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(54) **Title**: COMPOSITIONS AND METHODS FOR MODULATING GROWTH HORMONE RECEPTOR EXPRESSION

(57) **Abstract**: The present embodiments provide methods, compounds, and compositions for treating, preventing, ameliorating a disease associated with excess growth hormone using antisense compounds oligonucleotides targeted to growth hormone receptor (GHR).

COMPOSITIONS AND METHODS FOR MODULATING GROWTH HORMONE RECEPTOR EXPRESSION

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 BIOL0253WOSEQ_ST25.txt created April 27, 2015, which is 1.29 MB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

The present embodiments provide methods, compounds, and compositions for treating, preventing, or ameliorating a disease associated with excess growth hormone using antisense compounds or oligonucleotides targeted to growth hormone receptor (GHR).

Background

Growth hormone is produced in the pituitary and secreted into the bloodstream where it binds to growth hormone receptor (GHR) on many cell types, causing production of insulin-like growth factor-1 (IGF-1). IGF-1 is produced mainly in the liver, but also in adipose tissue and the kidney, and secreted into the bloodstream. Several disorders, such as acromegaly and gigantism, are associated with elevated growth hormone levels and/or elevated IGF-I levels in plasma and/or tissues.

Excessive production of growth hormone can lead to diseases such as acromegaly or gigantism. Acromegaly and gigantism are associated with excess growth hormone, often caused by a pituitary tumor, and affects 40-50 per million people worldwide with about 15,000 patients in each of the US and Europe and an annual incidence of about 4-5 per million people. Acromegaly and gigantism are initially characterized by abnormal growth of the hands and feet and bony changes in the facial features. Many of the growth related outcomes are mediated by elevated levels of serum IGF-1.

Summary

Embodiments provided herein relate to methods, compounds, and compositions for treating, preventing, or ameliorating a disease associated with excess growth hormone. Several embodiments provided herein are drawn to antisense compounds or oligonucleotides targeted to growth hormone receptor (GHR). Several embodiments are directed to treatment, prevention, or amelioration of acromegaly with antisense compounds or oligonucleotides targeted to growth hormone receptor (GHR).

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 invention, as claimed. 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 for the portions of the document discussed herein, as well as in their entirety.

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:

"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).

"2'-O-methoxyethyl" (also 2'-MOE and 2'-O$(CH_2)_2$-OCH_3) refers to an O-methoxy-ethyl modification at the 2' position of a furanose ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

"2'-MOE nucleoside" (also 2'-O-methoxyethyl nucleoside) means a nucleoside comprising a 2'-MOE modified sugar moiety.

"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..

"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.

"3' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 3'-most nucleotide of a particular antisense compound.

"5' target site" refers to the nucleotide of a target nucleic acid which is complementary to the 5'-most nucleotide of a particular antisense compound.

"5-methylcytosine" means a cytosine modified with a methyl group attached to the 5 position. A 5-methylcytosine is a modified nucleobase.

"About" means within ±10% of a value. For example, if it is stated, "the compounds affected at least about 70% inhibition of GHR", it is implied that GHR levels are inhibited within a range of 60% and 80%.

"Administration" or "administering" refers to routes of introducing an antisense compound provided herein to a subject to perform its intended function. An example of a route of administration that can be used includes, but is not limited to parenteral administration, such as subcutaneous, intravenous, or intramuscular injection or infusion.

"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.

"Amelioration" refers to a lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. In certain embodiments, amelioration includes a delay or slowing in the

progression of one or more indicators of a condition or disease. The severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

"Animal" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

"Antisense activity" means any detectable or measurable activity attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid.

"Antisense compound" means an oligomeric compound that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding. Examples of antisense compounds include single-stranded and double-stranded compounds, such as, antisense oligonucleotides, siRNAs, shRNAs, ssRNAs, and occupancy-based compounds.

"Antisense inhibition" means reduction of target nucleic acid levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels in the absence of the antisense compound.

"Antisense mechanisms" are all those mechanisms involving hybridization of a compound with target nucleic acid, wherein the outcome or effect of the hybridization is either target degradation or target occupancy with concomitant stalling of the cellular machinery involving, for example, transcription or splicing.

"Antisense oligonucleotide" means a single-stranded oligonucleotide having a nucleobase sequence that permits hybridization to a corresponding region or segment of a target nucleic acid.

"Base complementarity" refers to the capacity for the precise base pairing of nucleobases of an antisense oligonucleotide with corresponding nucleobases in a target nucleic acid (i.e., hybridization), and is mediated by Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen binding between corresponding nucleobases.

"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.

"Bicyclic nucleic acid" or " BNA" or "BNA nucleosides" means a nucleoside having a sugar moiety comprising a bridge connecting two carbon atoms of the sugar ring, thereby forming a bicyclic ring system. In certain embodiments, the bridge connects the 4'-carbon and the 2'-carbon of the sugar ring.

"Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

"Carbohydrate" means a naturally occurring carbohydrate, a modified carbohydrate, or a carbohydrate derivative.

"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).

"Carbohydrate derivative" means any compound which may be synthesized using a carbohydrate as a starting material or intermediate.

"cEt" or "constrained ethyl" means a bicyclic sugar moiety comprising a bridge connecting the 4'-carbon and the 2'-carbon, wherein the bridge has the formula: 4'-$CH(CH_3)$-O-2'.

"Constrained ethyl nucleoside" (also cEt nucleoside) means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-$CH(CH_3)$-O-2' bridge.

"Chemically distinct region" refers to a region of an antisense compound that is in some way chemically different than another region of the same antisense compound. For example, a region having 2'-O-methoxyethyl nucleotides is chemically distinct from a region having nucleotides without 2'-O-methoxyethyl modifications.

"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.

"Chimeric antisense compounds" means antisense compounds that have at least 2 chemically distinct regions, each position having a plurality of subunits.

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

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

"Co-administration" means administration of two or more pharmaceutical agents to an individual. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate

pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration encompasses parallel or sequential administration.

"Complementarity" means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

"Comprise," "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

"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.

"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 "$GalNAc3\text{-}1_a$" 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.

"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.

"Contiguous nucleobases" means nucleobases immediately adjacent to each other.

"Constrained ethyl nucleoside" or "cEt" means a nucleoside comprising a bicyclic sugar moiety comprising a 4'-$CH(CH_3)$-O-2'bridge.

"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).

"Designing" or "Designed to" refer to the process of designing an oligomeric compound that specifically hybridizes with a selected nucleic acid molecule.

"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.

"Diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, in drugs that are injected, the diluent may be liquid, e.g. saline solution.

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

"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.

"Downstream" refers to the relative direction towards the 3' end or C-terminal end of a nucleic acid.

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

"Effective amount" in the context of modulating an activity or of treating or preventing a condition means the administration of that amount of pharmaceutical agent to a subject in need of such modulation, treatment, or prophylaxis, either in a single dose or as part of a series, that is effective for modulation of that effect, or for treatment or prophylaxis or improvement of that condition. The effective amount may vary among individuals depending on the health and physical condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual's medical condition, and other relevant factors.

"Efficacy" means the ability to produce a desired effect.

"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.

"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.

"Fully complementary" or "100% complementary" means each nucleobase of a first nucleic acid has a complementary nucleobase in a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a target nucleic acid is a second nucleic acid.

"Furanosyl" means a structure comprising a 5-membered ring comprising four carbon atoms and one oxygen atom.

"Gapmer" means a chimeric antisense compound in which an internal region having a plurality of nucleosides that support RNase H cleavage is positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions. The internal region may be referred to as the "gap" and the external regions may be referred to as the "wings."

"Growth Hormone Receptor (GHR)" means any nucleic acid or protein of GHR. "GHR nucleic acid" means any nucleic acid encoding GHR. For example, in certain embodiments, a GHR nucleic acid includes a DNA sequence encoding GHR, an RNA sequence transcribed from DNA encoding GHR (including genomic DNA comprising introns and exons), including a non-protein encoding (*i.e.* non-coding) RNA sequence, and an mRNA sequence encoding GHR. "GHR mRNA" means an mRNA encoding a GHR protein.

"GHR specific inhibitor" refers to any agent capable of specifically inhibiting GHR RNA and/or GHR protein expression or activity at the molecular level. For example, GHR specific inhibitors include nucleic acids (including antisense compounds), peptides, antibodies, small molecules, and other agents capable of inhibiting the expression of GHR RNA and/or GHR protein.

"Halo" and "halogen," mean an atom selected from fluorine, chlorine, bromine and iodine.

"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.

"Hybridization" means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense oligonucleotide and a nucleic acid target.

"Identifying an animal having, or at risk for having, a disease, disorder and/or condition" means identifying an animal having been diagnosed with the disease, disorder and/or condition or identifying an animal predisposed to develop the disease, disorder and/or condition. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments.

"Immediately adjacent" means there are no intervening elements between the immediately adjacent elements.

"Individual" means a human or non-human animal selected for treatment or therapy.

"Inhibiting the expression or activity" refers to a reduction, blockade of the expression or activity and does not necessarily indicate a total elimination of expression or activity.

"Internucleoside linkage" refers to the chemical bond between nucleosides.

"Internucleoside neutral linking group" means a neutral linking group that directly links two nucleosides.

"Internucleoside phosphorus linking group" means a phosphorus linking group that directly links two nucleosides.

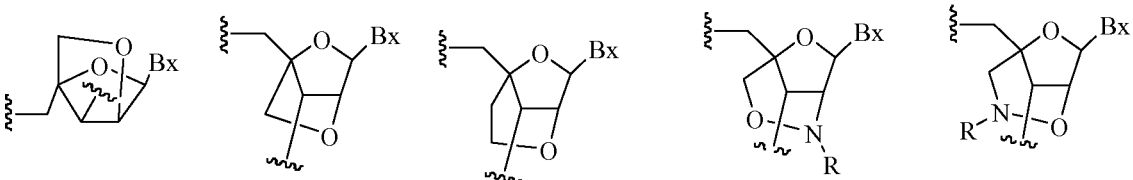
"Lengthened" antisense oligonucleotides are those that have one or more additional nucleosides relative to an antisense oligonucleotide disclosed herein.

"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.

"Linked deoxynucleoside" means a nucleic acid base (A, G, C, T, U) substituted by deoxyribose linked by a phosphate ester to form a nucleotide.

"Linked nucleosides" means adjacent nucleosides linked together by an internucleoside linkage.

"Locked nucleic acid nucleoside" or "LNA" "Locked nucleic acid" or " LNA" or "LNA nucleosides" means nucleic acid monomers having a bridge connecting two carbon atoms between the 4' and 2'position of the nucleoside sugar unit, thereby forming a bicyclic sugar. Examples of such bicyclic sugar include, but are not limited to A) α-L-Methyleneoxy (4'-CH_2-O-2') LNA , (B) β-D-Methyleneoxy (4'-CH_2-O-2') LNA , (C) Ethyleneoxy (4'-$(CH_2)_2$-O-2') LNA , (D) Aminooxy (4'-CH_2-O-N(R)-2') LNA and (E) Oxyamino (4'-CH_2-N(R)-O-2') LNA, as depicted below.



