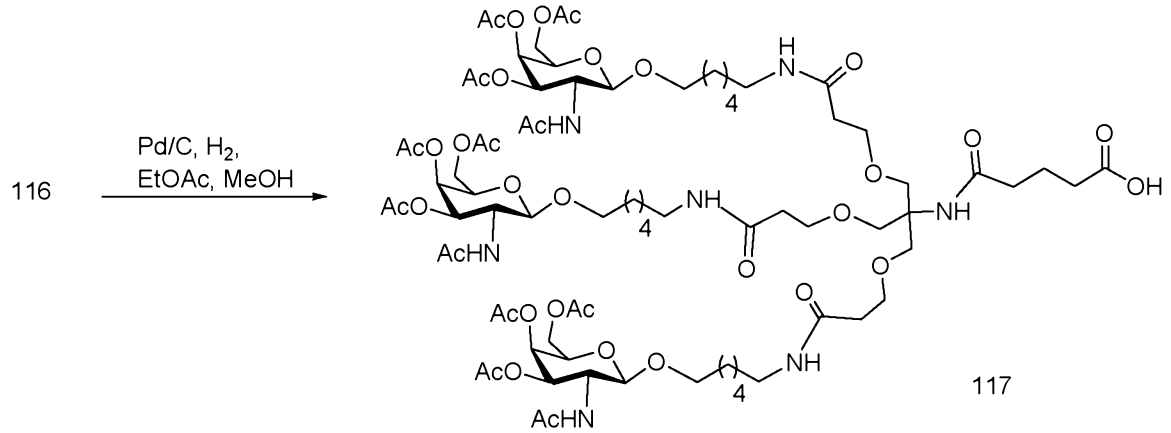
Compound 112 (5 g, 8.6 mmol) was dissolved in 1:1 methanol/ethyl acetate (22 mL/22 mL). Palladium hydroxide on carbon (0.5 g) was added. The reaction mixture was stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite and washed the pad with 1:1 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.

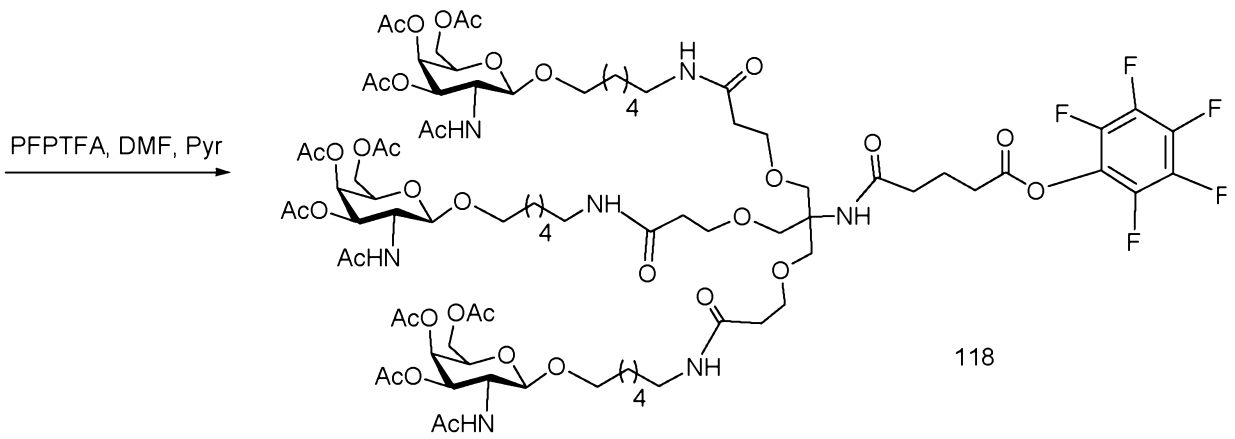
Compound 113 (1.25 g, 2.7 mmol), HBTU (3.2 g, 8.4 mmol) and DIEA (2.8 mL, 16.2 mmol) were dissolved in anhydrous DMF (17 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 105a (3.77 g, 8.4 mmol) in anhydrous DMF (20 mL) was added. The reaction was 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 ^{1}H NMR analysis.

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 ^{1}H NMR analysis.

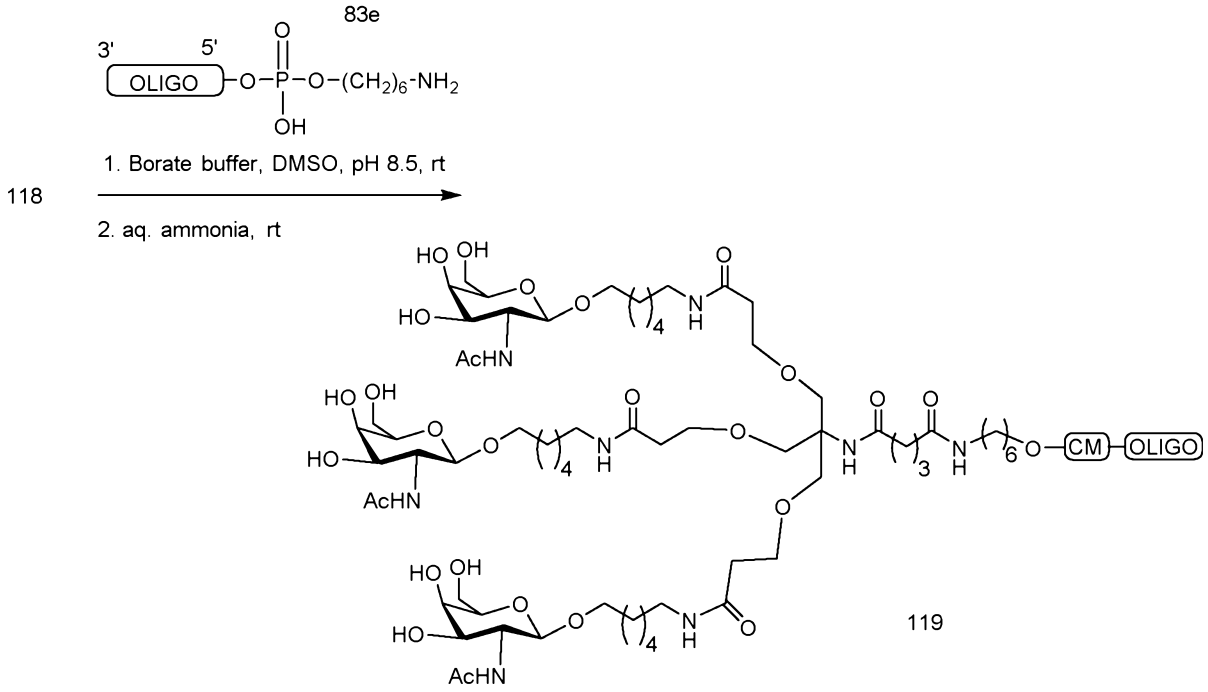
Compound 83a (0.17 g, 0.75 mmol), HBTU (0.31 g, 0.83 mmol) and DIEA (0.26 mL, 1.5 mmol) were dissolved in anhydrous DMF (5 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 115 (1.22 g, 0.75 mmol) in anhydrous DMF was added and the reaction was stirred 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 ^{1}H NMR analysis.





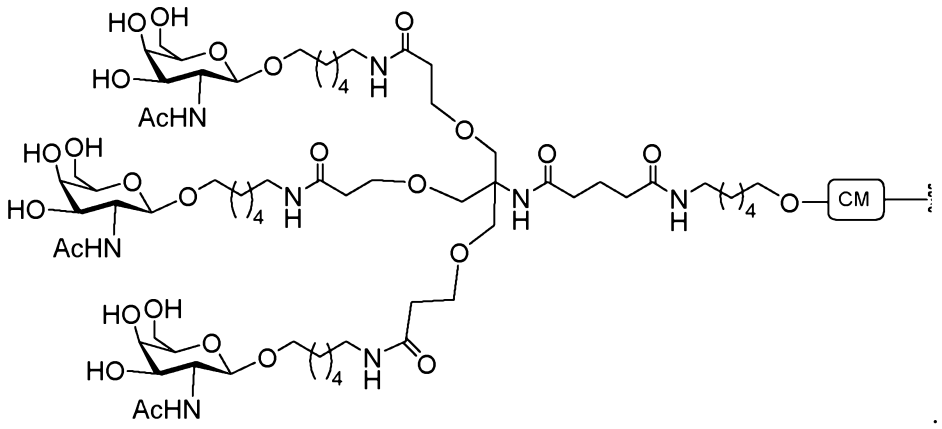
Compound 116 (0.74 g, 0.4 mmol) was dissolved in 1:1 methanol/ethyl acetate (5 mL/5 mL). Palladium on carbon (wet, 0.074 g) was added. The reaction mixture was flushed with hydrogen and stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite. The 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 ^{1}H NMR analysis.

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 ^{1}H and ^{1}H and ^{19}F NMR.

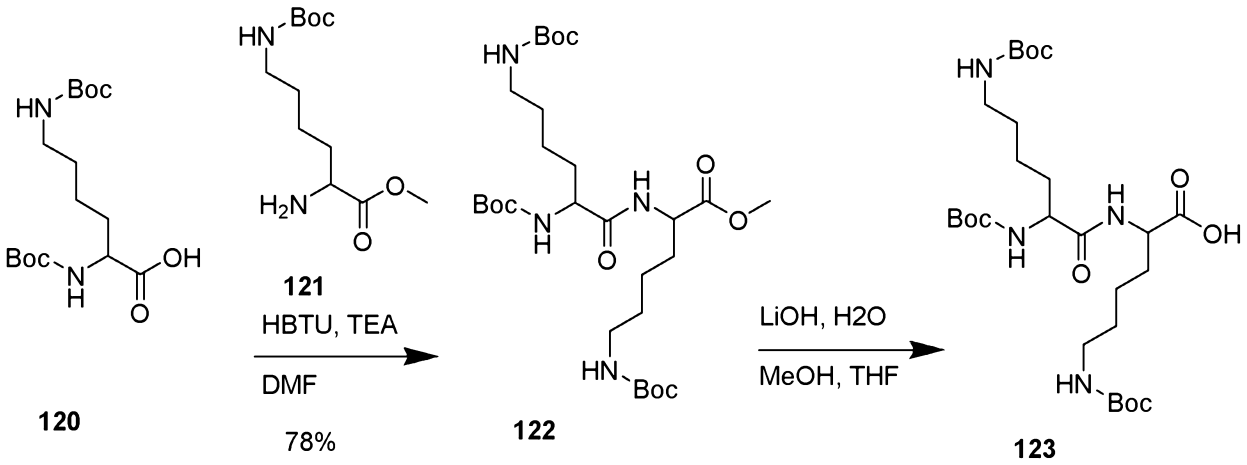


Oligomeric Compound 119, comprising a $GalNAc_3$-7 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-7 ($GalNAc_3$-7_a) can be combined with any cleavable moiety to provide a variety of conjugate groups.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

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



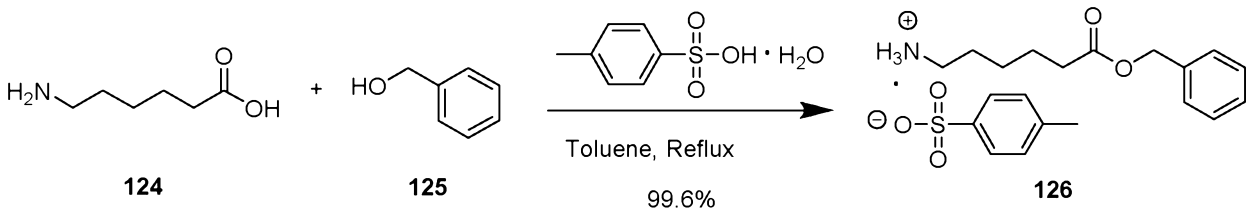
Example 49: Preparation of Oligonucleotide 132 Comprising GalNAc$_3$-5



Compound 120 (14.01 g, 40 mmol) and HBTU (14.06 g, 37 mmol) were dissolved in anhydrous DMF (80 mL). Triethylamine (11.2 mL, 80.35 mmol) was added and stirred for 5 min. The reaction mixture was cooled in an ice bath and a solution of compound 121 (10 g, mmol) in anhydrous DMF (20 mL) was added. Additional triethylamine (4.5 mL, 32.28 mmol) was added and the reaction mixture was stirred for 18 h under an argon atmosphere. The reaction was monitored by TLC (ethyl acetate:hexane; 1:1; Rf = 0.47). The solvent was removed under reduced pressure. The residue was taken up in EtOAc (300 mL) and washed with 1M $NaHSO_4$ (3 x 150 mL), aqueous saturated $NaHCO_3$ solution (3 x 150 mL) and brine (2 x 100 mL). Organic layer was dried with Na_2SO_4. Drying agent was removed by filtration and organic layer was concentrated by rotary evaporation. Crude mixture was purified by silica gel column chromatography and eluted by using 35 – 50% EtOAc in hexane to yield a compound 122 (15.50 g, 78.13%). The structure was confirmed by LCMS and ^{1}H NMR analysis. Mass *m/z* 589.3 $[M + H]^+$.

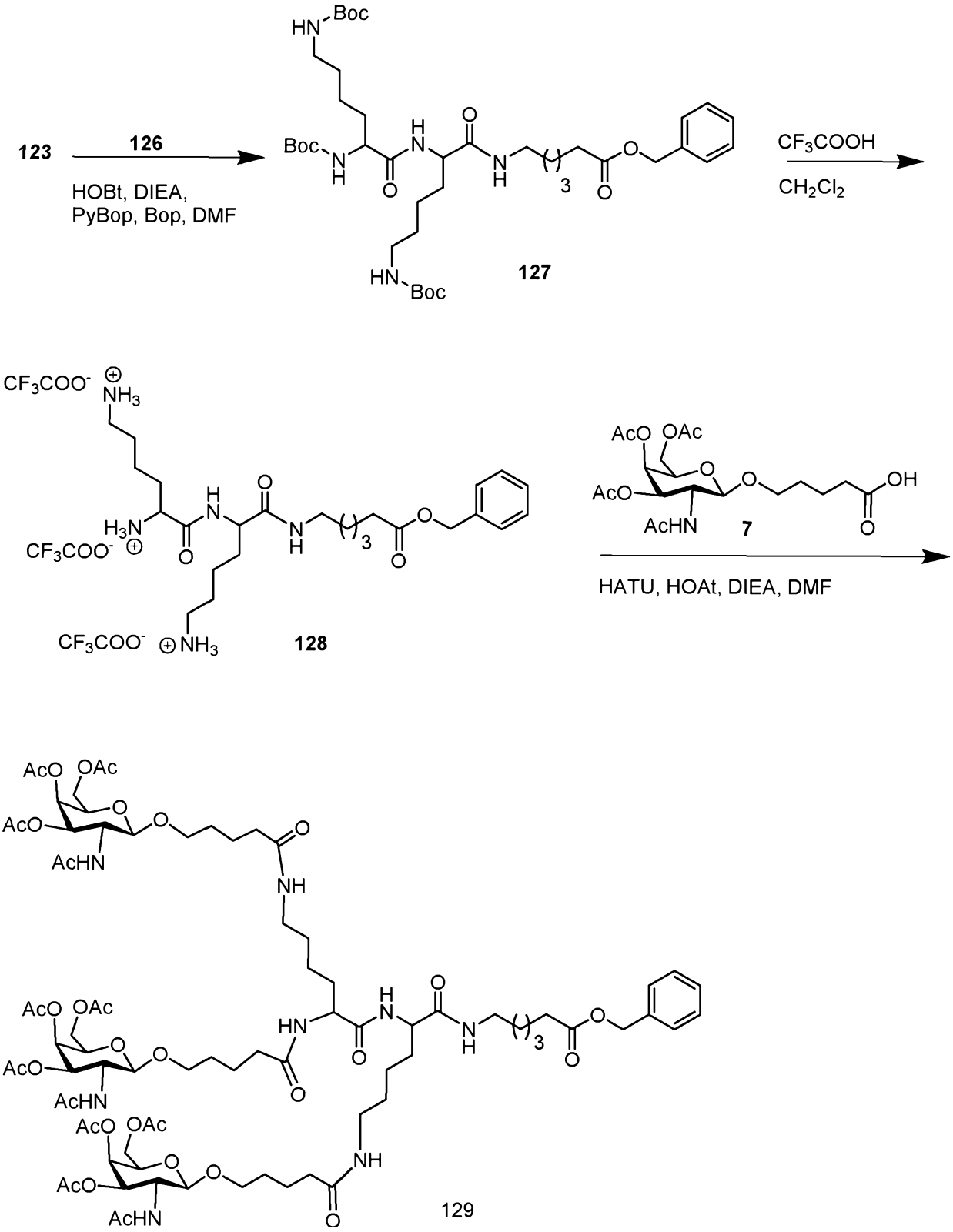
A solution of LiOH (92.15 mmol) in water (20 mL) and THF (10 mL) was added to a cooled solution of Compound 122 (7.75 g,13.16 mmol) dissolved in methanol (15 mL). The reaction mixture was stirred at

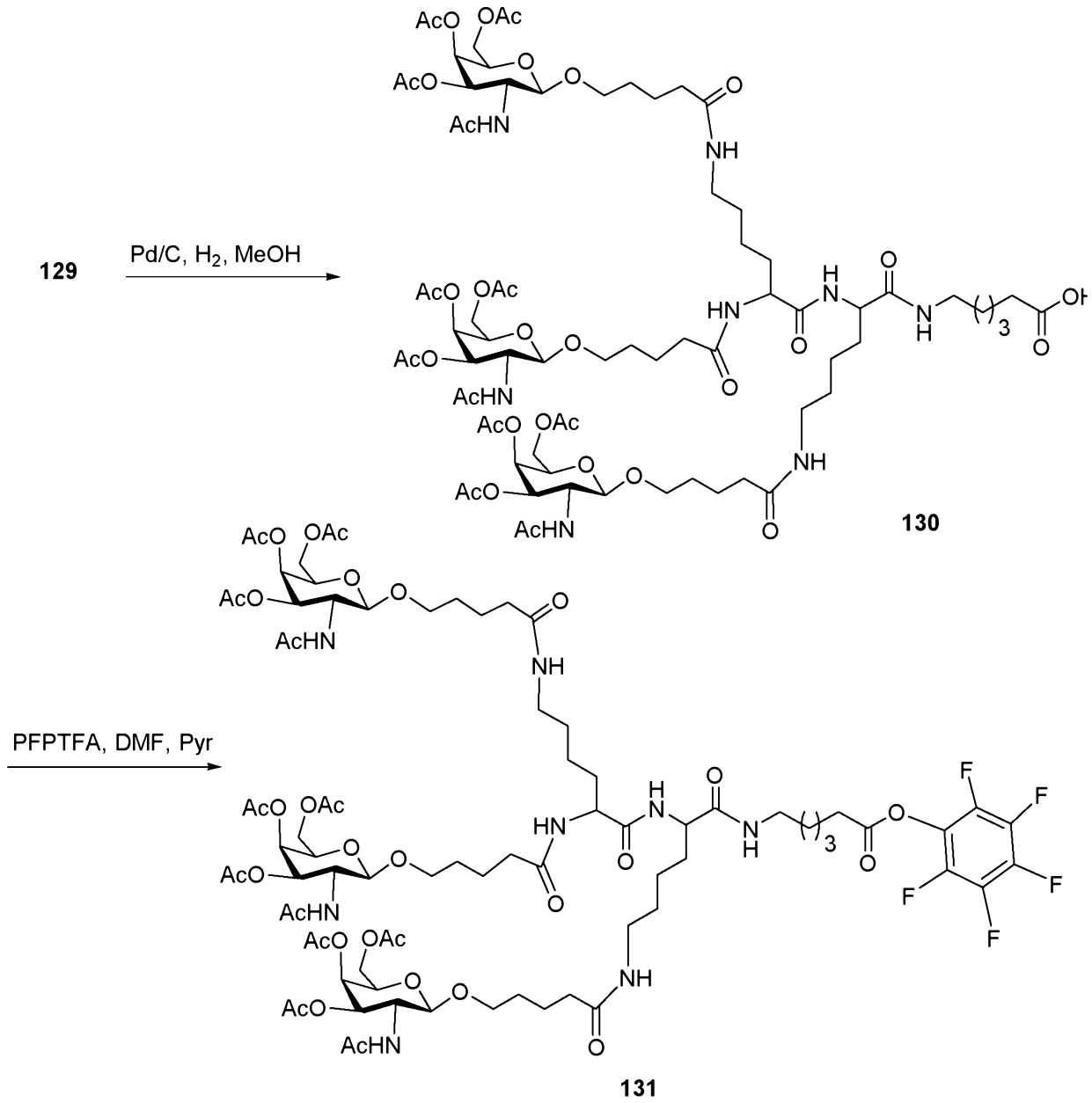
room temperature for 45 min. and monitored by TLC (EtOAc:hexane; 1:1). The reaction mixture was concentrated to half the volume under reduced pressure. The remaining solution was cooled an ice bath and neutralized by adding concentrated HCl. The reaction mixture was diluted, extracted with EtOAc (120 mL) and washed with brine (100 mL). An emulsion formed and cleared upon standing overnight. The organic layer was separated dried (Na_2SO_4), filtered and evaporated to yield Compound 123 (8.42 g). Residual salt is the likely cause of excess mass. LCMS is consistent with structure. Product was used without any further purification. M.W.cal:574.36; M.W.fd:575.3 $[M + H]^+$.



124 125 126

Compound 126 was synthesized following the procedure described in the literature (*J. Am. Chem. Soc.* 2011, *133*, 958-963).


123
126
HOBt, DIEA,
PyBop, Bop, DMF
127
CF3COOH
CH2Cl2
128
7
HATU, HOAt, DIEA, DMF
129



Compound 123 (7.419 g, 12.91 mmol), HOBt (3.49 g, 25.82 mmol) and compound 126 (6.33 g, 16.14 mmol) were dissolved in and DMF (40 mL) and the resulting reaction mixture was cooled in an ice bath. To this *N*,*N*-Diisopropylethylamine (4.42 mL, 25.82 mmol), PyBop (8.7 g, 16.7 mmol) followed by Bop coupling reagent (1.17 g, 2.66 mmol) were added under an argon atmosphere. The ice bath was removed and the solution was allowed to warm to room temperature. The reaction was completed after 1 h as determined by TLC (DCM:MeOH:AA; 89:10:1). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with 1 M $NaHSO_4$ (3x100 mL), aqueous saturated $NaHCO_3$ (3x100 mL) and brine (2x100 mL). The organic phase separated dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography with a gradient of 50% hexanes/EtOAC to 100% EtOAc to yield Compound 127 (9.4 g) as a white foam. LCMS and ^1H NMR

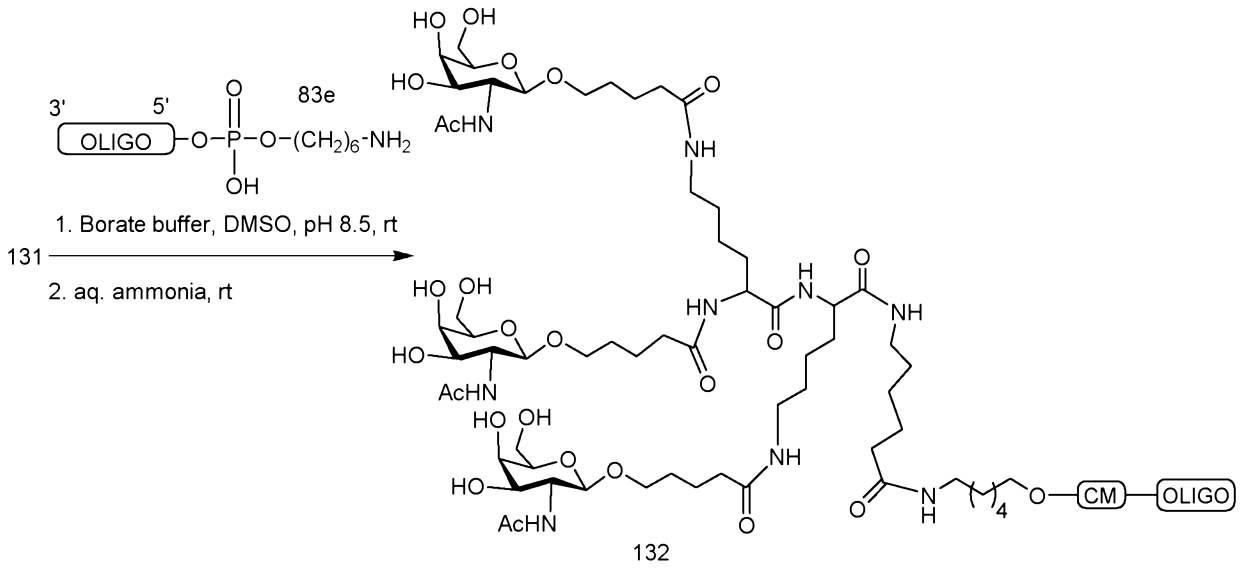
were consistent with structure. Mass *m/z* 778.4 $[M + H]^+$.

Trifluoroacetic acid (12 mL) was added to a solution of compound 127 (1.57 g, 2.02 mmol) in dichloromethane (12 mL) and stirred at room temperature for 1 h. The reaction mixture was co-evaporated with toluene (30 mL) under reduced pressure to dryness. The residue obtained was co-evaporated twice with acetonitrile (30 mL) and toluene (40 mL) to yield Compound 128 (1.67 g) as trifluoro acetate salt and used for next step without further purification. LCMS and ^{1}H NMR were consistent with structure. Mass *m/z* 478.2 $[M + H]^+$.

Compound 7 (0.43 g, 0.963 mmol), HATU (0.35 g, 0.91 mmol), and HOAt (0.035 g, 0.26 mmol) were combined together and dried for 4 h over P_2O_5 under reduced pressure in a round bottom flask and then dissolved in anhydrous DMF (1 mL) and stirred for 5 min. To this a solution of compound 128 (0.20 g, 0.26 mmol) in anhydrous DMF (0.2 mL) and *N*,*N*-Diisopropylethylamine (0.2 mL) was added. The reaction mixture was stirred at room temperature under an argon atmosphere. The reaction was complete after 30 min as determined by LCMS and TLC (7% MeOH/DCM). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (30 mL) and washed with 1 M $NaHSO_4$ (3x20 mL), aqueous saturated $NaHCO_3$ (3 x 20 mL) and brine (3x20 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 5-15% MeOH in dichloromethane to yield Compound 129 (96.6 mg). LC MS and ^{1}H NMR are consistent with structure. Mass *m/z* 883.4 $[M + 2H]^+$.

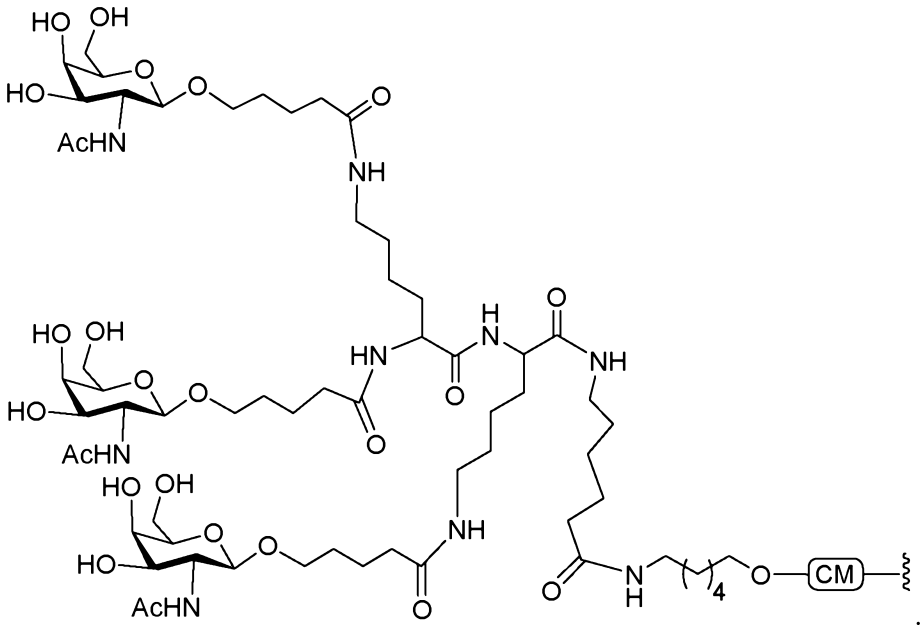
Compound 129 (0.09 g, 0.051 mmol) was dissolved in methanol (5 mL) in 20 mL scintillation vial. To this was added a small amount of 10% Pd/C (0.015 mg) and the reaction vessel was flushed with H_2 gas. The reaction mixture was stirred at room temperature under H_2 atmosphere for 18 h. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with methanol. The filtrate washings were pooled together and concentrated under reduced pressure to yield Compound 130 (0.08 g). LCMS and ^{1}H NMR were consistent with structure. The product was used without further purification. Mass *m/z* 838.3 $[M + 2H]^+$.

To a 10 mL pointed round bottom flask were added compound 130 (75.8 mg, 0.046 mmol), 0.37 M pyridine/DMF (200 µL) and a stir bar. To this solution was added 0.7 M pentafluorophenyl trifluoroacetate/DMF (100 µL) drop wise with stirring. The reaction was completed after 1 h as determined by LC MS. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (~ 10 mL). The organic layer was partitioned against $NaHSO_4$ (1 M, 10 mL) , aqueous saturated $NaHCO_3$ (10 mL) and brine (10 mL) three times each. The organic phase separated and dried over Na_2SO_4, filtered and concentrated to yield Compound 131 (77.7 mg). LCMS is consistent with structure. Used without further purification. Mass *m/z* 921.3 $[M + 2H]^+$.

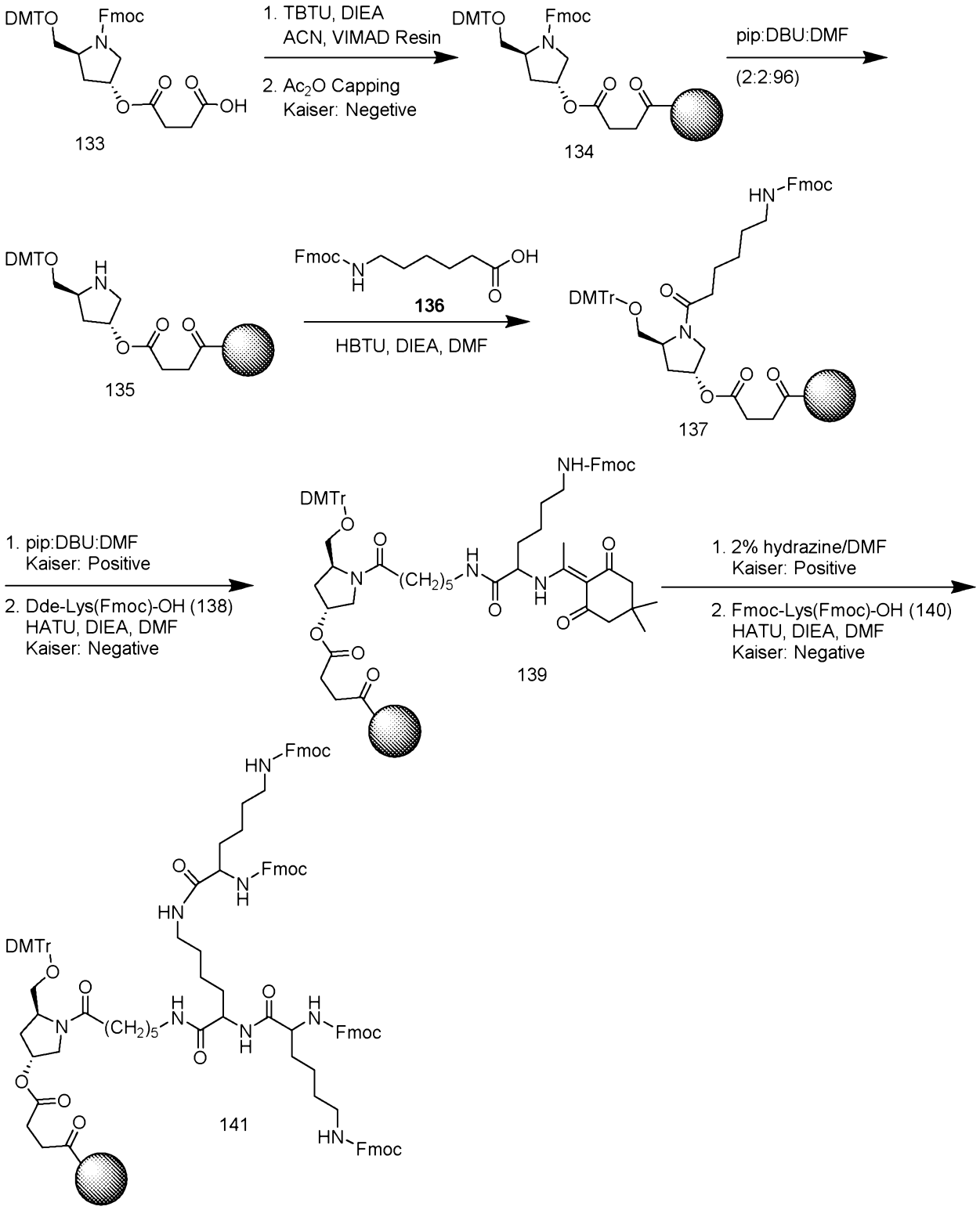


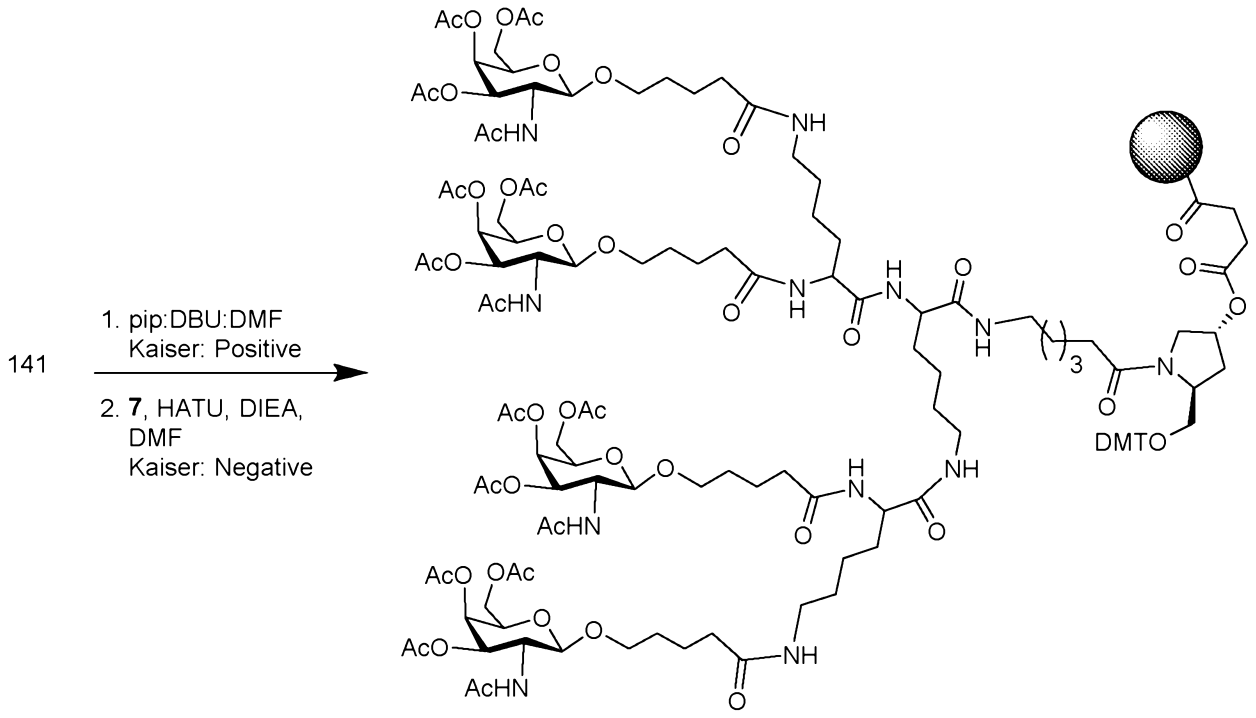
Oligomeric Compound 132, comprising a $GalNAc_3$-5 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-5 ($GalNAc_3$-5_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-.