(A) (B) (C) (D) (E)

As used herein, LNA compounds include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the sugar wherein each of the bridges independently comprises 1 or from 2 to 4 linked groups independently selected from -$[C(R_1)(R_2)]_n$-, -$C(R_1)$=$C(R_2)$-, -$C(R_1)$=N-, -$C(=NR_1)$-, -C(=O)-, -C(=S)-, -O-, -$Si(R_1)_2$-, -$S(=O)_x$- and -$N(R_1)$-; wherein: x is 0, 1, or 2; n is 1, 2, 3, or 4; each R_1 and R_2 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, a heterocycle radical, a 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.

Examples of 4'- 2' bridging groups encompassed within the definition of LNA include, but are not limited to one of formulae: -$[C(R_1)(R_2)]_n$-, -$[C(R_1)(R_2)]_n$-O-, -$C(R_1R_2)$-$N(R_1)$-O- or –$C(R_1R_2)$-O-$N(R_1)$-. Furthermore, other bridging groups encompassed with the definition of LNA are 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-$N(R_1)$-2' and 4'-CH_2-$N(R_1)$-O-2'- bridges, wherein each R_1 and R_2 is, independently, H, a protecting group or C_1-C_{12} alkyl.

Also included within the definition of LNA according to the invention are LNAs in which the 2'-hydroxyl group of the ribosyl sugar ring is connected to the 4' carbon atom of the sugar ring, thereby forming a methyleneoxy (4'-CH_2-O-2') bridge to form the bicyclic sugar moiety. The bridge can also be a methylene (-CH_2-) group connecting the 2' oxygen atom and the 4' carbon atom, for which the term methyleneoxy (4'-CH_2-O-2') LNA is used. Furthermore; in the case of the bicylic sugar moiety having an ethylene bridging group in this position, the term ethyleneoxy (4'-CH_2CH_2-O-2') LNA is used. α -L-methyleneoxy (4'-CH_2-O-2'), an isomer of methyleneoxy (4'-CH_2-O-2') LNA is also encompassed within the definition of LNA, as used herein.

"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.

"Mismatch" or "non-complementary nucleobase" refers to the case when a nucleobase of a first nucleic acid is not capable of pairing with the corresponding nucleobase of a second or target nucleic acid.

"Modified carbohydrate" means any carbohydrate having one or more chemical modifications relative to naturally occurring carbohydrates.

"Modified internucleoside linkage" refers to a substitution or any change from a naturally occurring internucleoside bond (i.e. a phosphodiester internucleoside bond).

"Modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U).

"Modified nucleoside" means a nucleoside having, independently, a modified sugar moiety and/or modified nucleobase.

"Modified nucleotide" means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, or modified nucleobase.

"Modified oligonucleotide" means an oligonucleotide comprising at least one modified internucleoside linkage, a modified sugar, and/or a modified nucleobase.

"Modified sugar" means substitution and/or any change from a natural sugar moiety. "Modified sugar moiety" means a substituted sugar moiety or a sugar surrogate.

"Modulating" refers to changing or adjusting a feature in a cell, tissue, organ or organism. For example, modulating GHR mRNA can mean to increase or decrease the level of GHR mRNA and/or GHR protein in a cell, tissue, organ or organism. A "modulator" effects the change in the cell, tissue, organ or organism. For example, a GHR antisense compound can be a modulator that decreases the amount of GHR mRNA and/or GHR protein in a cell, tissue, organ or organism.

"MOE" means $-OCH_2CH_2OCH_3$.

"Monomer" refers to a single unit of an oligomer. Monomers include, but are not limited to, nucleosides and nucleotides, whether naturally occuring or modified.

"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.

"Motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

"Natural sugar moiety" means a sugar moiety found in DNA (2'-H) or RNA (2'-OH). "Naturally occurring sugar moiety" means a ribofuranosyl as found in naturally occurring RNA or a deoxyribofuranosyl as found in naturally occurring DNA.

"Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

"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.

"Non-complementary nucleobase" refers to a pair of nucleobases that do not form hydrogen bonds with one another or otherwise support hybridization.

"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.

"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.

"Nucleic acid" refers to molecules composed of monomeric nucleotides. A nucleic acid includes, but is not limited to, ribonucleic acids (RNA), deoxyribonucleic acids (DNA), single-stranded nucleic acids, and double-stranded nucleic acids.

"Nucleobase" means a heterocyclic moiety capable of pairing with a base of another nucleic acid.

"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.

"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.

"Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, and/or nucleobase modification.

"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.

"Nucleoside mimetic" includes those structures used to replace the sugar or the sugar and the base and not necessarily the linkage at one or more positions of an oligomeric compound such as for example nucleoside mimetics having morpholino, cyclohexenyl, cyclohexyl, tetrahydropyranyl, bicyclo or tricyclo

sugar mimetics, *e.g.*, non furanose sugar units. Nucleotide mimetic includes those structures used to replace the nucleoside and the linkage at one or more positions of an oligomeric compound such as for example peptide nucleic acids or morpholinos (morpholinos linked by -N(H)-C(=O)-O- or other non-phosphodiester linkage). Sugar surrogate overlaps with the slightly broader term nucleoside mimetic but is intended to indicate replacement of the sugar unit (furanose ring) only. The tetrahydropyranyl rings provided herein are illustrative of an example of a sugar surrogate wherein the furanose sugar group has been replaced with a tetrahydropyranyl ring system. "Mimetic" refers to groups that are substituted for a sugar, a nucleobase, and/or internucleoside linkage. Generally, a mimetic is used in place of the sugar or sugar-internucleoside linkage combination, and the nucleobase is maintained for hybridization to a selected target.

"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.

"Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

"Off-target effect" refers to an unwanted or deleterious biological effect associated with modulation of RNA or protein expression of a gene other than the intended target nucleic acid.

"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.

"Oligonucleoside" means an oligonucleotide in which the internucleoside linkages do not contain a phosphorus atom.

"Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

"Parenteral administration" means administration through injection or infusion. Parenteral administration includes subcutaneous administration, intravenous administration, intramuscular

administration, intraarterial administration, intraperitoneal administration, or intracranial administration, e.g. intrathecal or intracerebroventricular administration.

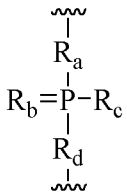
"Peptide" means a molecular formed by linking at least two amino acids by amide bonds. Without limitation, as used herein, peptide refers to polypeptides and proteins.

"Pharmaceutical agent" means a substance that provides a therapeutic benefit when administered to an individual. For example, in certain embodiments, a conjugated antisense oligonucleotide targeted to GHR is a pharmaceutical agent.

"Pharmaceutical composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition may comprise one or more active pharmaceutical agents and a sterile aqueous solution.

"Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

"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.

"Phosphorothioate linkage" means a linkage between nucleosides where the phosphodiester bond is modified by replacing one of the non-bridging oxygen atoms with a sulfur atom. A phosphorothioate linkage is a modified internucleoside linkage.

"Portion" means a defined number of contiguous (i.e., linked) nucleobases of a nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an antisense compound

"Prevent" refers to delaying or forestalling the onset, development or progression of a disease, disorder, or condition for a period of time from minutes to indefinitely. Prevent also means reducing the risk of developing a disease, disorder, or condition.

"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).

"Prophylactically effective amount" refers to an amount of a pharmaceutical agent that provides a prophylactic or preventative benefit to an animal.

"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.

"Region" is defined as a portion of the target nucleic acid having at least one identifiable structure, function, or characteristic.

"Ribonucleotide" means a nucleotide having a hydroxy at the 2' position of the sugar portion of the nucleotide. Ribonucleotides may be modified with any of a variety of substituents.

"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).

"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.

"Salts" mean a physiologically and pharmaceutically acceptable salt of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

"Segments" are defined as smaller or sub-portions of regions within a target nucleic acid.

"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.

"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.

"Side effects" means physiological disease and/or conditions attributable to a treatment other than the desired effects. In certain embodiments, side effects include injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, myopathies, and malaise. For example, increased aminotransferase levels in serum may

indicate liver toxicity or liver function abnormality. For example, increased bilirubin may indicate liver toxicity or liver function abnormality.

"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.

"Sites," as used herein, are defined as unique nucleobase positions within a target nucleic acid.

"Slows progression" means decrease in the development of the said disease.

"Specifically hybridizable" refers to an antisense compound having a sufficient degree of complementarity between an antisense oligonucleotide and a target nucleic acid to induce a desired effect, while exhibiting minimal or no effects on non-target nucleic acids under conditions in which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays and therapeutic treatments.

"Stringent hybridization conditions" or "stringent conditions" refer to conditions under which an oligomeric compound will hybridize to its target sequence, but to a minimal number of other sequences.

"Subject" means a human or non-human animal selected for treatment or therapy.

"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.

"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.

"Sugar moiety" means a naturally occurring sugar moiety or a modified sugar moiety of a nucleoside.

"Sugar motif" means a pattern of sugar modifications in an oligonucleotide or a region thereof.

"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.

"Target" refers to a protein, the modulation of which is desired.

"Target gene" refers to a gene encoding a target.

"Targeting" or "targeted" means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

"Target nucleic acid," "target RNA," "target RNA transcript" and "nucleic acid target" all mean a nucleic acid capable of being targeted by antisense compounds. "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.

"Target region" means a portion of a target nucleic acid to which one or more antisense compounds is targeted.

"Target segment" means the sequence of nucleotides of a target nucleic acid to which an antisense compound is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment.

"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.

"Terminal internucleoside linkage" means the linkage between the last two nucleosides of an oligonucleotide or defined region thereof.

"Therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual.

"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.

"Treat" refers to administering a pharmaceutical composition to an animal in order to effect an alteration or improvement of a disease, disorder, or condition in the animal. In certain embodiments, one or more pharmaceutical compositions can be administered to the animal.

"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.

"Unmodified" nucleobases 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).

"Unmodified nucleotide" means a nucleotide composed of naturally occuring nucleobases, sugar moieties, and internucleoside linkages. In certain embodiments, an unmodified nucleotide is an RNA nucleotide (i.e. β-D-ribonucleosides) or a DNA nucleotide (i.e. β-D-deoxyribonucleoside).

"Upstream" refers to the relative direction towards the 5' end or N-terminal end of a nucleic acid.

"Wing segment" means a plurality of nucleosides modified to impart to an oligonucleotide properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by in vivo nucleases.

Certain Embodiments

Certain embodiments provide methods, compounds and compositions for inhibiting growth hormone receptor (GHR) expression.

Certain embodiments provide antisense compounds targeted to a GHR nucleic acid. In certain embodiments, the GHR nucleic acid has the sequence set forth in GENBANK Accession No. NM_000163.4 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No

X06562.1 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. DR006395.1 (incorporated herein as SEQ ID NO: 4), GENBANK Accession No. DB052048.1 (incorporated herein as SEQ ID NO: 5), GENBANK Accession No. AF230800.1 (incorporated herein as SEQ ID NO: 6), the complement of GENBANK Accession No. AA398260.1 (incorporated herein as SEQ ID NO: 7), GENBANK Accession No. BC136496.1 (incorporated herein as SEQ ID NO: 8), GENBANK Accession No. NM_001242399.2 (incorporated herein as SEQ ID NO: 9), GENBANK Accession No. NM_001242400.2 (incorporated herein as SEQ ID NO: 10), GENBANK Accession No. NM_001242401.3 (incorporated herein as SEQ ID NO: 11), GENBANK Accession No. NM_001242402.2 (incorporated herein as SEQ ID NO: 12), GENBANK Accession No. NM_001242403.2 (incorporated herein as SEQ ID NO: 13), GENBANK Accession No. NM_001242404.2 (incorporated herein as SEQ ID NO: 14), GENBANK Accession No. NM_001242405.2 (incorporated herein as SEQ ID NO: 15), GENBANK Accession No. NM_001242406.2 (incorporated herein as SEQ ID NO: 16), GENBANK Accession No. NM_001242460.1 (incorporated herein as SEQ ID NO: 17), GENBANK Accession NM_001242461.1 (incorporated herein as SEQ ID NO: 18), or GENBANK Accession No. NM_001242462.1 (incorporated herein as SEQ ID NO: 19).