The structure of $GalNAc_3$-5 ($GalNAc_3$-5_a-CM-) is shown below:



Example 50: Preparation of Oligonucleotide 144 Comprising GalNAc$_4$-11



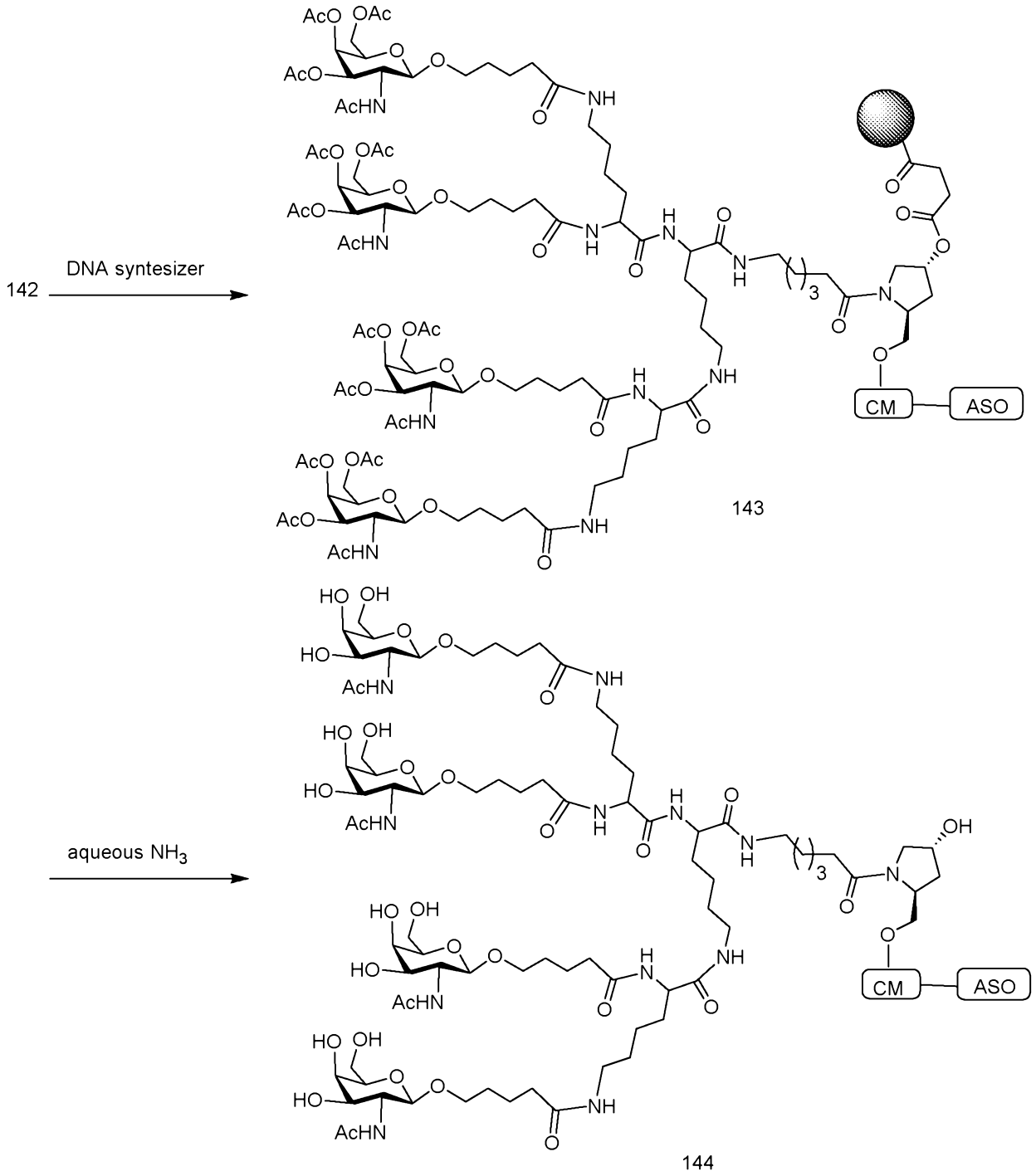


142

Synthesis of Compound 134. To a Merrifield flask was added aminomethyl VIMAD resin (2.5 g, 450 μmol/g) that was washed with acetonitrile, dimethylformamide, dichloromethane and acetonitrile. The resin was swelled in acetonitrile (4 mL). Compound 133 was pre-activated in a 100 mL round bottom flask by adding 20 (1.0 mmol, 0.747 g), TBTU (1.0 mmol, 0.321 g), acetonitrile (5 mL) and DIEA (3.0 mmol, 0.5 mL). This solution was allowed to stir for 5 min and was then added to the Merrifield flask with shaking. The suspension was allowed to shake for 3 h. The reaction mixture was drained and the resin was washed with acetonitrile, DMF and DCM. New resin loading was quantitated by measuring the absorbance of the DMT cation at 500 nm (extinction coefficient = 76000) in DCM and determined to be 238 μmol/g. The resin was capped by suspending in an acetic anhydride solution for ten minutes three times.

The solid support bound compound 141 was synthesized using iterative Fmoc-based solid phase peptide synthesis methods. A small amount of solid support was withdrawn and suspended in aqueous ammonia (28-30 wt%) for 6 h. The cleaved compound was analyzed by LC-MS and the observed mass was consistent with structure. Mass *m/z* 1063.8 $[M + 2H]^+$.

The solid support bound compound 142 was synthesized using solid phase peptide synthesis methods.



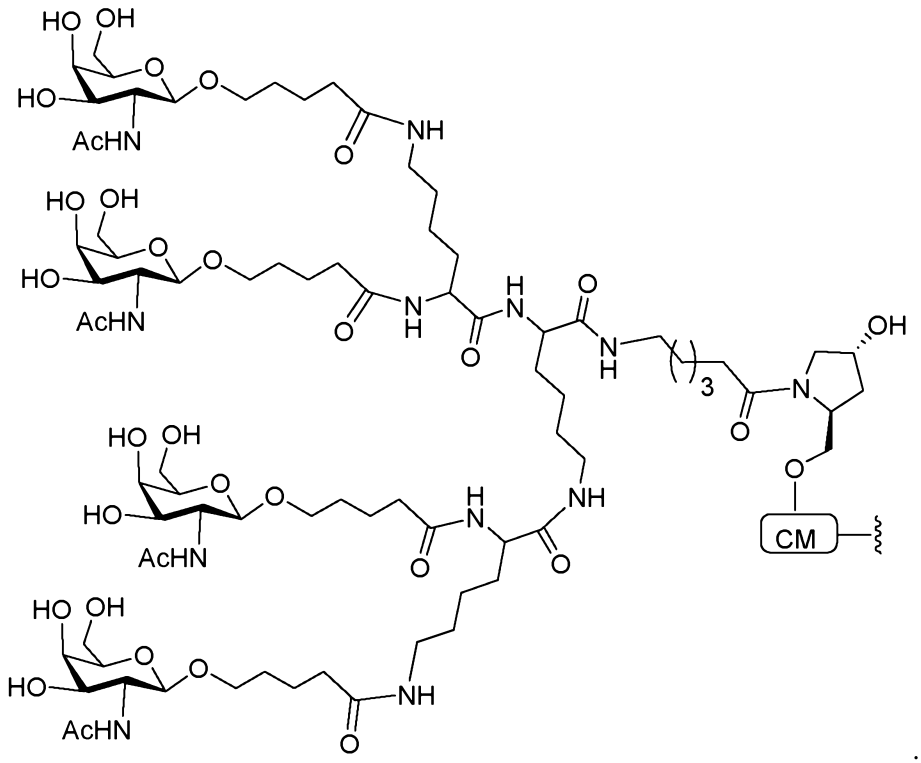
The solid support bound compound 143 was synthesized using standard solid phase synthesis on a DNA synthesizer.

The solid support bound compound 143 was suspended in aqueous ammonia (28-30 wt%) and heated at 55 °C for 16 h. The solution was cooled and the solid support was filtered. The filtrate was concentrated and the residue dissolved in water and purified by HPLC on a strong anion exchange column. The fractions containing full length compound 144 were pooled together and desalted. The resulting $GalNAc_4$-11

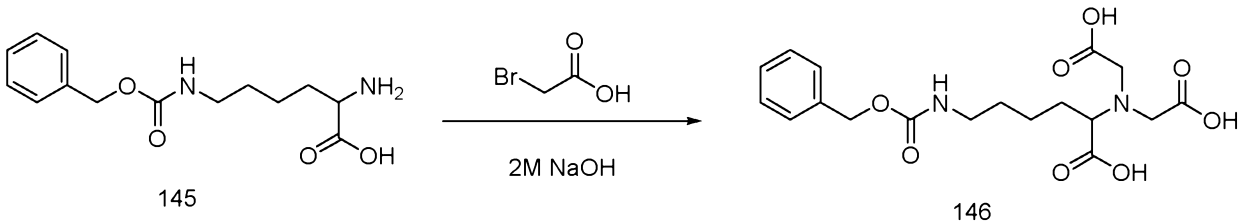
conjugated oligomeric compound was analyzed by LC-MS and the observed mass was consistent with structure.

The $GalNAc_4$ cluster portion of the conjugate group $GalNAc_4$-11 ($GalNAc_4$-11_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)-.

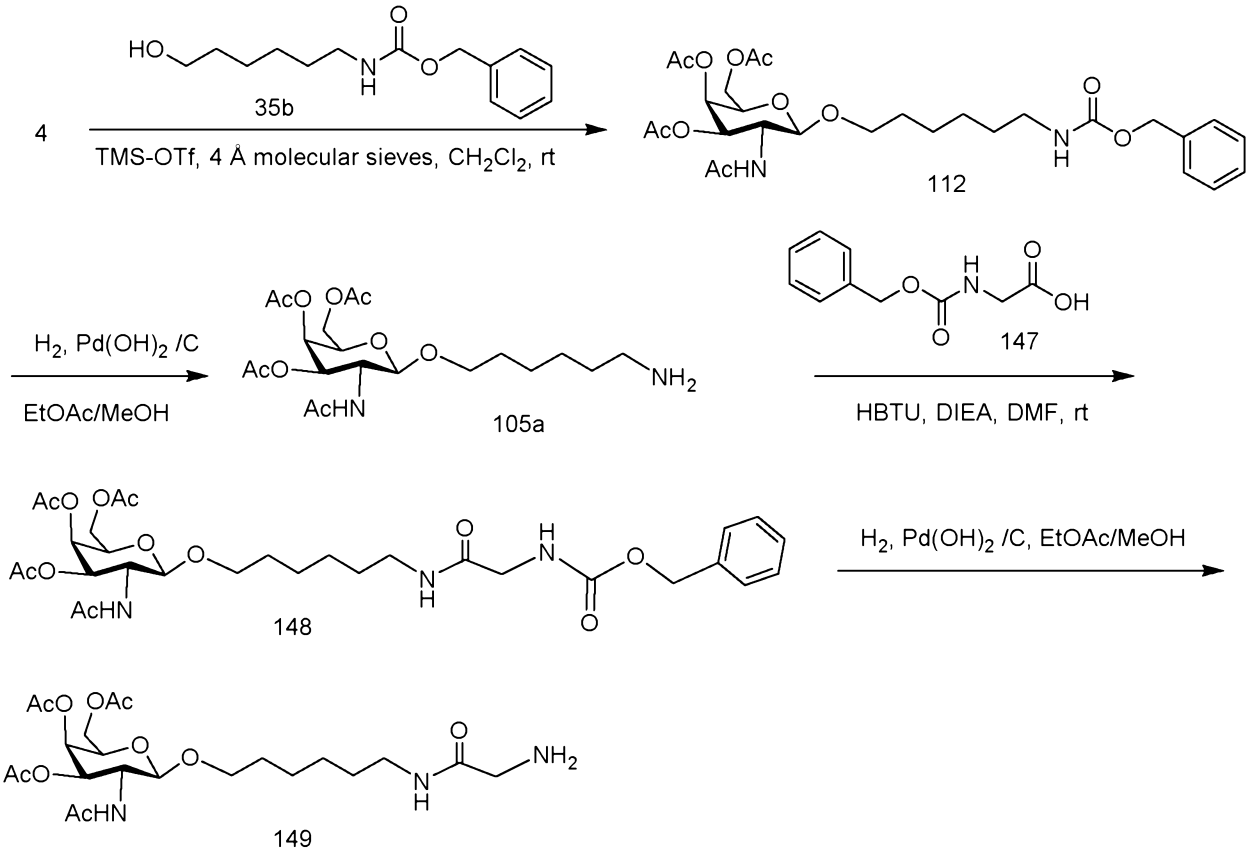
The structure of $GalNAc_4$-11 ($GalNAc_4$-11_a-CM) is shown below:



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



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



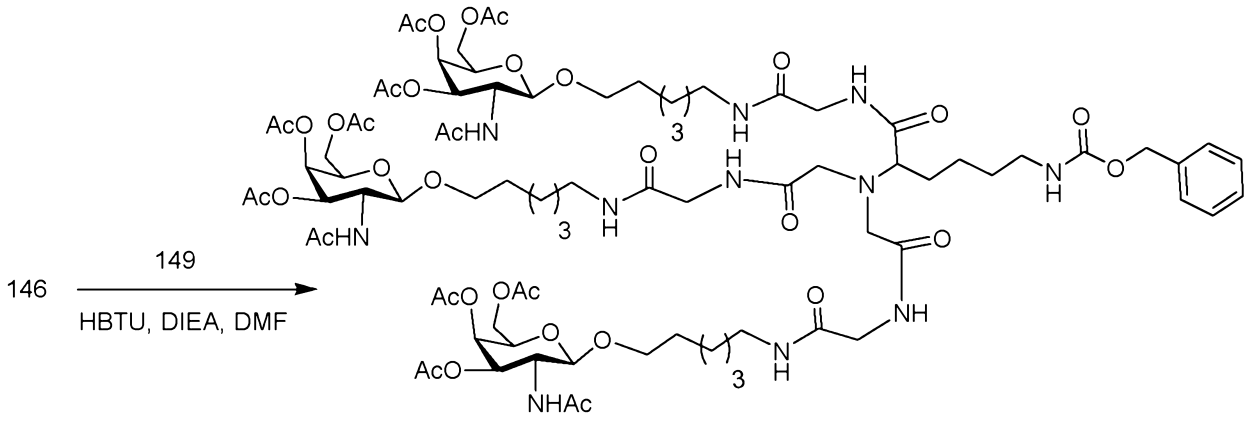
Compound 4 (15 g, 45.55 mmol) and compound 35b (14.3 grams, 57 mmol) were dissolved in CH_2Cl_2 (200 ml). Activated molecular sieves (4 Å. 2 g, powdered) were added, and the reaction was allowed to stir for 30 minutes under nitrogen atmosphere. TMS-OTf was added (4.1 ml, 22.77 mmol) and the reaction 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.

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.

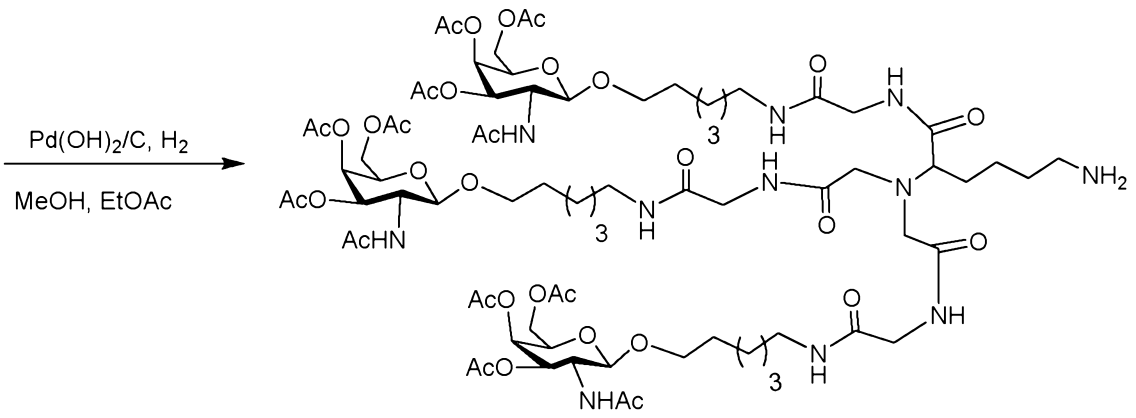
Compound 147 (2.31 g, 11 mmol) was dissolved in anhydrous DMF (100 mL). *N*,*N*-Diisopropylethylamine (DIEA, 3.9 mL, 22 mmol) was added, followed by HBTU (4 g, 10.5 mmol). The

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.

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.



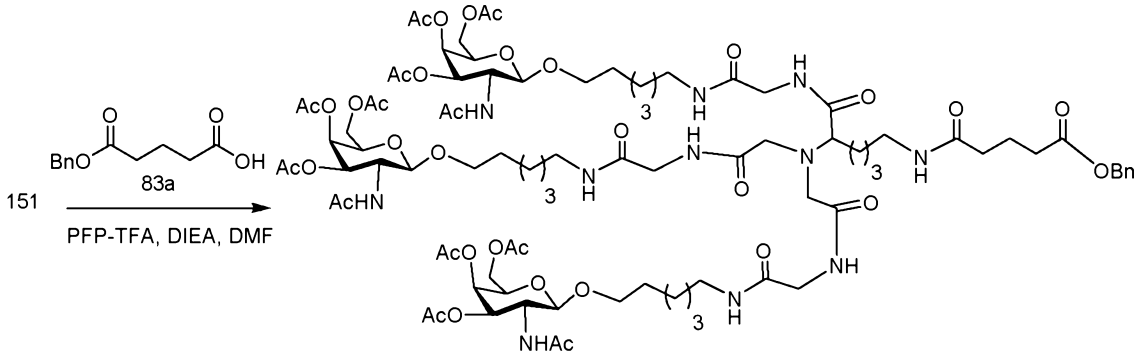
150



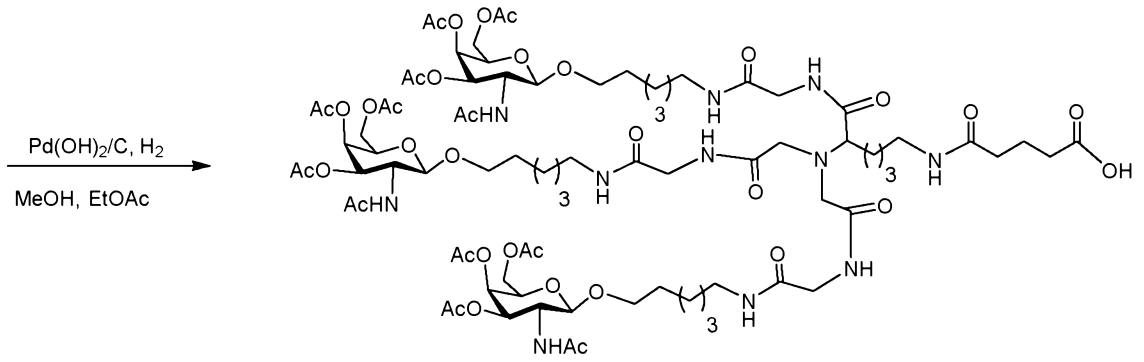
151

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.

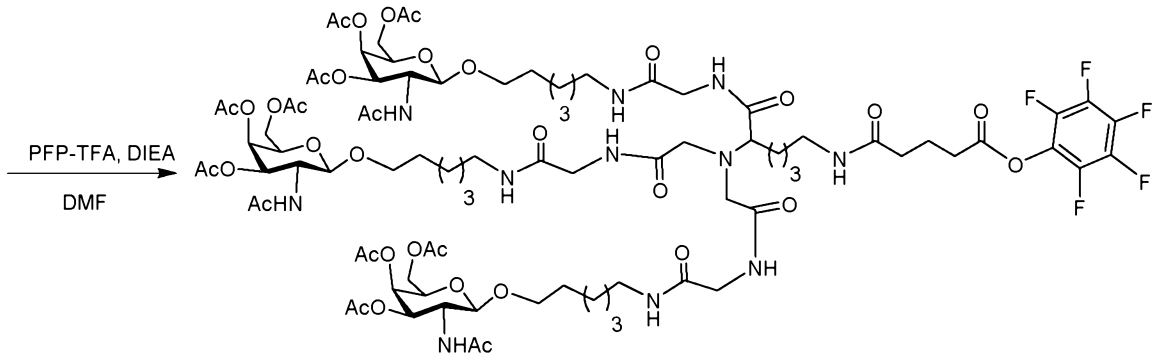
Compound 150 (0.62 g) was dissolved in 1:1 MeOH/ EtOAc (5 L). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (60 mg). Hydrogen gas was bubbled through the solution for 30 minutes. Upon completion (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



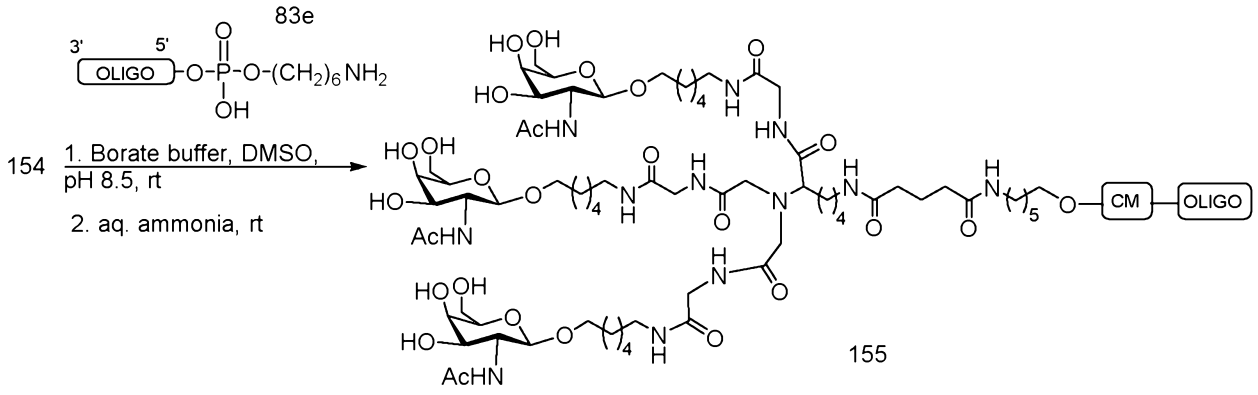
154

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 ^{1}H NMR were consistent with the desired product.

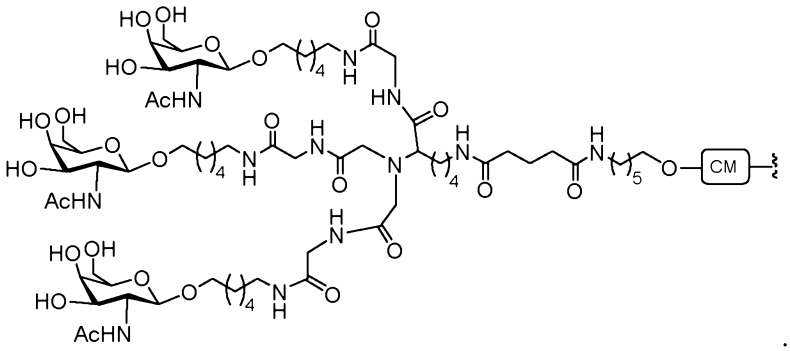
Compound 152 (0.35 g, 0.182 mmol) was dissolved in 1:1 MeOH/EtOAc (10 mL). The reaction mixture was purged by bubbling a stream of argon thru the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (35 mg). Hydrogen gas was bubbled thru the solution for 30 minutes. 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.

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 ^{1}H NMR were consistent with the desired product.

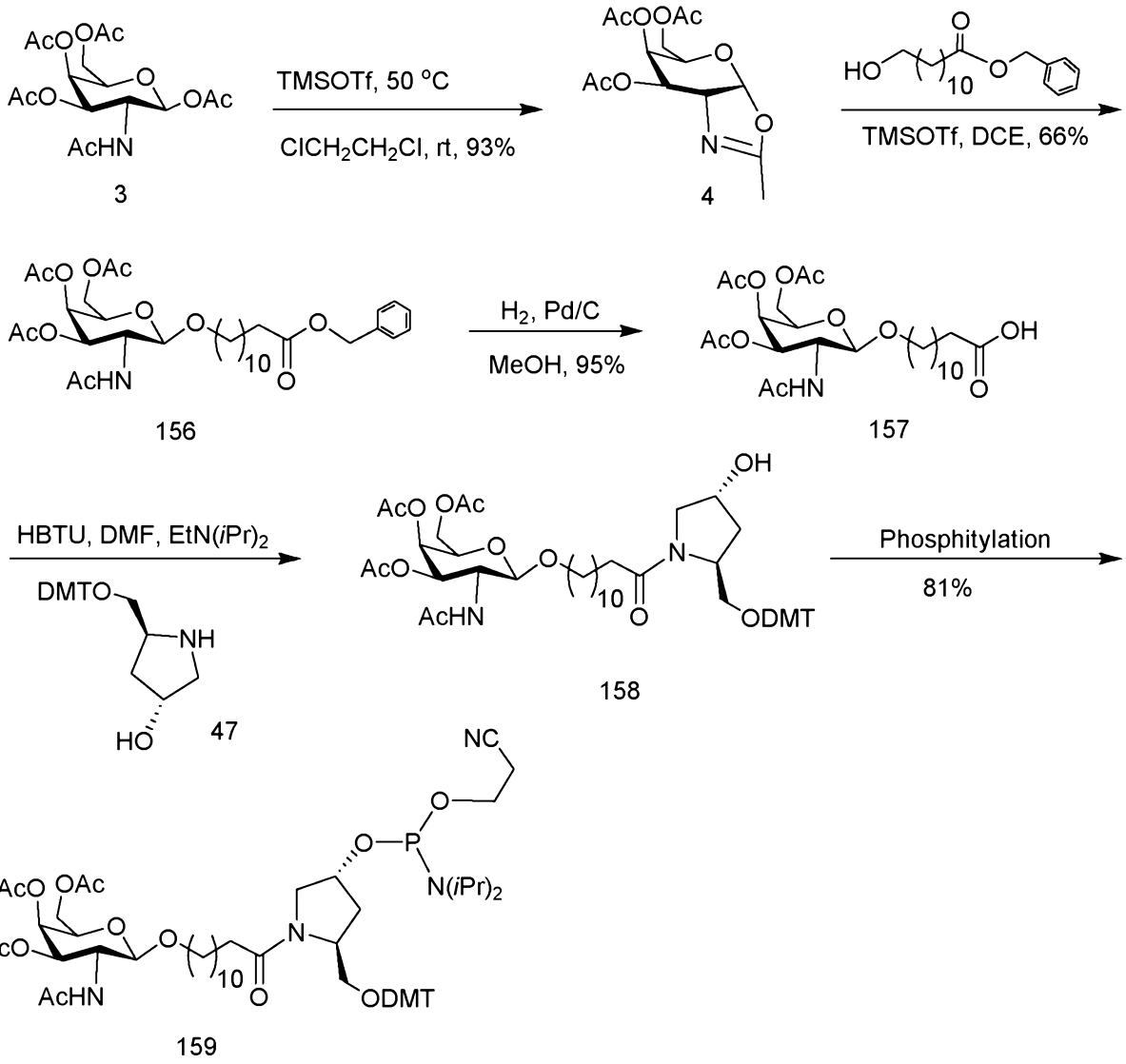


Oligomeric Compound 155, comprising a $GalNAc_3$-6 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-6 ($GalNAc_3$-6_a) can be combined with any cleavable moiety to provide a variety of conjugate groups.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

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



Example 52: Preparation of Oligonucleotide 160 Comprising GalNAc$_3$-9



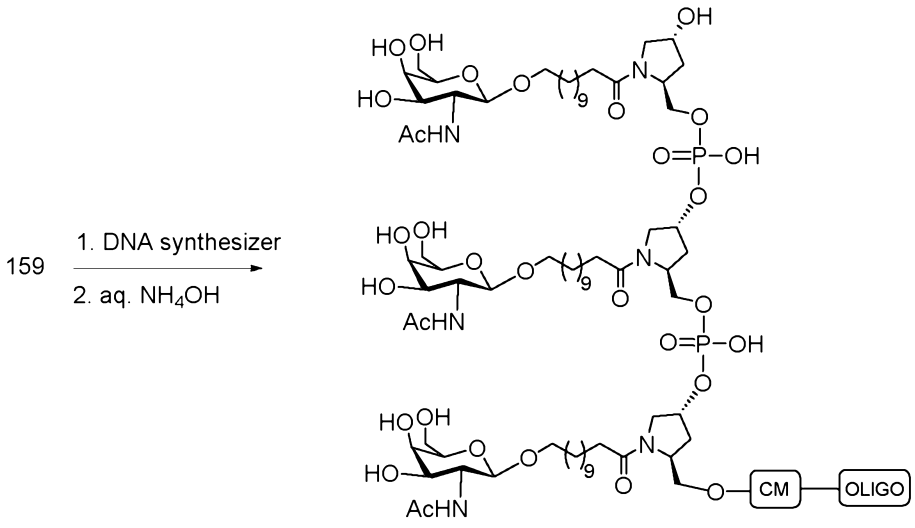
Compound 156 was synthesized following the procedure described in the literature (*J. Med. Chem.* 2004, *47*, 5798-5808).

Compound 156, (18.60 g, 29.28 mmol) was dissolved in methanol (200 mL). Palladium on carbon (6.15 g, 10 wt%, loading (dry basis), matrix carbon powder, wet) was added. The reaction mixture was stirred at room temperature under hydrogen for 18 h. The reaction mixture was filtered through a pad of

celite and the celite pad was washed thoroughly with methanol. The combined filtrate was washed and concentrated to dryness. The residue was purified by silica gel column chromatography and eluted with 5-10 % methanol in dichloromethane to yield Compound 157 (14.26 g, 89%). Mass *m/z* 544.1 $[M-H]^-$.

Compound 157 (5 g, 9.17 mmol) was dissolved in anhydrous DMF (30 mL). HBTU (3.65 g, 9.61 mmol) and *N*,*N*-Diisopropylethylamine (13.73 mL, 78.81 mmol) were added and the reaction mixture was stirred at room temperature for 5 minutes. To this a solution of compound 47 (2.96 g, 7.04 mmol) was added. The reaction was stirred at room temperature for 8 h. The reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution. The mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried (Na_2SO_4), filtered and evaporated. The residue obtained was purified by silica gel column chromatography and eluted with 50% ethyl acetate in hexane to yield compound 158 (8.25g, 73.3%). The structure was confirmed by MS and ^1H NMR analysis.

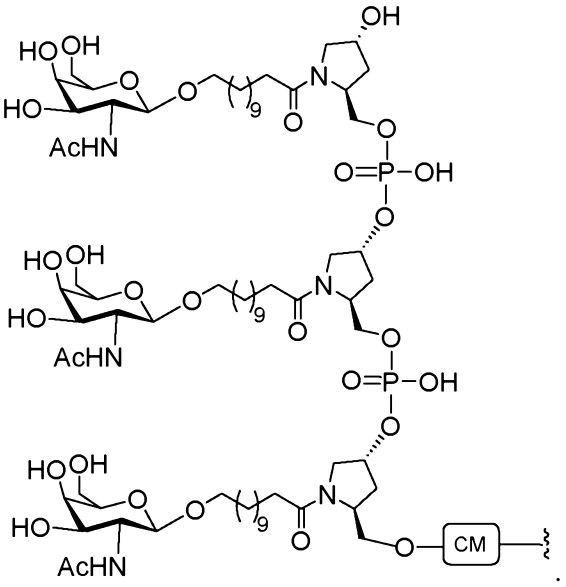
Compound 158 (7.2 g, 7.61 mmol) was dried over P_2O_5 under reduced pressure. The dried compound was dissolved in anhydrous DMF (50 mL). To this 1H-tetrazole (0.43 g, 6.09 mmol) and *N*-methylimidazole (0.3 mL, 3.81 mmol) and 2-cyanoethyl-*N*,*N*,*N*',*N*'-tetraisopropyl phosphorodiamidite (3.65 mL, 11.50 mmol) were added. The reaction mixture was stirred t under an argon atmosphere for 4 h. The reaction mixture was diluted with ethyl acetate (200 mL). The reaction mixture was washed with saturated $NaHCO_3$ and brine. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography and eluted with 50-90 % ethyl acetate in hexane to yield Compound 159 (7.82 g, 80.5%). The structure was confirmed by LCMS and ^{31}P NMR analysis.



160

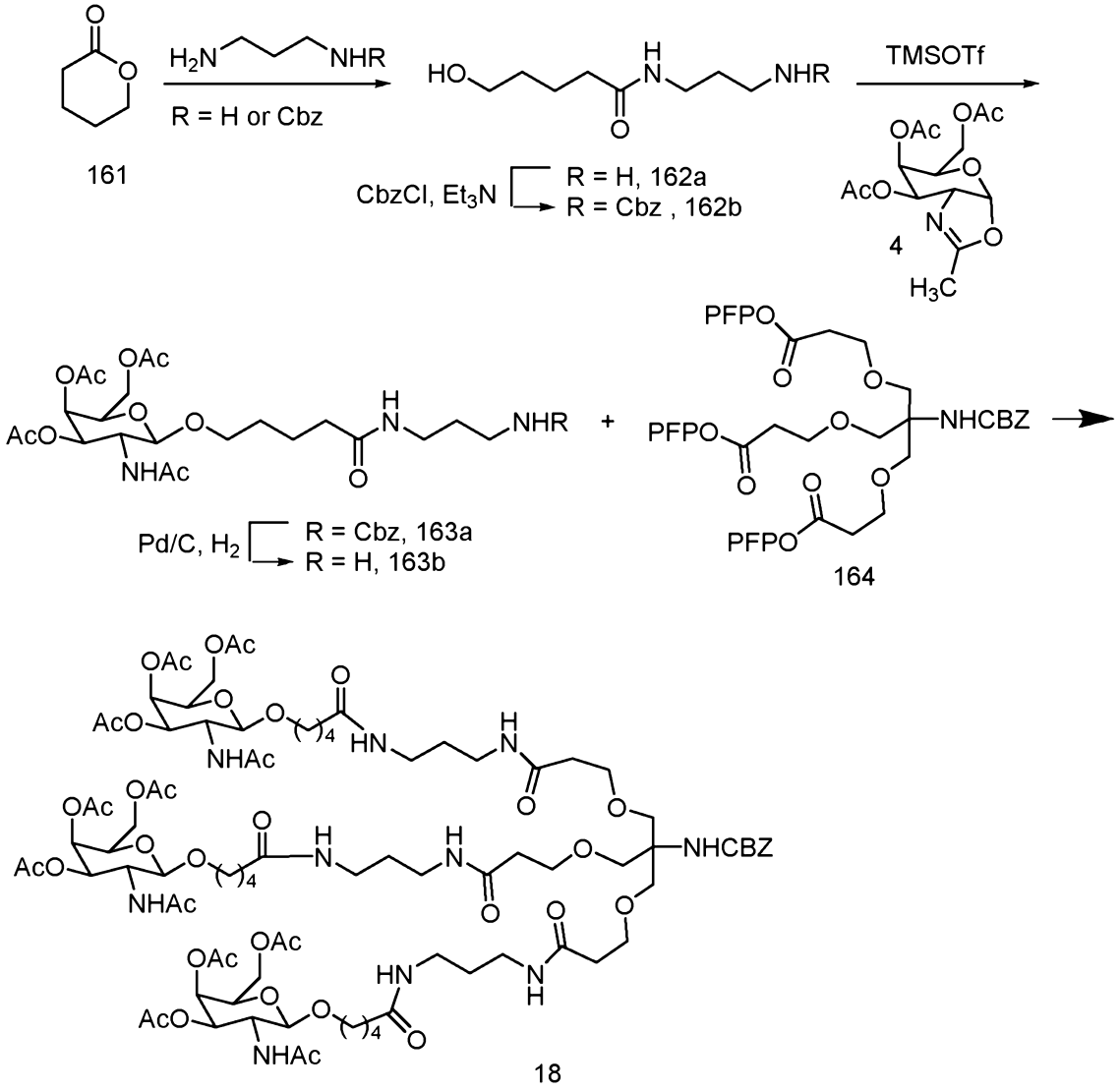
Oligomeric Compound 160, comprising a $GalNAc_3$-9 conjugate group, was prepared using standard oligonucleotide synthesis procedures. Three units of compound 159 were coupled to the solid support, followed by nucleotide phosphoramidites. Treatment of the protected oligomeric compound with aqueous ammonia yielded compound 160. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-9 ($GalNAc_3$-

9_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)-. The structure of $GalNAc_3$-9 ($GalNAc_3$-9_a-CM) is shown below:



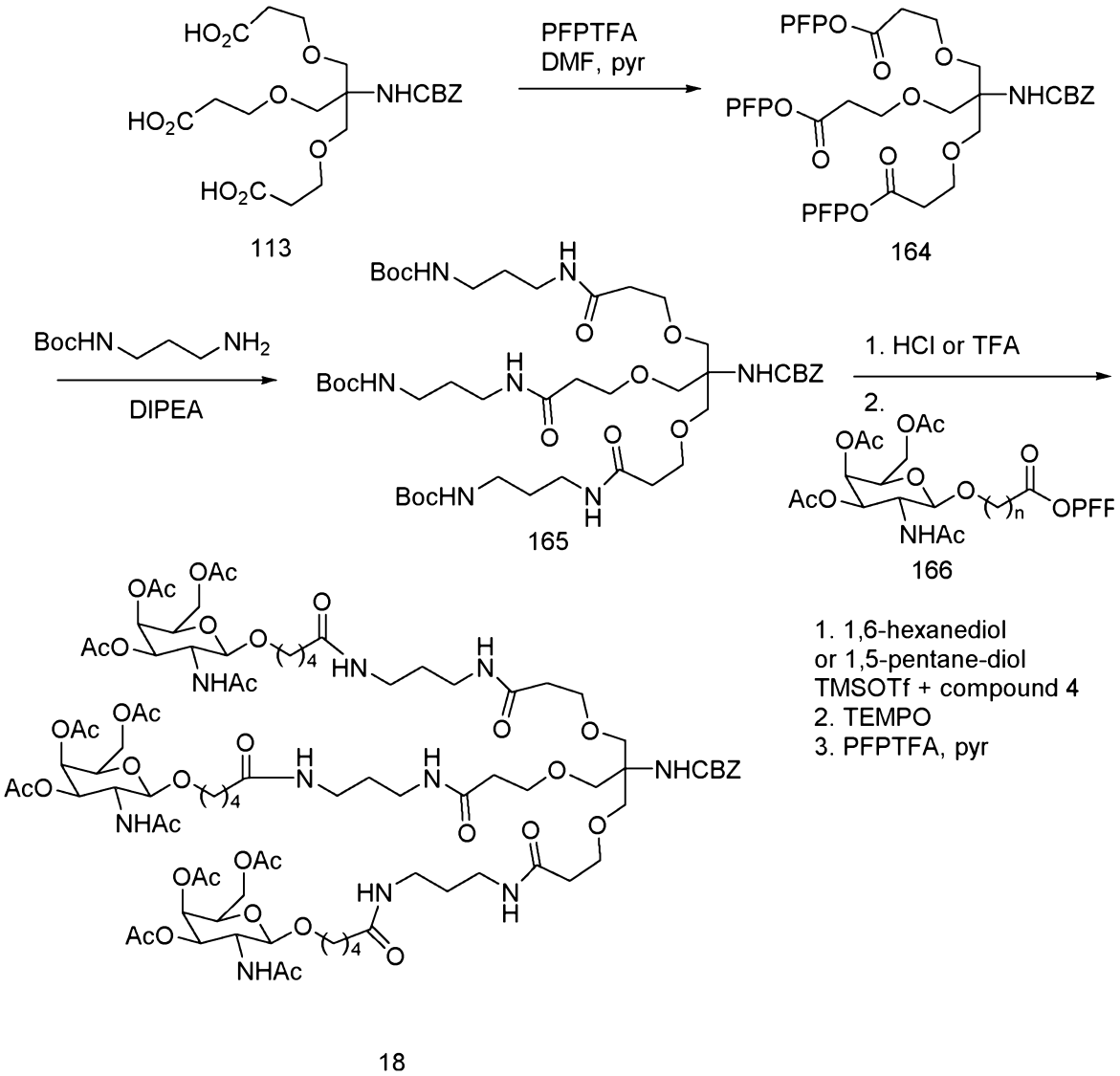
5

Example 53: Alternate procedure for preparation of Compound 18 (GalNAc$_3$-1a and GalNAc$_3$-3a)



Lactone 161 was reacted with diamino propane (3-5 eq) or Mono-Boc protected diamino propane (1 eq) to provide alcohol 162a or 162b. When unprotected propanediamine was used for the above reaction, the excess diamine was removed by evaporation under high vacuum and the free amino group in 162a was protected using CbzCl to provide 162b as a white solid after purification by column chromatography. Alcohol 162b was further reacted with compound 4 in the presence of TMSOTf to provide 163a which was converted to 163b by removal of the Cbz group using catalytic hydrogenation. The pentafluorophenyl (PFP) ester 164 was prepared by reacting triacid 113 (see Example 48) with PFPTFA (3.5 eq) and pyridine (3.5 eq) in DMF (0.1 to 0.5 M). The triester 164 was directly reacted with the amine 163b (3–4 eq) and DIPEA (3–4 eq) to provide Compound 18. The above method greatly facilitates purification of intermediates and minimizes the formation of byproducts which are formed using the procedure described in Example 4.

Example 54: Alternate procedure for preparation of Compound 18 (GalNAc$_3$-1a and GalNAc$_3$-3a)



The triPFP ester 164 was prepared from acid 113 using the procedure outlined in example 53 above and reacted with mono-Boc protected diamine to provide 165 in essentially quantitative yield. The Boc groups were removed with hydrochloric acid or trifluoroacetic acid to provide the triamine which was reacted with the PFP activated acid 166 in the presence of a suitable base such as DIPEA to provide Compound 18.

The PFP protected Gal-NAc acid 166 was prepared from the corresponding acid by treatment with PFPTFA (1-1.2 eq) and pyridine (1-1.2 eq) in DMF. The precursor acid in turn was prepared from the corresponding alcohol by oxidation using TEMPO (0.2 eq) and BAIB in acetonitrile and water. The precursor alcohol was prepared from sugar intermediate 4 by reaction with 1,6-hexanediol (or 1,5-pentanediol or other diol for other n values) (2-4 eq) and TMSOTf using conditions described previously in example 47.

Example 55: Dose-dependent study of oligonucleotides comprising either a 3' or 5'-conjugate group (comparison of GalNAc$_3$-1, 3, 8 and 9) targeting SRB-1 *in vivo*

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 either the 3' or 5' terminus of the respective oligonucleotide by a phosphodiester linked 2'-deoxyadenosine nucleoside (cleavable moiety).

Table 39

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	none	108
ISIS 655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	5/10/5	**GalNAc$_3$-1**	110
ISIS 664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-9_a$**	5/10/5	**GalNAc$_3$-9**	110
ISIS 661161	**GalNAc$_3$-3$_{a\text{-}o'}A_{do}$** $G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-3**	109
ISIS 665001	**GalNAc$_3$-8$_{a\text{-}o'}A_{do}$** $G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-8**	109

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 β-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.

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9. The structure of GalNAc$_3$-9 was shown previously in Example 52. The structure of GalNAc$_3$-3 was shown previously in Example 39. The structure of GalNAc$_3$-8 was shown previously in Example 47.

Treatment

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, 664078, 661161, 665001 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.

As illustrated in Table 40, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. Indeed, the antisense oligonucleotides comprising the phosphodiester linked $GalNAc_3$-1 and $GalNAc_3$-9 conjugates at the 3' terminus (ISIS 655861 and ISIS 664078) and the $GalNAc_3$-3 and $GalNAc_3$-8 conjugates linked at the 5' terminus (ISIS 661161 and ISIS 665001) showed substantial improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 353382). Furthermore, ISIS 664078, comprising a $GalNAc_3$-9 conjugate at the 3' terminus was essentially equipotent compared to ISIS 655861, which comprises a $GalNAc_3$-1 conjugate at the 3' terminus. The 5' conjugated antisense oligonucleotides, ISIS 661161 and ISIS 665001, comprising a $GalNAc_3$-3 or $GalNAc_3$-9, respectively, had increased potency compared to the 3' conjugated antisense oligonucleotides (ISIS 655861 and ISIS 664078).

Table 40

ASOs containing $GalNAc_3$-1, 3, 8 or 9 targeting SRB-1

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	Conjugate
Saline	n/a	100	
353382	3	88	none
	10	68	
	30	36	
655861	0.5	98	**$GalNac_3$ -1** (3')
	1.5	76	
	5	31	
	15	20	
664078	0.5	88	**$GalNac_3$-9** (3')
	1.5	85	
	5	46	
	15	20	
661161	0.5	92	**$GalNac_3$-3** (5')
	1.5	59	
	5	19	
	15	11	
665001	0.5	100	**$GalNac_3$-8** (5')
	1.5	73	
	5	29	
	15	13	

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 the table below.

Table 41

ISIS No.	Dosage mg/kg	ALT	AST	Total Bilirubin	BUN	Conjugate
Saline		24	59	0.1	37.52	
353382	3	21	66	0.2	34.65	none
	10	22	54	0.2	34.2	
	30	22	49	0.2	33.72	
655861	0.5	25	62	0.2	30.65	**GalNac$_3$-1** (3')
	1.5	23	48	0.2	30.97	
	5	28	49	0.1	32.92	
	15	40	97	0.1	31.62	
664078	0.5	40	74	0.1	35.3	**GalNac$_3$-9** (3')
	1.5	47	104	0.1	32.75	
	5	20	43	0.1	30.62	
	15	38	92	0.1	26.2	
661161	0.5	101	162	0.1	34.17	**GalNac$_3$-3** (5')
	1.5 g	42	100	0.1	33.37	
	5 g	23	99	0.1	34.97	
	15	53	83	0.1	34.8	
665001	0.5	28	54	0.1	31.32	**GalNac$_3$-8** (5')
	1.5	42	75	0.1	32.32	
	5	24	42	0.1	31.85	
	15	32	67	0.1	31.	

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*

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	108
ISIS 655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	5/10/5	**GalNAc$_3$-1**	110
ISIS 664507	**GalNAc$_3$-2$_{a\text{-}o'}$$A_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-2**	109
ISIS 661161	**GalNAc$_3$-3$_{a\text{-}o'}$$A_{do}$** $G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-3**	109
ISIS 666224	**GalNAc$_3$-5$_{a\text{-}o'}$$A_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$	5/10/5	**GalNAc$_3$-5**	109

	$^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$			
ISIS 666961	**GalNAc$_3$-6$_{a}$-$_{o}$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-6**	109
ISIS 666981	**GalNAc$_3$-7$_{a}$-$_{o}$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-7**	109
ISIS 666881	**GalNAc$_3$-10$_{a}$-$_{o}$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-10**	109

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 β-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.

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

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.

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	
	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	

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	
666961	0.5	17	63	0.2	26	**GalNAc$_3$-6** (5')
	1.5	23	68	0.2	26	
	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 57: Duration of action study of oligonucleotides comprising a 3'-conjugate group targeting ApoC III *in vivo*

Mice were injected once with the doses indicated below and monitored over the course of 42 days for ApoC-III and plasma triglycerides (Plasma TG) levels. The study was performed using 3 transgenic mice that express human APOC-III in each group.

Table 45

Modified ASO targeting ApoC III

ASO	Sequence (5' to 3')	Linkages	SEQ ID No.
ISIS 304801	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	PS	32
ISIS 647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}$ $A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	PS	111
ISIS 647536	$A_{es}G_{eo}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}$ $A_{ds}G_{ds}{}^{m}C_{ds}T_{eo}T_{eo}T_{es}A_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	PO/PS	111

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 β-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.

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9.

Table 46

ApoC III mRNA (% Saline on Day 1) and Plasma TG Levels (% Saline on Day 1)

ASO	Dose	Target	Day 3	Day 7	Day 14	Day 35	Day 42
Saline	0 mg/kg	ApoC-III	98	100	100	95	116
ISIS 304801	30 mg/kg	ApoC-III	28	30	41	65	74
ISIS 647535	10 mg/kg	ApoC-III	16	19	25	74	94
ISIS 647536	10 mg/kg	ApoC-III	18	16	17	35	51
Saline	0 mg/kg	Plasma TG	121	130	123	105	109
ISIS 304801	30 mg/kg	Plasma TG	34	37	50	69	69
ISIS 647535	10 mg/kg	Plasma TG	18	14	24	18	71
ISIS 647536	10 mg/kg	Plasma TG	21	19	15	32	35

As can be seen in the table above the duration of action increased with addition of the 3'-conjugate group compared to the unconjugated oligonucleotide. There was a further increase in the duration of action for the conjugated mixed PO/PS oligonucleotide 647536 as compared to the conjugated full PS oligonucleotide 647535.

Example 58: Dose-dependent study of oligonucleotides comprising a 3'-conjugate group (comparison of $GalNAc_3$-1 and $GalNAc_4$-11) targeting SRB-1 *in vivo*

The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice. Unconjugated ISIS 440762 was included as an unconjugated standard. Each of the conjugate groups were attached at the 3' terminus of the respective oligonucleotide by a phosphodiester linked 2'-deoxyadenosine nucleoside cleavable moiety.

The structure of $GalNAc_3$-1_a was shown previously in Example 9. The structure of $GalNAc_3$-11_a was shown previously in Example 50.

Treatment

Six week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 440762, 651900, 663748 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.

As illustrated in Table 47, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. The antisense oligonucleotides comprising the phosphodiester linked $GalNAc_3$-1 and $GalNAc_4$-11 conjugates at the 3' terminus (ISIS 651900 and ISIS 663748) showed substantial

improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 440762). The two conjugated oligonucleotides, $GalNAc_3$-1 and $GalNAc_4$-11, were equipotent.

Table 47

Modified ASO targeting SRB-1

ASO	Sequence (5' to 3')	Dose mg/kg	% Saline control	SEQ ID No.
Saline			100	
ISIS 440762	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	0.6	73.45	104
		2	59.66	
		6	23.50	
ISIS 651900	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	0.2	62.75	112
		0.6	29.14	
		2	8.61	
		6	5.62	
ISIS 663748	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do'}\text{-}GalNAc_4\text{-}11_a}$	0.2	63.99	112
		0.6	33.53	
		2	7.58	
		6	5.52	

Capital letters indicate the nucleobase for each nucleoside and ^{m}C indicates a 5-methyl cytosine. Subscripts: "e" indicates a 2'-MOE modified nucleoside; "k" indicates 6'-*(S)*-CH_3 bicyclic nucleoside; "d" indicates a β-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.

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 48 below.

Table 48

ISIS No.	Dosage mg/kg	ALT	AST	Total Bilirubin	BUN	Conjugate
Saline		30	76	0.2	40	
440762	0.60	32	70	0.1	35	none
	2	26	57	0.1	35	
	6	31	48	0.1	39	
651900	0.2	32	115	0.2	39	**$GalNac_3$-1** (3')
	0.6	33	61	0.1	35	
	2	30	50	0.1	37	
	6	34	52	0.1	36	
663748	0.2	28	56	0.2	36	**$GalNac_4$-11** (3')
	0.6	34	60	0.1	35	
	2	44	62	0.1	36	

	6	38	71	0.1	33	

Example 59: Effects of GalNAc$_3$-1 conjugated ASOs targeting FXI *in vivo*

The oligonucleotides listed below were tested in a multiple dose study for antisense inhibition of FXI in mice. ISIS 404071 was included as an unconjugated standard. Each of the conjugate groups was attached at the 3' terminus of the respective oligonucleotide by a phosphodiester linked 2'-deoxyadenosine nucleoside cleavable moiety.

Table 49

Modified ASOs targeting FXI

ASO	Sequence (5' to 3')	Linkages	SEQ ID No.
ISIS 404071	$T_{es}G_{es}G_{es}T_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{es}G_{es}A_{es}G_{es}G_{e}$	PS	115
ISIS 656172	$T_{es}G_{es}G_{es}T_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{es}G_{es}A_{es}G_{es}G_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-1_a$**	PS	113
ISIS 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$_3-1_a$**	PO/PS	113

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 β-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.

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9.

Treatment

Six week old male Balb/c mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously twice a week for 3 weeks at the dosage shown below with ISIS 404071, 656172, 656173 or with PBS treated control. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration to determine the liver FXI mRNA levels using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. Plasma FXI protein levels were also measured using ELISA. FXI 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 FXI mRNA levels for each treatment group. The data was normalized to PBS-treated control and is denoted as "% PBS". The ED$_{50}$s were measured using similar methods as described previously and are presented below.

Table 50

Factor XI mRNA (% Saline)

ASO	Dose mg/kg	% Control	Conjugate	Linkages

Saline		100	none	
ISIS 404071	3	92	none	PS
	10	40		
	30	15		
ISIS 656172	0.7	74	**GalNAc$_3$-1**	PS
	2	33		
	6	9		
ISIS 656173	0.7	49	**GalNAc$_3$-1**	PO/PS
	2	22		
	6	1		

As illustrated in Table 50, treatment with antisense oligonucleotides lowered FXI mRNA levels in a dose-dependent manner. The oligonucleotides comprising a 3'-GalNAc$_3$-1 conjugate group showed substantial improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 404071). Between the two conjugated oligonucleotides an improvement in potency was further provided by substituting some of the PS linkages with PO (ISIS 656173).

As illustrated in Table 50a, treatment with antisense oligonucleotides lowered FXI protein levels in a dose-dependent manner. The oligonucleotides comprising a 3'-GalNAc$_3$-1 conjugate group showed substantial improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 404071). Between the two conjugated oligonucleotides an improvement in potency was further provided by substituting some of the PS linkages with PO (ISIS 656173).

Table 50a

Factor XI protein (% Saline)

ASO	Dose mg/kg	Protein (% Control)	Conjugate	Linkages
Saline		100	none	
ISIS 404071	3	127	none	PS
	10	32		
	30	3		
ISIS 656172	0.7	70	**GalNAc$_3$-1**	PS
	2	23		
	6	1		
ISIS 656173	0.7	45	**GalNAc$_3$-1**	PO/PS
	2	6		
	6	0		

Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Total bilirubin, total albumin, CRE 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 the table below.

Table 51

ISIS No.	Dosage mg/kg	ALT	AST	Total Albumin	Total Bilirubin	CRE	BUN	Conjugate
Saline		71.8	84.0	3.1	0.2	0.2	22.9	
404071	3	152.8	176.0	3.1	0.3	0.2	23.0	none
	10	73.3	121.5	3.0	0.2	0.2	21.4	
	30	82.5	92.3	3.0	0.2	0.2	23.0	
656172	0.7	62.5	111.5	3.1	0.2	0.2	23.8	**GalNac$_3$-1** (3')
	2	33.0	51.8	2.9	0.2	0.2	22.0	
	6	65.0	71.5	3.2	0.2	0.2	23.9	
656173	0.7	54.8	90.5	3.0	0.2	0.2	24.9	**GalNac$_3$-1** (3')
	2	85.8	71.5	3.2	0.2	0.2	21.0	
	6	114.0	101.8	3.3	0.2	0.2	22.7	

Example 60: Effects of conjugated ASOs targeting SRB-1 *in vitro*

The oligonucleotides listed below were tested in a multiple dose study for antisense inhibition of SRB-1 in primary mouse hepatocytes. ISIS 353382 was included as an unconjugated standard. Each of the conjugate groups were attached at the 3' or 5' terminus of the respective oligonucleotide by a phosphodiester linked 2'-deoxyadenosine nucleoside cleavable moiety.

Table 52

Modified ASO targeting SRB-1

ASO	Sequence (5' to 3')	Motif	Conjugate	SEQ ID No.
ISIS 353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	none	108
ISIS 655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	5/10/5	**GalNAc$_3$-1**	110
ISIS 655862	$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	5/10/5	**GalNAc$_3$-1**	110
ISIS 661161	**GalNAc$_3$-3$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-3**	109
ISIS 665001	**GalNAc$_3$-8$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-8**	109
ISIS 664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-9_a$**	5/10/5	**GalNAc$_3$-9**	110
ISIS 666961	**GalNAc$_3$-6$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-6**	109
ISIS 664507	**GalNAc$_3$-2$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-2**	109
ISIS 666881	**GalNAc$_3$-10$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-10**	109
ISIS 666224	**GalNAc$_3$-5$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-5**	109
ISIS 666981	**GalNAc$_3$-7$_{a\text{-}o'}$A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-7**	109

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 β-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.

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9. The structure of GalNAc$_3$-3a was shown previously in Example 39. The structure of GalNAc$_3$-8a was shown previously in Example 47. The structure of GalNAc$_3$-9a was shown previously in Example 52. The structure of GalNAc$_3$-6a was shown previously in Example 51. The structure of GalNAc$_3$-2a was shown previously in Example 37. The structure of GalNAc$_3$-10a was shown previously in Example 46. The structure of GalNAc$_3$-5a was shown previously in Example 49. The structure of GalNAc$_3$-7a was shown previously in Example 48.

Treatment

The oligonucleotides listed above were tested *in vitro* in primary mouse hepatocyte cells plated at a density of 25,000 cells per well and treated with 0.03, 0.08, 0.24, 0.74, 2.22, 6.67 or 20 nM modified oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and mRNA levels were measured by quantitative real-time PCR and the SRB-1 mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®.

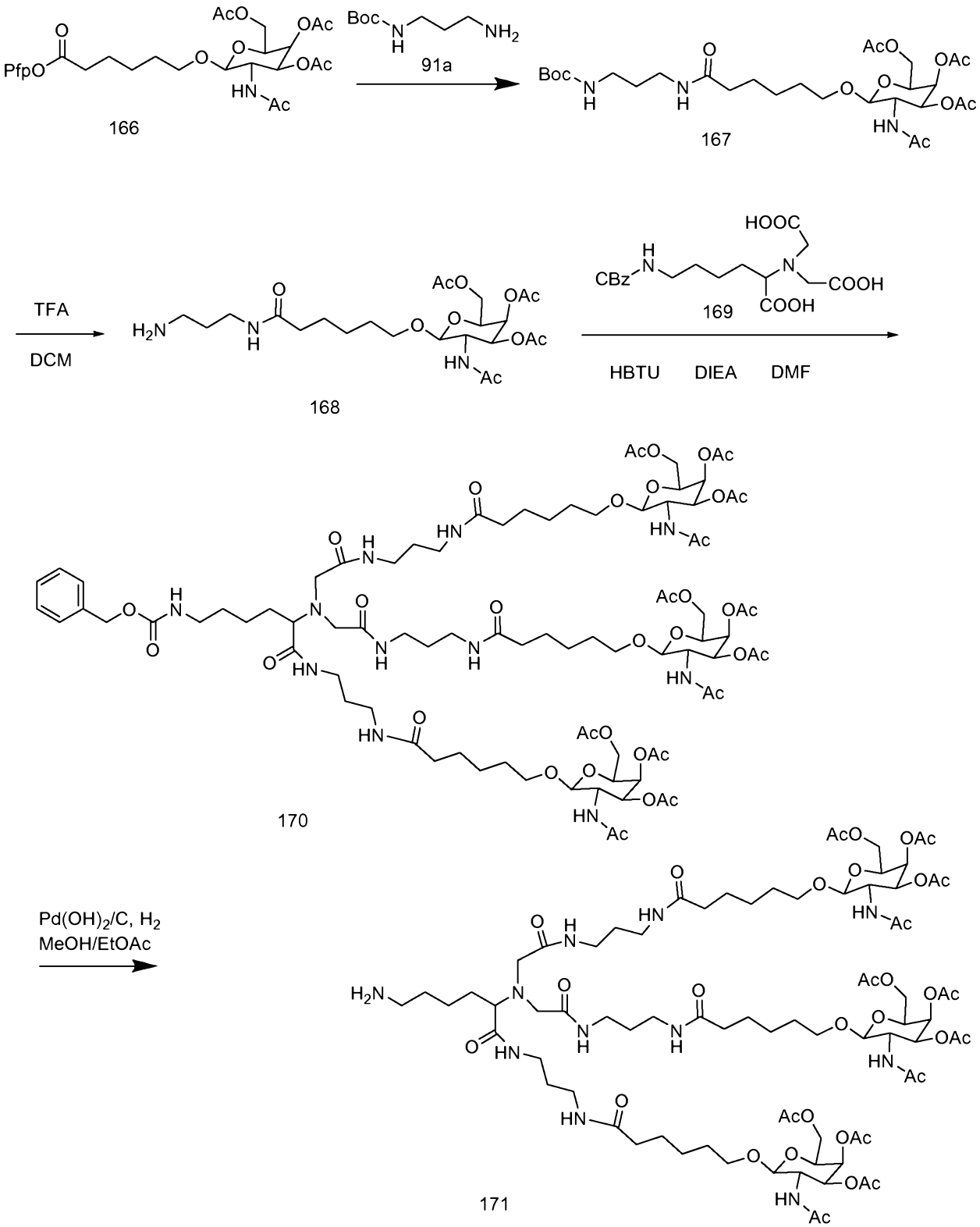
The IC_{50} was calculated using standard methods and the results are presented in Table 53. The results show that, under free uptake conditions in which no reagents or electroporation techniques are used to artificially promote entry of the oligonucleotides into cells, the oligonucleotides comprising a GalNAc conjugate were significantly more potent in hepatocytes than the parent oligonucleotide (ISIS 353382) that does not comprise a GalNAc conjugate.

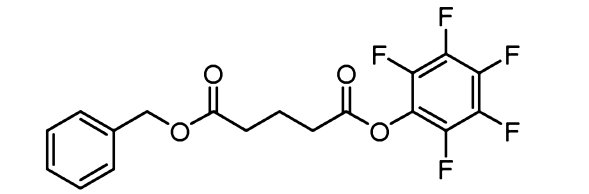
Table 53

ASO	IC_{50} (nM)	Internucleoside linkages	Conjugate	SEQ ID No.
ISIS 353382	190[a]	PS	none	108
ISIS 655861	11[a]	PS	**GalNAc$_3$-1**	110
ISIS 655862	3	PO/PS	**GalNAc$_3$-1**	110
ISIS 661161	15[a]	PS	**GalNAc$_3$-3**	109
ISIS 665001	20	PS	**GalNAc$_3$-8**	109
ISIS 664078	55	PS	**GalNAc$_3$-9**	110
ISIS 666961	22[a]	PS	**GalNAc$_3$-6**	109
ISIS 664507	30	PS	**GalNAc$_3$-2**	109
ISIS 666881	30	PS	**GalNAc$_3$-10**	109
ISIS 666224	30[a]	PS	**GalNAc$_3$-5**	109
ISIS 666981	40	PS	**GalNAc$_3$-7**	109

[a]Average of multiple runs.

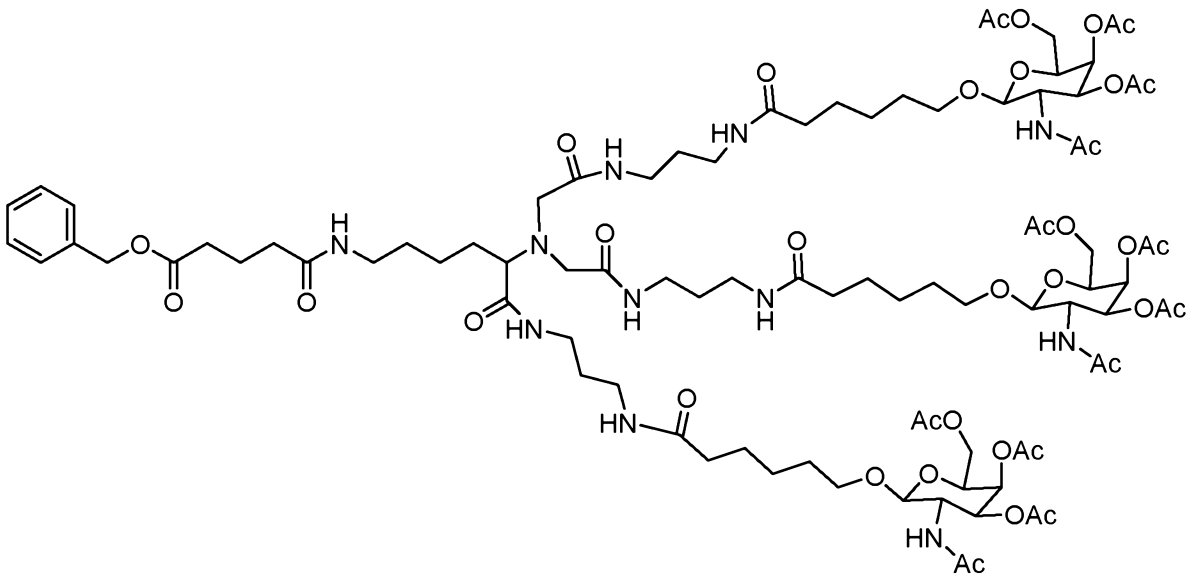
Example 61: Preparation of oligomeric compound 175 comprising $GalNAc_3$-12



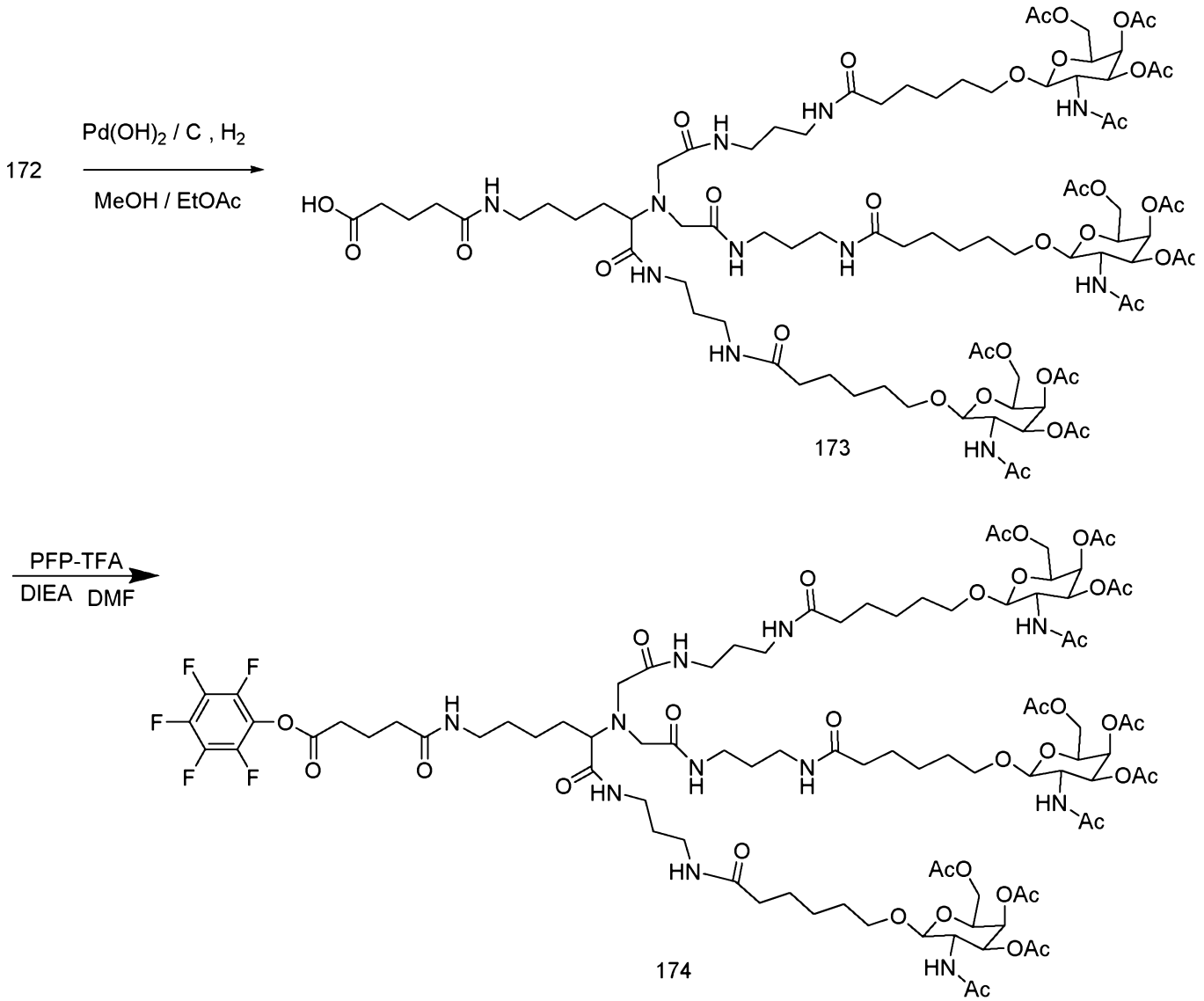


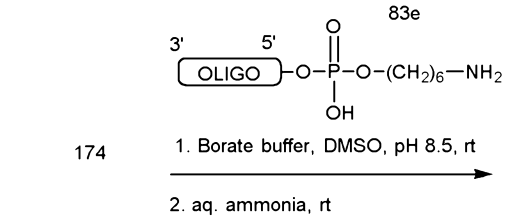
benzyl (perfluorophenyl) glutarate

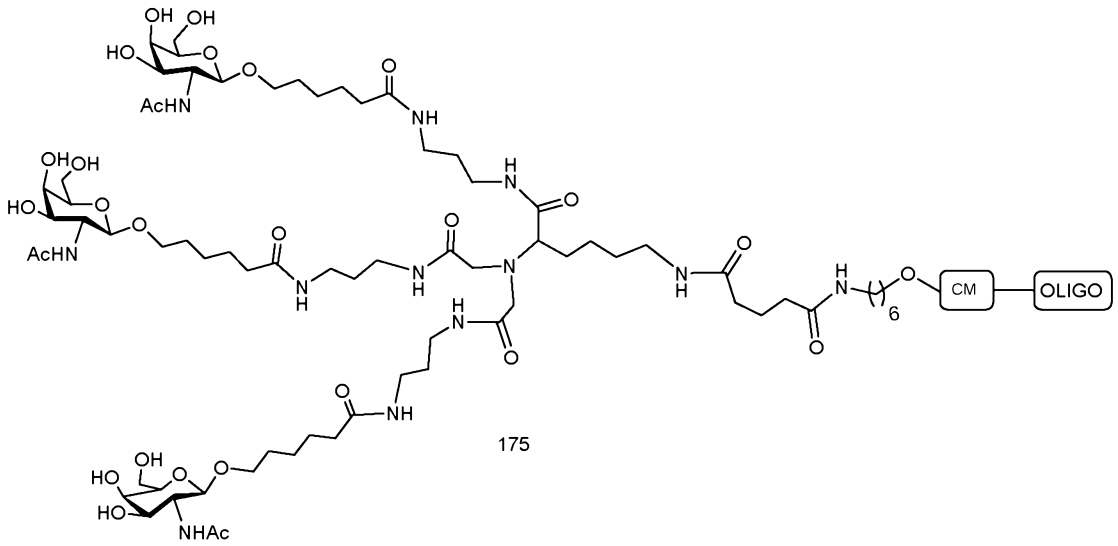
DMF



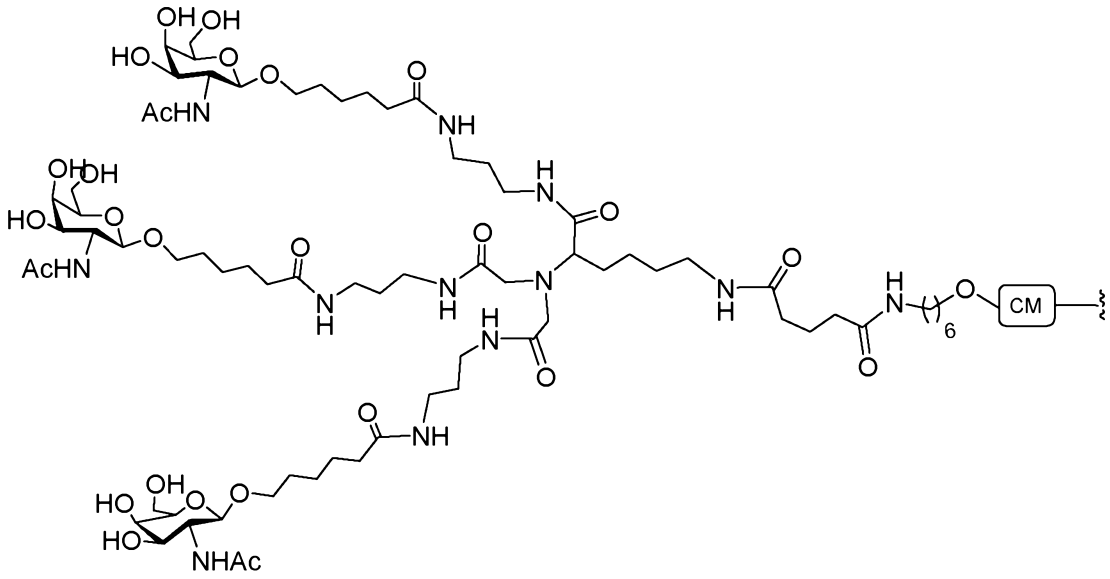
172


172
Pd(OH)2 / C , H2
MeOH / EtOAc
173
PFP-TFA
DIEA DMF
174

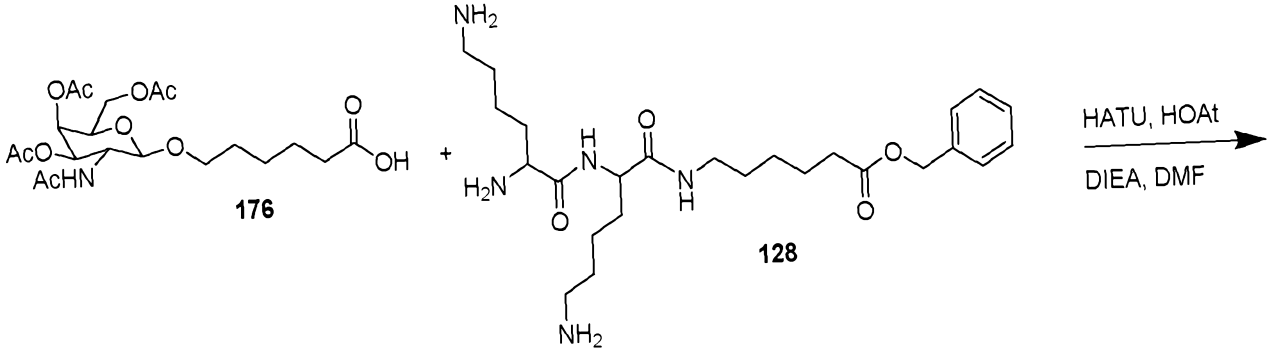


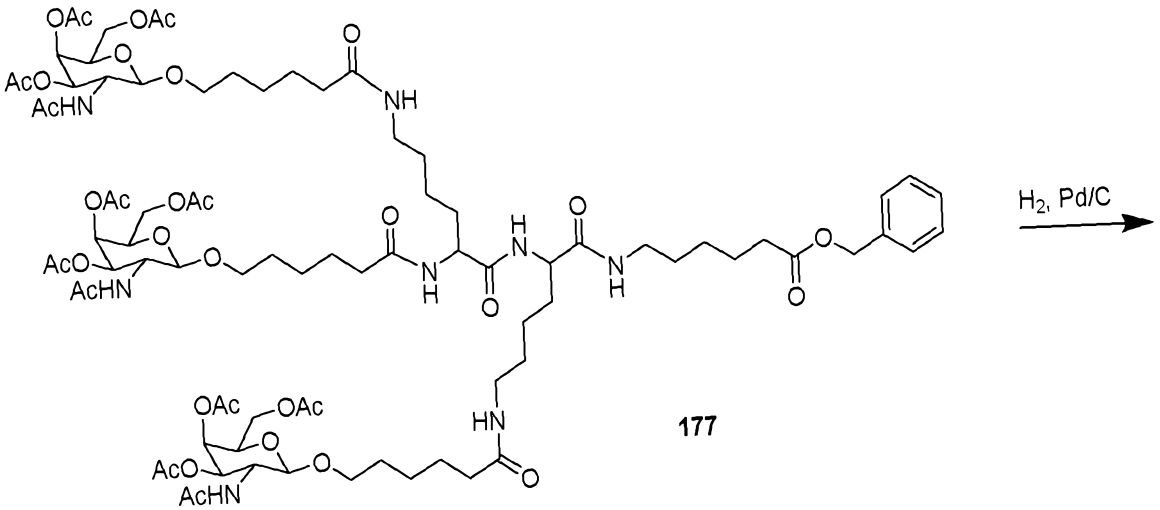


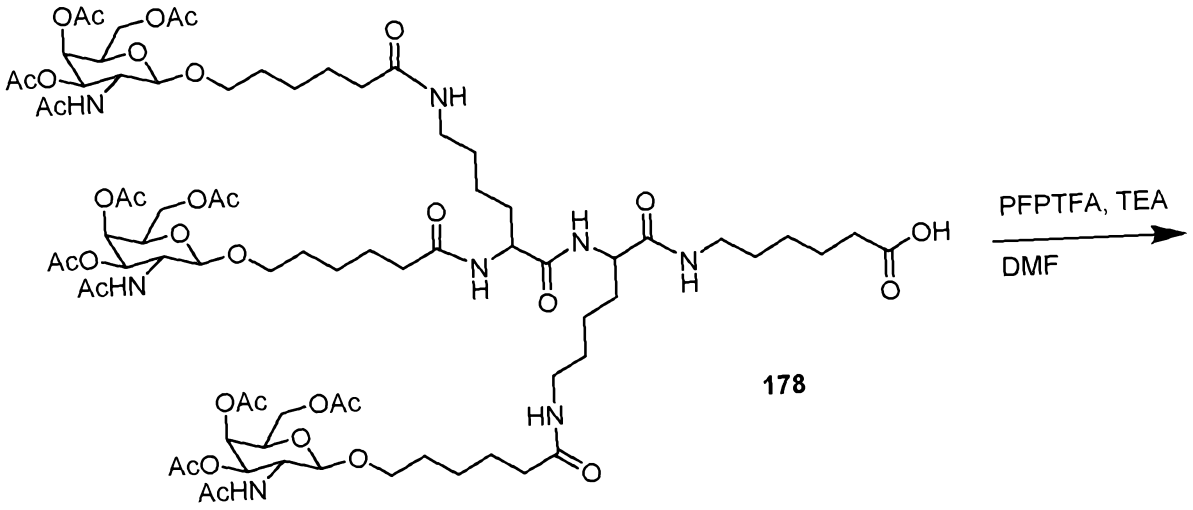
Compound 169 is commercially available. Compound 172 was prepared by addition of benzyl (perfluorophenyl) glutarate to compound 171. The benzyl (perfluorophenyl) glutarate was prepared by adding PFP-TFA and DIEA to 5-(benzyloxy)-5-oxopentanoic acid in DMF. Oligomeric compound 175, comprising a $GalNAc_3$-12 conjugate group, was prepared from compound 174 using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-12 ($GalNAc_3$-12_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In a certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-12 ($GalNAc_3$-12_a-CM-) is shown below:

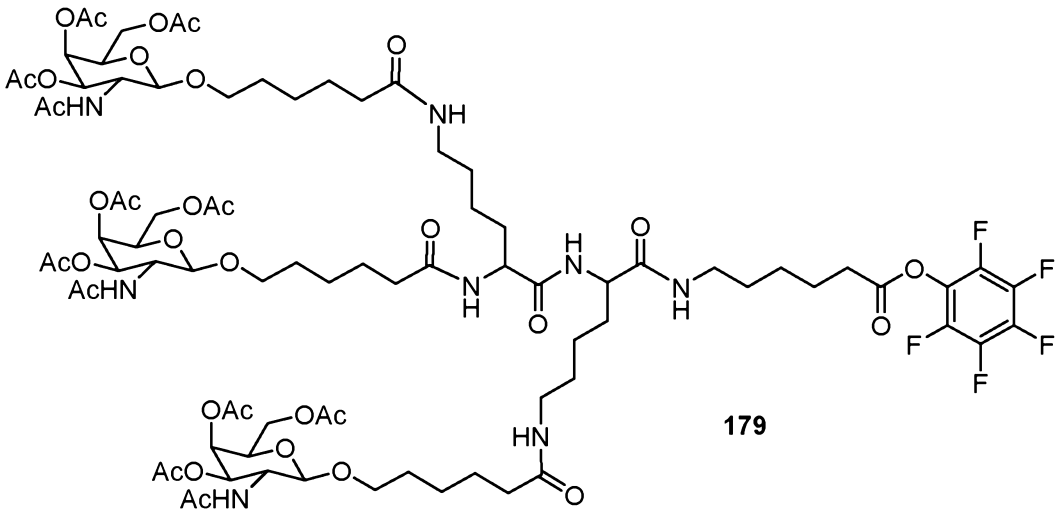


Example 62: Preparation of oligomeric compound 180 comprising GalNAc$_3$-13

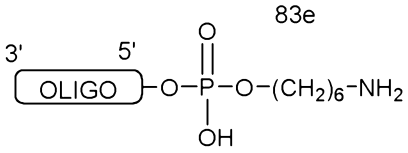

OAc
OAc
AcO
AcHN
OH
176
NH2
H2N
128
HATU, HOAt
DIEA, DMF


177
H2, Pd/C


178
PFPTFA, TEA
DMF

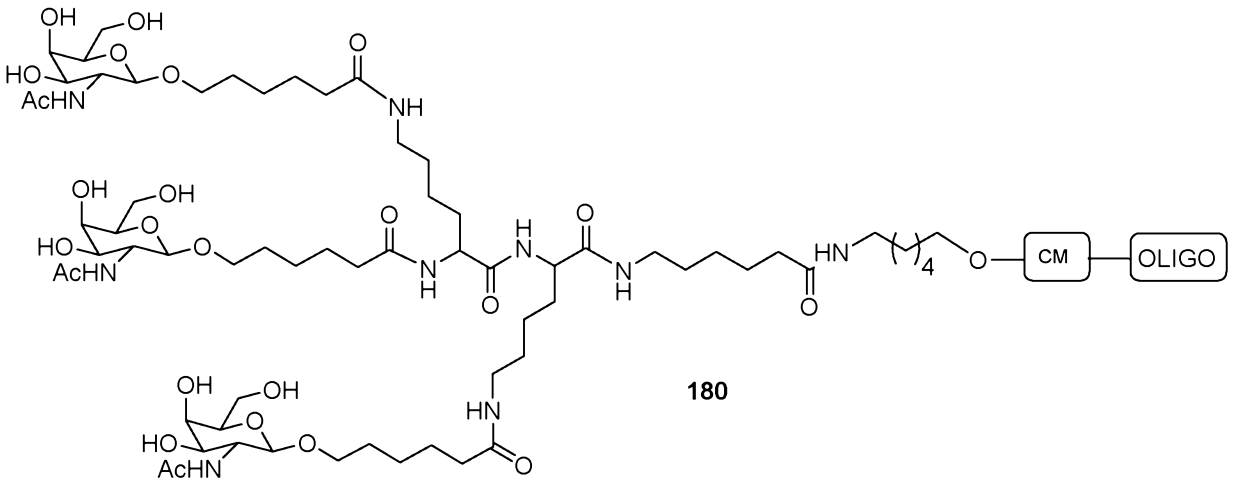


179



1. Borate buffer, DMSO, pH 8.5, rt

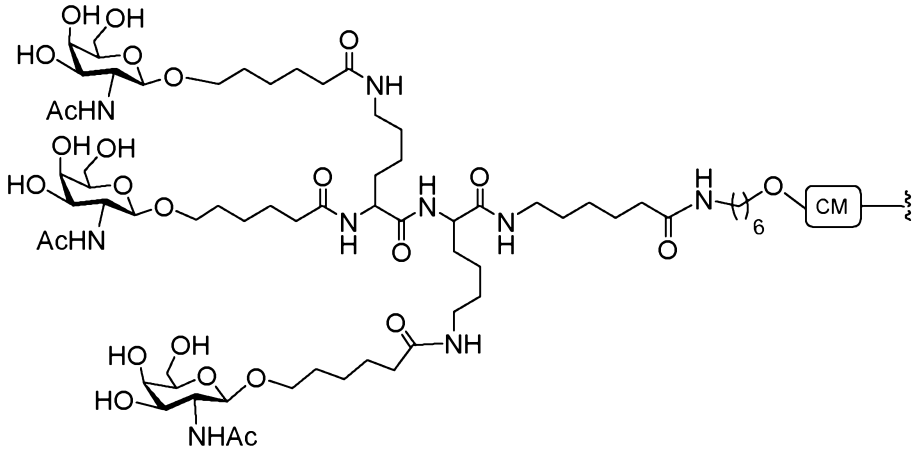
2. aq. ammonia, rt



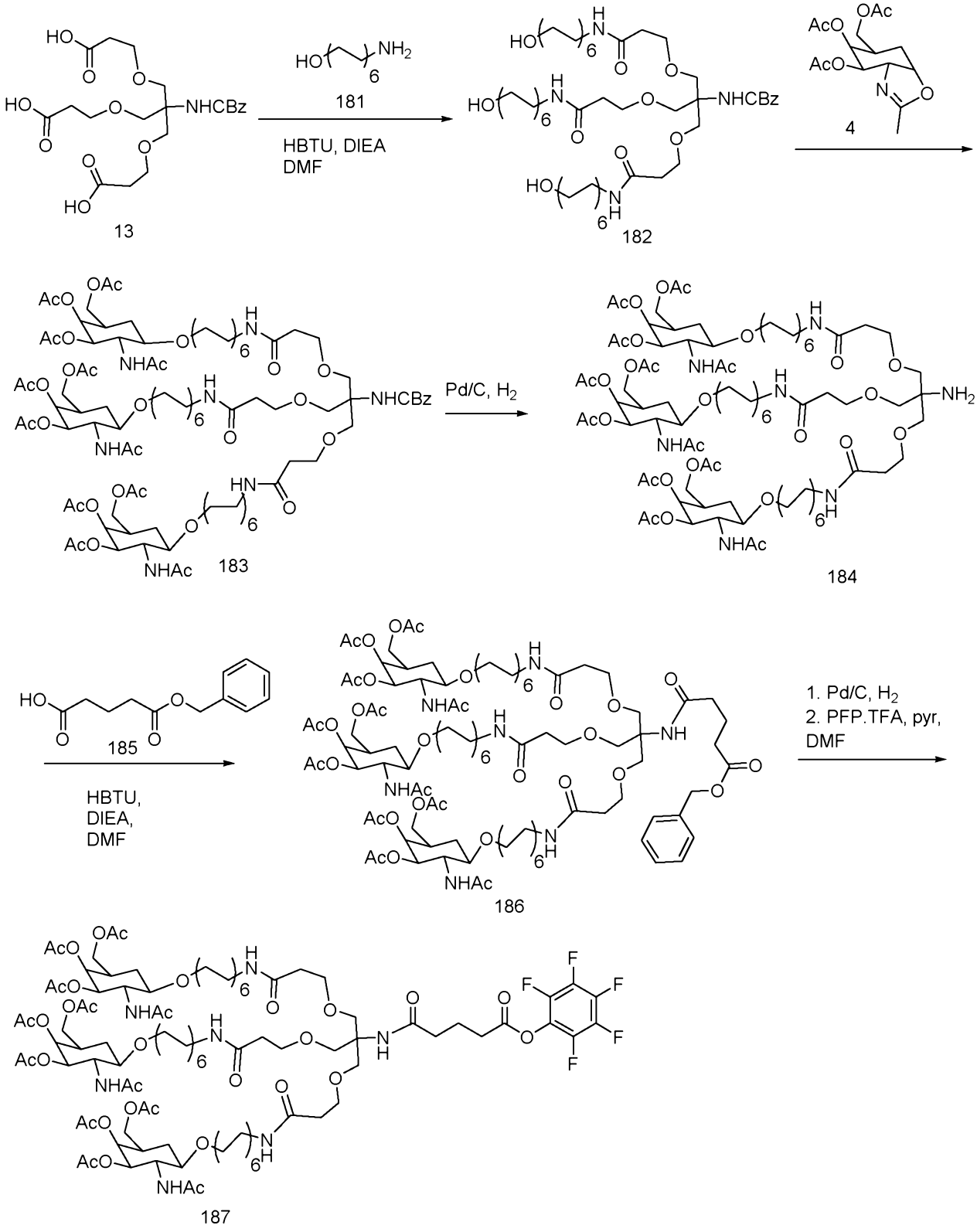
180

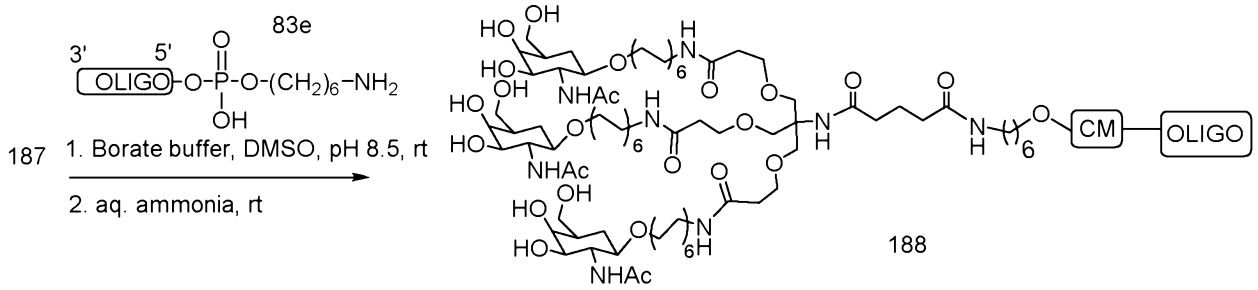
Compound 176 was prepared using the general procedure shown in Example 2. Oligomeric compound 180, comprising a $GalNAc_3$-13 conjugate group, was prepared from compound 177 using the general procedures illustrated in Example 49. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-13 ($GalNAc_3$-13_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In a

certainembodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-13 ($GalNAc_3$-13_a-CM-) is shown below:

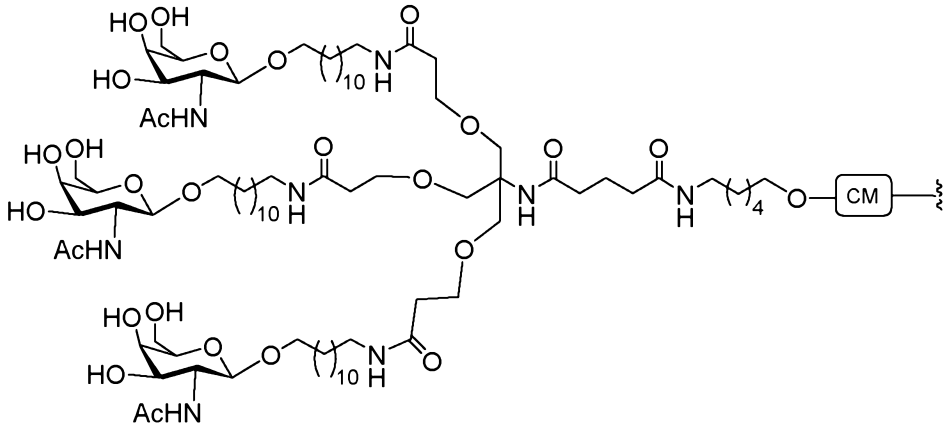


Example 63: Preparation of oligomeric compound 188 comprising $GalNAc_3$-14

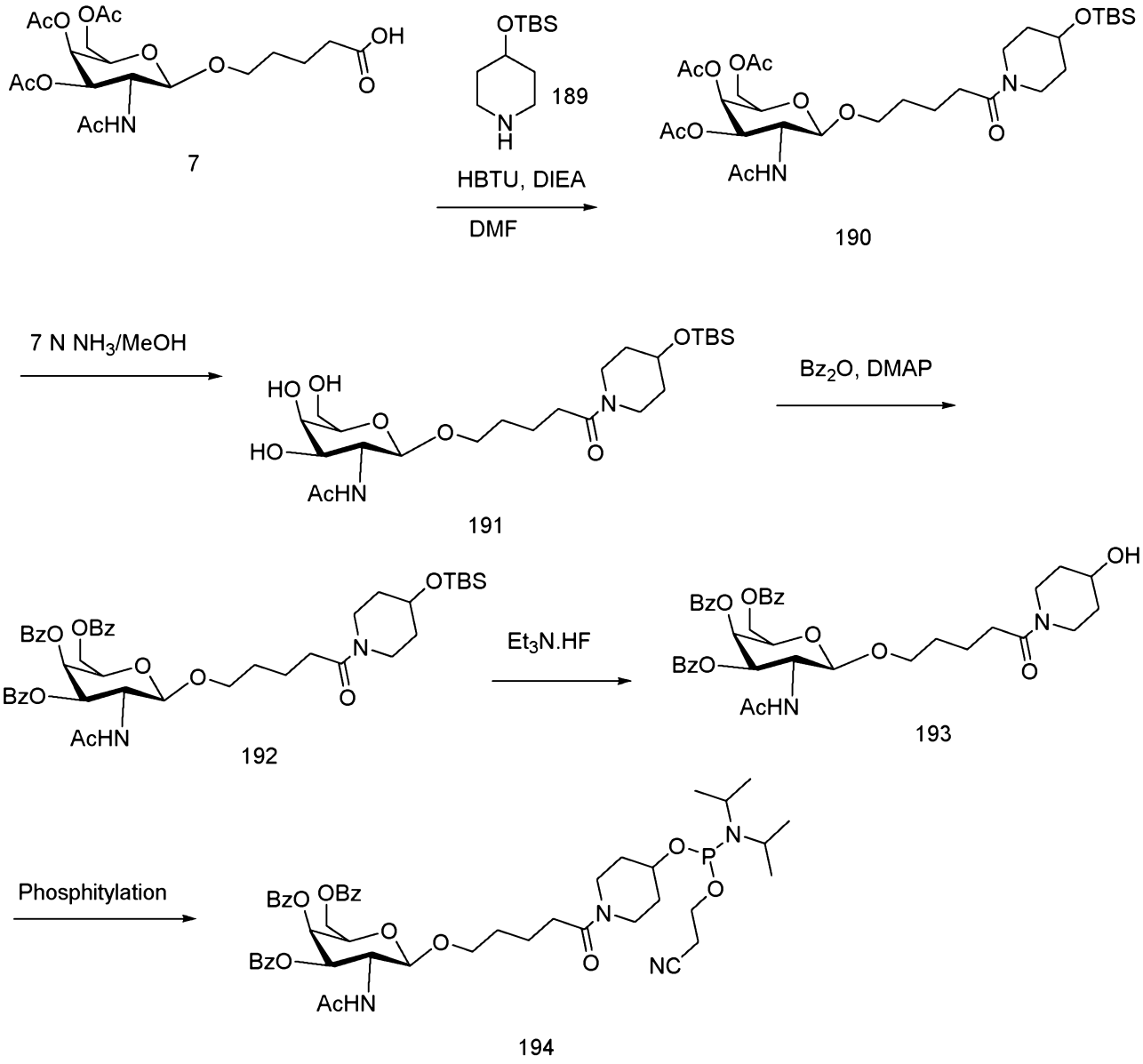

13
181
HBTU, DIEA
DMF
182
4
Pd/C, H2
183
184
185
HBTU,
DIEA,
DMF
186
1. Pd/C, H2
2. PFP.TFA, pyr,
DMF
187

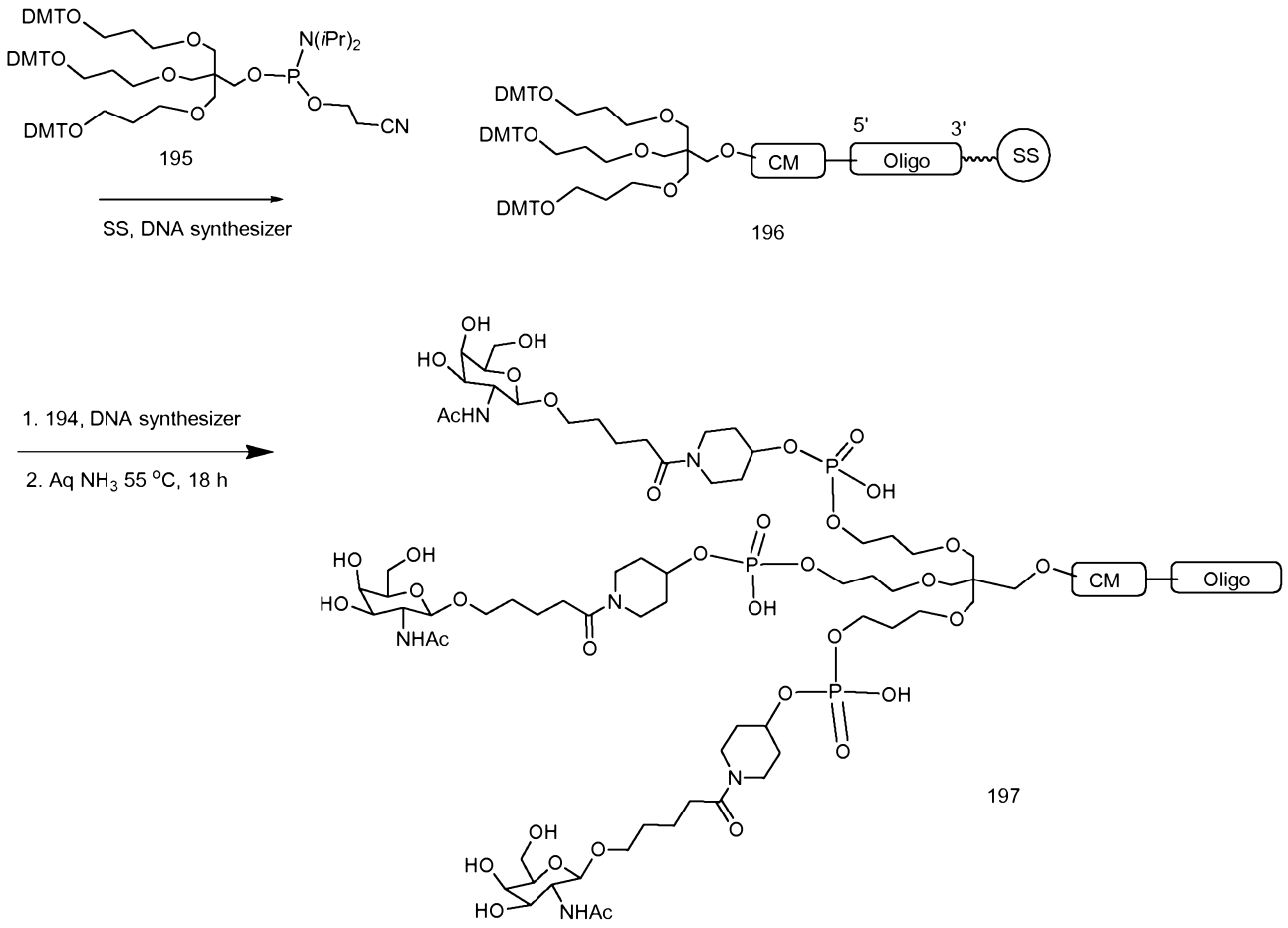


Compounds 181 and 185 are commercially available. Oligomeric compound 188, comprising a $GalNAc_3$-14 conjugate group, was prepared from compound 187 using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-14 ($GalNAc_3$-14_a) can be combined 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)-. The structure of $GalNAc_3$-14 ($GalNAc_3$-14_a-CM-) is shown below:

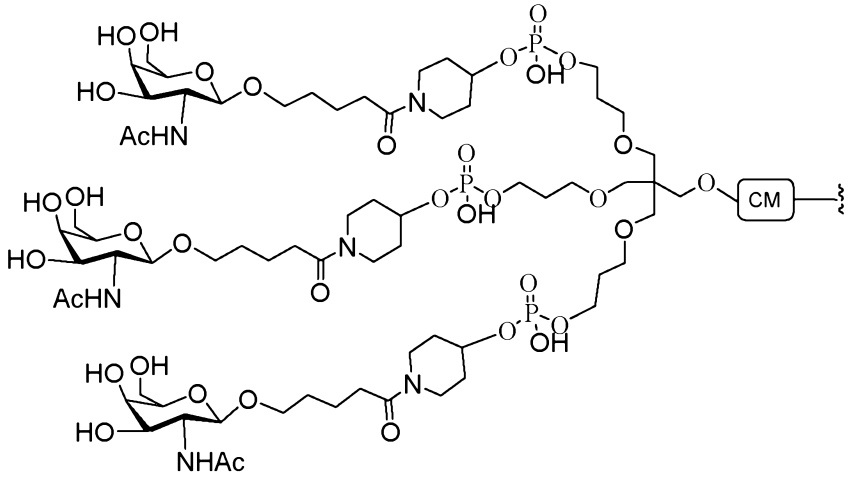


Example 64: Preparation of oligomeric compound 197 comprising $GalNAc_3$-15


AcO
OAc
O
AcO
AcHN
OH
O
7
OTBS
189
N
H
HBTU, DIEA
DMF
OTBS
190
7 N NH3/MeOH
HO
OH
HO
191
Bz2O, DMAP
BzO
OBz
BzO
192
Et3N.HF
193
OH
Phosphitylation
P
NC
194



Compound 189 is commercially available. Compound 195 was prepared using the general procedure shown in Example 31. Oligomeric compound 197, comprising a $GalNAc_3$-15 conjugate group, was prepared from compounds 194 and 195 using standard oligonucleotide synthesis procedures. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-15 ($GalNAc_3$-15_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)-. The structure of $GalNAc_3$-15 ($GalNAc_3$-15_a-CM-) is shown below:



Example 65: Dose-dependent study of oligonucleotides comprising a 5'-conjugate group (comparison of GalNAc$_3$-3, 12, 13, 14, and 15) targeting SRB-1 *in vivo*

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 GalNAc$_3$ conjugate groups was attached at the 5' terminus of the respective oligonucleotide by a phosphodiester linked 2'-deoxyadenosine nucleoside (cleavable moiety).

Table 54

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	Conjugate	SEQ ID No.
353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	none	108
661161	**GalNAc$_3$-3$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-3	109
671144	**GalNAc$_3$-12$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-12	109
670061	**GalNAc$_3$-13$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-13	109
671261	**GalNAc$_3$-14$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-14	109
671262	**GalNAc$_3$-15$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-15	109

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 β-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.

The structure of $GalNAc_3$-3_a was shown previously in Example 39. The structure of $GalNAc_3$-12a was shown previously in Example 61. The structure of $GalNAc_3$-13a was shown previously in Example 62. The structure of $GalNAc_3$-14a was shown previously in Example 63. The structure of $GalNAc_3$-15a was shown previously in Example 64.

Treatment

Six to eight week old C57bl6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once or twice at the dosage shown below with ISIS 353382, 661161, 671144, 670061, 671261, 671262, or with saline. Mice that were dosed twice received the second dose three days after the first dose. 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.

As illustrated in Table 55, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. No significant differences in target knockdown were observed between animals that received a single dose and animals that received two doses (see ISIS 353382 dosages 30 and 2 x 15 mg/kg; and ISIS 661161 dosages 5 and 2 x 2.5 mg/kg). The antisense oligonucleotides comprising the phosphodiester linked $GalNAc_3$-3, 12, 13, 14, and 15 conjugates showed substantial improvement in potency compared to the unconjugated antisense oligonucleotide (ISIS 335382).

Table 55

SRB-1 mRNA (% Saline)

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	ED_{50} (mg/kg)	Conjugate
Saline	n/a	100.0	n/a	n/a
353382	3	85.0	22.4	none
	10	69.2		
	30	34.2		
	2 x 15	36.0		
661161	0.5	87.4	2.2	$GalNAc_3$-3
	1.5	59.0		
	5	25.6		
	2 x 2.5	27.5		
	15	17.4		
671144	0.5	101.2	3.4	$GalNAc_3$-12
	1.5	76.1		
	5	32.0		
	15	17.6		
670061	0.5	94.8	2.1	$GalNAc_3$-13
	1.5	57.8		
	5	20.7		

	15	13.3		
671261	0.5	110.7	4.1	$GalNAc_3$-14
	1.5	81.9		
	5	39.8		
	15	14.1		
671262	0.5	109.4	9.8	$GalNAc_3$-15
	1.5	99.5		
	5	69.2		
	15	36.1		

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 changes in body weights were evaluated with no significant differences from the saline group (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 56 below.

Table 56

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	Conjugate
Saline	n/a	28	60	0.1	39	n/a
353382	3	30	77	0.2	36	none
	10	25	78	0.2	36	
	30	28	62	0.2	35	
	2 x 15	22	59	0.2	33	
661161	0.5	39	72	0.2	34	$GalNAc_3$-3
	1.5	26	50	0.2	33	
	5	41	80	0.2	32	
	2 x 2.5	24	72	0.2	28	
	15	32	69	0.2	36	
671144	0.5	25	39	0.2	34	$GalNAc_3$-12
	1.5	26	55	0.2	28	
	5	48	82	0.2	34	
	15	23	46	0.2	32	
670061	0.5	27	53	0.2	33	$GalNAc_3$-13
	1.5	24	45	0.2	35	
	5	23	58	0.1	34	
	15	24	72	0.1	31	
671261	0.5	69	99	0.1	33	$GalNAc_3$-14
	1.5	34	62	0.1	33	
	5	43	73	0.1	32	
	15	32	53	0.2	30	
671262	0.5	24	51	0.2	29	$GalNAc_3$-15
	1.5	32	62	0.1	31	
	5	30	76	0.2	32	
	15	31	64	0.1	32	

Example 66: Effect of various cleavable moieties on antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a 5'-$GalNAc_3$ cluster

The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice. Each of the $GalNAc_3$ conjugate groups was attached at the 5' terminus of the respective oligonucleotide by a phosphodiester linked nucleoside (cleavable moiety (CM)).

Table 57

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
661161	**$GalNAc_3$-3_{a-o},A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	A_d	109
670699	**$GalNAc_3$-3_{a-o},T_{do}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	T_d	116
670700	**$GalNAc_3$-3_{a-o},A_{eo}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	A_e	109
670701	**$GalNAc_3$-3_{a-o},T_{eo}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	T_e	116
671165	**$GalNAc_3$-13_{a-o},A_{do}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-13a	A_d	109

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 β-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.

The structure of $GalNAc_3$-3_a was shown previously in Example 39. The structure of $GalNAc_3$-13a was shown previously in Example 62.

Treatment

Six to eight week old C57bl6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 661161, 670699, 670700, 670701, 671165, 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.

As illustrated in Table 58, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. The antisense oligonucleotides comprising various cleavable moieties all showed similar potencies.

Table 58

SRB-1 mRNA (% Saline)

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100.0	n/a	n/a
661161	0.5	87.8	$GalNAc_3$-3a	A_d
	1.5	61.3		
	5	33.8		
	15	14.0		
670699	0.5	89.4	$GalNAc_3$-3a	T_d
	1.5	59.4		
	5	31.3		
	15	17.1		
670700	0.5	79.0	$GalNAc_3$-3a	A_e
	1.5	63.3		
	5	32.8		
	15	17.9		
670701	0.5	79.1	$GalNAc_3$-3a	T_e
	1.5	59.2		
	5	35.8		
	15	17.7		
671165	0.5	76.4	$GalNAc_3$-13a	A_d
	1.5	43.2		
	5	22.6		
	15	10.0		

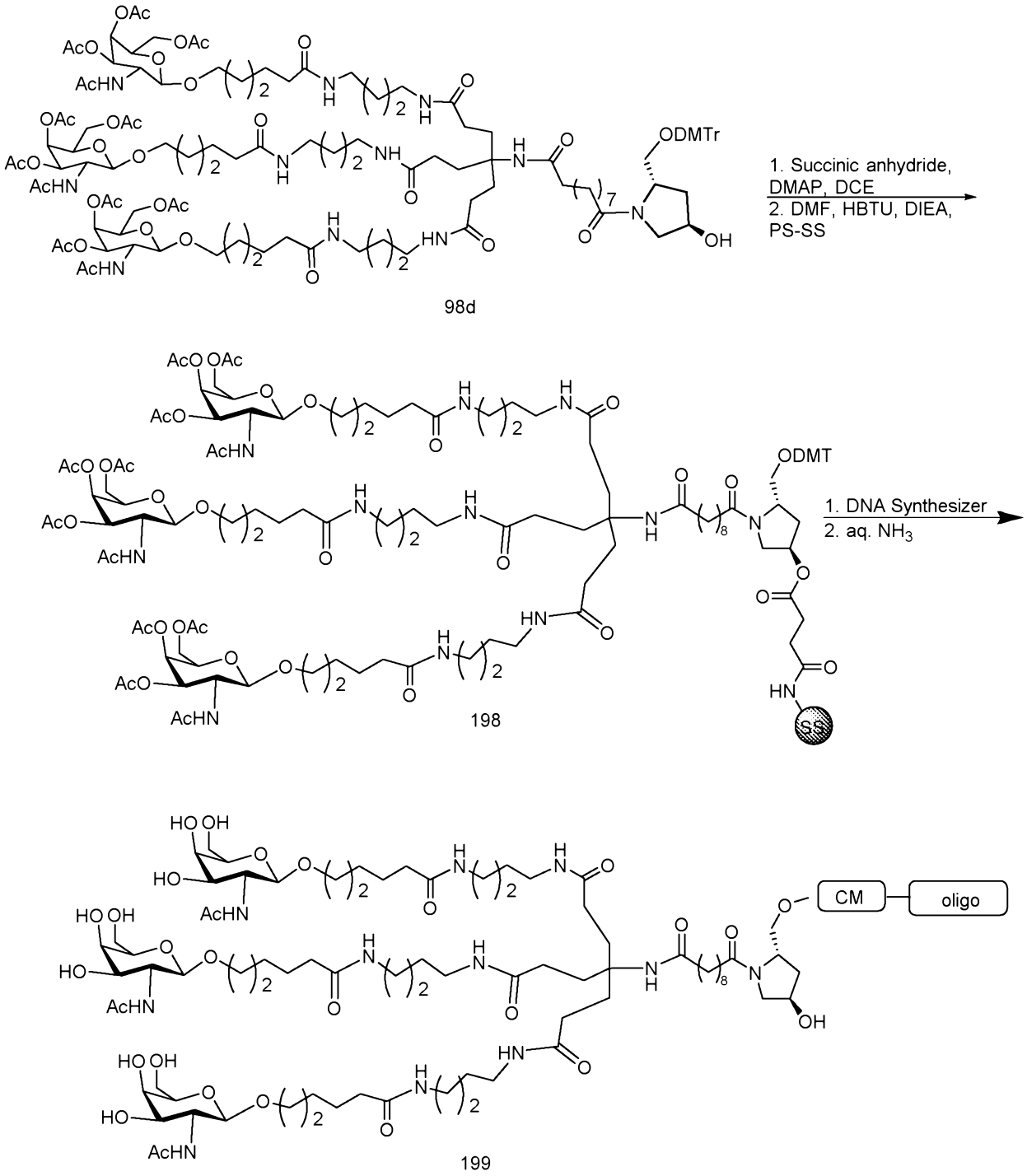
Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Total bilirubin and BUN were also evaluated. The changes in body weights were evaluated with no significant differences from the saline group (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 56 below.