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and has a nucleobase sequence comprising at least 9 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and has a nucleobase sequence comprising at least 10 contiguous nucleobases of the nucleobase sequences of any of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and has a nucleobase sequence comprising at least 11 contiguous nucleobases of the nucleobase sequences of any of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and has a nucleobase sequence comprising at least 12 contiguous nucleobases of the nucleobase sequences of any of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and has a nucleobase sequence comprising the nucleobase sequences of any of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of the nucleobase sequences of any one of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides complementary within nucleotides 30-51, 63-82, 103-118, 143-159, 164-197, 206-259, 361-388, 554-585, 625-700, 736-776, 862-887, 923-973, 978-996, 1127-1142, 1170-1195, 1317-1347, 1360-1383, 1418-1449, 1492-1507, 1524-1548, 1597-1634, 1641-1660, 1683-1698, 1744-1768, 1827-1860, 1949-2002, 2072-2092, 2095-2110, 2306-2321, 2665-2683, 2685-2719, 2739-2770, 2859-2880, 2941-2960, 2963-2978, 3037-3052, 3205-3252, 3306-3332, 3371-3386, 3518-3542, 3975-3990, 4041-4087, 4418-4446, 4528-4546, 7231-7246, 7570-7585, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 11020-11035, 11793-11808, 12214-12229, 12474-12489, 12905-12920, 13400-13415, 13717-13732, 14149-14164, 14540-14555, 15264-15279, 15849-15864, 16530-16545, 17377-17392, 17581-17596, 17943-17958, 18353-18368, 18636-18651, 19256-19271, 19814-19829, 20365-20380, 20979-20994, 21566-21581, 22150-22165, 22803-22818, 29049-29064, 29554-29569, 30245-30260, 30550-30565, 30915-30930, 31468-31483, 32366-32381, 32897-32912, 33187-33202, 33780-33795, 34407-34422, 34846-34861, 35669-35684, 36312-36327, 36812-36827, 37504-37519, 38841-38856, 40250-40265, 40706-40721, 40922-40937, 41424-41439, 41999-42014, 42481-42496, 42700-42715, 43291-43306, 43500-43515, 43947-43962, 44448-44463, 45162-45177, 46010-46025, 46476-46491, 47447-47462, 47752-47767, 48001-48016, 48423-48438, 50195-50210, 50470-50485, 51104-51119, 51756-51771, 52015-52030, 52230-52245, 52588-52603, 53532-53547, or 54645-54660 of SEQ ID NO: 1, wherein said modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases 100% complementary to an equal length portion of nucleobases 30-51, 63-82, 103-118, 143-159, 164-197, 206-259, 361-388, 554-585, 625-700, 736-776, 862-887, 923-973, 978-996, 1127-1142, 1170-1195, 1317-1347, 1360-1383, 1418-1449, 1492-1507, 1524-1548, 1597-1634, 1641-1660, 1683-1698, 1744-1768, 1827-1860, 1949-2002, 2072-2092, 2095-2110, 2306-2321, 2665-2683, 2685-2719, 2739-2770, 2859-2880, 2941-2960, 2963-2978, 3037-3052, 3205-3252, 3306-3332, 3371-3386, 3518-3542, 3975-3990, 4041-4087, 4418-4446, 4528-4546, 7231-7246, 7570-7585, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 11020-11035, 11793-11808, 12214-12229, 12474-12489, 12905-12920, 13400-13415, 13717-13732, 14149-14164, 14540-14555, 15264-15279, 15849-

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Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides complementary within nucleotides 2571-2586, 2867-3059, 3097-3116, 3341-3695, 4024-4039, 4446-4894, 5392-5817, 6128-6265, 6499-6890, 7231-7246, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 10660-10679, 11020-11035, 11793-12229, 12469-12920, 13351-13415, 13717-13732, 14149-14164, 14361-14555, 14965-15279, 15849-16001, 16253-16272, 16447-16545, 17130-17149, 17377-17669, 17927-17958, 18353-18368, 18636-18773, 19661-19918, 20288-20470, 20979-20994, 21215-21606, 21820-21837, 22150-22165, 22518-22536, 22803-22818, 26494-26522, 29049-29069, 29323-29489, 30550-30565, 30915-31191, 31468-31483, 32363-32382, 32827-33202, 33635-33795, 34138-34157, 34407-34422, 34845-34864, 35466-35485, 35669-35684, 36023-36042, 36266-36327, 36721-36827, 37032-37130, 37276-37295, 37504-37675, 38094-38118, 38841-38856, 39716-40538, 40706-40937, 41164-41183, 41342-41439, 42141-42164, 42700-42760, 43173-43537, 43765-46025, 46476-46532, 48423-48438, 50072-50210, 50470-50485, 50719-51234, 51747-51797, 52015-52143, 52230-52245, 52573-52652, 53466-54660, 54886-54901, 63751-64662, 64882-65099, 65363-65378, 65600-65615, 65988-66183, 66566-66581, 66978-67080, 67251-67270, 67662-67929, 68727-68742, 69203-69242, 69565-69620, 69889-70145, 70352-70584, 70925-71071, 71314-71329, 71617-71769, 72107-72241, 72584-72670, 73061-73076, 73350-73369, 73689-73723, 74107-74131, 74317-74557, 74947-75009, 75192-75207, 75979-76066, 76410-77095, 77292-77307, 77638-77869, 78122-78326, 79006-79021, 79478-79505, 80277-80292, 80575-80939, 81207-81222, 81524-81543, 81761-81776, 82233-82248, 82738-83198, 83330-83416, 83884-84063, 84381-85964, 86220-86392, 86554-86655, 86901-86920, 87181-87262, 88063-88082, 88293-88308, 88605-88967, 89160-89175, 89940-90255, 90473-90528, 91073-91088, 91273-91292, 91647-91662, 91930-92126, 92356-92371, 93190-93443, 93762-94111, 94374-94389, 94581-94653, 94839-94858, 95292-95583, 95829-95844, 96137-96503, 96793-97013, 97539-97554, 97800-97889, 98132-98151, 98624-98672, 98810-99115, 99258-99273, 99478-99503, 99791-99858, 100281-100300, 100406-100421, 100742-100828, 101080-101103, 101242-101320, 101788-101906, 102549-102568, 103566-103625, 104067-104086, 104277-104858, 105255-105274, 106147-106364, 106632-106647, 106964-107735, 108514-108788, 109336-109505, 109849-109864, 110403-110442, 110701-110974, 111203-111322, 112030-

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Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases 100% complementary to an equal length portion of nucleobases 2571-2586, 2867-3059, 3097-3116, 3341-3695, 4024-4039, 4446-4894, 5392-5817, 6128-6265, 6499-6890, 7231-7246, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 10660-10679, 11020-11035, 11793-12229, 12469-12920, 13351-13415, 13717-13732, 14149-14164, 14361-14555, 14965-15279, 15849-16001, 16253-16272, 16447-16545, 17130-17149, 17377-17669, 17927-17958, 18353-18368, 18636-18773, 19661-19918, 20288-20470, 20979-20994, 21215-21606, 21820-21837, 22150-22165, 22518-22536, 22803-22818, 26494-26522, 29049-29069, 29323-29489, 30550-30565, 30915-31191, 31468-31483, 32363-32382, 32827-33202, 33635-33795, 34138-34157, 34407-34422, 34845-34864, 35466-35485, 35669-35684, 36023-36042, 36266-36327, 36721-36827, 37032-37130, 37276-37295, 37504-37675, 38094-38118, 38841-38856, 39716-40538, 40706-40937, 41164-41183, 41342-41439, 42141-42164, 42700-42760, 43173-43537, 43765-46025, 46476-46532, 48423-48438, 50072-50210, 50470-50485, 50719-51234, 51747-51797, 52015-52143, 52230-52245, 52573-52652, 53466-54660, 54886-54901, 63751-64662, 64882-65099, 65363-65378, 65600-65615, 65988-66183, 66566-66581, 66978-67080, 67251-67270, 67662-67929, 68727-68742, 69203-69242, 69565-69620, 69889-70145, 70352-70584, 70925-71071, 71314-71329, 71617-71769, 72107-72241, 72584-72670, 73061-73076, 73350-73369, 73689-73723, 74107-74131, 74317-74557, 74947-75009, 75192-75207, 75979-76066, 76410-77095, 77292-77307, 77638-77869, 78122-78326, 79006-79021, 79478-79505, 80277-80292, 80575-80939, 81207-81222, 81524-81543, 81761-81776, 82233-82248, 82738-83198, 83330-83416, 83884-84063, 84381-85964, 86220-86392, 86554-86655, 86901-86920, 87181-87262, 88063-88082, 88293-88308, 88605-88967, 89160-89175, 89940-90255, 90473-90528, 91073-91088, 91273-91292, 91647-91662, 91930-92126, 92356-92371, 93190-93443, 93762-94111, 94374-94389, 94581-94653, 94839-94858, 95292-95583, 95829-95844, 96137-96503, 96793-97013, 97539-97554, 97800-97889, 98132-98151, 98624-98672, 98810-99115, 99258-99273, 99478-99503, 99791-99858, 100281-100300, 100406-100421, 100742-100828, 101080-101103, 101242-101320, 101788-101906, 102549-102568, 103566-

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Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NOs: 20-2295.

Certain embodiments provide a compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of the nucleobase sequence of any one of SEQ ID NOs: 20-2295.

In certain embodiments, a compound comprising an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to a growth hormone receptor nucleic acid and is complementary within the following nucleotide regions of SEQ ID NO: 1: 30-51, 63-82, 103-118, 143-159, 164-197, 206-259, 361-388, 554-585, 625-700, 736-776, 862-887, 923-973, 978-996, 1127-1142, 1170-1195, 1317-1347, 1360-1383, 1418-1449, 1492-1507, 1524-1548, 1597-1634, 1641-1660, 1683-1698, 1744-1768, 1827-1860, 1949-2002, 2072-2092, 2095-2110, 2306-2321, 2665-2683, 2685-2719, 2739-2770, 2859-2880, 2941-2960, 2963-2978, 3037-3052, 3205-3252, 3306-3332, 3371-3386, 3518-3542, 3975-3990, 4041-4087, 4418-4446, 4528-4546, 7231-7246, 7570-7585, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 11020-11035, 11793-11808, 12214-12229, 12474-12489, 12905-12920, 13400-13415, 13717-13732, 14149-14164, 14540-14555, 15264-15279, 15849-15864, 16530-16545, 17377-17392, 17581-17596, 17943-17958, 18353-18368, 18636-18651, 19256-19271, 19814-19829, 20365-20380, 20979-20994, 21566-21581, 22150-22165, 22803-22818, 29049-29064, 29554-29569, 30245-30260, 30550-30565, 30915-30930, 31468-31483, 32366-32381, 32897-32912, 33187-33202, 33780-33795, 34407-34422,

34846-34861, 35669-35684, 36312-36327, 36812-36827, 37504-37519, 38841-38856, 40250-40265, 40706-40721, 40922-40937, 41424-41439, 41999-42014, 42481-42496, 42700-42715, 43291-43306, 43500-43515, 43947-43962, 44448-44463, 45162-45177, 46010-46025, 46476-46491, 47447-47462, 47752-47767, 48001-48016, 48423-48438, 50195-50210, 50470-50485, 51104-51119, 51756-51771, 52015-52030, 52230-52245, 52588-52603, 53532-53547, or 54645-54660.

In certain embodiments, a compound comprising an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to a growth hormone receptor nucleic acid and targets the following nucleotide regions of SEQ ID NO: 1: 30-51, 63-82, 103-118, 143-159, 164-197, 206-259, 361-388, 554-585, 625-700, 736-776, 862-887, 923-973, 978-996, 1127-1142, 1170-1195, 1317-1347, 1360-1383, 1418-1449, 1492-1507, 1524-1548, 1597-1634, 1641-1660, 1683-1698, 1744-1768, 1827-1860, 1949-2002, 2072-2092, 2095-2110, 2306-2321, 2665-2683, 2685-2719, 2739-2770, 2859-2880, 2941-2960, 2963-2978, 3037-3052, 3205-3252, 3306-3332, 3371-3386, 3518-3542, 3975-3990, 4041-4087, 4418-4446, 4528-4546, 7231-7246, 7570-7585, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 11020-11035, 11793-11808, 12214-12229, 12474-12489, 12905-12920, 13400-13415, 13717-13732, 14149-14164, 14540-14555, 15264-15279, 15849-15864, 16530-16545, 17377-17392, 17581-17596, 17943-17958, 18353-18368, 18636-18651, 19256-19271, 19814-19829, 20365-20380, 20979-20994, 21566-21581, 22150-22165, 22803-22818, 29049-29064, 29554-29569, 30245-30260, 30550-30565, 30915-30930, 31468-31483, 32366-32381, 32897-32912, 33187-33202, 33780-33795, 34407-34422, 34846-34861, 35669-35684, 36312-36327, 36812-36827, 37504-37519, 38841-38856, 40250-40265, 40706-40721, 40922-40937, 41424-41439, 41999-42014, 42481-42496, 42700-42715, 43291-43306, 43500-43515, 43947-43962, 44448-44463, 45162-45177, 46010-46025, 46476-46491, 47447-47462, 47752-47767, 48001-48016, 48423-48438, 50195-50210, 50470-50485, 51104-51119, 51756-51771, 52015-52030, 52230-52245, 52588-52603, 53532-53547, or 54645-54660.

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to a region of a growth hormone receptor nucleic acid. In certain embodiments, such compounds or oligonucleotides targeted to a region of a GHR nucleic acid have a contiguous nucleobase portion that is complementary to an equal length nucleobase portion of the region. For example, the portion can be at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobases portion complementary to an equal length portion of a region recited herein. In certain embodiments, such compounds or oligonucleotide target the following nucleotide regions of SEQ ID NO: 1: 30-51, 63-82, 103-118, 143-159, 164-197, 206-259, 361-388, 554-585, 625-700, 736-776, 862-887, 923-973, 978-996, 1127-1142, 1170-1195, 1317-1347, 1360-1383, 1418-1449, 1492-1507, 1524-1548, 1597-1634, 1641-1660, 1683-1698, 1744-1768, 1827-1860, 1949-2002, 2072-2092, 2095-2110, 2306-2321, 2665-2683, 2685-2719, 2739-2770, 2859-2880, 2941-2960, 2963-2978, 3037-3052, 3205-3252, 3306-3332, 3371-3386, 3518-3542, 3975-3990, 4041-4087, 4418-4446, 4528-4546, 7231-7246, 7570-7585, 8395-8410, 9153-

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In certain embodiments, a compound comprising an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to a growth hormone receptor nucleic acid is complementary within the following nucleotide regions of SEQ ID NO: 2: 2571-2586, 2867-3059, 3097-3116, 3341-3695, 4024-4039, 4446-4894, 5392-5817, 6128-6265, 6499-6890, 7231-7246, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 10660-10679, 11020-11035, 11793-12229, 12469-12920, 13351-13415, 13717-13732, 14149-14164, 14361-14555, 14965-15279, 15849-16001, 16253-16272, 16447-16545, 17130-17149, 17377-17669, 17927-17958, 18353-18368, 18636-18773, 19661-19918, 20288-20470, 20979-20994, 21215-21606, 21820-21837, 22150-22165, 22518-22536, 22803-22818, 26494-26522, 29049-29069, 29323-29489, 30550-30565, 30915-31191, 31468-31483, 32363-32382, 32827-33202, 33635-33795, 34138-34157, 34407-34422, 34845-34864, 35466-35485, 35669-35684, 36023-36042, 36266-36327, 36721-36827, 37032-37130, 37276-37295, 37504-37675, 38094-38118, 38841-38856, 39716-40538, 40706-40937, 41164-41183, 41342-41439, 42141-42164, 42700-42760, 43173-43537, 43765-46025, 46476-46532, 48423-48438, 50072-50210, 50470-50485, 50719-51234, 51747-51797, 52015-52143, 52230-52245, 52573-52652, 53466-54660, 54886-54901, 63751-64662, 64882-65099, 65363-65378, 65600-65615, 65988-66183, 66566-66581, 66978-67080, 67251-67270, 67662-67929, 68727-68742, 69203-69242, 69565-69620, 69889-70145, 70352-70584, 70925-71071, 71314-71329, 71617-71769, 72107-72241, 72584-72670, 73061-73076, 73350-73369, 73689-73723, 74107-74131, 74317-74557, 74947-75009, 75192-75207, 75979-76066, 76410-77095, 77292-77307, 77638-77869, 78122-78326, 79006-79021, 79478-79505, 80277-80292, 80575-80939, 81207-81222, 81524-81543, 81761-81776, 82233-82248, 82738-83198, 83330-83416, 83884-84063, 84381-85964, 86220-86392, 86554-86655, 86901-86920, 87181-87262, 88063-88082, 88293-88308, 88605-88967, 89160-89175, 89940-90255, 90473-90528, 91073-91088, 91273-91292, 91647-91662, 91930-92126, 92356-92371, 93190-93443, 93762-94111, 94374-94389, 94581-94653, 94839-94858, 95292-95583, 95829-95844, 96137-96503, 96793-97013, 97539-97554, 97800-97889, 98132-98151, 98624-98672, 98810-99115, 99258-99273, 99478-99503, 99791-99858, 100281-100300, 100406-100421, 100742-100828, 101080-101103, 101242-101320, 101788-101906, 102549-102568, 103566-103625, 104067-104086,

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In certain embodiments, a compound comprising an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to a growth hormone receptor nucleic acid targets the following nucleotide regions of SEQ ID NO: 2: : 2571-2586, 2867-3059, 3097-3116, 3341-3695, 4024-4039, 4446-4894, 5392-5817, 6128-6265, 6499-6890, 7231-7246, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 10660-10679, 11020-11035, 11793-12229, 12469-12920, 13351-13415, 13717-13732, 14149-14164, 14361-14555, 14965-15279, 15849-16001, 16253-16272, 16447-16545, 17130-17149, 17377-17669, 17927-17958, 18353-18368, 18636-18773, 19661-19918, 20288-20470, 20979-20994, 21215-21606, 21820-21837, 22150-22165, 22518-22536, 22803-22818, 26494-26522, 29049-29069, 29323-29489, 30550-30565, 30915-31191, 31468-31483, 32363-32382, 32827-33202, 33635-33795, 34138-34157, 34407-34422, 34845-34864, 35466-35485, 35669-35684, 36023-36042, 36266-36327, 36721-36827, 37032-37130, 37276-37295, 37504-37675, 38094-38118, 38841-38856, 39716-40538, 40706-40937, 41164-41183, 41342-41439, 42141-42164, 42700-42760, 43173-43537, 43765-46025, 46476-46532, 48423-48438, 50072-50210, 50470-50485, 50719-51234, 51747-51797, 52015-52143, 52230-52245, 52573-52652, 53466-54660, 54886-54901, 63751-64662, 64882-65099, 65363-65378, 65600-65615, 65988-66183, 66566-66581, 66978-67080, 67251-67270, 67662-67929, 68727-68742, 69203-69242, 69565-69620, 69889-70145, 70352-70584, 70925-71071, 71314-71329, 71617-71769, 72107-72241, 72584-72670, 73061-73076, 73350-73369, 73689-73723, 74107-74131, 74317-74557, 74947-75009, 75192-75207, 75979-76066, 76410-77095, 77292-77307, 77638-77869, 78122-78326, 79006-79021, 79478-79505, 80277-80292, 80575-80939, 81207-81222, 81524-81543, 81761-81776, 82233-82248, 82738-83198, 83330-83416, 83884-84063, 84381-85964, 86220-86392, 86554-86655, 86901-86920, 87181-87262, 88063-88082, 88293-88308, 88605-88967, 89160-89175, 89940-90255, 90473-90528, 91073-91088, 91273-91292, 91647-91662, 91930-92126, 92356-92371, 93190-93443, 93762-94111, 94374-94389, 94581-94653, 94839-94858, 95292-95583, 95829-95844, 96137-96503, 96793-97013, 97539-97554, 97800-97889, 98132-98151, 98624-98672, 98810-99115, 99258-99273, 99478-99503, 99791-99858, 100281-100300, 100406-100421, 100742-100828, 101080-101103, 101242-

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234466, 234876-234918, 235258-235328, 235770-235785, 236071-236213, 236684-237196, 237585-237698, 237949-237557, 244873-244897, 245319-245334, 245701-245780, 246152-246523, 246936-247031, 247203-247240, 247431-247450, 247644-247659, 248223-248363, 248694-248762, 249494-249509, 250001-250020, 250693-250708, 251214-251233, 251601-251637, 251950-252060, 252665-252680, 252838-252863, 253140-253166, 253594-253819, 254036-254083, 254246-254345, 254641-254660, 254905-254920, 255397-255422, 255618-255633, 255992-256704, 257018-257092, 257317-257332, 257818-259305, 259500-259515, 261294-261656, 262021-262036, 262453-262779, 263338-266518, 266861-267131, 267375-268051, 268366-269447, 270038-271850, 271950-271969, 272631-274145, 274205-275747, 275808-276636, 276932-277064, 277391-278380, 278932-279063, 279303-281001, 281587-281610, 282229-283668, 290035-290474, 290924-292550, 292860-294408, 295475-297012, 297587-298115, 298161-298418, 298489-298738, 299082-299187, 299276-299669, 299723-299749, 299788-300504, or 300835-301295.