Table 59

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	$GalNAc_3$ Cluster	CM
Saline	n/a	24	64	0.2	31	n/a	n/a
661161	0.5	25	64	0.2	31	$GalNAc_3$-3a	A_d
	1.5	24	50	0.2	32		
	5	26	55	0.2	28		
	15	27	52	0.2	31		
670699	0.5	42	83	0.2	31	$GalNAc_3$-3a	T_d
	1.5	33	58	0.2	32		
	5	26	70	0.2	29		
	15	25	67	0.2	29		
670700	0.5	40	74	0.2	27	$GalNAc_3$-3a	A_e
	1.5	23	62	0.2	27		
	5	24	49	0.2	29		
	15	25	87	0.1	25		

670701	0.5	30	77	0.2	27	$GalNAc_3$-3a	T_e
	1.5	22	55	0.2	30		
	5	81	101	0.2	25		
	15	31	82	0.2	24		
671165	0.5	44	84	0.2	26	$GalNAc_3$-13a	A_d
	1.5	47	71	0.1	24		
	5	33	91	0.2	26		
	15	33	56	0.2	29		

Example 67: Preparation of oligomeric compound 199 comprising GalNAc$_3$-16

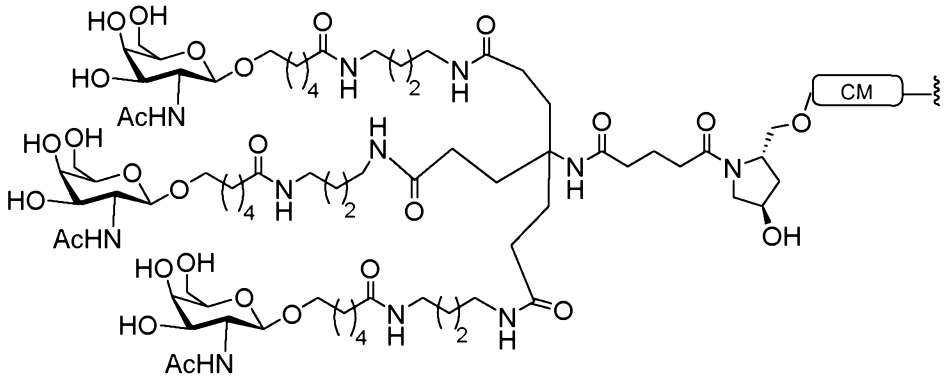


98d

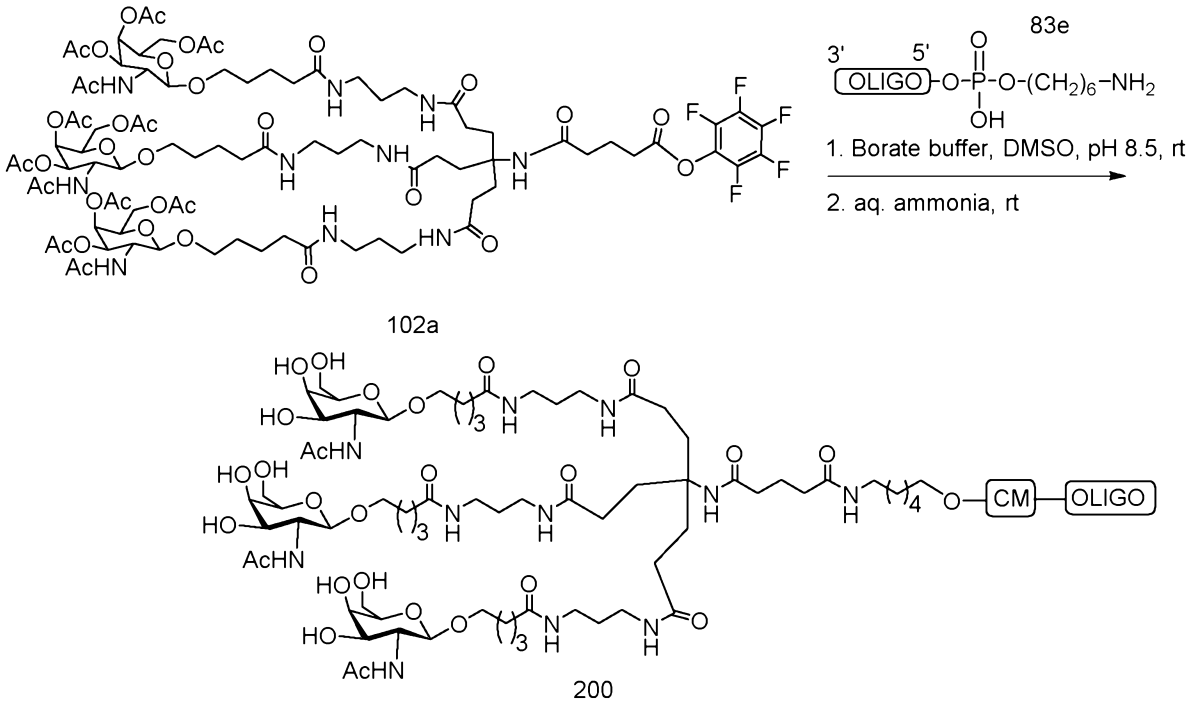
198

199

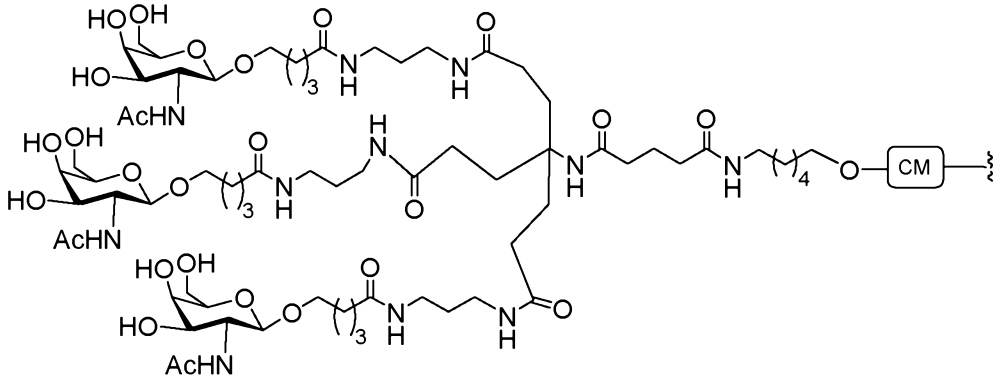
Oligomeric compound 199, comprising a GalNAc$_3$-16 conjugate group, is prepared using the general procedures illustrated in Examples 7 and 9. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-16 (GalNAc$_3$-16$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A$_d$-P(=O)(OH)-.The structure of GalNAc$_3$-16 (GalNAc$_3$-16$_a$-CM-) is shown below:



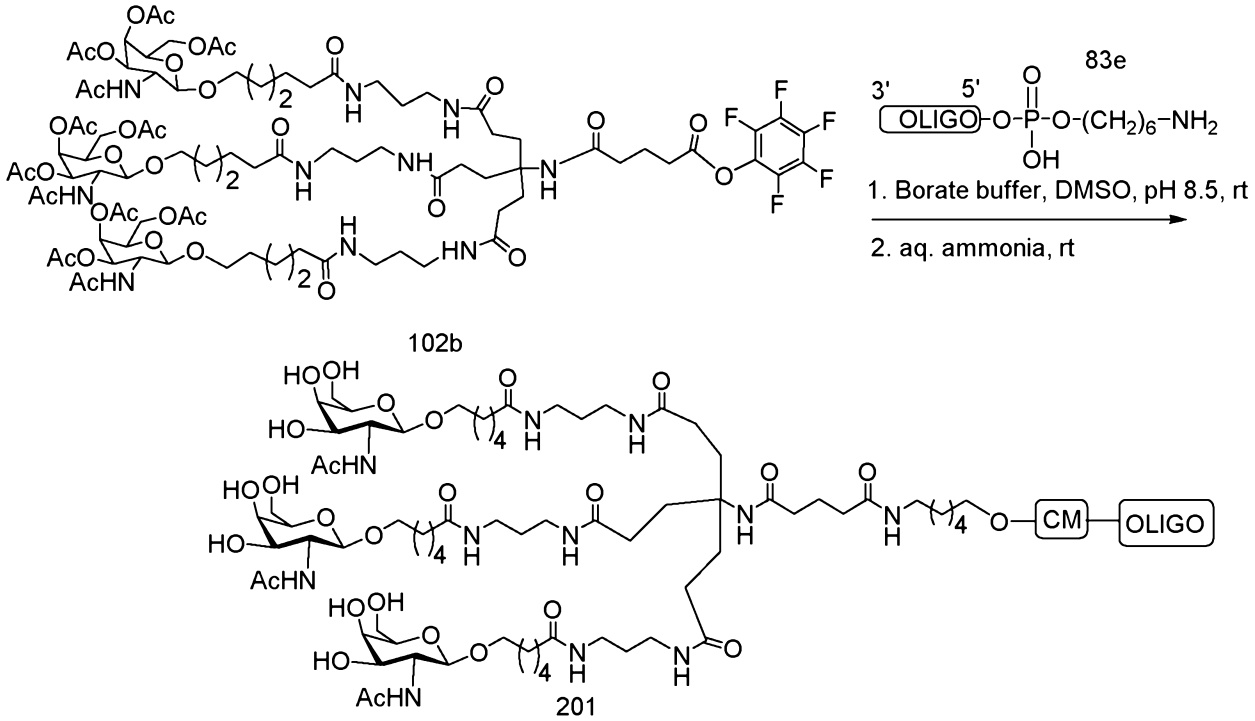
Example 68: Preparation of oligomeric compound 200 comprising GalNAc$_3$-17



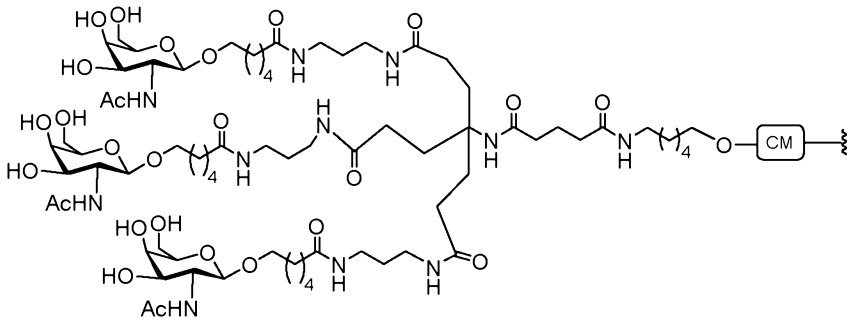
Oligomeric compound 200, comprising a GalNAc$_3$-17 conjugate group, was prepared using the general procedures illustrated in Example 46. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-17 (GalNAc$_3$-17$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A$_d$-P(=O)(OH)-. The structure of GalNAc$_3$-17 (GalNAc$_3$-17$_a$-CM-) is shown below:



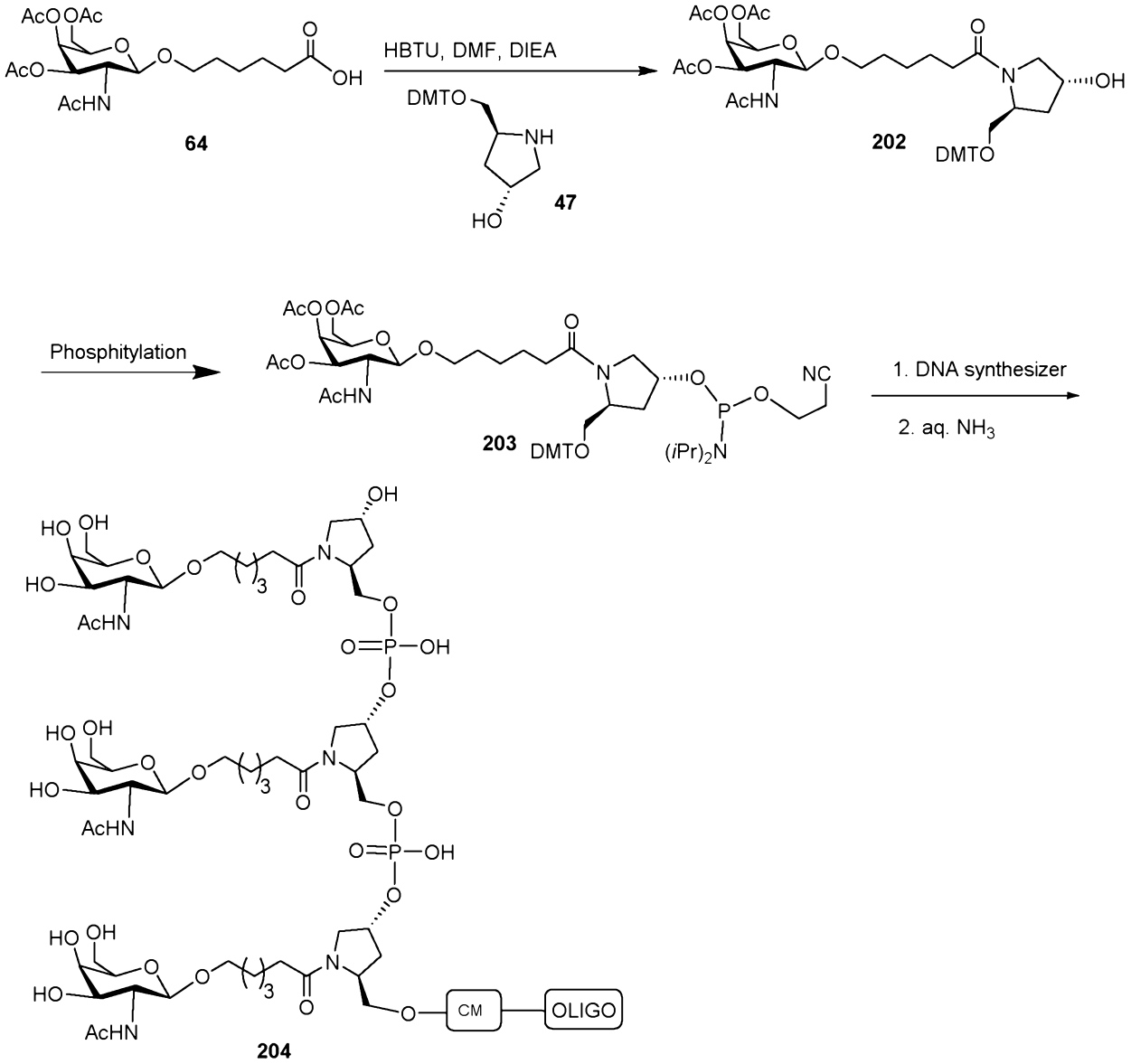
Example 69: Preparation of oligomeric compound 201 comprising GalNAc$_3$-18



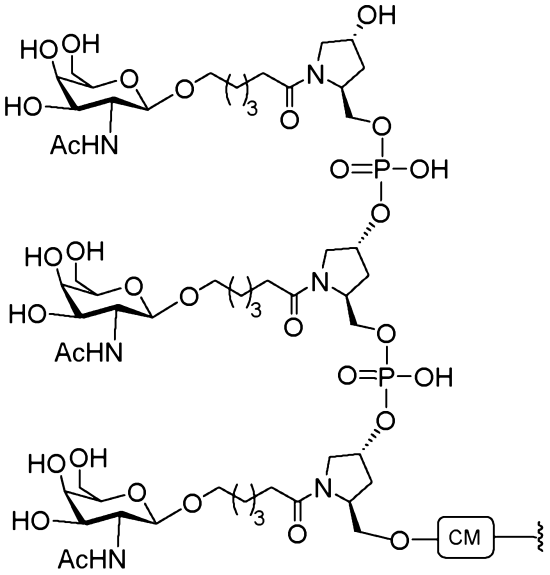
Oligomeric compound 201, comprising a GalNAc$_3$-18 conjugate group, was prepared using the general procedures illustrated in Example 46. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-18 (GalNAc$_3$-18$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A$_d$-P(=O)(OH)-. The structure of GalNAc$_3$-18 (GalNAc$_3$-18$_a$-CM-) is shown below:



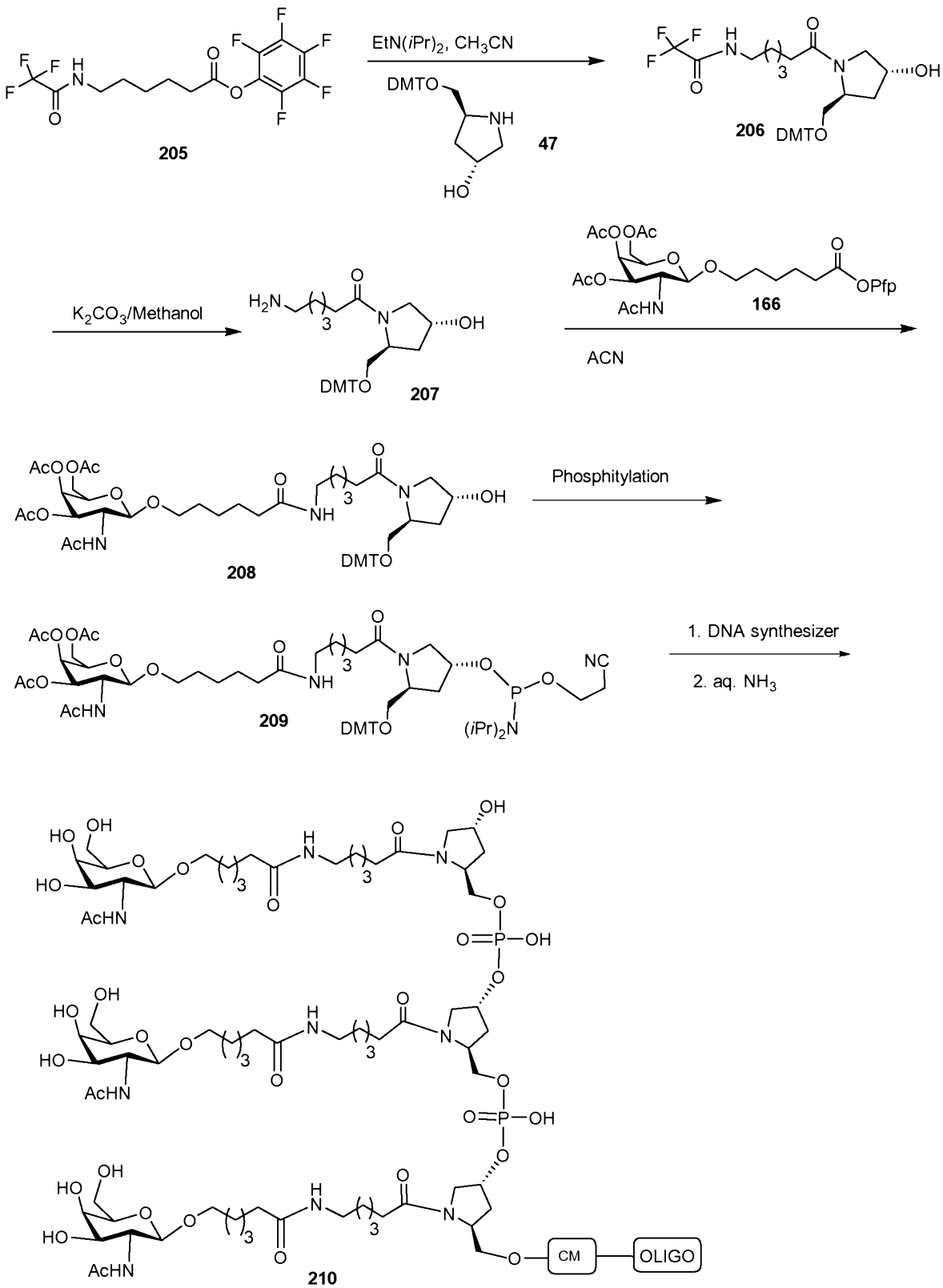
Example 70: Preparation of oligomeric compound 204 comprising GalNAc$_3$-19



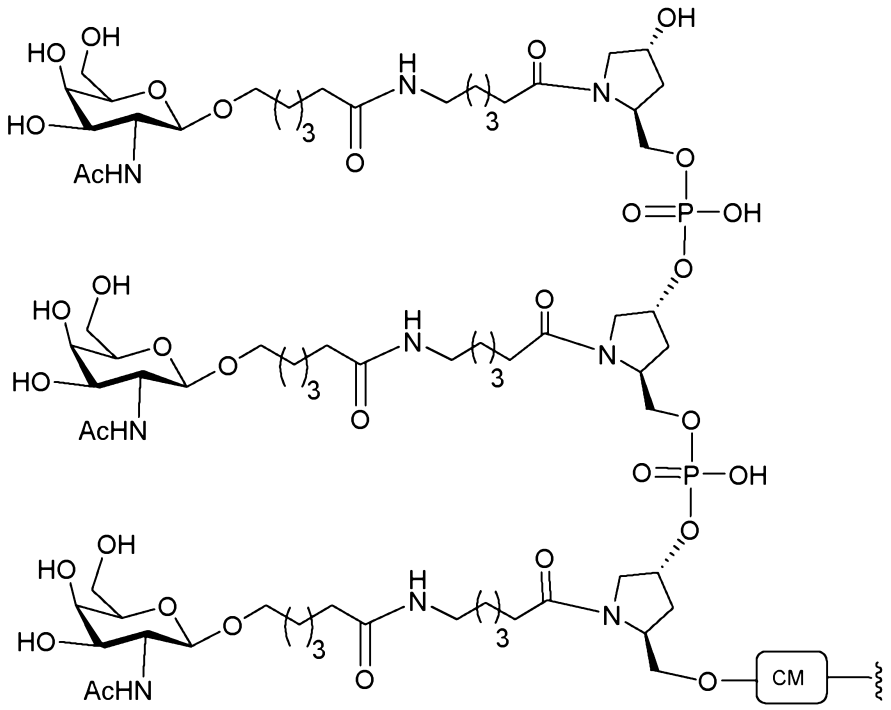
Oligomeric compound 204, comprising a GalNAc$_3$-19 conjugate group, was prepared from compound 64 using the general procedures illustrated in Example 52. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-19 (GalNAc$_3$-19$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A$_d$-P(=O)(OH)-. The structure of GalNAc$_3$-19 (GalNAc$_3$-19$_a$-CM-) is shown below:


HO
OH
HO
AcHN
O
O
3
O
N
OH
O
O=P–OH
O
HO
OH
HO
AcHN
O
O
3
O
N
O
O=P–OH
O
HO
OH
HO
AcHN
O
O
3
O
N
O
CM

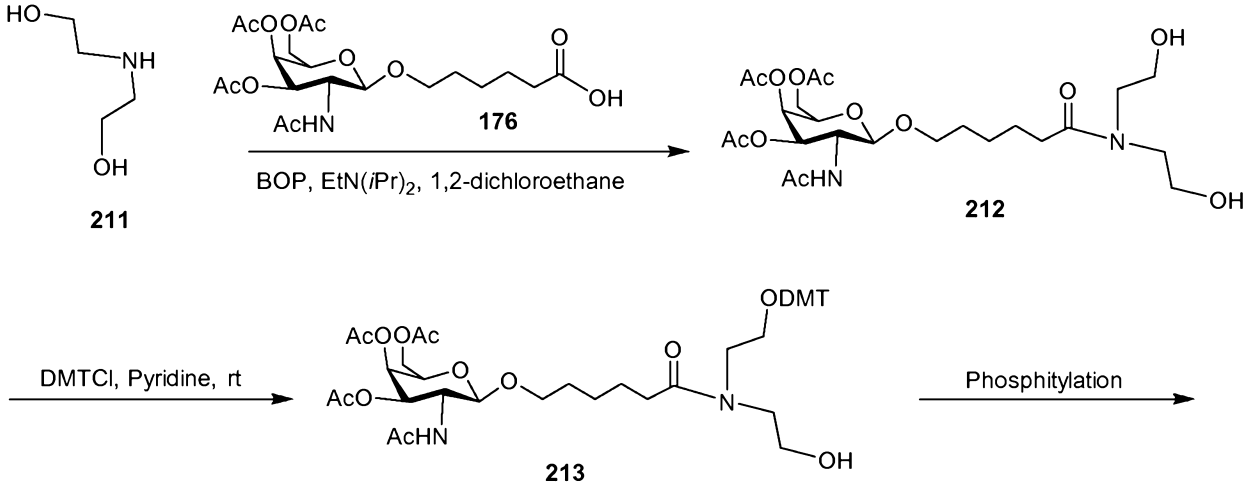
Example 71: Preparation of oligomeric compound 210 comprising GalNAc$_3$-20

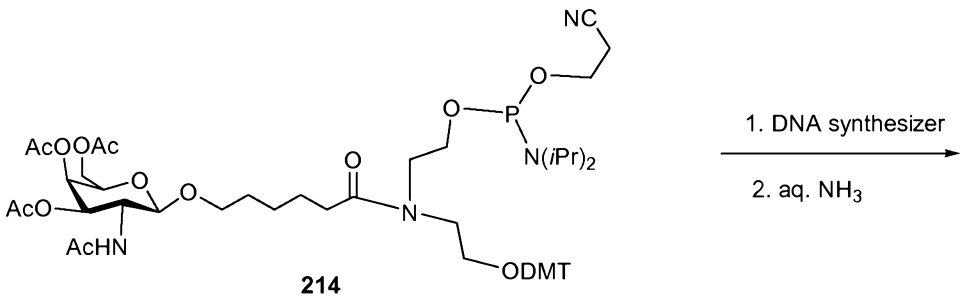


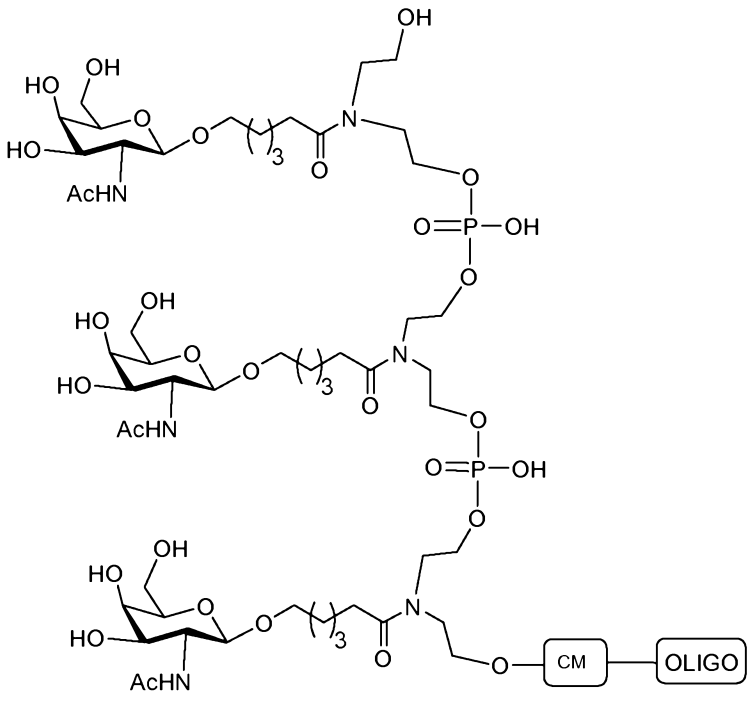
Compound 205 was prepared by adding PFP-TFA and DIEA to 6-(2,2,2-trifluoroacetamido)hexanoic acid in acetonitrile ,which was prepared by adding triflic anhydride to 6-aminohexanoic acid. The reaction mixture was heated to 80 °C, then lowered to rt. Oligomeric compound 210, comprising a $GalNAc_3$-20 conjugate group, was prepared from compound 208 using the general procedures illustrated in Example 52. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-20 ($GalNAc_3$-20_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)-. The structure of $GalNAc_3$-20 ($GalNAc_3$-20_a-CM-) is shown below:



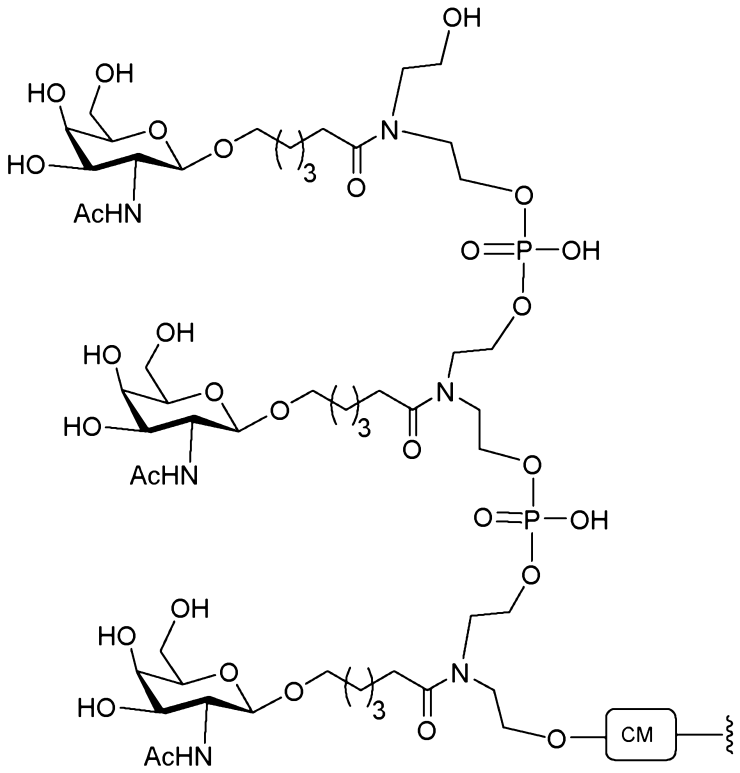
Example 72: Preparation of oligomeric compound 215 comprising GalNAc$_3$-21



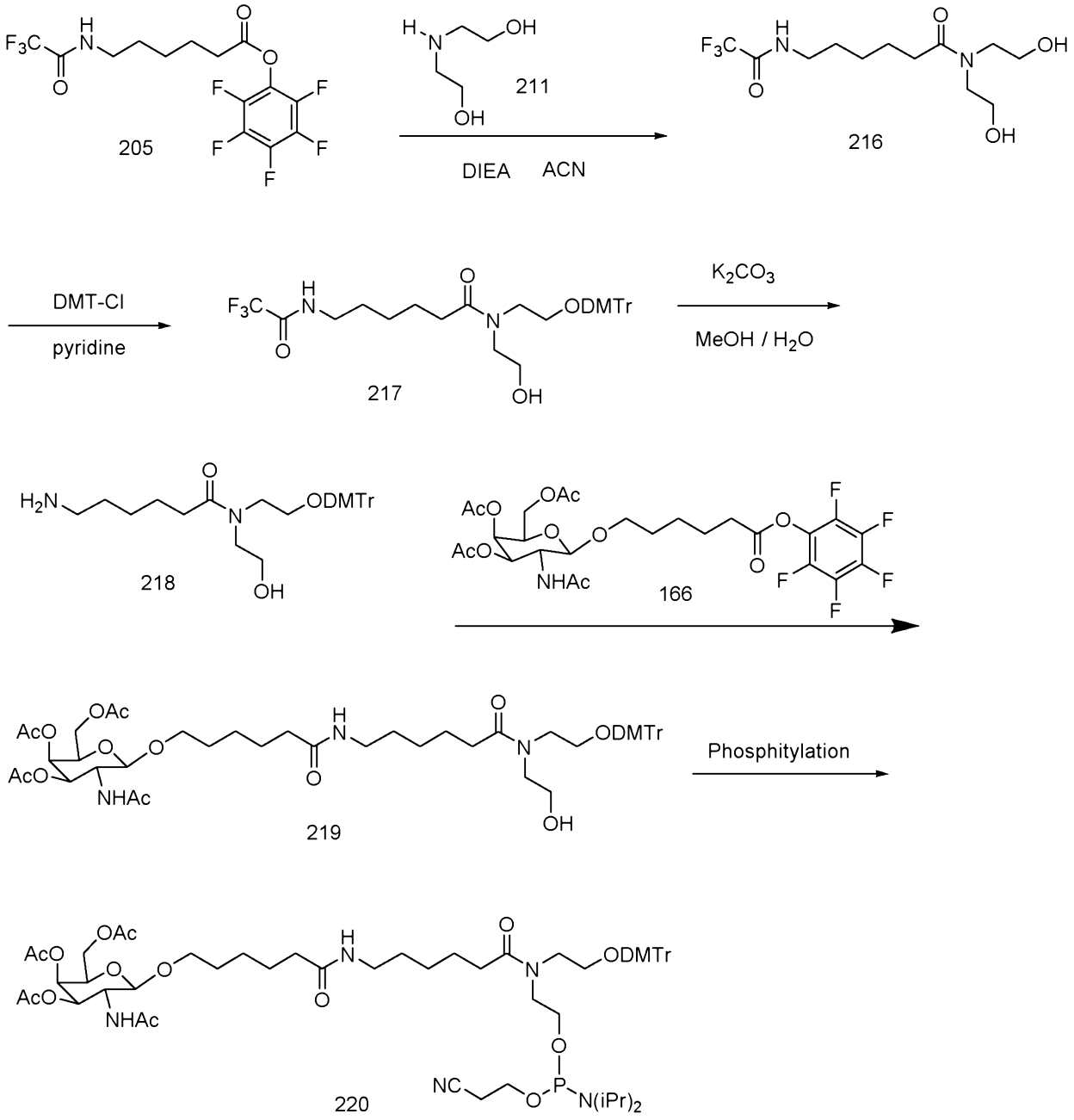


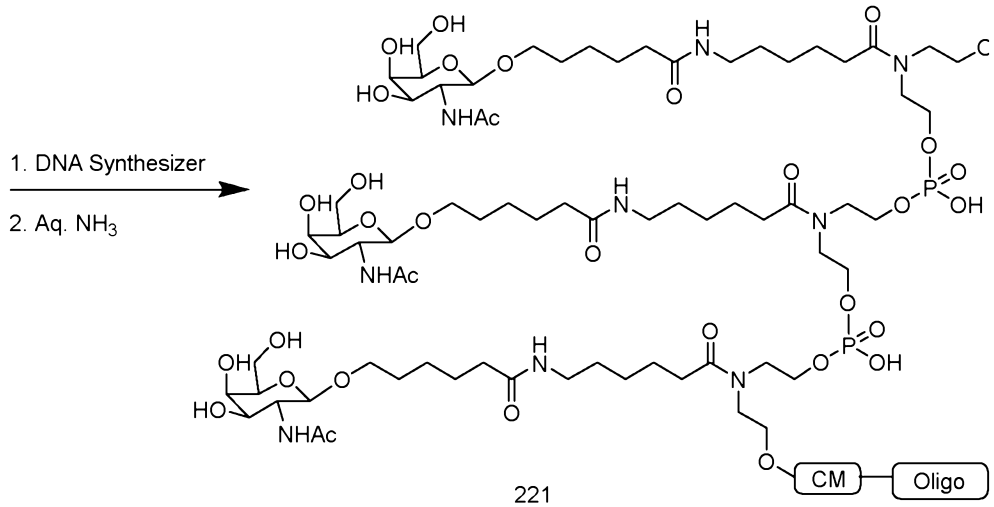


Compound 211 is commercially available. Oligomeric compound 215, comprising a $GalNAc_3$-21 conjugate group, was prepared from compound 213 using the general procedures illustrated in Example 52. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-21 ($GalNAc_3$-21_a) can be combined with 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)-. The structure of $GalNAc_3$-21 ($GalNAc_3$-21_a-CM-) is shown below:



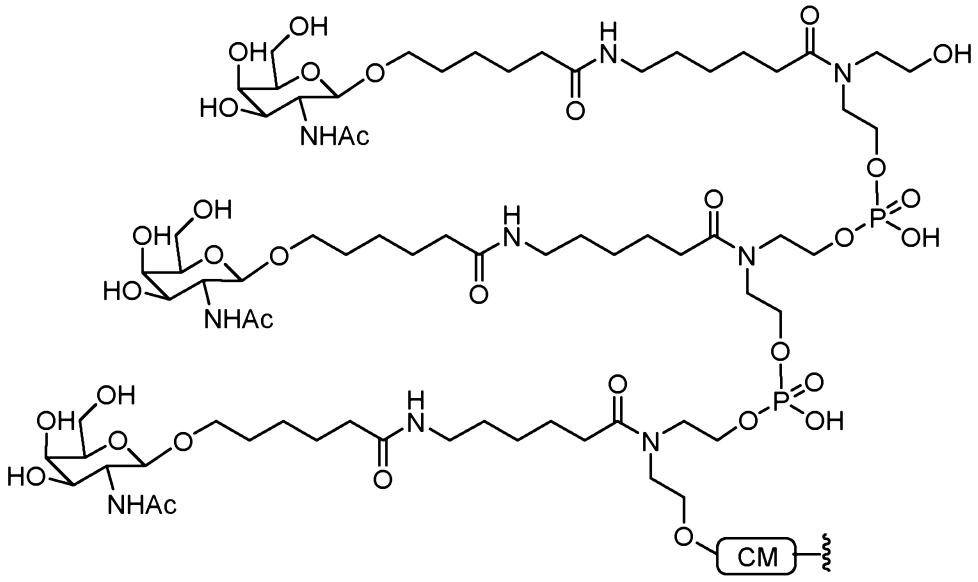
Example 73: Preparation of oligomeric compound 221 comprising GalNAc$_3$-22





221

Compound 220 was prepared from compound 219 using diisopropylammonium tetrazolide. Oligomeric compound 221, comprising a $GalNAc_3$-21 conjugate group, is prepared from compound 220 using the general procedure illustrated in Example 52. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-22 ($GalNAc_3$-22_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)-. The structure of $GalNAc_3$-22 ($GalNAc_3$-22_a-CM-) is shown below:



Example 74: Effect of various cleavable moieties on antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a 5'-$GalNAc_3$ conjugate

The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice. Each of the $GalNAc_3$ conjugate groups was attached at the 5' terminus of the respective oligonucleotide.