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to a region of a growth hormone receptor nucleic acid. In certain embodiments, such compounds or oligonucleotides targeted to a region of a GHR nucleic acid have a contiguous nucleobase portion that is complementary to an equal length nucleobase portion of the region. For example, the portion can be at least an 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous nucleobases portion complementary to an equal length portion of a region recited herein. In certain embodiments, such compounds or oligonucleotide target the following nucleotide regions of SEQ ID NO: 2: : 2571-2586, 2867-3059, 3097-3116, 3341-3695, 4024-4039, 4446-4894, 5392-5817, 6128-6265, 6499-6890, 7231-7246, 8395-8410, 9153-9168, 9554-9569, 9931-9946, 10549-10564, 10660-10679, 11020-11035, 11793-12229, 12469-12920, 13351-13415, 13717-13732, 14149-14164, 14361-14555, 14965-15279, 15849-16001, 16253-16272, 16447-16545, 17130-17149, 17377-17669, 17927-17958, 18353-18368, 18636-18773, 19661-19918, 20288-20470, 20979-20994, 21215-21606, 21820-21837, 22150-22165, 22518-22536, 22803-22818, 26494-26522, 29049-29069, 29323-29489, 30550-30565, 30915-31191, 31468-31483, 32363-32382, 32827-33202, 33635-33795, 34138-34157, 34407-34422, 34845-34864, 35466-35485, 35669-35684, 36023-36042, 36266-36327, 36721-36827, 37032-37130, 37276-37295, 37504-37675, 38094-38118, 38841-38856, 39716-40538, 40706-40937, 41164-41183, 41342-41439, 42141-42164, 42700-42760, 43173-43537, 43765-46025, 46476-46532, 48423-48438, 50072-50210, 50470-50485, 50719-51234, 51747-51797, 52015-52143, 52230-52245, 52573-52652, 53466-54660, 54886-54901, 63751-64662, 64882-65099, 65363-65378, 65600-65615, 65988-66183, 66566-66581, 66978-67080, 67251-67270, 67662-67929, 68727-68742, 69203-69242, 69565-69620, 69889-70145, 70352-70584, 70925-71071, 71314-71329, 71617-71769, 72107-72241, 72584-72670, 73061-73076, 73350-73369, 73689-73723, 74107-74131, 74317-74557, 74947-75009, 75192-75207, 75979-76066, 76410-77095, 77292-77307, 77638-77869, 78122-78326, 79006-79021, 79478-79505, 80277-80292, 80575-80939, 81207-81222, 81524-81543, 81761-81776, 82233-82248, 82738-83198, 83330-

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218541, 218734-21219037, 219342-219633, 219886-220705, 221044-221059, 221483-221607, 221947-221962, 222569-222584, 222914-222998, 223436-223451, 223948-224122, 224409-224430, 224717-224769, 225133-225148, 225436-225761, 226785-226898, 227025-227040, 227218-227251, 227485-227500, 227914-228837, 229174-229189, 229423-229438, 229615-229640, 230042-230057, 230313-230595, 231218-231345, 231817-232037, 232088-232408, 232823-232848, 232884-232899, 233210-233225, 233623-233646, 234447-234466, 234876-234918, 235258-235328, 235770-235785, 236071-236213, 236684-237196, 237585-237698, 237949-237557, 244873-244897, 245319-245334, 245701-245780, 246152-246523, 246936-247031, 247203-247240, 247431-247450, 247644-247659, 248223-248363, 248694-248762, 249494-249509, 250001-250020, 250693-250708, 251214-251233, 251601-251637, 251950-252060, 252665-252680, 252838-252863, 253140-253166, 253594-253819, 254036-254083, 254246-254345, 254641-254660, 254905-254920, 255397-255422, 255618-255633, 255992-256704, 257018-257092, 257317-257332, 257818-259305, 259500-259515, 261294-261656, 262021-262036, 262453-262779, 263338-266518, 266861-267131, 267375-268051, 268366-269447, 270038-271850, 271950-271969, 272631-274145, 274205-275747, 275808-276636, 276932-277064, 277391-278380, 278932-279063, 279303-281001, 281587-281610, 282229-283668, 290035-290474, 290924-292550, 292860-294408, 295475-297012, 297587-298115, 298161-298418, 298489-298738, 299082-299187, 299276-299669, 299723-299749, 299788-300504, or 300835-301295.

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to target intron 1 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 3058-144965 (intron 1) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 2 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 145047-208139 (intron 2) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 3 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 208206-267991 (intron 3) of a growth hormone receptor nucleic acid having the nucleobase

sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 4 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 268122-274018 (intron 4) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 5 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 274192-278925 (intron 5) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 6 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 279105-290308 (intron 6) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 7 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 290475-292530 (intron 7) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 8 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 292622-297153 (intron 8) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, a compound comprises an antisense compound or oligonucleotide and a conjugate group, wherein the antisense compound or oligonucleotide is targeted to intron 9 of a growth hormone receptor nucleic acid. In certain aspects, antisense compounds or oligonucleotides target within nucleotides 297224-297554 (intron 9) of a growth hormone receptor nucleic acid having the nucleobase sequence of SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000).

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises at least one modified internucleoside linkage, at least one modified sugar, and/or at least one modified nucleobase.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises at least one modified sugar. In certain aspects, at least one modified sugar comprises a 2'-O-methoxyethyl group. In certain aspects, at least one modified sugar is a bicyclic sugar, such as a 4'-CH(CH3)-O-2' group, a 4'-CH2-O-2' group, or a 4'-(CH2)2-O-2'group.

In certain aspects, the modified oligonucleotide comprises at least one modified internucleoside linkage, such as a phosphorothioate internucleoside linkage.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises at least one modified nucleobase, such as 5-methylcytosine.

In certain embodiments, any of the foregoing compounds or oligonucleotides comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

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

Certain embodiments provide a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides having a nucleobase sequence comprising the sequence recited in SEQ ID NO: 918, 479, 703, 1800, 1904, 2122, 2127, or 2194.

In certain aspects, the modified oligonucleotide has a nucleobase sequence comprising the sequence recited in SEQ ID NOs: 918, 479 or 703, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

In certain aspects, the modified oligonucleotide has a nucleobase sequence comprising the sequence recited in SEQ ID NOs: 1800, 1904, 2122, 2127, or 2194, wherein the modified oligonucleotide comprises of nucleosides that have either a MOE sugar modification, an (S)-cEt sugar modification, or a deoxy modification; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

In certain embodiments, a compound comprises a single-stranded modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has a nucleobase sequence comprising the sequence recited in SEQ ID NOs: 918, 479 or 703, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

In certain embodiments, a compound comprises a single-stranded modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 16 linked nucleosides and has a nucleobase sequence comprising the sequence recited in SEQ ID NOs: 1800, 1904, 2122, 2127, or 2194, wherein the modified oligonucleotide comprises of nucleosides that have either a MOE sugar modification, an (S)-cEt sugar modification, or a deoxy modification; wherein each internucleoside linkage is a phosphorothioate linkage; and wherein each cytosine is a 5-methylcytosine.

In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR and a conjugate group. For instance, in certain embodiments, a compound comprises ISIS 532401and a conjugate group.

In any of the foregoing embodiments, the compound or oligonucleotide can be at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to a nucleic acid encoding growth hormone receptor.

In any of the foregoing embodiments, the nucleic acid encoding growth hormone receptor can comprise the nucleotide sequence of any one of SEQ ID NOs: 1-19.

In any of the foregoing embodiments, the compound or oligonucleotide can be single-stranded.

In any of the foregoing embodiments, the compound or oligonucleotide can be double-stranded.

In certain embodiments, at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

In certain embodiments, at least one modified internucleoside linkage of the modified oligonucleotide is a phosphorothioate internucleoside linkage.

In certain embodiments, the modified oligonucleotide comprises at least 1, 2, 3, 4, 5, 6, or 7 phosphodiester internucleoside linkages.

In certain embodiments, each internucleoside linkage of the modified oligonucleotide is selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

In certain embodiments, each internucleoside linkage of the modified oligonucleotide is a phosphorothioate linkage.

In certain embodiments, at least one nucleoside of the modified oligonucleotide comprises a modified nucleobase.

In certain embodiments, the modified nucleobase is a 5-methylcytosine.

In certain embodiments, the modified oligonucleotide comprises at least one modified sugar.

In certain embodiments, the modified sugar is a 2' modified sugar, a BNA, or a THP.

In certain embodiments, the modified sugar is any of a 2'-O-methoxyethyl, 2'-O-methyl, a constrained ethyl, a LNA, or a 3'-fluoro-HNA.

In certain embodiments, the compound comprises at least one 2'-O-methoxyethyl nucleoside, 2'-O-methyl nucleoside, constrained ethyl nucleoside, LNA nucleoside, or 3'-fluoro-HNA nucleoside.

In certain embodiments, the modified oligonucleotide comprises:

a gap segment consisting of 10 linked deoxynucleosides;

a 5' wing segment consisting of 5 linked nucleosides; and

a 3' wing segment consisting of 5 linked nucleosides;

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

In certain embodiments, the modified oligonucleotide consists of 20 linked nucleosides.

In certain embodiments, the modified oligonucleotide consists of 19 linked nucleosides.

In certain embodiments, the modified oligonucleotide consists of 18 linked nucleosides.

Certain embodiments provide compounds consisting of a conjugate group and a modified oligonucleotide according to the following formula: mCes mCes Aes mCes mCes Tds Tds Tds Gds Gds Gds Tds Gds Ads Ads Tes Aes Ges mCes Ae; wherein,