Table 60

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	n/a	n/a	108
661161	**$GalNAc_3$-3_{a-o},A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	A_d	109
666904	**$GalNAc_3$-3_{a-o},**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	PO	108
675441	**$GalNAc_3$-17_{a-o},A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-17a	A_d	109
675442	**$GalNAc_3$-18_{a-o},A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-18a	A_d	109

In all tables, 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 β-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.

The structure of $GalNAc_3$-3_a was shown previously in Example 39. The structure of $GalNAc_3$-17a was shown previously in Example 68, and the structure of $GalNAc_3$-18a was shown in Example 69.

Treatment

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 60 or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration to determine the 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.

As illustrated in Table 61, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. The antisense oligonucleotides comprising a GalNAc conjugate showed similar potencies and were significantly more potent than the parent oligonucleotide lacking a GalNAc conjugate.

Table 61

SRB-1 mRNA (% Saline)

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100.0	n/a	n/a

353382	3	79.38	n/a	n/a
	10	68.67		
	30	40.70		
661161	0.5	79.18	$GalNAc_3$-3a	A_d
	1.5	75.96		
	5	30.53		
	15	12.52		
666904	0.5	91.30	$GalNAc_3$-3a	PO
	1.5	57.88		
	5	21.22		
	15	16.49		
675441	0.5	76.71	$GalNAc_3$-17a	A_d
	1.5	63.63		
	5	29.57		
	15	13.49		
675442	0.5	95.03	$GalNAc_3$-18a	A_d
	1.5	60.06		
	5	31.04		
	15	19.40		

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 (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 62 below.

Table 62

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	$GalNAc_3$ Cluster	CM
Saline	n/a	26	59	0.16	42	n/a	n/a
353382	3	23	58	0.18	39	n/a	n/a
	10	28	58	0.16	43		
	30	20	48	0.12	34		
661161	0.5	30	47	0.13	35	$GalNAc_3$-3a	A_d
	1.5	23	53	0.14	37		
	5	26	48	0.15	39		
	15	32	57	0.15	42		
666904	0.5	24	73	0.13	36	$GalNAc_3$-3a	PO
	1.5	21	48	0.12	32		
	5	19	49	0.14	33		
	15	20	52	0.15	26		
675441	0.5	42	148	0.21	36	$GalNAc_3$-17a	A_d
	1.5	60	95	0.16	34		
	5	27	75	0.14	37		
	15	24	61	0.14	36		
675442	0.5	26	65	0.15	37	$GalNAc_3$-18a	A_d
	1.5	25	64	0.15	43		
	5	27	69	0.15	37		
	15	30	84	0.14	37		

Example 75: Pharmacokinetic analysis of oligonucleotides comprising a 5'-conjugate group

The PK of the ASOs in Tables 54, 57 and 60 above was evaluated using liver samples that were obtained following the treatment procedures described in Examples 65, 66, and 74. The liver samples were minced and extracted using standard protocols and analyzed by IP-HPLC-MS alongside an internal standard. The combined tissue level (μg/g) of all metabolites was measured by integrating the appropriate UV peaks, and the tissue level of the full-length ASO missing the conjugate ("parent," which is Isis No. 353382 in this case) was measured using the appropriate extracted ion chromatograms (EIC).

Table 63

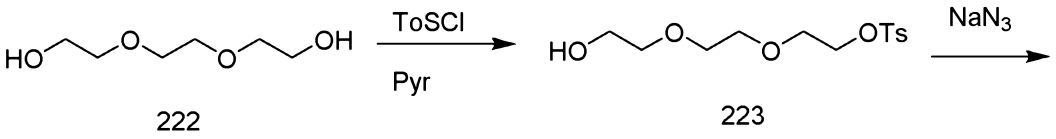
PK Analysis in Liver

ISIS No.	Dosage (mg/kg)	Total Tissue Level by UV (μg/g)	Parent ASO Tissue Level by EIC (μg/g)	$GalNAc_3$ Cluster	CM
353382	3	8.9	8.6	n/a	n/a
	10	22.4	21.0		
	30	54.2	44.2		
661161	5	32.4	20.7	$GalNAc_3$-3a	A_d
	15	63.2	44.1		
671144	5	20.5	19.2	$GalNAc_3$-12a	A_d
	15	48.6	41.5		
670061	5	31.6	28.0	$GalNAc_3$-13a	A_d
	15	67.6	55.5		
671261	5	19.8	16.8	$GalNAc_3$-14a	A_d
	15	64.7	49.1		
671262	5	18.5	7.4	$GalNAc_3$-15a	A_d
	15	52.3	24.2		
670699	5	16.4	10.4	$GalNAc_3$-3a	T_d
	15	31.5	22.5		
670700	5	19.3	10.9	$GalNAc_3$-3a	A_e
	15	38.1	20.0		
670701	5	21.8	8.8	$GalNAc_3$-3a	T_e
	15	35.2	16.1		
671165	5	27.1	26.5	$GalNAc_3$-13a	A_d
	15	48.3	44.3		
666904	5	30.8	24.0	$GalNAc_3$-3a	PO
	15	52.6	37.6		
675441	5	25.4	19.0	$GalNAc_3$-17a	A_d
	15	54.2	42.1		
675442	5	22.2	20.7	$GalNAc_3$-18a	A_d
	15	39.6	29.0		

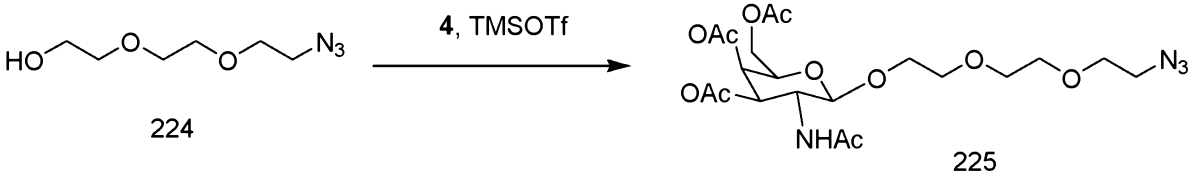
The results in Table 63 above show that there were greater liver tissue levels of the oligonucleotides comprising a $GalNAc_3$ conjugate group than of the parent oligonucleotide that does not comprise a $GalNAc_3$ conjugate group (ISIS 353382) 72 hours following oligonucleotide administration, particularly when taking into consideration the differences in dosing between the oligonucleotides with and without a $GalNAc_3$ conjugate group. Furthermore, by 72 hours, 40-98% of each oligonucleotide comprising a $GalNAc_3$ conjugate

group was metabolized to the parent compound, indicating that the $GalNAc_3$ conjugate groups were cleaved from the oligonucleotides.

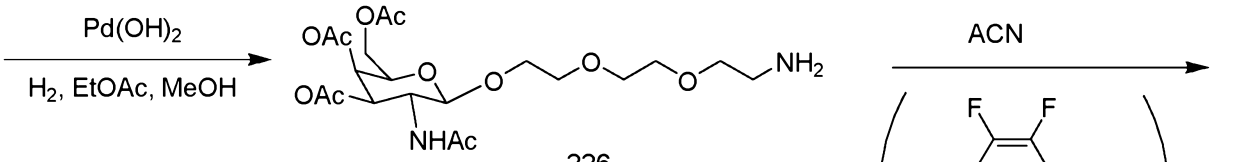
Example 76: Preparation of oligomeric compound 230 comprising $GalNAc_3$-23



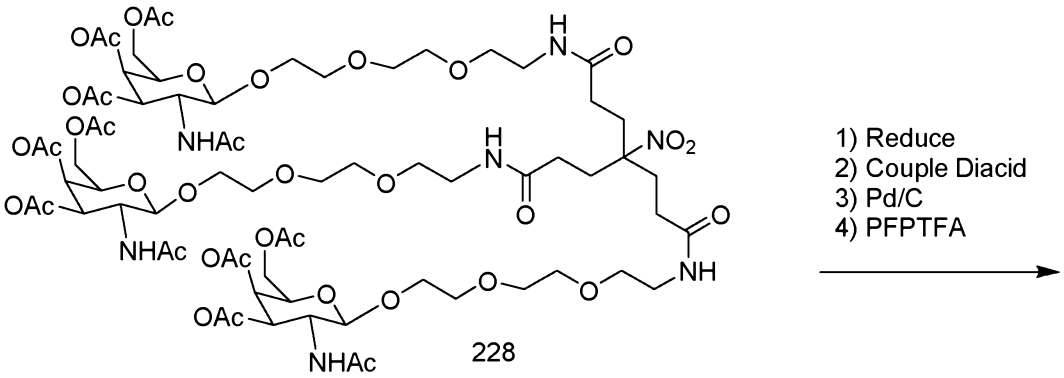
222 223



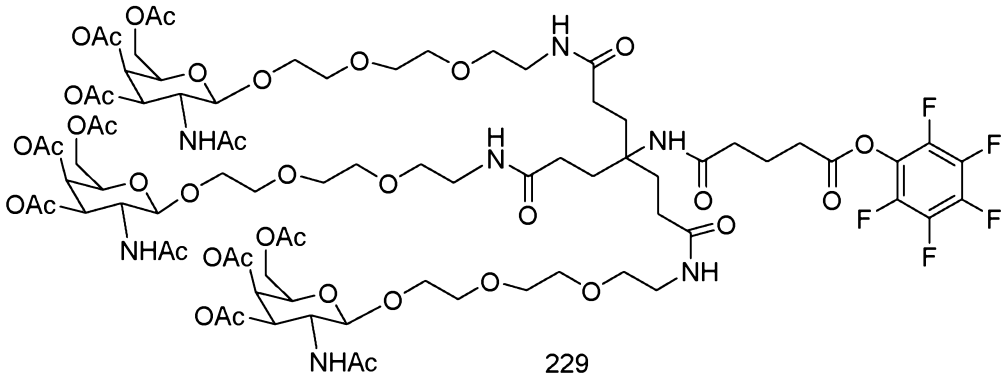
224 225



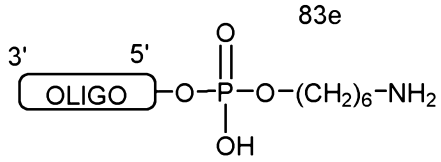
226 227



228

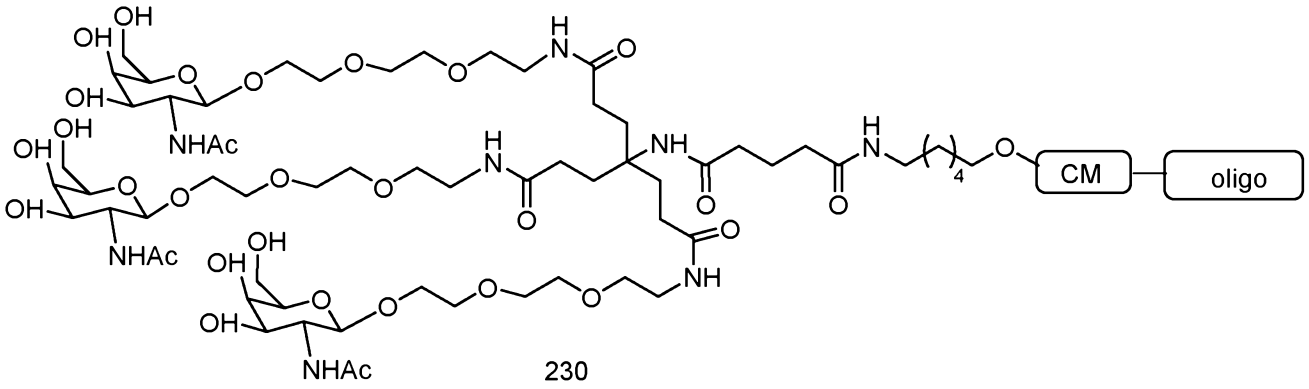


229



1. Borate buffer, DMSO, pH 8.5, rt

2. aq. ammonia, rt



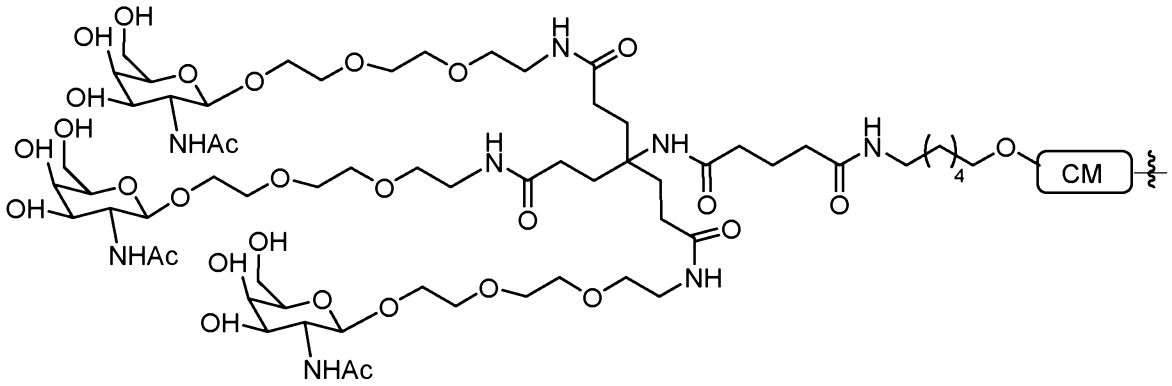
230

Compound 222 is commercially available. 44.48 ml (0.33 mol) of compound 222 was treated with tosyl chloride (25.39 g, 0.13 mol) in pyridine (500mL) for 16 hours. The reaction was then evaporated to an oil, dissolved in EtOAc and washed with water, sat. $NaHCO_3$, brine, and dried over Na_2SO_4. The ethyl acetate was concentrated to dryness and purified by column chromatography, eluted with EtOAc/hexanes (1:1) followed by 10% methanol in CH_2Cl_2 to give compound 223 as a colorless oil. LCMS and NMR were consistent with the structure. 10 g (32.86 mmol) of 1-Tosyltriethylene glycol (compound 223) was treated with sodium azide (10.68 g, 164.28 mmol) in DMSO (100mL) at room temperature for 17 hours. The reaction mixture was then poured onto water, and extracted with EtOAc. The organic layer was washed with water three times and dried over Na_2SO_4. The organic layer was concentrated to dryness to give 5.3g of compound 224 (92%). LCMS and NMR were consistent with the structure. 1-Azidotriethylene glycol (compound 224, 5.53 g, 23.69 mmol) and compound 4 (6 g, 18.22 mmol) were treated with 4A molecular sieves (5g), and TMSOTf (1.65 ml, 9.11 mmol) in dichloromethane (100mL) under an inert atmosphere. After 14 hours, the reaction was filtered to remove the sieves, and the organic layer was washed with sat. $NaHCO_3$, water, brine, and dried over Na_2SO_4. The organic layer was concentrated to dryness and purified by column chromatography, eluted with a gradient of 2 to 4% methanol in dichloromethane to give compound 225. LCMS and NMR were consistent with the structure. Compound 225 (11.9 g, 23.59 mmol) was hydrogenated in EtOAc/Methanol (4:1, 250mL) over Pearlman's catalyst. After 8 hours, the catalyst was

removed by filtration and the solvents removed to dryness to give compound 226. LCMS and NMR were consistent with the structure.

In order to generate compound 227, a solution of nitromethanetrispropionic acid (4.17 g, 15.04 mmol) and Hunig's base (10.3 ml, 60.17 mmol) in DMF (100mL) were treated dropwise with pentaflourotrifluoro acetate (9.05 ml, 52.65 mmol). After 30 minutes, the reaction was poured onto ice water and extracted with EtOAc. The organic layer was washed with water, brine, and dried over Na_2SO_4. The organic layer was concentrated to dryness and then recrystallized from heptane to give compound 227 as a white solid. LCMS and NMR were consistent with the structure. Compound 227 (1.5 g, 1.93 mmol) and compound 226 (3.7 g, 7.74 mmol) were stirred at room temperature in acetonitrile (15 mL) for 2 hours. The reaction was then evaporated to dryness and purified by column chromatography, eluting with a gradient of 2 to10% methanol in dichloromethane to give compound 228. LCMS and NMR were consistent with the structure. Compound 228 (1.7 g, 1.02 mmol) was treated with Raney Nickel (about 2g wet) in ethanol (100mL) in an atmosphere of hydrogen. After 12 hours, the catalyst was removed by filtration and the organic layer was evaporated to a solid that was used directly in the next step. LCMS and NMR were consistent with the structure. This solid (0.87 g, 0.53 mmol) was treated with benzylglutaric acid (0.18 g, 0.8 mmol), HBTU (0.3 g, 0.8 mmol) and DIEA (273.7 µl, 1.6 mmol) in DMF (5mL). After 16 hours, the DMF was removed under reduced pressure at 65°C to an oil, and the oil was dissolved in dichloromethane. The organic layer was washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. After evaporation of the organic layer, the compound was purified by column chromatography and eluted with a gradient of 2 to 20% methanol in dichloromethane to give the coupled product. LCMS and NMR were consistent with the structure. The benzyl ester was deprotected with Pearlman's catalyst under a hydrogen atmosphere for 1 hour. The catalyst was them removed by filtration and the solvents removed to dryness to give the acid. LCMS and NMR were consistent with the structure. The acid (486 mg, 0.27 mmol) was dissolved in dry DMF (3 mL). Pyridine (53.61 µl, 0.66 mmol) was added and the reaction was purged with argon. Pentaflourotriflouro acetate (46.39 µl, 0.4 mmol) was slowly added to the reaction mixture. The color of the reaction changed from pale yellow to burgundy, and gave off a light smoke which was blown away with a stream of argon. The reaction was allowed to stir at room temperature for one hour (completion of reaction was confirmed by LCMS). The solvent was removed under reduced pressure (rotovap) at 70 °C. The residue was diluted with DCM and washed with 1N $NaHSO_4$, brine, saturated sodium bicarbonate and brine again. The organics were dried over Na_2SO_4, filtered, and were concentrated to dryness to give 225 mg of compound 229 as a brittle yellow foam. LCMS and NMR were consistent with the structure.

Oligomeric compound 230, comprising a $GalNAc_3$-23 conjugate group, was prepared from compound 229 using the general procedure illustrated in Example 46. The $GalNAc_3$ cluster portion of the $GalNAc_3$-23 conjugate group ($GalNAc_3$-23_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. The structure of $GalNAc_3$-23 ($GalNAc_3$-23_a-CM) is shown below:



Example 77: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a GalNAc$_3$ conjugate

The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Table 64

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No.
661161	**GalNAc$_3$-3$_{a\text{-}o}$,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$_{e}$	GalNAc$_3$-3a	A$_d$	109
666904	**GalNAc$_3$-3$_{a\text{-}o}$,**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$_{e}$	GalNAc$_3$-3a	PO	108
673502	**GalNAc$_3$-10$_{a\text{-}o}$,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$_{e}$	GalNAc$_3$-10a	A$_d$	109
677844	**GalNAc$_3$-9$_{a\text{-}o}$,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$_{e}$	GalNAc$_3$-9a	A$_d$	109
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$_{e}$	GalNAc$_3$-23a	A$_d$	109
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$_{eo}$**A$_{do}$,-GalNAc$_3$-1$_a$**	GalNAc$_3$-1a	A$_d$	110
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$_{do}$,-GalNAc$_3$-19$_a$**	GalNAc$_3$-19a	A$_d$	110
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$_{es}$^{m}C$_{es}$ ^{m}C$_{es}$T$_{es}$T$_{eo}$**A$_{do}$,-GalNAc$_3$-20$_a$**	GalNAc$_3$-20a	A$_d$	110

The structure of GalNAc$_3$-1$_a$ was shown previously in Example 9, GalNAc$_3$-3$_a$ was shown in Example 39, GalNAc$_3$-9a was shown in Example 52, GalNAc$_3$-10a was shown in Example 46, 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.

Treatment

Six to eight week old C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were each injected subcutaneously once at a dosage shown below with an oligonucleotide listed in Table 64 or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration to determine the 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.

As illustrated in Table 65, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner.

Table 65

SRB-1 mRNA (% Saline)

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100.0	n/a	n/a
661161	0.5	89.18	$GalNAc_3$-3a	A_d
	1.5	77.02		
	5	29.10		
	15	12.64		
666904	0.5	93.11	$GalNAc_3$-3a	PO
	1.5	55.85		
	5	21.29		
	15	13.43		
673502	0.5	77.75	$GalNAc_3$-10a	A_d
	1.5	41.05		
	5	19.27		
	15	14.41		
677844	0.5	87.65	$GalNAc_3$-9a	A_d
	1.5	93.04		
	5	40.77		
	15	16.95		
677843	0.5	102.28	$GalNAc_3$-23a	A_d
	1.5	70.51		
	5	30.68		
	15	13.26		
655861	0.5	79.72	$GalNAc_3$-1a	A_d
	1.5	55.48		
	5	26.99		
	15	17.58		
677841	0.5	67.43	$GalNAc_3$-19a	A_d
	1.5	45.13		
	5	27.02		
	15	12.41		
677842	0.5	64.13	$GalNAc_3$-20a	A_d
	1.5	53.56		
	5	20.47		
	15	10.23		

Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were also measured using standard protocols. Total bilirubin and BUN were also evaluated. Changes in body weights were evaluated, with no significant change from the saline group (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 66 below.

Table 66

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	$GalNAc_3$ Cluster	CM
Saline	n/a	21	45	0.13	34	n/a	n/a
661161	0.5	28	51	0.14	39	$GalNAc_3$-3a	A_d
	1.5	23	42	0.13	39		
	5	22	59	0.13	37		
	15	21	56	0.15	35		
666904	0.5	24	56	0.14	37	$GalNAc_3$-3a	PO
	1.5	26	68	0.15	35		
	5	23	77	0.14	34		
	15	24	60	0.13	35		
673502	0.5	24	59	0.16	34	$GalNAc_3$-10a	A_d
	1.5	20	46	0.17	32		
	5	24	45	0.12	31		
	15	24	47	0.13	34		
677844	0.5	25	61	0.14	37	$GalNAc_3$-9a	A_d
	1.5	23	64	0.17	33		
	5	25	58	0.13	35		
	15	22	65	0.14	34		
677843	0.5	53	53	0.13	35	$GalNAc_3$-23a	A_d
	1.5	25	54	0.13	34		
	5	21	60	0.15	34		
	15	22	43	0.12	38		
655861	0.5	21	48	0.15	33	$GalNAc_3$-1a	A_d
	1.5	28	54	0.12	35		
	5	22	60	0.13	36		
	15	21	55	0.17	30		
677841	0.5	32	54	0.13	34	$GalNAc_3$-19a	A_d
	1.5	24	56	0.14	34		
	5	23	92	0.18	31		
	15	24	58	0.15	31		
677842	0.5	23	61	0.15	35	$GalNAc_3$-20a	A_d
	1.5	24	57	0.14	34		
	5	41	62	0.15	35		
	15	24	37	0.14	32		

Example 78: Antisense inhibition *in vivo* by oligonucleotides targeting Angiotensinogen comprising a $GalNAc_3$ conjugate

The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of Angiotensinogen (AGT) in normotensive Sprague Dawley rats.

Table 67

Modified ASOs targeting AGT

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
552668	$^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}G_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}G_{es}G_{es}A_{es}T_{e}$	n/a	n/a	117
669509	$^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}G_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}G_{es}G_{es}A_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	$GalNAc_3$-1_a	A_d	118

The structure of $GalNAc_3$-1_a was shown previously in Example 9.

Treatment

Six week old, male Sprague Dawley rats were each injected subcutaneously once per week at a dosage shown below, for a total of three doses, with an oligonucleotide listed in Table 67 or with PBS. Each treatment group consisted of 4 animals. The rats were sacrificed 72 hours following the final dose. AGT liver mRNA levels were measured using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. AGT plasma protein levels were measured using the Total Angiotensinogen ELISA (Catalog # JP27412, IBL International, Toronto, ON) with plasma diluted 1:20,000. The results below are presented as the average percent of AGT mRNA levels in liver or AGT protein levels in plasma for each treatment group, normalized to the PBS control.

As illustrated in Table 68, treatment with antisense oligonucleotides lowered AGT liver mRNA and plasma protein levels in a dose-dependent manner, and the oligonucleotide comprising a GalNAc conjugate was significantly more potent than the parent oligonucleotide lacking a GalNAc conjugate.

Table 68

AGT liver mRNA and plasma protein levels

ISIS No.	Dosage (mg/kg)	AGT liver mRNA (% PBS)	AGT plasma protein (% PBS)	$GalNAc_3$ Cluster	CM
PBS	n/a	100	100	n/a	n/a
552668	3	95	122	n/a	n/a
	10	85	97		
	30	46	79		
	90	8	11		
669509	0.3	95	70	$GalNAc_3$-1a	A_d
	1	95	129		
	3	62	97		
	10	9	23		

Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in plasma and body weights were also measured at time of sacrifice using standard protocols. The results are shown in Table 69 below.

Table 69

Liver transaminase levels and rat body weights

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Body Weight (% of baseline)	$GalNAc_3$ Cluster	CM
PBS	n/a	51	81	186	n/a	n/a
552668	3	54	93	183	n/a	n/a
	10	51	93	194		
	30	59	99	182		
	90	56	78	170		
669509	0.3	53	90	190	$GalNAc_3$-1a	A_d
	1	51	93	192		
	3	48	85	189		
	10	56	95	189		

Example 79: Duration of action *in vivo* of oligonucleotides targeting APOC-III comprising a $GalNAc_3$ conjugate

The oligonucleotides listed in Table 70 below were tested in a single dose study for duration of action in mice.

Table 70

Modified ASOs targeting APOC-III

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
304801	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}$ $T_{es}A_{es}T_{e}$	n/a	n/a	32
647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}$ $T_{es}A_{es}T_{eo}$**$A_{do'}$-GalNAc$_3$-1$_a$**	$GalNAc_3$-1a	A_d	111
663083	**GalNAc$_3$-3$_a$-$_o$'A_{do}**$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-3a	A_d	119
674449	**GalNAc$_3$-7$_a$-$_o$'A_{do}**$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-7a	A_d	119
674450	**GalNAc$_3$-10$_a$-$_o$'A_{do}**$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-10a	A_d	119
674451	**GalNAc$_3$-13$_a$-$_o$'A_{do}**$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-13a	A_d	119

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

Six to eight week old transgenic mice that express human APOC-III were each injected subcutaneously once with an oligonucleotide listed in Table 70 or with PBS. Each treatment group consisted of 3 animals. Blood was drawn before dosing to determine baseline and at 72 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, and 6 weeks following the dose. Plasma triglyceride and APOC-III protein levels were measured as described in Example 20. The results below are presented as the average percent of plasma triglyceride and APOC-III levels for each treatment group, normalized to baseline levels, showing that the oligonucleotides comprising a GalNAc conjugate group exhibited a longer duration of action than the parent oligonucleotide without a conjugate group (ISIS 304801) even though the dosage of the parent was three times the dosage of the oligonucleotides comprising a GalNAc conjugate group.

Table 71
Plasma triglyceride and APOC-III protein levels in transgenic mice

ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	Triglycerides (% baseline)	APOC-III protein (% baseline)	$GalNAc_3$ Cluster	CM
PBS	n/a	3	97	102	n/a	n/a
		7	101	98		
		14	108	98		
		21	107	107		
		28	94	91		
		35	88	90		
		42	91	105		
304801	30	3	40	34	n/a	n/a
		7	41	37		
		14	50	57		
		21	50	50		
		28	57	73		
		35	68	70		
		42	75	93		
647535	10	3	36	37	$GalNAc_3$-1a	A_d
		7	39	47		
		14	40	45		
		21	41	41		
		28	42	62		
		35	69	69		
		42	85	102		
663083	10	3	24	18	$GalNAc_3$-3a	A_d
		7	28	23		
		14	25	27		
		21	28	28		
		28	37	44		
		35	55	57		
		42	60	78		
674449	10	3	29	26	$GalNAc_3$-7a	A_d
		7	32	31		

		14	38	41		
		21	44	44		
		28	53	63		
		35	69	77		
		42	78	99		
674450	10	3	33	30	$GalNAc_3$-10a	A_d
		7	35	34		
		14	31	34		
		21	44	44		
		28	56	61		
		35	68	70		
		42	83	95		
674451	10	3	35	33	$GalNAc_3$-13a	A_d
		7	24	32		
		14	40	34		
		21	48	48		
		28	54	67		
		35	65	75		
		42	74	97		

Example 80: Antisense inhibition *in vivo* by oligonucleotides targeting Alpha-1 Antitrypsin (A1AT) comprising a $GalNAc_3$ Conjugate

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	120
656326	$A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	$GalNAc_3$-1a	A_d	121
678381	$\mathbf{GalNAc_3\text{-}3_a\text{-}_{o'}A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	$GalNAc_3$-3a	A_d	122
678382	$\mathbf{GalNAc_3\text{-}7_a\text{-}_{o'}A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	$GalNAc_3$-7a	A_d	122
678383	$\mathbf{GalNAc_3\text{-}10_a\text{-}_{o'}A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	$GalNAc_3$-10a	A_d	122
678384	$\mathbf{GalNAc_3\text{-}13_a\text{-}_{o'}A_{do}}A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_e$	$GalNAc_3$-13a	A_d	122

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

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.

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		

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

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

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	108
655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do}$-GalNAc$_3-1_a$**	PS	GalNAc$_3$-1$_a$	A_d	40	110
661161	**GalNAc$_3$-3$_a$-$_o$,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$_3$-3$_a$	A_d	40	109
661162	**GalNAc$_3$-3$_a$-$_o$,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$_3$-3$_a$	A_d	8	109
664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do}$-GalNAc$_3-9_a$**	PS	GalNAc$_3$-9$_a$	A_d	20	110
665001	**GalNAc$_3$-8$_a$-$_o$,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$_3$-8$_a$	A_d	70	109
666224	**GalNAc$_3$-5$_a$-$_o$,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$_3$-5$_a$	A_d	80	109
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	108
666881	**GalNAc$_3$-10$_a$-$_o$,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$_3$-10$_a$	A_d	30	109
666904	**GalNAc$_3$-3$_a$-$_o$,**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	GalNAc$_3$-3$_a$	PO	9	108
666924	**GalNAc$_3$-3$_a$-$_o$,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$_3$-3$_a$	T_d	15	123
666961	**GalNAc$_3$-6$_a$-$_o$,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$_3$-6$_a$	A_d	150	109
666981	**GalNAc$_3$-7$_a$-$_o$,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$_3$-7$_a$	A_d	20	109
670061	**GalNAc$_3$-13$_a$-$_o$,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$_3$-13$_a$	A_d	30	109
670699	**GalNAc$_3$-3$_a$-$_o$,T_{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$_3$-3$_a$	T_d	15	116
670700	**GalNAc$_3$-3$_a$-$_o$,A_{eo}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T$	PO/PS	GalNAc$_3$-3$_a$	A_e	30	109

670701	**GalNAc$_3$-3$_a$-$_o$,T$_{eo}$**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	116
671144	**GalNAc$_3$-12$_a$-$_o$,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$_3$ -12$_a$	A$_d$	40	109
671165	**GalNAc$_3$-13$_a$-$_o$,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	PO/PS	GalNAc$_3$ -13$_a$	A$_d$	8	109
671261	**GalNAc$_3$-14$_a$-$_o$,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$_3$ -14$_a$	A$_d$	>250	109
671262	**GalNAc$_3$-15$_a$-$_o$,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$_3$ -15$_a$	A$_d$	>250	109
673501	**GalNAc$_3$-7$_a$-$_o$,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$_3$ -7$_a$	A$_d$	30	109
673502	**GalNAc$_3$-10$_a$-$_o$,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$_3$ -10$_a$	A$_d$	8	109
675441	**GalNAc$_3$-17$_a$-$_o$,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$_3$ -17$_a$	A$_d$	30	109
675442	**GalNAc$_3$-18$_a$-$_o$,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$_3$ -18$_a$	A$_d$	20	109
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$_{do}$,-GalNAc$_3$-19$_a$**	PS	GalNAc$_3$ -19$_a$	A$_d$	40	110
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$_{es}$^{m}C$_{es}$^{m}C$_{es}$T$_{es}$T$_{eo}$**A$_{do}$,-GalNAc$_3$-20$_a$**	PS	GalNAc$_3$ -20$_a$	A$_d$	30	110
677843	**GalNAc$_3$-23$_a$-$_o$,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	109

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$_3$-13$_a$ 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

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	$T_{es}G_{es}G_{es}T_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{es}G_{es}$ $A_{es}G_{es}G_{e}$	n/a	n/a	115
656173	$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}$ $A_{es}G_{es}G_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	$GalNAc_3\text{-}1_a$	A_d	113
663086	$\mathbf{GalNAc_3\text{-}3_{a\text{-}o'}A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}3_a$	A_d	124
678347	$\mathbf{GalNAc_3\text{-}7_{a\text{-}o'}A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}7_a$	A_d	124
678348	$\mathbf{GalNAc_3\text{-}10_{a\text{-}o'}A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}10_a$	A_d	124
678349	$\mathbf{GalNAc_3\text{-}13_{a\text{-}o'}A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}13_a$	A_d	124

The structure of $GalNAc_3\text{-}1_a$ was shown previously in Example 9, $GalNAc_3\text{-}3_a$ was shown in Example 39, $GalNAc_3\text{-}7_a$ was shown in Example 48, $GalNAc_3\text{-}10_a$ was shown in Example 46, and $GalNAc_3\text{-}13_a$ was shown in Example 62.

Treatment

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.

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	115
	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	113
	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	124
	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	124
	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	124
	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	124
	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

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

Treatment

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	115
		10	47			
		17	52			
656173	6	3	1	$GalNAc_3$-1a	A_d	113
		10	3			
		17	21			
663086	6	3	1	$GalNAc_3$-3a	A_d	124

		10	2			
		17	9			
678347	6	3	1	$GalNAc_3$-7a	A_d	124
		10	1			
		17	8			
678348	6	3	1	$GalNAc_3$-10a	A_d	124
		10	1			
		17	6			
678349	6	3	1	$GalNAc_3$-13a	A_d	124
		10	1			
		17	5			

Example 85: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a $GalNAc_3$ Conjugate

Oligonucleotides listed in Table 76 were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Treatment

Six to eight week old C57BL/6 mice were each injected subcutaneously once per week at a dosage shown below, for a total of three doses, with an oligonucleotide listed in Table 76 or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 48 hours following the final administration to determine the 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 liver SRB-1 mRNA levels for each treatment group, normalized to the saline control.

As illustrated in Tables 80 and 81, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner.

Table 80

SRB-1 mRNA in liver

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100	n/a	n/a
655861	0.1	94	$GalNAc_3$-1a	A_d
	0.3	119		
	1	68		
	3	32		
661161	0.1	120	$GalNAc_3$-3a	A_d
	0.3	107		
	1	68		
	3	26		
666881	0.1	107	$GalNAc_3$-10a	A_d
	0.3	107		
	1	69		
	3	27		
666981	0.1	120	$GalNAc_3$-7a	A_d

	0.3	103		
	1	54		
	3	21		
670061	0.1	118	$GalNAc_3$-13a	A_d
	0.3	89		
	1	52		
	3	18		
677842	0.1	119	$GalNAc_3$-20a	A_d
	0.3	96		
	1	65		
	3	23		

Table 81

SRB-1 mRNA in liver

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
661161	0.1	107	$GalNAc_3$-3a	A_d
	0.3	95		
	1	53		
	3	18		
677841	0.1	110	$GalNAc_3$-19a	A_d
	0.3	88		
	1	52		
	3	25		

Liver transaminase levels, total bilirubin, BUN, and body weights were also measured using standard protocols. Average values for each treatment group are shown in Table 82 below.

Table 82

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	BUN (mg/dL)	Body Weight (% baseline)	$GalNAc_3$ Cluster	CM
Saline	n/a	19	39	0.17	26	118	n/a	n/a
655861	0.1	25	47	0.17	27	114	$GalNAc_3$-1a	A_d
	0.3	29	56	0.15	27	118		
	1	20	32	0.14	24	112		
	3	27	54	0.14	24	115		
661161	0.1	35	83	0.13	24	113	$GalNAc_3$-3a	A_d
	0.3	42	61	0.15	23	117		
	1	34	60	0.18	22	116		
	3	29	52	0.13	25	117		
666881	0.1	30	51	0.15	23	118	$GalNAc_3$-10a	A_d
	0.3	49	82	0.16	25	119		
	1	23	45	0.14	24	117		
	3	20	38	0.15	21	112		
666981	0.1	21	41	0.14	22	113	$GalNAc_3$-7a	A_d
	0.3	29	49	0.16	24	112		
	1	19	34	0.15	22	111		
	3	77	78	0.18	25	115		
670061	0.1	20	63	0.18	24	111	$GalNAc_3$-13a	A_d

	0.3	20	57	0.15	21	115		
	1	20	35	0.14	20	115		
	3	27	42	0.12	20	116		
677842	0.1	20	38	0.17	24	114	$GalNAc_3$-20a	A_d
	0.3	31	46	0.17	21	117		
	1	22	34	0.15	21	119		
	3	41	57	0.14	23	118		

Example 86: Antisense inhibition *in vivo* by oligonucleotides targeting TTR comprising a $GalNAc_3$ cluster

Oligonucleotides listed in Table 83 below were tested in a dose-dependent study for antisense inhibition of human transthyretin (TTR) in transgenic mice that express the human TTR gene.