A = an adenine,

mC = a 5'-methylcytosine

G = a guanine,

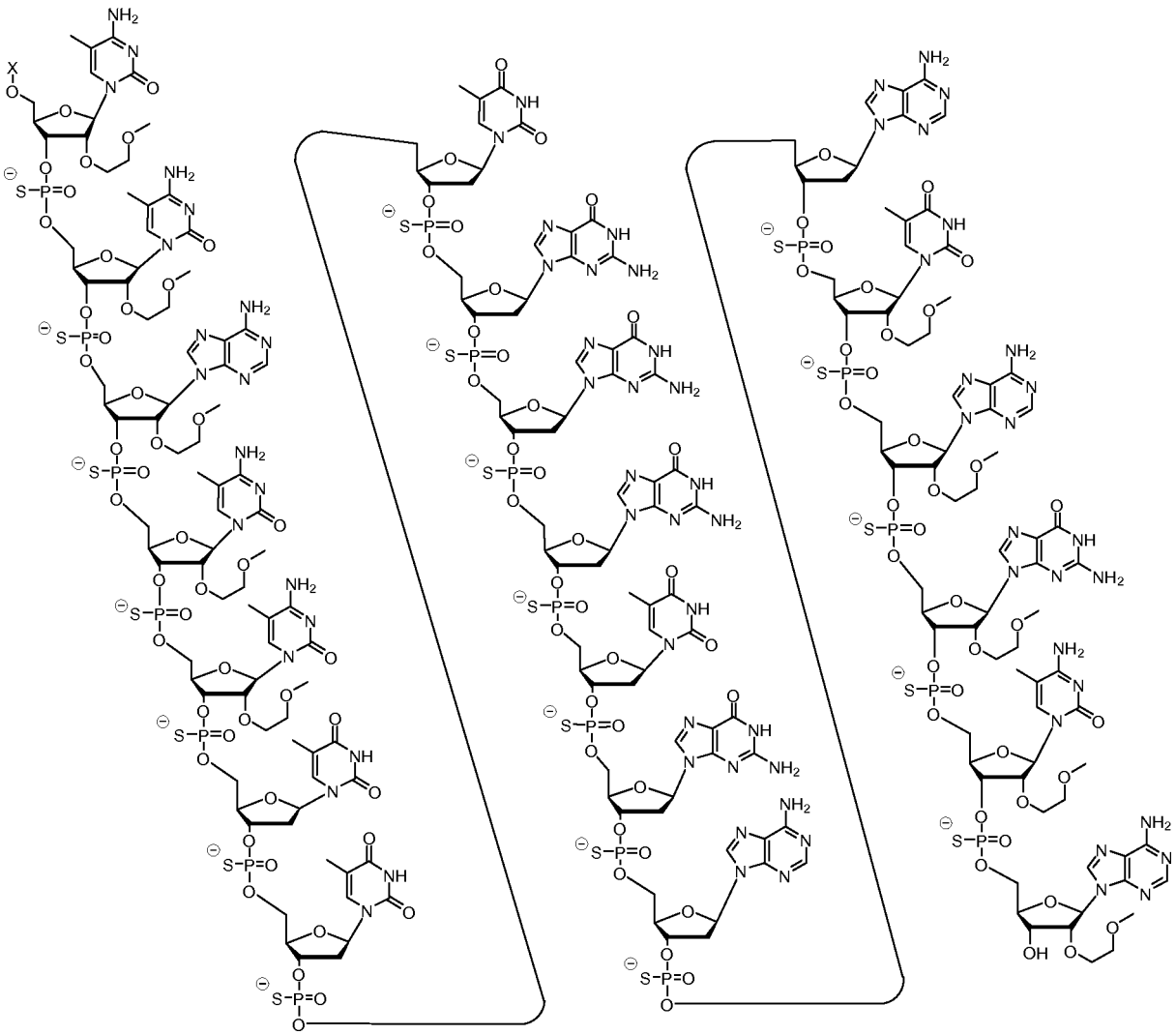
T = a thymine,

e = a 2'-O-methoxyethyl modified nucleoside,

d = a 2'-deoxynucleoside, and

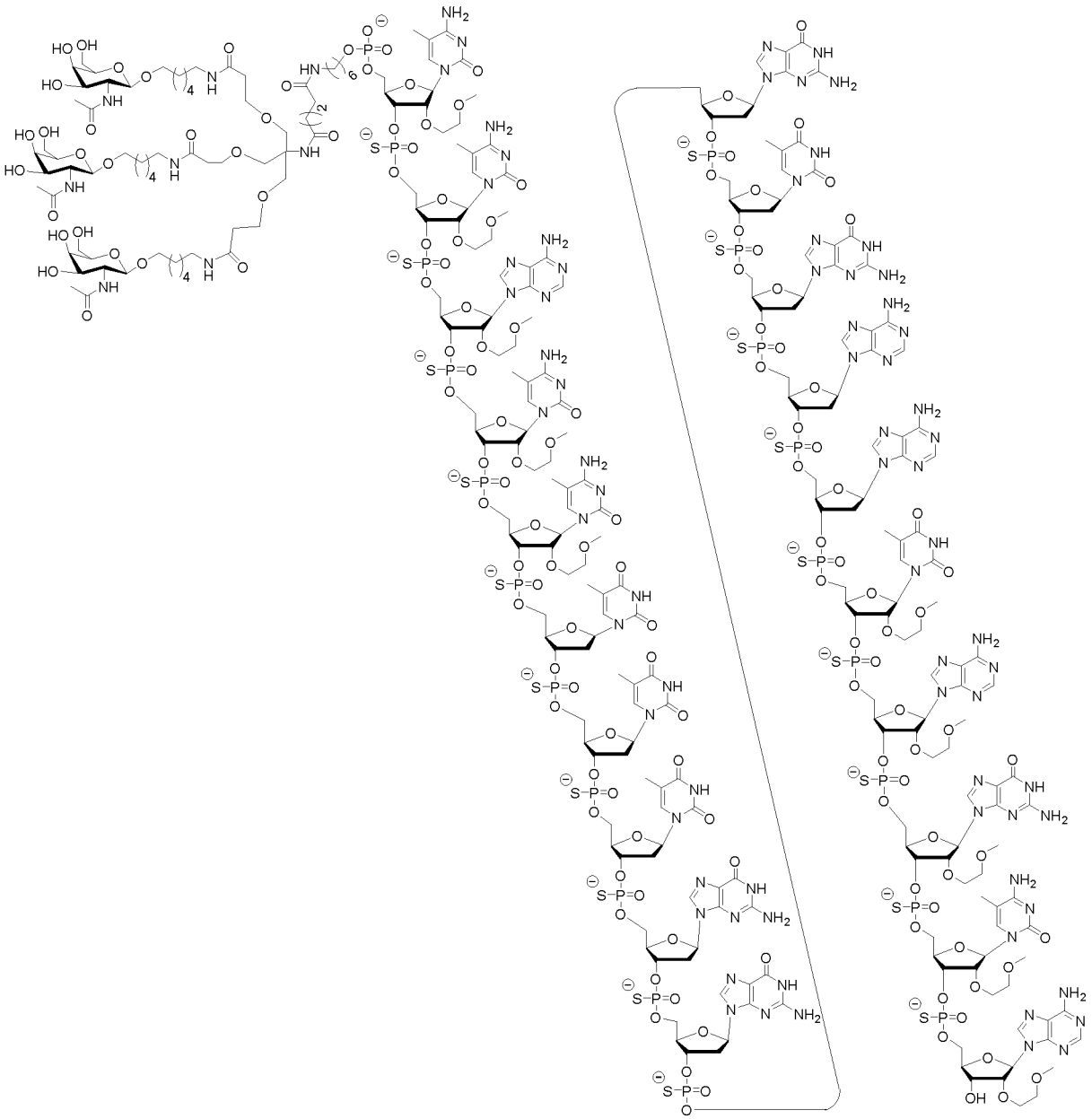
s = a phosphorothioate internucleoside linkage.

In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc on the 5' end. For instance, in certain embodiments, a compound comprises ISIS 532401 conjugated to GalNAc on the 5' end. . In further embodiments, the compound has the following chemical structure comprising or consisting of ISIS 532401 with 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:

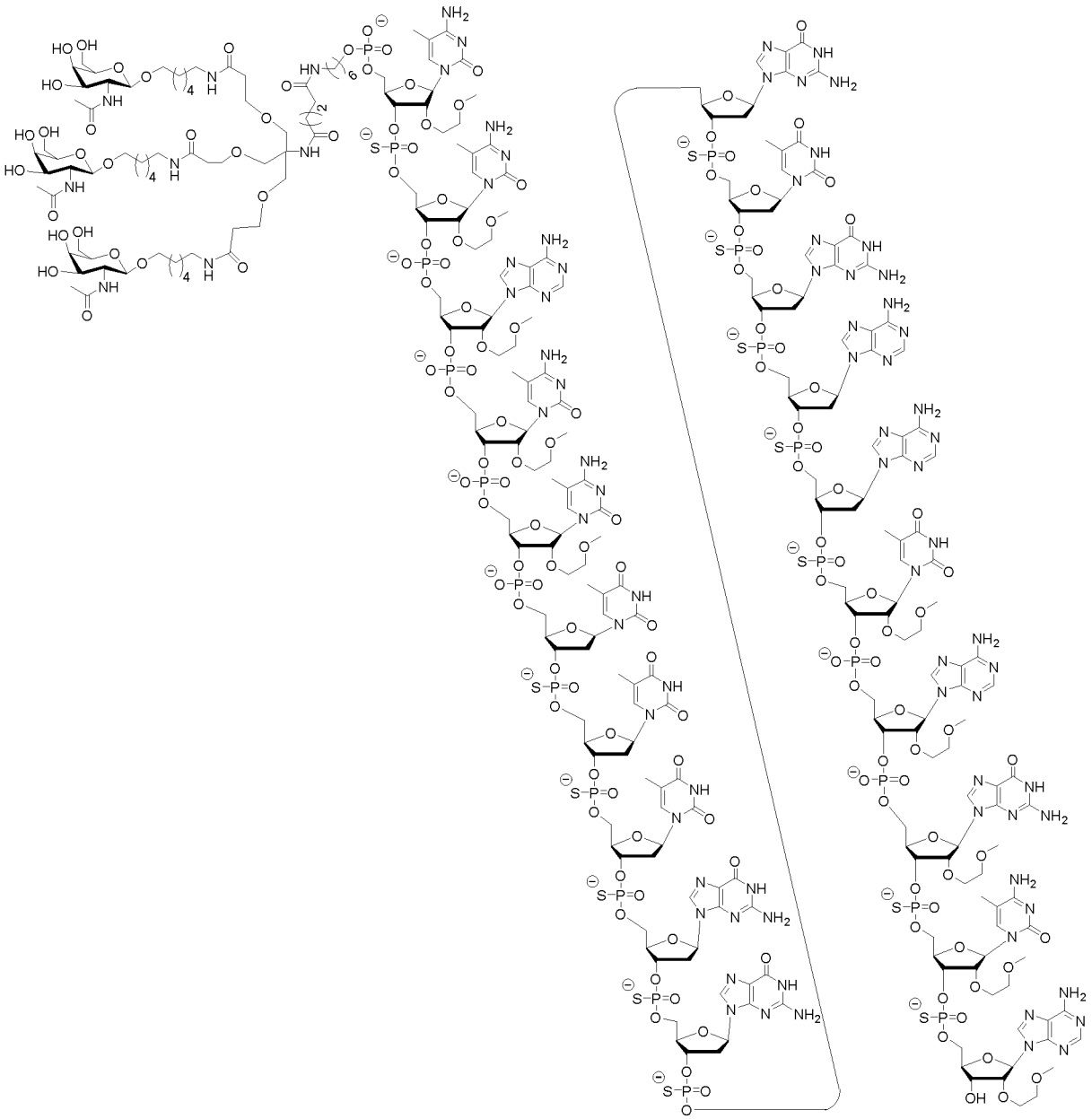


wherein X is a conjugate group comprising GalNAc.