Treatment

Eight week old TTR transgenic mice were each injected subcutaneously once per week for three weeks, for a total of three doses, with an oligonucleotide and dosage listed in the tables below or with PBS. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration. Tail bleeds were performed at various time points throughout the experiment, and plasma TTR protein, ALT, and AST levels were measured and reported in Tables 85-87. After the animals were sacrificed, plasma ALT, AST, and human TTR levels were measured, as were body weights, organ weights, and liver human TTR mRNA levels. TTR protein levels were measured using a clinical analyzer (AU480, Beckman Coulter, CA). Real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) were used according to standard protocols to determine liver human TTR mRNA levels. The results presented in Tables 84-87 are the average values for each treatment group. The mRNA levels are the average values relative to the average for the PBS group. Plasma protein levels are the average values relative to the average value for the PBS group at baseline. Body weights are the average percent weight change from baseline until sacrifice for each individual treatment group. Organ weights shown are normalized to the animal's body weight, and the average normalized organ weight for each treatment group is then presented relative to the average normalized organ weight for the PBS group.

In Tables 84-87, "BL" indicates baseline, measurements that were taken just prior to the first dose. As illustrated in Tables 84 and 85, treatment with antisense oligonucleotides lowered TTR expression levels in a dose-dependent manner. The oligonucleotides comprising a GalNAc conjugate were more potent than the parent lacking a GalNAc conjugate (ISIS 420915). Furthermore, the oligonucleotides comprising a GalNAc conjugate and mixed PS/PO internucleoside linkages were even more potent than the oligonucleotide comprising a GalNAc conjugate and full PS linkages.

Table 83

Oligonucleotides targeting human TTR

Isis No.	Sequence 5' to 3'	Linkages	GalNAc cluster	CM	SEQ ID No.
420915	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}$ $A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS	n/a	n/a	74
660261	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}$ $A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-1_a$**	PS	GalNAc$_3$-1a	A_d	125
682883	**GalNAc$_3$-3$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}$ $T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-3a	PO	74
682884	**GalNAc$_3$-7$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}$ $T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-7a	PO	74
682885	**GalNAc$_3$-10$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}$ $A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-10a	PO	74
682886	**GalNAc$_3$-13$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}$ $A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-13a	PO	74
684057	$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}$ $A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-19_a$**	PS/PO	GalNAc$_3$-19a	A_d	125

The legend for Table 85 can be found in Example 74. The structure of GalNAc$_3$-1 was shown in Example 9. The structure of GalNAc$_3$-3$_a$ was shown in Example 39. The structure of GalNAc$_3$-7$_a$ was shown in Example 48. The structure of GalNAc$_3$-10$_a$ was shown in Example 46. The structure of GalNAc$_3$-13$_a$ was shown in Example 62. The structure of GalNAc$_3$-19$_a$ was shown in Example 70.

Table 84

Antisense inhibition of human TTR *in vivo*

Isis No.	Dosage (mg/kg)	TTR mRNA (% PBS)	Plasma TTR protein (% PBS)	GalNAc cluster	CM	SEQ ID No.
PBS	n/a	100	100	n/a	n/a	
420915	6	99	95	n/a	n/a	74
	20	48	65			
	60	18	28			
660261	0.6	113	87	GalNAc$_3$-1a	A_d	125
	2	40	56			
	6	20	27			
	20	9	11			

Table 85

Antisense inhibition of human TTR *in vivo*

Isis No.	Dosage (mg/kg)	TTR mRNA (% PBS)	Plasma TTR protein (% PBS at BL)				GalNAc cluster	CM	SEQ ID No.
			BL	Day 3	Day 10	Day 17 (After sac)			
PBS	n/a	100	100	96	90	114	n/a	n/a	
420915	6	74	106	86	76	83	n/a	n/a	74
	20	43	102	66	61	58			
	60	24	92	43	29	32			
682883	0.6	60	88	73	63	68	GalNAc$_3$-3a	PO	74
	2	18	75	38	23	23			
	6	10	80	35	11	9			

682884	0.6	56	88	78	63	67	$GalNAc_3$-7a	PO	74
	2	19	76	44	25	23			
	6	15	82	35	21	24			
682885	0.6	60	92	77	68	76	$GalNAc_3$-10a	PO	74
	2	22	93	58	32	32			
	6	17	85	37	25	20			
682886	0.6	57	91	70	64	69	$GalNAc_3$-13a	PO	74
	2	21	89	50	31	30			
	6	18	102	41	24	27			
684057	0.6	53	80	69	56	62	$GalNAc_3$-19a	A_d	125
	2	21	92	55	34	30			
	6	11	82	50	18	13			

Table 86

Transaminase levels, body weight changes, and relative organ weights

Isis No.	Dosage (mg/kg)	ALT (U/L)				AST (U/L)				Body (% BL)	Liver (% PBS)	Spleen (% PBS)	Kidney (% PBS)	SEQ ID No.
		BL	Day 3	Day 10	Day 17	BL	Day 3	Day 10	Day 17					
PBS	n/a	33	34	33	24	58	62	67	52	105	100	100	100	n/a
420915	6	34	33	27	21	64	59	73	47	115	99	89	91	74
	20	34	30	28	19	64	54	56	42	111	97	83	89	
	60	34	35	31	24	61	58	71	58	113	102	98	95	
660261	0.6	33	38	28	26	70	71	63	59	111	96	99	92	125
	2	29	32	31	34	61	60	68	61	118	100	92	90	
	6	29	29	28	34	58	59	70	90	114	99	97	95	
	20	33	32	28	33	64	54	68	95	114	101	106	92	

Table 87

Transaminase levels, body weight changes, and relative organ weights

Isis No.	Dosage (mg/kg)	ALT (U/L)				AST (U/L)				Body (% BL)	Liver (% PBS)	Spleen (% PBS)	Kidney (% PBS)	SEQ ID No.
		BL	Day 3	Day 10	Day 17	BL	Day 3	Day 10	Day 17					
PBS	n/a	32	34	37	41	62	78	76	77	104	100	100	100	n/a
420915	6	32	30	34	34	61	71	72	66	102	103	102	105	74
	20	41	34	37	33	80	76	63	54	106	107	135	101	
	60	36	30	32	34	58	81	57	60	106	105	104	99	
682883	0.6	32	35	38	40	53	81	74	76	104	101	112	95	74
	2	38	39	42	43	71	84	70	77	107	98	116	99	
	6	35	35	41	38	62	79	103	65	105	103	143	97	
682884	0.6	33	32	35	34	70	74	75	67	101	100	130	99	74
	2	31	32	38	38	63	77	66	55	104	103	122	100	
	6	38	32	36	34	65	85	80	62	99	105	129	95	
682885	0.6	39	26	37	35	63	63	77	59	100	109	109	112	74
	2	30	26	38	40	54	56	71	72	102	98	111	102	
	6	27	27	34	35	46	52	56	64	102	98	113	96	
682886	0.6	30	40	34	36	58	87	54	61	104	99	120	101	74
	2	27	26	34	36	51	55	55	69	103	91	105	92	
	6	40	28	34	37	107	54	61	69	109	100	102	99	

684057	0.6	35	26	33	39	56	51	51	69	104	99	110	102	125
	2	33	32	31	40	54	57	56	87	103	100	112	97	
	6	39	33	35	40	67	52	55	92	98	104	121	108	

Example 87: Duration of action *in vivo* by single doses of oligonucleotides targeting TTR comprising a $GalNAc_3$ cluster

ISIS numbers 420915 and 660261 (see Table 83) were tested in a single dose study for duration of action in mice. ISIS numbers 420915, 682883, and 682885 (see Table 83) were also tested in a single dose study for duration of action in mice.

Treatment

Eight week old, male transgenic mice that express human TTR were each injected subcutaneously once with 100 mg/kg ISIS No. 420915 or 13.5 mg/kg ISIS No. 660261. Each treatment group consisted of 4 animals. Tail bleeds were performed before dosing to determine baseline and at days 3, 7, 10, 17, 24, and 39 following the dose. Plasma TTR protein levels were measured as described in Example 86. The results below are presented as the average percent of plasma TTR levels for each treatment group, normalized to baseline levels.

Table 88

Plasma TTR protein levels

ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	TTR (% baseline)	$GalNAc_3$ Cluster	CM	SEQ ID No.
420915	100	3	30	n/a	n/a	74
		7	23			
		10	35			
		17	53			
		24	75			
		39	100			
660261	13.5	3	27	$GalNAc_3$-1a	A_d	125
		7	21			
		10	22			
		17	36			
		24	48			
		39	69			

Treatment

Female transgenic mice that express human TTR were each injected subcutaneously once with 100 mg/kg ISIS No. 420915, 10.0 mg/kg ISIS No. 682883, or 10.0 mg/kg 682885. Each treatment group consisted of 4 animals. Tail bleeds were performed before dosing to determine baseline and at days 3, 7, 10, 17, 24, and 39 following the dose. Plasma TTR protein levels were measured as described in Example 86.

The results below are presented as the average percent of plasma TTR levels for each treatment group, normalized to baseline levels.

Table 89

Plasma TTR protein levels

ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	TTR (% baseline)	$GalNAc_3$ Cluster	CM	SEQ ID No.
420915	100	3	48	n/a	n/a	74
		7	48			
		10	48			
		17	66			
		31	80			
682883	10.0	3	45	$GalNAc_3$-3a	PO	74
		7	37			
		10	38			
		17	42			
		31	65			
682885	10.0	3	40	$GalNAc_3$-10a	PO	74
		7	33			
		10	34			
		17	40			
		31	64			

The results in Tables 88 and 89 show that the oligonucleotides comprising a GalNAc conjugate are more potent with a longer duration of action than the parent oligonucleotide lacking a conjugate (ISIS 420915).

Example 88: Splicing modulation *in vivo* by oligonucleotides targeting SMN comprising a $GalNAc_3$ conjugate

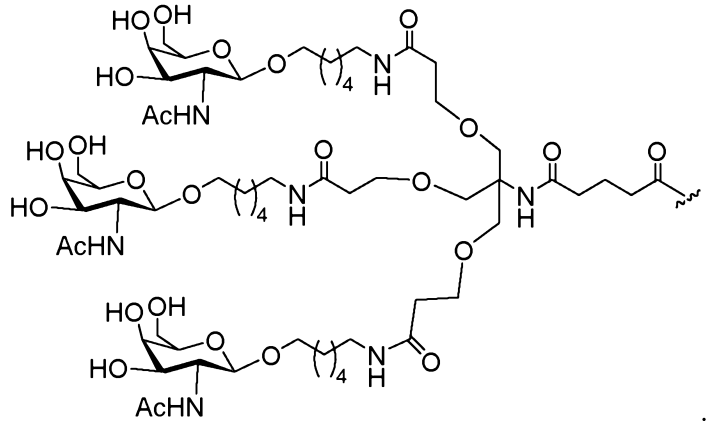
The oligonucleotides listed in Table 90 were tested for splicing modulation of human survival of motor neuron (SMN) in mice.

Table 90

Modified ASOs targeting SMN

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
387954	$A_{es}T_{es}T_{es}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}T_{es}T_{es}{}^{m}C_{es}A_{es}T_{es}A_{es}A_{es}T_{es}G_{es}{}^{m}C_{es}T_{es}G_{es}G_{e}$	n/a	n/a	126
699819	**$GalNAc_3$-7_{a}-$_{o}$'**$A_{es}T_{es}T_{es}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}T_{es}T_{es}{}^{m}C_{es}A_{es}T_{es}A_{es}A_{es}T_{es}G_{es}{}^{m}C_{es}T_{es}G_{es}G_{e}$	$GalNAc_3$-7a	PO	126
699821	**$GalNAc_3$-7_{a}-$_{o}$'**$A_{es}T_{eo}T_{eo}{}^{m}C_{eo}A_{eo}{}^{m}C_{eo}T_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{eo}T_{eo}A_{eo}A_{eo}T_{eo}G_{eo}{}^{m}C_{eo}T_{es}G_{es}G_{e}$	$GalNAc_3$-7a	PO	126
700000	$A_{es}T_{es}T_{es}{}^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}T_{es}T_{es}{}^{m}C_{es}A_{es}T_{es}A_{es}A_{es}T_{es}G_{es}{}^{m}C_{es}T_{es}G_{es}G_{eo}$**$A_{do}$'-$GalNAc_3$-$1_{a}$**	$GalNAc_3$-1a	A_d	127
703421	X-ATT^{m}CA^{m}CTTT^{m}CATAATG^{m}CTGG	n/a	n/a	126
703422	**$GalNAc_3$-7_{b}-**X-ATT^{m}CA^{m}CTTT^{m}CATAATG^{m}CTGG	$GalNAc_3$-7b	n/a	126

The structure of $GalNAc_3$-7_a was shown previously in Example 48. "X" indicates a 5' primary amine generated by Gene Tools (Philomath, OR), and $GalNAc_3$-7_b indicates the structure of $GalNAc_3$-7_a lacking the $-NH-C_6-O$ portion of the linker as shown below:



ISIS numbers 703421 and 703422 are morphlino oligonucleotides, wherein each nucleotide of the two oligonucleotides is a morpholino nucleotide.

Treatment

Six week old transgenic mice that express human SMN were injected subcutaneously once with an oligonucleotide listed in Table 91 or with saline. Each treatment group consisted of 2 males and 2 females. The mice were sacrificed 3 days following the dose to determine the liver human SMN mRNA levels both with and without exon 7 using real-time PCR according to standard protocols. Total RNA was measured using Ribogreen reagent. The SMN mRNA levels were normalized to total mRNA, and further normalized to the averages for the saline treatment group. The resulting average ratios of SMN mRNA including exon 7 to SMN mRNA missing exon 7 are shown in Table 91. The results show that fully modified oligonucleotides that modulate splicing and comprise a GalNAc conjugate are significantly more potent in altering splicing in the liver than the parent oligonucleotides lacking a GlaNAc conjugate. Furthermore, this trend is maintained for multiple modification chemistries, including 2'-MOE and morpholino modified oligonucleotides.

Table 91

Effect of oligonucleotides targeting human SMN *in vivo*

ISIS No.	Dose (mg/kg)	+Exon 7 / -Exon 7	$GalNAc_3$ Cluster	CM	SEQ ID No.
Saline	n/a	1.00	n/a	n/a	n/a
387954	32	1.65	n/a	n/a	126
387954	288	5.00	n/a	n/a	126
699819	32	7.84	$GalNAc_3$-7a	PO	126
699821	32	7.22	$GalNAc_3$-7a	PO	126
700000	32	6.91	$GalNAc_3$-1a	A_d	127
703421	32	1.27	n/a	n/a	126
703422	32	4.12	$GalNAc_3$-7b	n/a	126

Example 89: Antisense inhibition *in vivo* by oligonucleotides targeting Apolipoprotein A (Apo(a)) comprising a GalNAc$_3$ conjugate

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	25
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	25

The structure of GalNAc$_3$-7$_a$ was shown in Example 48.

Treatment

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.

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 90: Antisense inhibition *in vivo* by oligonucleotides targeting TTR comprising a $GalNAc_3$ cluster

Oligonucleotides listed in Table 95 below were tested in a dose-dependent study for antisense inhibition of human transthyretin (TTR) in transgenic mice that express the human TTR gene.

Treatment

TTR transgenic mice were each injected subcutaneously once per week for three weeks, for a total of three doses, with an oligonucleotide and dosage listed in Table 96 or with PBS. Each treatment group consisted of 4 animals. Prior to the first dose, a tail bleed was performed to determine plasma TTR protein levels at baseline (BL). The mice were sacrificed 72 hours following the final administration. TTR protein levels were measured using a clinical analyzer (AU480, Beckman Coulter, CA). Real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) were used according to standard protocols to determine liver human TTR mRNA levels. The results presented in Table 96 are the average values for each treatment group. The mRNA levels are the average values relative to the average for the PBS group. Plasma protein levels are the average values relative to the average value for the PBS group at baseline. "BL" indicates baseline, measurements that were taken just prior to the first dose. As illustrated in Table 96, treatment with antisense oligonucleotides lowered TTR expression levels in a dose-dependent manner. The oligonucleotides comprising a GalNAc conjugate were more potent than the parent lacking a GalNAc conjugate (ISIS 420915), and oligonucleotides comprising a phosphodiester or deoxyadenosine

cleavable moiety showed significant improvements in potency compared to the parent lacking a conjugate (see ISIS numbers 682883 and 666943 vs 420915 and see Examples 86 and 87).

Table 95

Oligonucleotides targeting human TTR

Isis No.	Sequence 5' to 3'	Linkages	GalNAc cluster	CM	SEQ ID No.
420915	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS	n/a	n/a	74
682883	**GalNAc$_3$-3$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-3a	PO	74
666943	**GalNAc$_3$-3$_{a\text{-}o}$,A$_{do}$**$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-3a	A$_d$	128
682887	**GalNAc$_3$-7$_{a\text{-}o}$,A$_{do}$**$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-7a	A$_d$	128
682888	**GalNAc$_3$-10$_{a\text{-}o}$,A$_{do}$**$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-10a	A$_d$	128
682889	**GalNAc$_3$-13$_{a\text{-}o}$,A$_{do}$**$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-13a	A$_d$	128

The legend for Table 95 can be found in Example 74. The structure of GalNAc$_3$-3$_a$ was shown in Example 39. The structure of GalNAc$_3$-7$_a$ was shown in Example 48. The structure of GalNAc$_3$-10$_a$ was shown in Example 46. The structure of GalNAc$_3$-13$_a$ was shown in Example 62.

Table 96

Antisense inhibition of human TTR *in vivo*

Isis No.	Dosage (mg/kg)	TTR mRNA (% PBS)	TTR protein (% BL)	GalNAc cluster	CM
PBS	n/a	100	124	n/a	n/a
420915	6	69	114	n/a	n/a
	20	71	86		
	60	21	36		
682883	0.6	61	73	GalNAc$_3$-3a	PO
	2	23	36		
	6	18	23		
666943	0.6	74	93	GalNAc$_3$-3a	A$_d$
	2	33	57		
	6	17	22		
682887	0.6	60	97	GalNAc$_3$-7a	A$_d$
	2	36	49		
	6	12	19		
682888	0.6	65	92	GalNAc$_3$-10a	A$_d$
	2	32	46		
	6	17	22		
682889	0.6	72	74	GalNAc$_3$-13a	A$_d$
	2	38	45		
	6	16	18		

Example 91: Antisense inhibition *in vivo* by oligonucleotides targeting Factor VII comprising a $GalNAc_3$ conjugate in non-human primates

Oligonucleotides listed in Table 97 below were tested in a non-terminal, dose escalation study for antisense inhibition of Factor VII in monkeys.

Treatment

Non-naïve monkeys were each injected subcutaneously on days 0, 15, and 29 with escalating doses of an oligonucleotide listed in Table 97 or with PBS. Each treatment group consisted of 4 males and 1 female. Prior to the first dose and at various time points thereafter, blood draws were performed to determine plasma Factor VII protein levels. Factor VII protein levels were measured by ELISA. The results presented in Table 98 are the average values for each treatment group relative to the average value for the PBS group at baseline (BL), the measurements taken just prior to the first dose. As illustrated in Table 98, treatment with antisense oligonucleotides lowered Factor VII expression levels in a dose-dependent manner, and the oligonucleotide comprising the GalNAc conjugate was significantly more potent in monkeys compared to the oligonucleotide lacking a GalNAc conjugate.

Table 97

Oligonucleotides targeting Factor VII

Isis No.	Sequence 5' to 3'	Linkages	GalNAc cluster	CM	SEQ ID No.
407935	$A_{es}T_{es}G_{es}{}^{m}C_{es}A_{es}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}$ $T_{es}{}^{m}C_{es}T_{es}G_{es}A_{e}$	PS	n/a	n/a	38
686892	**$GalNAc_3$-$10_{a\text{-}o}$**,$A_{es}T_{es}G_{es}{}^{m}C_{es}A_{es}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}$ $A_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}T_{es}G_{es}A_{e}$	PS	$GalNAc_3$-10a	PO	38

The legend for Table 97 can be found in Example 74. The structure of $GalNAc_3$-10_a was shown in Example 46.

Table 98

Factor VII plasma protein levels

ISIS No.	Day	Dose (mg/kg)	Factor VII (% BL)
407935	0	n/a	100
	15	10	87
	22	n/a	92
	29	30	77
	36	n/a	46
	43	n/a	43
686892	0	3	100
	15	10	56
	22	n/a	29
	29	30	19
	36	n/a	15

	43	n/a	11

Example 92: Antisense inhibition in primary hepatocytes by antisense oligonucleotides targeting Apo-CIII comprising a GalNAc$_3$ conjugate

Primary mouse hepatocytes were seeded in 96-well plates at 15,000 cells per well, and the oligonucleotides listed in Table 99, targeting mouse ApoC-III, were added at 0.46, 1.37, 4.12, or 12.35, 37.04, 111.11, or 333.33 nM or 1.00 μM. After incubation with the oligonucleotides for 24 hours, the cells were lysed and total RNA was purified using RNeasy (Qiagen). ApoC-III mRNA levels were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc.) according to standard protocols. IC_{50} values were determined using Prism 4 software (GraphPad). The results show that regardless of whether the cleavable moiety was a phosphodiester or a phosphodiester-linked deoxyadensoine, the oligonucleotides comprising a GalNAc conjugate were significantly more potent than the parent oligonucleotide lacking a conjugate.

Table 99

Inhibition of mouse APOC-III expression in mouse primary hepatocytes

ISIS No.	Sequence (5' to 3')	CM	IC_{50} (nM)	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	13.20	129
661180	$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}$ $A_{es}G_{es}{}^{m}C_{es}A_{eo}$ **A_{do}'-GalNAc$_3$-1$_a$**	A_d	1.40	130
680771	**GalNAc$_3$-3$_{a\text{-}o}$**,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}$ $A_{es}G_{es}{}^{m}C_{es}A_{e}$	PO	0.70	129
680772	**GalNAc$_3$-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	1.70	129
680773	**GalNAc$_3$-10$_{a\text{-}o}$**,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}$ $A_{es}G_{es}{}^{m}C_{es}A_{e}$	PO	2.00	129
680774	**GalNAc$_3$-13$_{a\text{-}o}$**,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}$ $A_{es}G_{es}{}^{m}C_{es}A_{e}$	PO	1.50	129
681272	**GalNAc$_3$-3$_{a\text{-}o}$**,$^{m}C_{es}A_{eo}G_{eo}{}^{m}C_{eo}T_{eo}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{eo}$ $A_{eo}G_{es}{}^{m}C_{es}A_{e}$	PO	< 0.46	129
681273	**GalNAc$_3$-3$_{a\text{-}o}$**,**A_{do}**$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}$ $^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	A_d	1.10	131
683733	$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}$ $A_{es}G_{es}{}^{m}C_{es}A_{eo}$**$A_{do}$'-GalNAc$_3-19_a$**	A_d	2.50	130

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, GalNAc$_3$-13$_a$ was shown in Example 62, and GalNAc$_3$-19$_a$ was shown in Example 70.

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

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	132
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	132
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	132
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	132
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	132
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	132
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	132

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

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.

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 94: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising 2'-sugar modifications and a 5'-GalNAc$_3$ conjugate

The oligonucleotides listed in Table 102 were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Table 102

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No.
353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	n/a	n/a	108
700989	$G_{ms}C_{ms}U_{ms}U_{ms}C_{ms}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}U_{ms}C_{ms}C_{ms}U_{ms}U_{m}$	n/a	n/a	133
666904	**GalNAc$_3$-3$_{a-o}$**,$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-3a	PO	108
700991	**GalNAc$_3$-7$_{a-o}$**,$G_{ms}C_{ms}U_{ms}U_{ms}C_{ms}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}U_{ms}C_{ms}C_{ms}U_{ms}U_{m}$	GalNAc$_3$-7a	PO	133

Subscript "m" indicates a 2'-O-methyl modified nucleoside. See Example 74 for complete table legend. 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

The study was completed using the protocol described in Example 93. Results are shown in Table 103 below and show that both the 2'-MOE and 2'-OMe modified oligonucleotides comprising a GalNAc conjugate were significantly more potent than the respective parent oligonucleotides lacking a conjugate. The results of the body weights, liver transaminases, total bilirubin, and BUN measurements indicated that the compounds were all well tolerated.

Table 103

SRB-1 mRNA

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% PBS)
PBS	n/a	100
353382	5	116
	15	58
	45	27
700989	5	120
	15	92
	45	46
666904	1	98
	3	45
	10	17
700991	1	118
	3	63
	10	14

Example 95: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising bicyclic nucleosides and a 5'-GalNAc$_3$ conjugate

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	104
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	104
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	104
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	104
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$_d$	112
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	104
699789	**GalNAc$_3$-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	104

Subscript "g" indicates a fluoro-HNA nucleoside, subscript "l" indicates a locked nucleoside comprising a 2'-O-CH_2-4' bridge. See the Example 74 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

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
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

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	25
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	25
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	25
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	25

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

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).

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 97: Modified oligonucleotides targeting TTR comprising a GalNAc$_3$ conjugate group

The oligonucleotides shown in Table 108 comprising a GalNAc conjugate were designed to target TTR.

Table 108
Modified oligonucleotides targeting TTR

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No
666941	**GalNAc$_3$-3$_{a\text{-}o}$,A$_{do}$** T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-3	A$_d$	128
666942	T_{es} $^{m}C_{eo}$ T_{eo} T_{eo} G_{eo} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{eo} T_{eo} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{eo}$ **A$_{do}$-GalNAc$_3$-3$_a$**	GalNAc$_3$-1	A$_d$	125
682876	**GalNAc$_3$-3$_{a\text{-}o}$,**T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-3	PO	74
682877	**GalNAc$_3$-7$_{a\text{-}o}$,**T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-7	PO	74
682878	**GalNAc$_3$-10$_{a\text{-}o}$,**T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-10	PO	74
682879	**GalNAc$_3$-13$_{a\text{-}o}$,**T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-13	PO	74
682880	**GalNAc$_3$-7$_{a\text{-}o}$,A$_{do}$** T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-7	A$_d$	128
682881	**GalNAc$_3$-10$_{a\text{-}o}$,A$_{do}$** T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-10	A$_d$	128
682882	**GalNAc$_3$-13$_{a\text{-}o}$,A$_{do}$** T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{e}$	GalNAc$_3$-13	A$_d$	128
684056	T_{es} $^{m}C_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^{m}C_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^{m}C_{es}$ $^{m}C_{es}$ $^{m}C_{eo}$ **A$_{do}$-GalNAc$_3$-19$_a$**	GalNAc$_3$-19	A$_d$	125

The legend for Table 108 can be found in Example 74. The structure of GalNAc$_3$-1 was shown in Example 9. The structure of GalNAc$_3$-3$_a$ was shown in Example 39. The structure of GalNAc$_3$-7$_a$ was shown in Example 48. The structure of GalNAc$_3$-10$_a$ was shown in Example 46. The structure of GalNAc$_3$-13$_a$ was shown in Example 62. The structure of GalNAc$_3$-19$_a$ was shown in Example 70.

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

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

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 ß-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% ß-mercaptoethanol. Lysates were transferred to round bottom assay tubes after a brief 10 min freeze/thaw cycle and assayed on a ɣ-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).

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
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*

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	25
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	25

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

Treatment

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
	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

The oligonucleotides listed in Table 112 were tested for inhibition of mouse APOC-III expression *in vivo*. C57Bl/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	129
			6	86	
			20	59	
			60	37	
680772	**GalNAc$_3$-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	129
			2	58	
			6	31	
			20	13	
696847	**GalNAc$_3$-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	129
			2	73	
			6	40	
			20	28	

The structure of GalNAc$_3$-7$_a$ was shown in Example 48.

Example 102: Distribution in liver of antisense oligonucleotides comprising a GalNAc conjugate

The liver distribution of ISIS 353382 (see Table 36) that does not comprise a GalNAc conjugate and ISIS 655861 (see Table 36) that does comprise a GalNAc conjugate was evaluated. Male balb/c mice were subcutaneously injected once with ISIS 353382 or 655861 at a dosage listed in Table 113. Each treatment group consisted of 3 animals except for the 18 mg/kg group for ISIS 655861, which consisted of 2 animals. The animals were sacrificed 48 hours following the dose to determine the liver distribution of the oligonucleotides. In order to measure the number of antisense oligonucleotide molecules per cell, a Ruthenium (II) tris-bipyridine tag (MSD TAG, Meso Scale Discovery) was conjugated to an oligonucleotide probe used to detect the antisense oligonucleotides. The results presented in Table 113 are the average concentrations of oligonucleotide for each treatment group in units of millions of oligonucleotide molecules per cell. The results show that at equivalent doses, the oligonucleotide comprising a GalNAc conjugate was present at higher concentrations in the total liver and in hepatocytes than the oligonucleotide that does not comprise a GalNAc conjugate. Furthermore, the oligonucleotide comprising a GalNAc conjugate was present at lower concentrations in non-parenchymal liver cells than the oligonucleotide that does not comprise a GalNAc conjugate. And while the concentrations of ISIS 655861 in hepatocytes and non-parenchymal liver cells were similar per cell, the liver is approximately 80% hepatocytes by volume. Thus, the majority of the

ISIS 655861 oligonucleotide that was present in the liver was found in hepatocytes, whereas the majority of the ISIS 353382 oligonucleotide that was present in the liver was found in non-parenchymal liver cells.

Table 113

ISIS No.	Dosage (mg/kg)	Concentration in whole liver (molecules*10^6 per cell)	Concentration in hepatocytes (molecules*10^6 per cell)	Concentration in non-parenchymal liver cells (molecules*10^6 per cell)
353382	3	9.7	1.2	37.2
	10	17.3	4.5	34.0
	20	23.6	6.6	65.6
	30	29.1	11.7	80.0
	60	73.4	14.8	98.0
	90	89.6	18.5	119.9
655861	0.5	2.6	2.9	3.2
	1	6.2	7.0	8.8
	3	19.1	25.1	28.5
	6	44.1	48.7	55.0
	18	76.6	82.3	77.1

Example 103: Duration of action *in vivo* of oligonucleotides targeting APOC-III comprising a GalNAc$_3$ conjugate

The oligonucleotides listed in Table 114 below were tested in a single dose study for duration of action in mice.

Table 114

Modified ASOs targeting APOC-III

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No.
304801	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	n/a	n/a	32
663084	**GalNAc$_3$-3$_a$-$_o$'A_{do}**$A_{es}G_{eo}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{eo}T_{eo}T_{es}A_{es}T_{e}$	GalNAc$_3$-3a	A_d	119
679241	$A_{es}G_{eo}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{eo}T_{eo}T_{es}A_{es}T_{eo}$**$A_{do}$'-GalNAc$_3-19_a$**	GalNAc$_3$-19a	A_d	111

The structure of GalNAc$_3$-3$_a$ was shown in Example 39, and GalNAc$_3$-19$_a$ was shown in Example 70.

Treatment

Female transgenic mice that express human APOC-III were each injected subcutaneously once with an oligonucleotide listed in Table 114 or with PBS. Each treatment group consisted of 3 animals. Blood was drawn before dosing to determine baseline and at 3, 7, 14, 21, 28, 35, and 42 days following the dose. Plasma triglyceride and APOC-III protein levels were measured as described in Example 20. The results in Table 115 are presented as the average percent of plasma triglyceride and APOC-III levels for each treatment group,

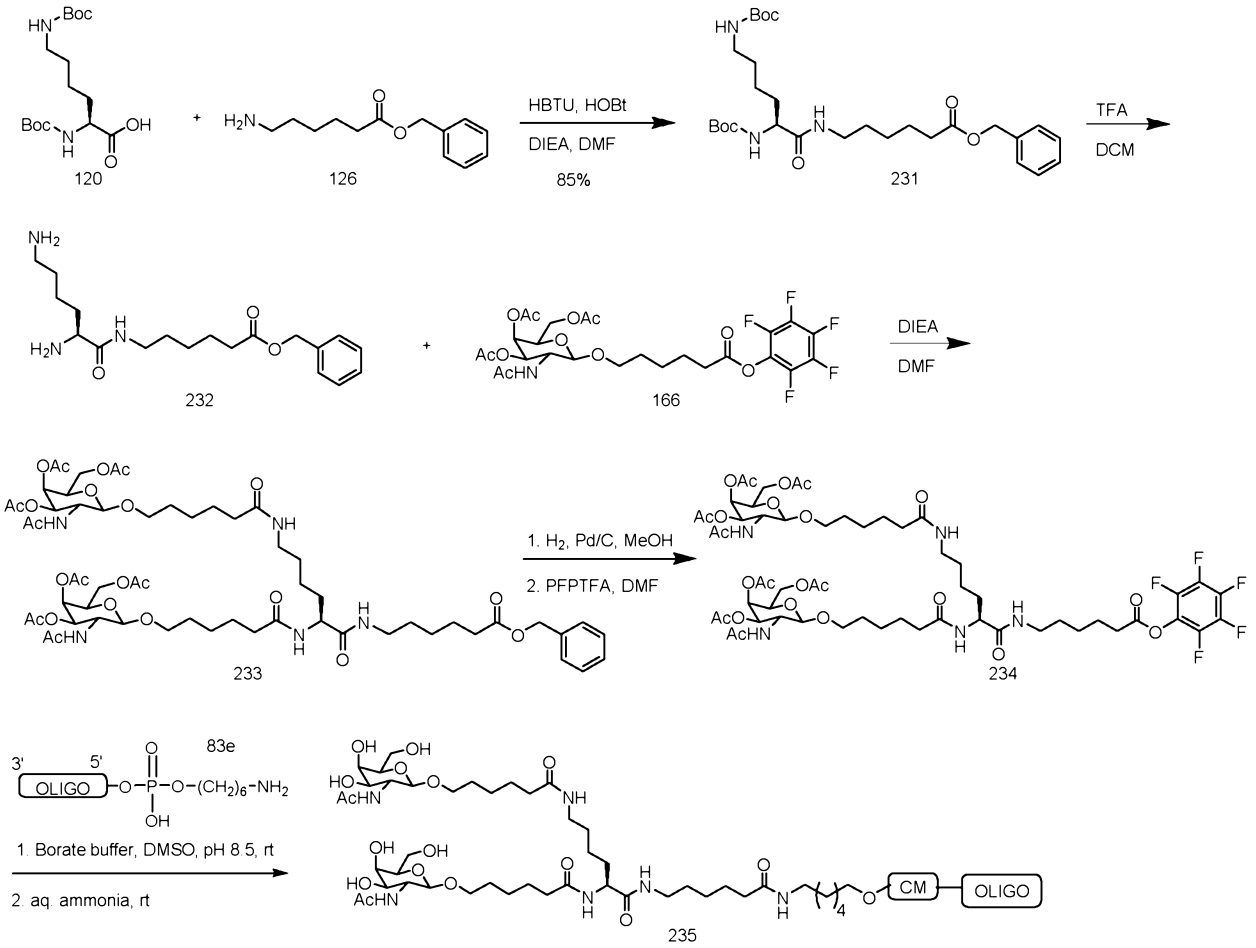
normalized to baseline levels. A comparison of the results in Table 71 of example 79 with the results in Table 115 below show that oligonucleotides comprising a mixture of phosphodiester and phosphorothioate internucleoside linkages exhibited increased duration of action than equivalent oligonucleotides comprising only phosphorothioate internucleoside linkages.

Table 115

Plasma triglyceride and APOC-III protein levels in transgenic mice

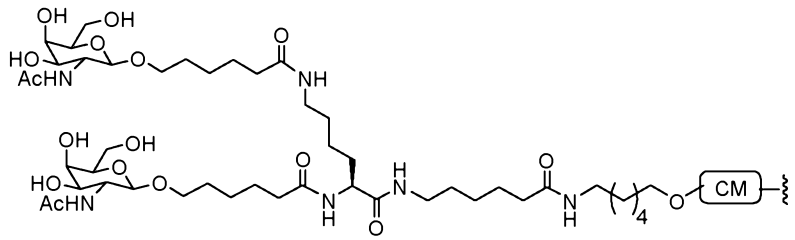
ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	Triglycerides (% baseline)	APOC-III protein (% baseline)	$GalNAc_3$ Cluster	CM
PBS	n/a	3	96	101	n/a	n/a
		7	88	98		
		14	91	103		
		21	69	92		
		28	83	81		
		35	65	86		
		42	72	88		
304801	30	3	42	46	n/a	n/a
		7	42	51		
		14	59	69		
		21	67	81		
		28	79	76		
		35	72	95		
		42	82	92		
663084	10	3	35	28	$GalNAc_3$-3a	A_d
		7	23	24		
		14	23	26		
		21	23	29		
		28	30	22		
		35	32	36		
		42	37	47		
679241	10	3	38	30	$GalNAc_3$-19a	A_d
		7	31	28		
		14	30	22		
		21	36	34		
		28	48	34		
		35	50	45		
		42	72	64		

Example 104: Synthesis of oligonucleotides comprising a 5'-GalNAc$_2$ conjugate

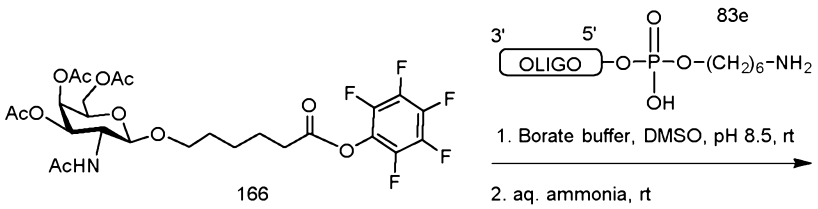


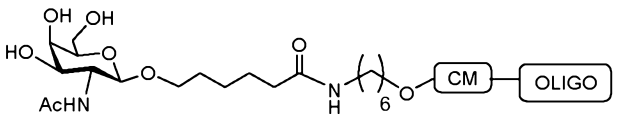
Compound 120 is commercially available, and the synthesis of compound 126 is described in Example 49. Compound 120 (1 g, 2.89 mmol), HBTU (0.39 g, 2.89 mmol), and HOBt (1.64 g, 4.33 mmol) were dissolved in DMF (10 mL. and *N,N*-diisopropylethylamine (1.75 mL, 10.1 mmol) were added. After about 5 min, aminohexanoic acid benzyl ester (1.36 g, 3.46 mmol) was added to the reaction. After 3h, the reaction mixture was poured into 100 mL of 1 M NaHSO4 and extracted with 2 x 50 mL ethyl acetate. Organic layers were combined and washed with 3 x 40 mL sat $NaHCO_3$ and 2 x brine, dried with Na_2SO_4, filtered and concentrated. The product was purified by silica gel column chromatography (DCM:EA:Hex , 1:1:1) to yield compound 231. LCMS and NMR were consistent with the structure. Compounds 231 (1.34 g, 2.438 mmol) was dissolved in dichloromethane (10 mL) and trifluoracetic acid (10 mL) was added. After stirring at room temperature for 2h, the reaction mixture was concentrated under reduced pressure and co-evaporated with toluene (3 x 10 mL). The residue was dried under reduced pressure to yield compound 232 as the trifuloracetate salt. The synthesis of compound 166 is described in Example 54. Compound 166 (3.39 g, 5.40 mmol) was dissolved in DMF (3 mL). A solution of compound 232 (1.3 g, 2.25 mmol) was dissolved in DMF (3 mL) and *N,N*-diisopropylethylamine (1.55 mL) was added. The reaction was stirred at room temperature for 30 minutes, then poured into water (80 mL) and the aqueous layer was extracted with

EtOAc (2x100 mL). The organic phase was separated and washed with sat. aqueous $NaHCO_3$ (3 x 80 mL), 1 M $NaHSO_4$ (3 x 80 mL) and brine (2 x 80 mL), then dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography to yield compound 233. LCMS and NMR were consistent with the structure. Compound 233 (0.59 g, 0.48 mmol) was dissolved in methanol (2.2 mL) and ethyl acetate (2.2 mL). Palladium on carbon (10 wt% Pd/C, wet , 0.07 g) was added, and the reaction mixture was stirred under hydrogen atmosphere for 3 h. The reaction mixture was filtered through a pad of Celite and concentrated to yield the carboxylic acid. The carboxylic acid (1.32 g, 1.15 mmol, cluster free acid) was dissolved in DMF (3.2 mL). To this *N,N*-diisopropylehtylamine (0.3 mL, 1.73 mmol) and PFPTFA (0.30 mL, 1.73 mmol) were added. After 30 min stirring at room temperature the reaction mixture was poured into water (40 mL) and extracted with EtOAc (2 x 50 mL). A standard work-up was completed as described above to yield compound 234. LCMS and NMR were consistent with the structure. Oligonucleotide 235 was prepared using the general procedure described in Example 46. The $GalNAc_2$ cluster portion ($GalNAc_2$-24_a) of the conjugate group $GalNAc_2$-24 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_2$-24 ($GalNAc_2$-24_a-CM) is shown below:



Example 105: Synthesis of oligonucleotides comprising a $GalNAc_1$-25 conjugate

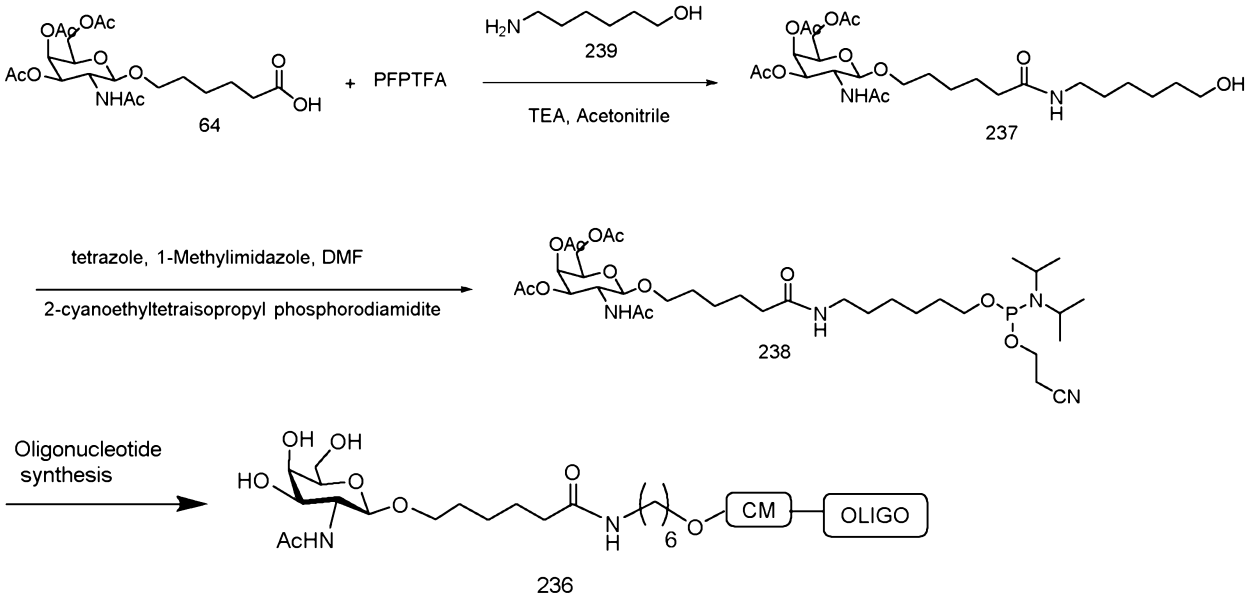




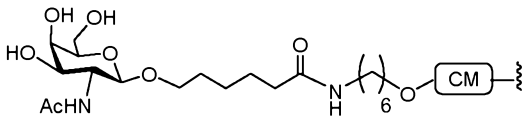
236

The synthesis of compound 166 is described in Example 54. Oligonucleotide 236 was prepared using the general procedure described in Example 46.

Alternatively, oligonucleotide 236 was synthesized using the scheme shown below, and compound 238 was used to form the oligonucleotide 236 using procedures described in Example 10.



The $GalNAc_1$ cluster portion ($GalNAc_1$-25_a) of the conjugate group $GalNAc_1$-25 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-25 ($GalNAc_1$-25_a-CM) is shown below:



Example 106: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a 5'-$GalNAc_2$ or a 5'-$GalNAc_3$ conjugate

Oligonucleotides listed in Tables 116 and 117 were tested in dose-dependent studies for antisense inhibition of SRB-1 in mice.

Treatment

Six to week old, male C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once with 2, 7, or 20 mg/kg of ISIS No. 440762; or with 0.2, 0.6, 2, 6, or 20 mg/kg of ISIS No. 686221, 686222, or 708561; 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 antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner, and the ED_{50} results are presented in Tables 116 and 117. Although previous studies showed that trivalent GalNAc-conjugated oligonucleotides were significantly more potent than divalent GalNAc-conjugated oligonucleotides, which were in turn significantly more potent than monovalent GalNAc conjugated oligonucleotides (*see*, e.g., Khorev et al., *Bioorg. & Med. Chem.*, Vol. 16, 5216-5231 (2008)), treatment with

antisense oligonucleotides comprising monovalent, divalent, and trivalent GalNAc clusters lowered SRB-1 mRNA levels with similar potencies as shown in Tables 116 and 117.

Table 116

Modified oligonucleotides targeting SRB-1

ISIS No.	Sequences (5' to 3')	GalNAc Cluster	ED_{50} (mg/kg)	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	4.7	104
686221	**$GalNAc_2$-24_a-$_o$,A_{do}**$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	$GalNAc_2$-24_a	0.39	114
686222	**$GalNAc_3$-13_a-$_o$,A_{do}**$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	$GalNAc_3$-13_a	0.41	114

See Example 93 for table legend. The structure of $GalNAc_3$-13a was shown in Example 62, and the structure of $GalNAc_2$-24a was shown in Example 104.

Table 117

Modified oligonucleotides targeting SRB-1

ISIS No.	Sequences (5' to 3')	GalNAc Cluster	ED_{50} (mg/kg)	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	5	104
708561	**$GalNAc_1$-25_a-$_o$,**$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{k}$	$GalNAc_1$-25_a	0.4	104

See Example 93 for table legend. The structure of $GalNAc_1$-25a was shown in Example 105.

The concentrations of the oligonucleotides in Tables 116 and 117 in liver were also assessed, using procedures described in Example 75. The results shown in Tables 117a and 117b below are the average total antisense oligonucleotide tissues levels for each treatment group, as measured by UV in units of μg oligonucleotide per gram of liver tissue. The results show that the oligonucleotides comprising a GalNAc conjugate group accumulated in the liver at significantly higher levels than the same dose of the oligonucleotide lacking a GalNAc conjugate group. Furthermore, the antisense oligonucleotides comprising one, two, or three GalNAc ligands in their respective conjugate groups all accumulated in the liver at similar levels. This result is surprising in view of the Khorev et al. literature reference cited above and is consistent with the activity data shown in Tables 116 and 117 above.

Table 117a

Liver concentrations of oligonucleotides comprising a $GalNAc_2$ or $GalNAc_3$ conjugate group

ISIS No.	Dosage (mg/kg)	[Antisense oligonucleotide] (μg/g)	GalNAc cluster	CM
440762	2	2.1	n/a	n/a
	7	13.1		
	20	31.1		
686221	0.2	0.9	$GalNAc_2$-24_a	A_d
	0.6	2.7		
	2	12.0		
	6	26.5		

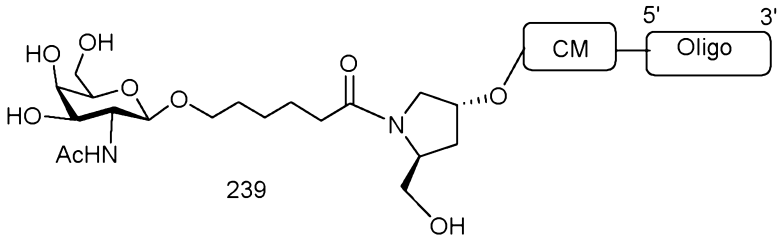
686222	0.2	0.5	$GalNAc_3$-13_a	A_d
	0.6	1.6		
	2	11.6		
	6	19.8		

Table 117b

Liver concentrations of oligonucleotides comprising a $GalNAc_1$ conjugate group

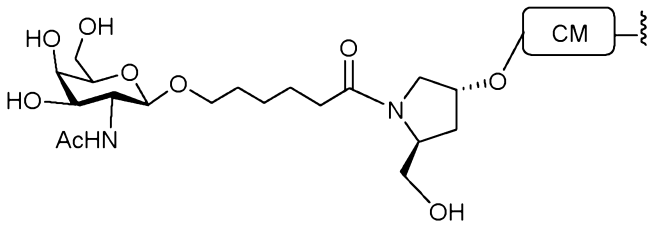
ISIS No.	Dosage (mg/kg)	[Antisense oligonucleotide] (μg/g)	GalNAc cluster	CM
440762	2	2.3	n/a	n/a
	7	8.9		
	20	23.7		
708561	0.2	0.4	$GalNAc_1$-25_a	PO
	0.6	1.1		
	2	5.9		
	6	23.7		
	20	53.9		

Example 107: Synthesis of oligonucleotides comprising a $GalNAc_1$-26 or $GalNAc_1$-27 conjugate



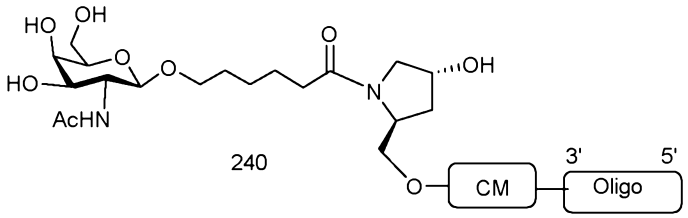
239

Oligonucleotide 239 is synthesized via coupling of compound 47 (see Example 15) to acid 64 (see Example 32) using HBTU and DIEA in DMF. The resulting amide containing compound is phosphitylated, then added to the 5'-end of an oligonucleotide using procedures described in Example 10. The $GalNAc_1$ cluster portion ($GalNAc_1$-26_a) of the conjugate group $GalNAc_1$-26 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-26 ($GalNAc_1$-26_a-CM) is shown below:

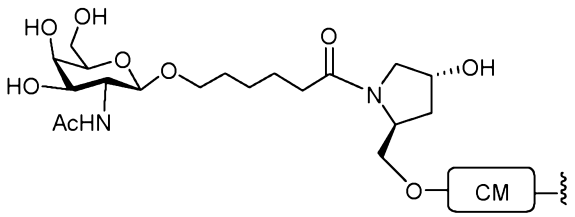


In order to add the $GalNAc_1$ conjugate group to the 3'-end of an oligonucleotide, the amide formed from the reaction of compounds 47 and 64 is added to a solid support using procedures described in Example

7. The oligonucleotide synthesis is then completed using procedures described in Example 9 in order to form oligonucleotide 240.



The $GalNAc_1$ cluster portion ($GalNAc_1$-27_a) of the conjugate group $GalNAc_1$-27 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-27 ($GalNAc_1$-27_a-CM) is shown below:



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

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	25
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	25
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	25
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	25
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	25
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	25
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	134

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

Treatment

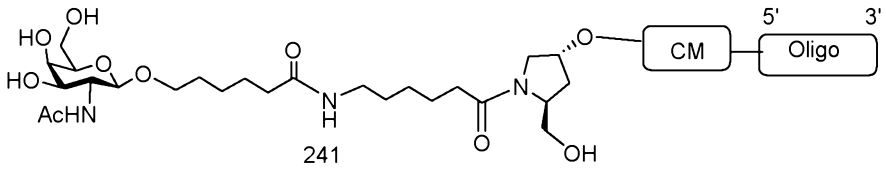
Male transgenic mice that express human Apo(a) were each injected subcutaneously once with an oligonucleotide and dosage listed in Table 119 or with PBS. Each treatment group consisted of 4 animals. Blood was drawn the day before dosing to determine baseline levels of Apo(a) protein in plasma and at 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

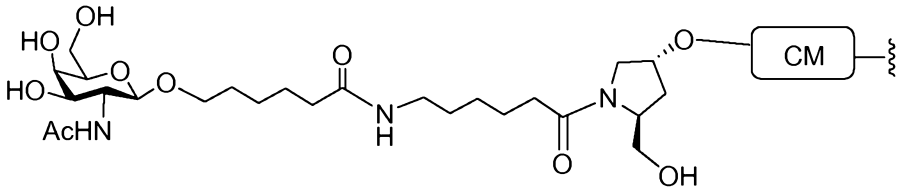
Apo(a) plasma protein levels

ISIS No.	Dosage (mg/kg)	Apo(a) at 1 week (% BL)
PBS	n/a	143
494372	50	58
681251	10	15
681255	10	14
681256	10	17
681257	10	24
681258	10	22
681260	10	26

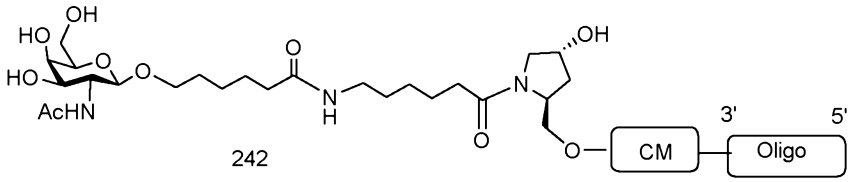
Example 109: Synthesis of oligonucleotides comprising a GalNAc$_1$-28 or GalNAc$_1$-29 conjugate



Oligonucleotide 241 is synthesized using procedures similar to those described in Example 71 to form the phosphoramidite intermediate, followed by procedures described in Example 10 to synthesize the oligonucleotide. The GalNAc$_1$ cluster portion (GalNAc$_1$-28$_a$) of the conjugate group GalNAc$_1$-28 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of GalNAc$_1$-28 (GalNAc$_1$-28$_a$-CM) is shown below:

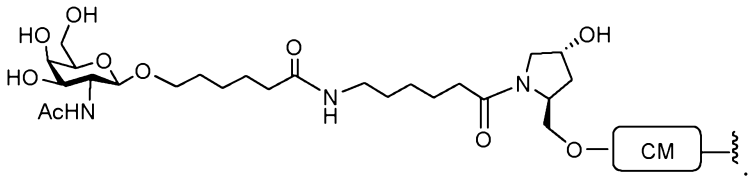


In order to add the $GalNAc_1$ conjugate group to the 3'-end of an oligonucleotide, procedures similar to those described in Example 71 are used to form the hydroxyl intermediate, which is then added to the solid support using procedures described in Example 7. The oligonucleotide synthesis is then completed using procedures described in Example 9 in order to form oligonucleotide 242.

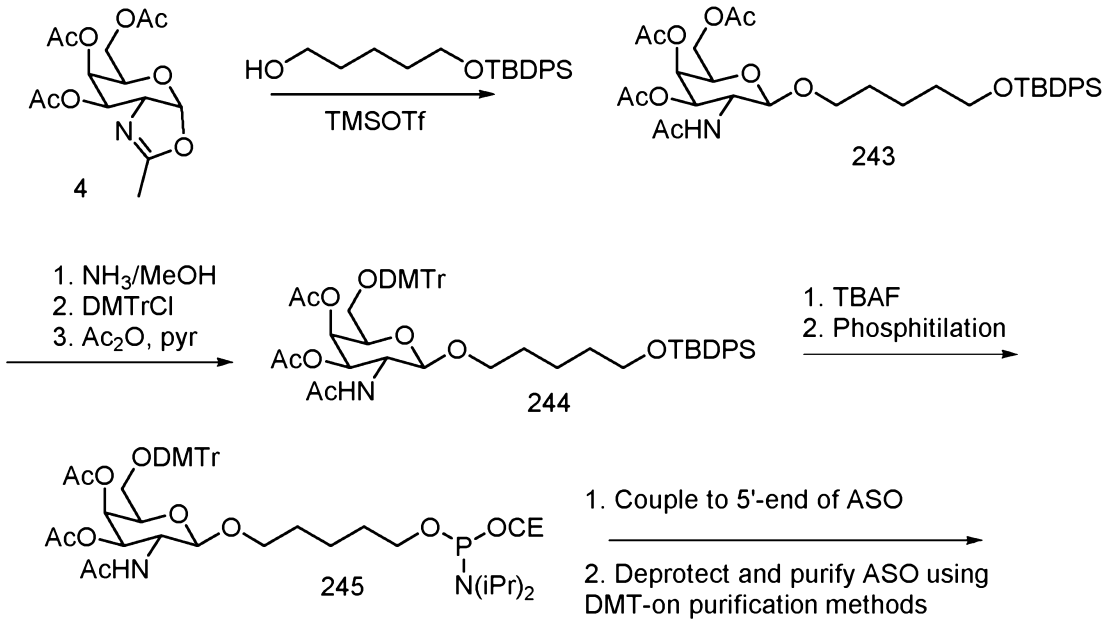


242

The $GalNAc_1$ cluster portion ($GalNAc_1$-29_a) of the conjugate group $GalNAc_1$-29 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-29 ($GalNAc_1$-29_a-CM) is shown below:



Example 110: Synthesis of oligonucleotides comprising a $GalNAc_1$-30 conjugate

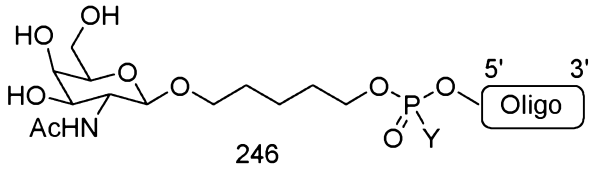


4

243

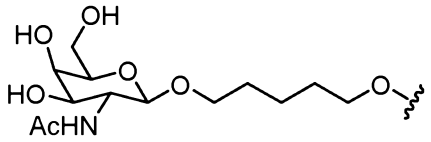
244

245

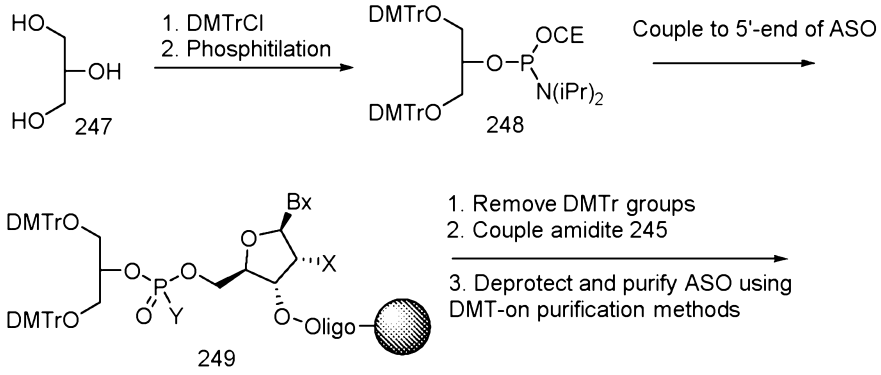


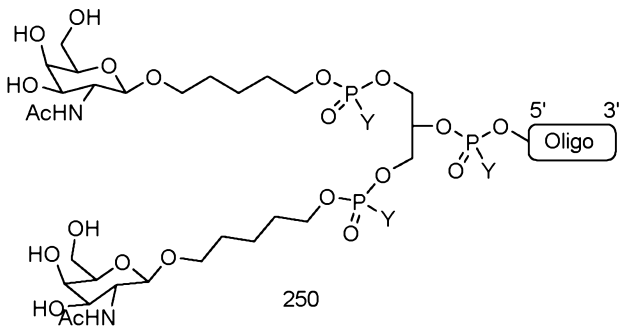
246

Oligonucleotide 246 comprising a $GalNAc_1$-30 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The $GalNAc_1$ cluster portion ($GalNAc_1$-30_a) of the conjugate group $GalNAc_1$-30 can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, Y is part of the cleavable moiety. In certain embodiments, Y is part of a stable moiety, and the cleavable moiety is present on the oligonucleotide. The structure of $GalNAc_1$-30_a is shown below:



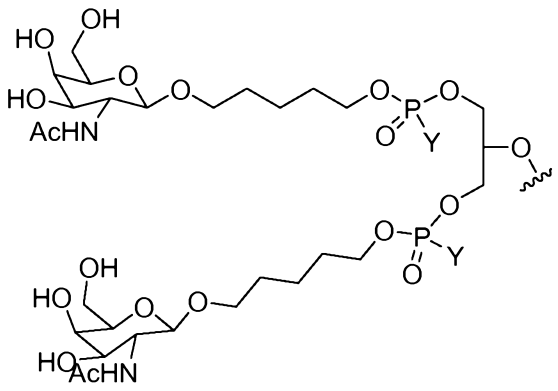
Example 111: Synthesis of oligonucleotides comprising a $GalNAc_2$-31 or $GalNAc_2$-32 conjugate



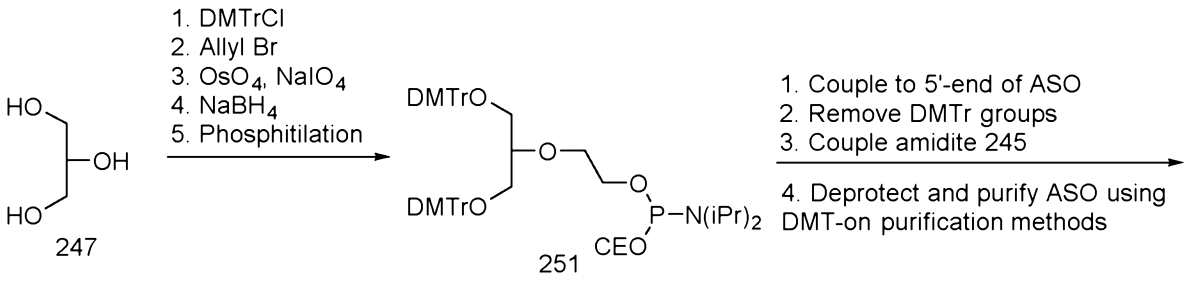


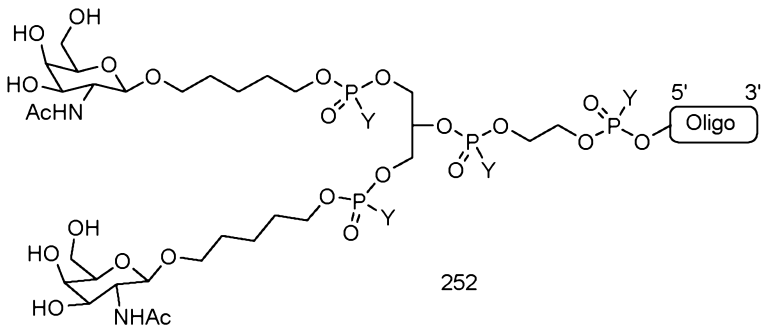
Oligonucleotide 250 comprising a $GalNAc_2$-31 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The $GalNAc_2$ cluster portion ($GalNAc_2$-31_a) of the conjugate group $GalNAc_2$-31 can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the Y-

containing group directly adjacent to the 5'-end of the oligonucleotide is part of the cleavable moiety. In certain embodiments, the Y-containing group directly adjacent to the 5'-end of the oligonucleotide is part of a stable moiety, and the cleavable moiety is present on the oligonucleotide. The structure of $GalNAc_2$-31_a is shown below:



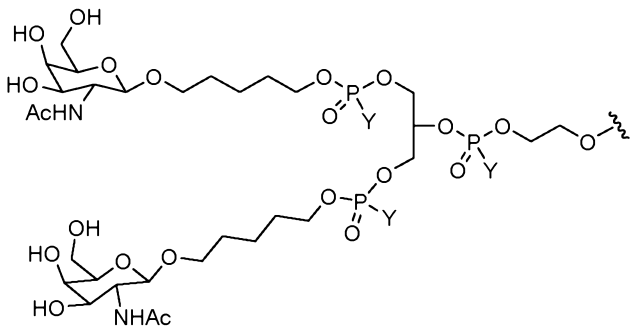
The synthesis of an oligonucleotide comprising a $GalNAc_2$-32 conjugate is shown below.





Oligonucleotide 252 comprising a $GalNAc_2$-32 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The $GalNAc_2$ cluster portion ($GalNAc_2$-32_a) of the conjugate group $GalNAc_2$-32 can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the Y-containing group directly adjacent to the 5'-end of the oligonucleotide is part of the cleavable moiety. In certain embodiments, the Y-containing group directly adjacent to the 5'-end of the oligonucleotide is part of a

stable moiety, and the cleavable moiety is present on the oligonucleotide. The structure of $GalNAc_2$-32_a is shown below:



Example 112: Modified oligonucleotides comprising a $GalNAc_1$ conjugate

The oligonucleotides in Table 120 targeting SRB-1 were synthesized with a $GalNAc_1$ conjugate group in order to further test the potency of oligonucleotides comprising conjugate groups that contain one GalNAc ligand.

Table 120

ISIS No.	Sequence (5' to 3')	GalNAc cluster	CM	SEQ ID NO.
711461	**$GalNAc_1$-$25_{a\text{-}o}$,A_{do}** G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-25_a	A_d	109
711462	**$GalNAc_1$-$25_{a\text{-}o}$,**G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-25_a	PO	108
711463	**$GalNAc_1$-$25_{a\text{-}o}$,**G_{es} $^mC_{eo}$ T_{eo} T_{eo} $^mC_{eo}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{eo} $^mC_{eo}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-25_a	PO	108
711465	**$GalNAc_1$-$26_{a\text{-}o}$,A_{do}** G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-26_a	A_d	109
711466	**$GalNAc_1$-$26_{a\text{-}o}$,**G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-26_a	PO	108
711467	**$GalNAc_1$-$26_{a\text{-}o}$,**G_{es} $^mC_{eo}$ T_{eo} T_{eo} $^mC_{eo}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{eo} $^mC_{eo}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-26_a	PO	108
711468	**$GalNAc_1$-$28_{a\text{-}o}$,A_{do}** G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-28_a	A_d	109
711469	**$GalNAc_1$-$28_{a\text{-}o}$,**G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-28_a	PO	108
711470	**$GalNAc_1$-$28_{a\text{-}o}$,**G_{es} $^mC_{eo}$ T_{eo} T_{eo} $^mC_{eo}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{eo} $^mC_{eo}$ $^mC_{es}$ T_{es} T_e	$GalNAc_1$-28_a	PO	108
713844	G_{es} $^mC_{es}$ T_{es} T_{es} $^mC_{es}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{es} $^mC_{es}$ $^mC_{es}$ T_{es} $T_{eo'}$-**$GalNAc_1$-27_a**	$GalNAc_1$-27_a	PO	108
713845	G_{es} $^mC_{eo}$ T_{eo} T_{eo} $^mC_{eo}$ A_{ds} G_{ds} T_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} $^mC_{ds}$ T_{ds} T_{eo} $^mC_{eo}$ $^mC_{es}$ T_{es} $T_{eo'}$-**$GalNAc_1$-27_a**	$GalNAc_1$-27_a	PO	108

713846	$G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{eo}$ **$A_{do'}$-GalNAc$_1$-27$_a$**	GalNAc$_1$-27$_a$	A_d	110
713847	$G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{eo'}$-**GalNAc$_1-29_a$**	GalNAc$_1$-29$_a$	PO	108
713848	$G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{eo'}$-**GalNAc$_1-29_a$**	GalNAc$_1$-29$_a$	PO	108
713849	$G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{eo}$ **$A_{do'}$-GalNAc$_1$-29$_a$**	GalNAc$_1$-29$_a$	A_d	110
713850	$G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{eo}$ **$A_{do'}$-GalNAc$_1$-29$_a$**	GalNAc$_1$-29$_a$	A_d	110

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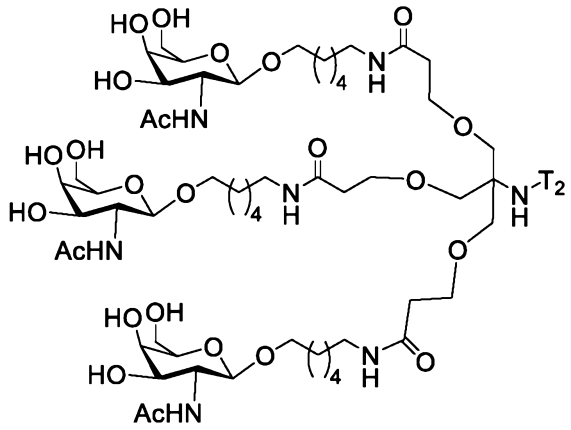
Claims:

1. A compound having the formula (XXVI):



(XXVI)

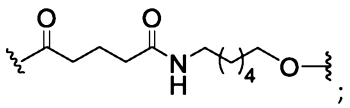
wherein:

T_2 is a group comprising a nucleoside, a nucleotide, a monomeric subunit, a reactive ester, a linker, a cleavable moiety or an oligomeric compound.

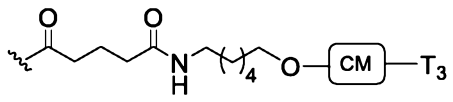
2. The compound of claim 1, wherein the linker comprises an amine, an amide, an ester, an ether, a pyrrolidine, PEG, a polyamide, or a disulfide bond.

3. The compound of claim 1, wherein the linker does not comprise a pyrrolidine.

4. The compound of any of claims 1 or 2, wherein the linker has the formula:



optionally, wherein T_2 has the formula:



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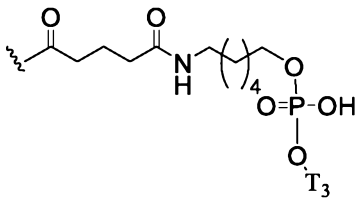
wherein:

CM is a cleavable moiety and T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound;

and/or, wherein T_2 has the formula:



wherein:

T_3 is a nucleoside, a nucleotide, a monomeric subunit, or an oligomeric compound.

5. The compound of any of claims 1 to 4, wherein T_2 or T_3 is a group comprising an oligomeric compound, and wherein the oligomeric compound is a modified oligonucleotide;
optionally, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides wherein at least one nucleoside is a modified nucleoside;
optionally, wherein the modified oligonucleotide comprises at least one modified nucleoside selected from among: a 2'-MOE nucleoside, a 2'-OMe nucleoside, a 2'-F nucleoside, a (4'-CH_2-O-2') bicyclic nucleoside, a (4'-$(CH_2)_2$-O-2') bicyclic nucleoside, a (4'-$C(CH_3)$H-O-2') bicyclic nucleoside; and a morpholino.

6. The compound of claim 5, wherein the modified oligonucleotide has a gapmer sugar motif comprising:

a 5'-region consisting of 2-8 linked 5'-region nucleosides, wherein at least two 5'-region nucleosides are modified nucleosides and wherein the 3'-most 5'-region nucleoside is a modified nucleoside;

a 3'-region consisting of 2-8 linked 3'-region nucleosides, wherein at least two 3'-region nucleosides are modified nucleosides and wherein the 5'-most 3'-region nucleoside is a modified nucleoside; and

a central region between the 5'-region and the 3'-region consisting of 5-10 linked central region nucleosides, each independently selected from among: a modified nucleoside and an

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unmodified deoxynucleoside, wherein the 5'-most central region nucleoside is an unmodified deoxynucleoside and the 3'-most central region nucleoside is an unmodified deoxynucleoside;

optionally wherein each 5'-region nucleoside is a modified nucleoside; each 3'-region nucleoside is a modified nucleoside; and each central region nucleoside is an unmodified deoxynucleoside.

7. The compound of claim 6, wherein the 5'-region consists of 2-5 linked 5'-region nucleosides; the 3'-region consists of 2-5 linked 3'-region nucleosides; and the central region consists of 8-10 central region nucleosides.

8. The compound of any of claims 5 to 7, wherein the modified oligonucleotide comprises at least one phosphorothioate internucleoside linkage;
and/or, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage;
and/or, wherein each internucleoside linkage of the modified oligonucleotide is either phosphorothioate internucleoside linkage or a phosphodiester internucleoside linkage.

9. The compound of any of claims 5 to 8, wherein the modified oligonucleotide is attached to the remainder of the compound at the 5'-end of the modified oligonucleotide;
or wherein the modified oligonucleotide is attached to the remainder of the compound at the 3'-end of the modified oligonucleotide.

10. The compound of any of claims 5 to 9, wherein the modified oligonucleotide is an antisense oligonucleotide.

11. The compound of claim any of claims 5 to 10, wherein the modified oligonucleotide is single-stranded or wherein the modified oligonucleotide is double-stranded.

12. The compound of any of claims 5 to 11, wherein the modified oligonucleotide activates the RISC pathway;
or wherein the modified oligonucleotide is an RNase H based antisense compound
or wherein the modified oligonucleotide alters splicing of a target pre-mRNA.

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13. The compound of any of claims 10 to 12, wherein the modified oligonucleotide is complementary to a target nucleic acid;
optionally wherein the target nucleic acid is selected from among: pre-mRNA, micro-RNA, or long non-coding RNA.

14. The compound of any of claims 10 to 13, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides;
optionally, wherein the modified oligonucleotide consists of 18 to 22 linked nucleosides;
optionally, wherein the modified oligonucleotide consists of 16 to 20 linked nucleosides.

15. A compound according to any of claims 5 to 14 for use in a method of treating a metabolic disorder or a cardiovascular disorder comprising administering the compound of any of claims 5 to 14 to a subject in need thereof.

16. A method of treating a metabolic disorder or a cardiovascular disorder, wherein the method comprises administering the compound of any of claims 5 to 14 to a subject in need thereof.

17. Use of the compound of any of claims 5 to 14 in the manufacture of a medicament for treating a metabolic disorder or a cardiovascular disorder.

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