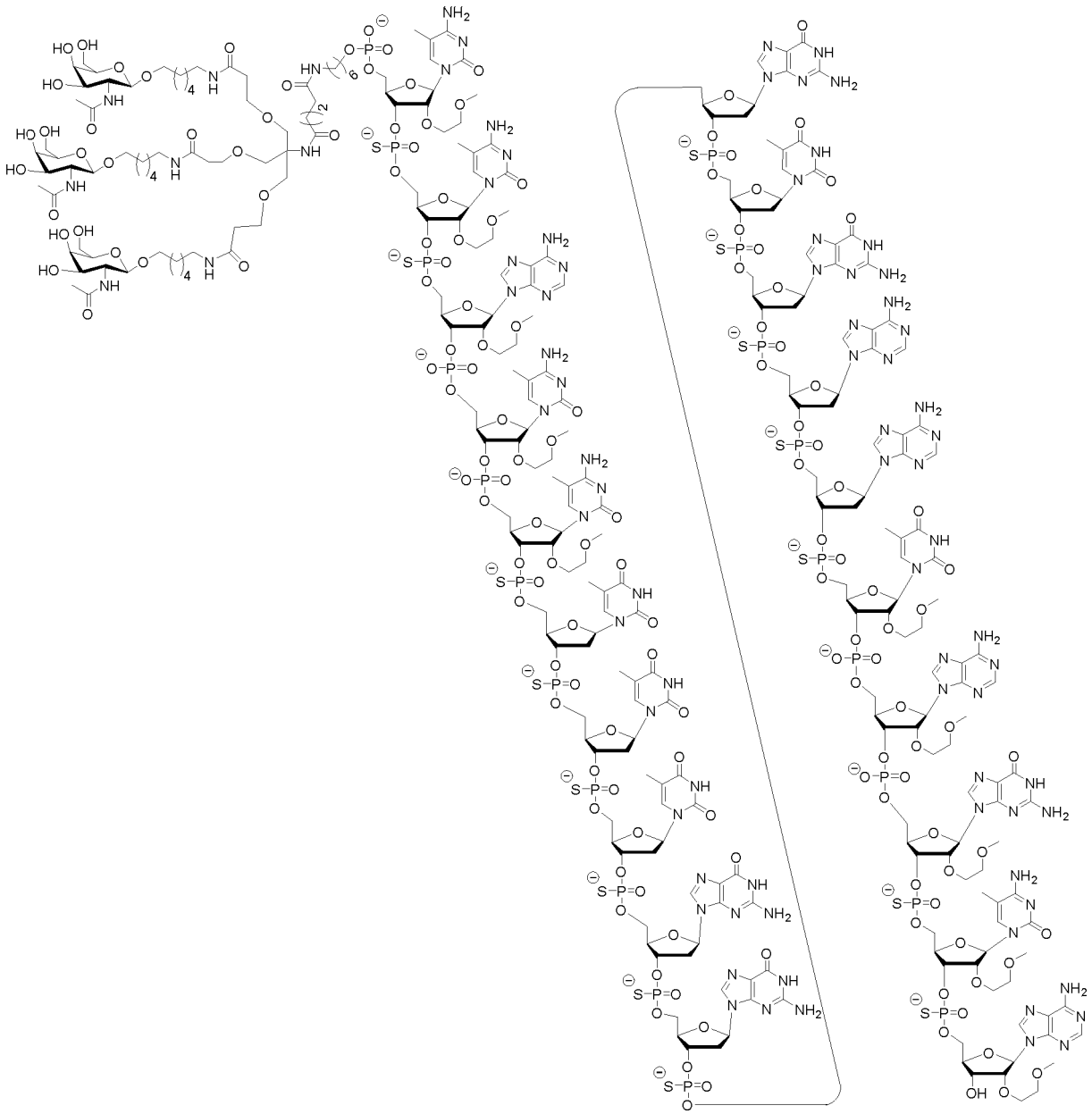
In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage. In further embodiments, a compound having the following chemical structure comprises or consists of ISIS 719223 with a 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:



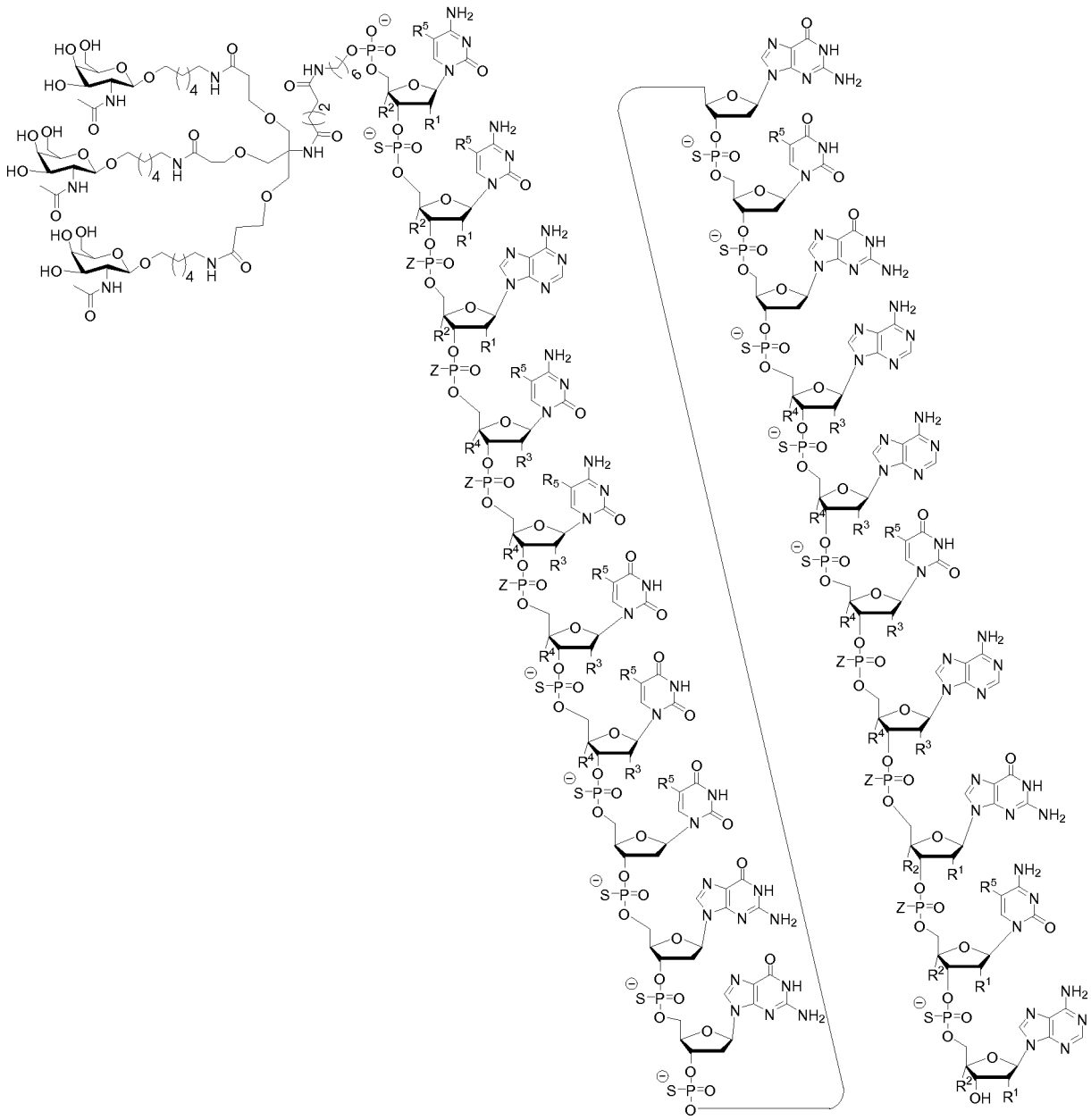
In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage or a phosphodiester linkage. In further embodiments, a compound having the following chemical structure comprises or consists of ISIS 719224 with a 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:



In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage or a phosphodiester linkage. In further embodiments, a compound having the following chemical structure comprises or consists of ISIS 766720 with a 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:



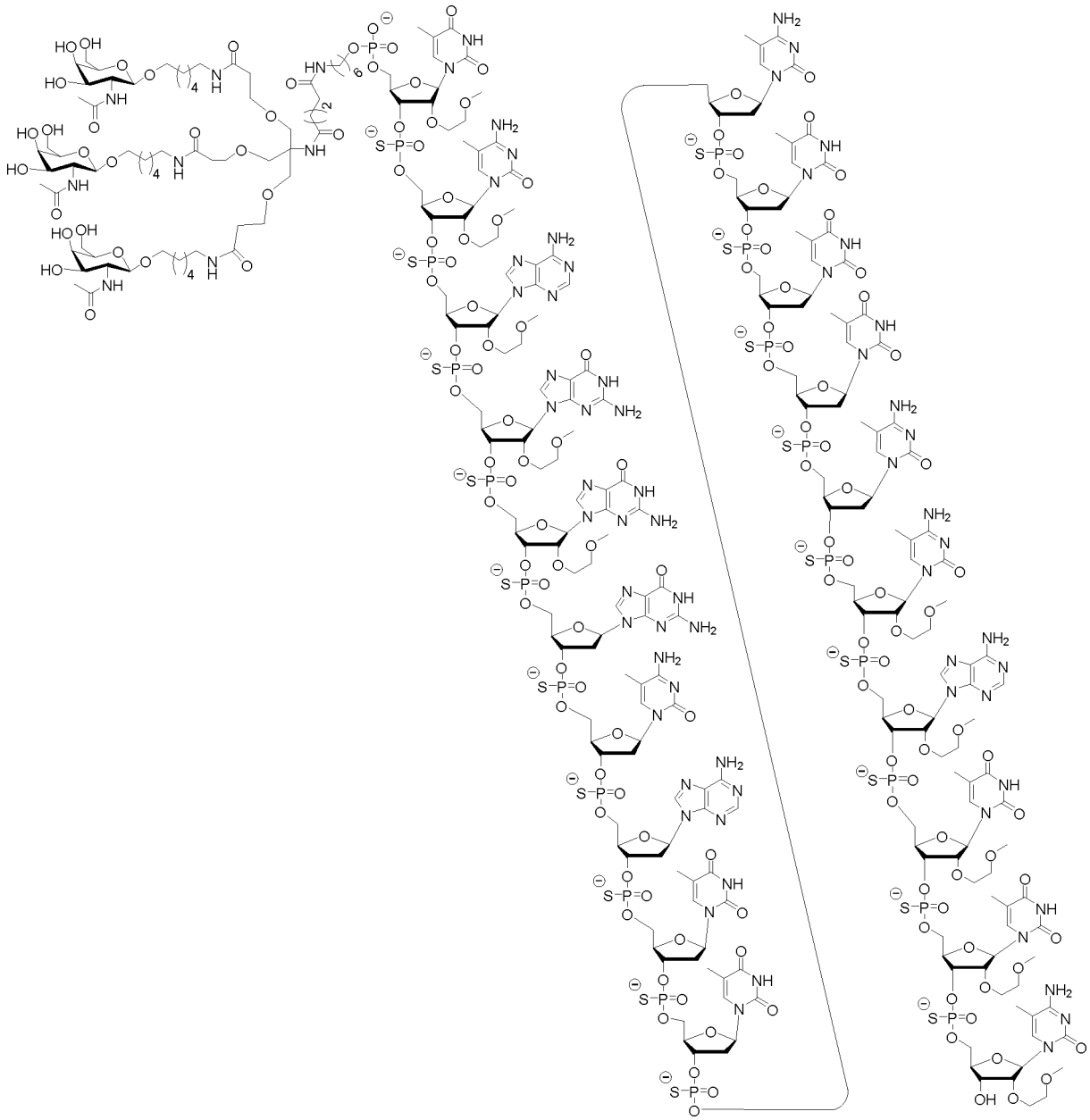
In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc. In further such embodiments, the compound comprises the sequence of ISIS 532401 conjugated to GalNAc, and is represented by the following chemical structure:



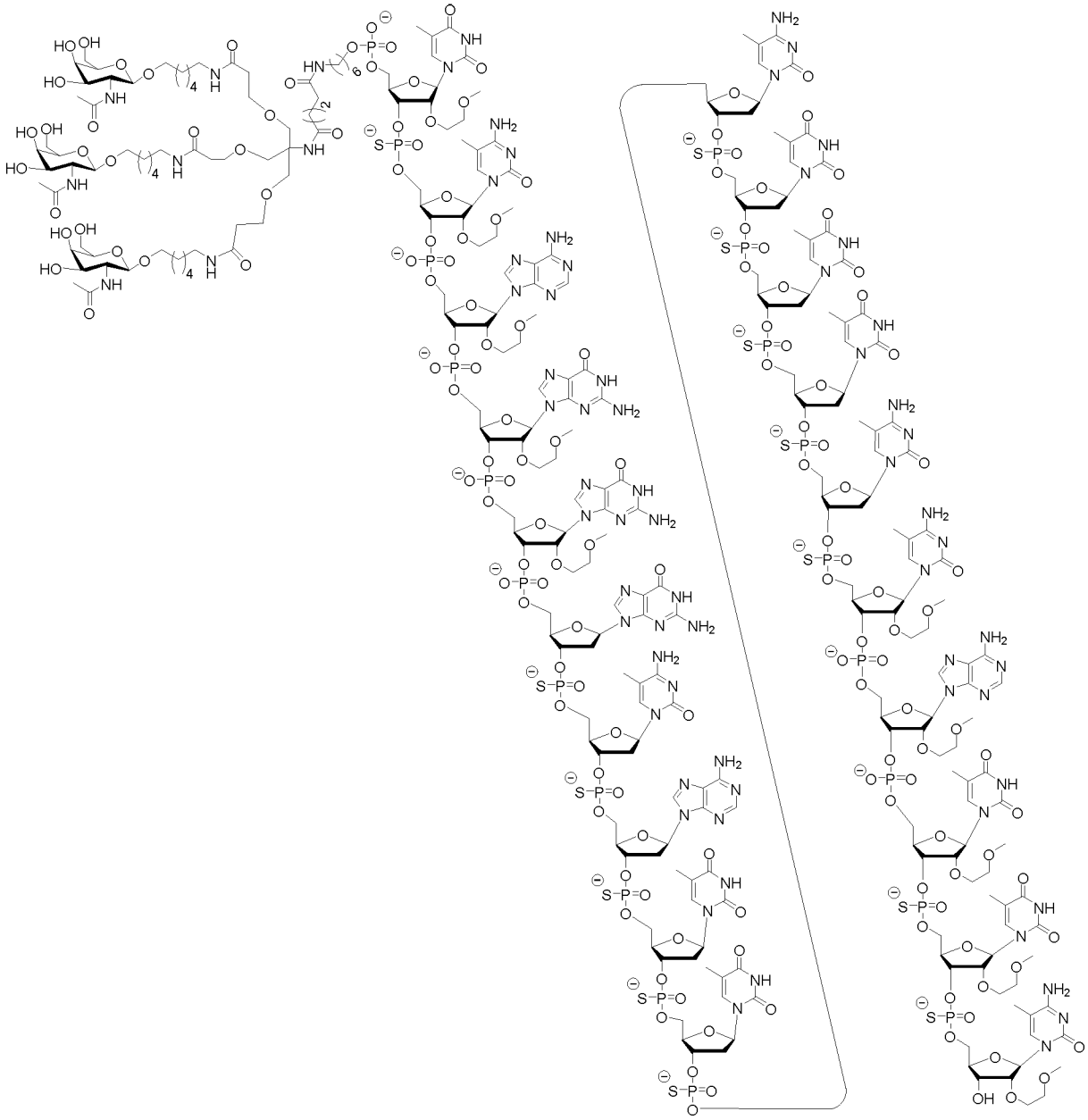
wherein either R^1 is $-OCH_2CH_2OCH_3$ (MOE)and R^2 is H; or R^1 and R^2 together form a bridge, wherein R^1 is –O- and R^2 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$, and R^1 and R^2 are directly connected such that the resulting bridge is selected from: $-O-CH_2-$, $-O-CH(CH_3)-$, and $-O-CH_2CH_2-$; and for each pair of R^3 and R^4 on the same ring, independently for each ring: either R^3 is selected from H and $-OCH_2CH_2OCH_3$ and R^4 is H; or R^3 and R^4 together form a bridge, wherein R^3 is –O-, and R^4 is $-CH_2-$, $-CH(CH_3)-$, or $-CH_2CH_2-$and R^3 and R^4 are directly connected such that the resulting bridge is selected from: $-O-CH_2-$, $-O-CH(CH_3)-$, and $-O-CH_2CH_2-$; and R^5 is selected from H and $-CH_3$; and Z is selected from S^- and O^-.

In certain embodiments, a compound comprises an antisense oligonucleotide having a nucleobase sequence of any of SEQ ID NOs disclosed in WO 2004/078922 and a conjugate group described herein. The

nucleobase sequences of all of the aforementioned referenced SEQ ID NOs are incorporated by reference herein. For example, a compound comprises an oligonucleotide disclosed in WO 2004/078922 conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage and has the following chemical structure:



For example, a compound comprises an oligonucleotide disclosed in WO 2004/078922 conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide compound is a phosphorothioate linkage or a phosphodiester linkage, and has the following chemical structure:



Certain embodiments provide a composition comprising the compound of any of the aforementioned embodiments or salt thereof and at least one of a pharmaceutically acceptable carrier or diluent. In certain aspects, the composition has a viscosity less than about 40 centipoise (cP), less than about 30 centipose (cP), less than about 20 centipose (cP), less than about 15 centipose (cP), or less than about 10 centipose (cP). In certain aspects, the composition having any of the aforementioned viscosities comprises a compound provided herein at a concentration of about 100 mg/mL, about 125 mg/mL, about 150 mg/mL, about 175 mg/mL, about 200 mg/mL, about 225 mg/mL, about 250 mg/mL, about 275 mg/mL, or about 300 mg/mL. In certain aspects, the composition having any of the aforementioned viscosities and/or compound

concentrations has a temperature of room temperature or about 20°C, about 21°C, about 22°C, about 23°C, about 24°C, about 25°C, about 26°C, about 27°C, about 28°C, about 29°C, or about 30°C.

Certain embodiments provide a method of treating a disease associated with excess growth hormone in a human comprising administering to the human a therapeutically effective amount of the compound or composition of any of the aforementioned embodiments, thereby treating the disease associated with excess growth hormone. In certain aspects, the disease associated with excess growth hormone is acromegaly. In certain aspects, the treatment reduces IGF-1 levels.

Certain embodiments provide a method of preventing a disease associated with excess growth hormone in a human comprising administering to the human a therapeutically effective amount of a compound or composition of any of the aforementioned embodiments, thereby preventing the disease associated with excess growth hormone. In certain embodiments, the disease associated with excess growth hormone is acromegaly.

Certain embodiments provide a method of reducing growth hormone receptor (GHR) levels in a human comprising administering to the human a therapeutically effective amount of the compound or composition of any of the aforementioned embodiments, thereby reducing GHR levels in the human. In certain aspects, the human has a disease associated with excess growth hormone. In certain aspects, the disease associated with excess growth hormone is acromegaly.

In certain aspects, the foregoing methods comprise co-administering the compound or composition and a second agent. In certain aspects, the compound or composition and the second agent are administered concomitantly.

Antisense compounds

Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, and siRNAs. An oligomeric compound may be "antisense" to a target nucleic acid, meaning that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

In certain embodiments, an antisense compound has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted. In certain such embodiments, an antisense oligonucleotide has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted.

In certain embodiments, an antisense compound is 10 to 30 subunits in length. In certain embodiments, an antisense compound is 12 to 30 subunits in length. In certain embodiments, an antisense compound is 12 to 22 subunits in length. In certain embodiments, an antisense compound is 14 to 30

subunits in length. In certain embodiments, an antisense compound is 14 to 20 subunits in length. In certain embodiments, an antisense compoun is 15 to 30 subunits in length. In certain embodiments, an antisense compound is 15 to 20 subunits in length. In certain embodiments, an antisense compound is 16 to 30 subunits in length. In certain embodiments, an antisense compound is 16 to 20 subunits in length. In certain embodiments, an antisense compound is 17 to 30 subunits in length. In certain embodiments, an antisense compound is 17 to 20 subunits in length. In certain embodiments, an antisense compound is 18 to 30 subunits in length. In certain embodiments, an antisense compound is 18 to 21 subunits in length. In certain embodiments, an antisense compound is 18 to 20 subunits in length. In certain embodiments, an antisense compound is 20 to 30 subunits in length. In other words, such antisense compounds are from 12 to 30 linked subunits, 14 to 30 linked subunits, 14 to 20 subunits, 15 to 30 subunits, 15 to 20 subunits, 16 to 30 subunits, 16 to 20 subunits, 17 to 30 subunits, 17 to 20 subunits, 18 to 30 subunits, 18 to 20 subunits, 18 to 21 subunits, 20 to 30 subunits, or 12 to 22 linked subunits, respectively. In certain embodiments, an antisense compound is 14 subunits in length. In certain embodiments, an antisense compound is 16 subunits in length. In certain embodiments, an antisense compound is 17 subunits in length. In certain embodiments, an antisense compound is 18 subunits in length. In certain embodiments, an antisense compound is 19 subunits in length. In certain embodiments, an antisense compound is 20 subunits in length. In other embodiments, the antisense compound is 8 to 80, 12 to 50, 13 to 30, 13 to 50, 14 to 30, 14 to 50, 15 to 30, 15 to 50, 16 to 30, 16 to 50, 17 to 30, 17 to 50, 18 to 22, 18 to 24, 18 to 30, 18 to 50, 19 to 22, 19 to 30, 19 to 50, or 20 to 30 linked subunits. In certain such embodiments, the antisense compounds are 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, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 linked subunits in length, or a range defined by any two of the above values. In some embodiments the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleotides.

In certain embodiments antisense oligonucleotides may be shortened or truncated. For example, a single subunit may be deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated antisense compound targeted to a GHR nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the antisense compound. Alternatively, the deleted nucleosides may be dispersed throughout the antisense compound, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

When a single additional subunit is present in a lengthened antisense compound, the additional subunit may be located at the 5' or 3' end of the antisense compound. When two or more additional subunits are present, the added subunits may be adjacent to each other, for example, in an antisense compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the antisense compound. Alternatively, the added subunits may be dispersed throughout the antisense compound, for

example, in an antisense compound having one subunit added to the 5' end and one subunit added to the 3' end.

It is possible to increase or decrease the length of an antisense compound, such as an antisense oligonucleotide, and/or introduce mismatch bases without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of antisense oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Antisense oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the antisense oligonucleotides were able to direct specific cleavage of the target mRNA, albeit to a lesser extent than the antisense oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase antisense oligonucleotides, including those with 1 or 3 mismatches.

Gautschi *et al.* (*J. Natl. Cancer Inst.* 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL *in vitro* and *in vivo*. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity *in vivo*.

Maher and Dolnick (*Nuc. Acid. Res.* 16:3341-3358,1988) tested a series of tandem 14 nucleobase antisense oligonucleotides, and a 28 and 42 nucleobase antisense oligonucleotides comprised of the sequence of two or three of the tandem antisense oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase antisense oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase antisense oligonucleotides.

Certain Antisense Compound Motifs and Mechanisms

In certain embodiments, antisense compounds have chemically modified subunits arranged in patterns, or motifs, to confer to the antisense compounds properties such as enhanced inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Chimeric antisense compounds typically contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of a chimeric antisense compound may confer another desired property e.g., serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

Antisense activity may result from any mechanism involving the hybridization of the antisense compound (e.g., oligonucleotide) with a target nucleic acid, wherein the hybridization ultimately results in a biological effect. In certain embodiments, the amount and/or activity of the target nucleic acid is modulated.

In certain embodiments, the amount and/or activity of the target nucleic acid is reduced. In certain embodiments, hybridization of the antisense compound to the target nucleic acid ultimately results in target nucleic acid degradation. In certain embodiments, hybridization of the antisense compound to the target nucleic acid does not result in target nucleic acid degradation. In certain such embodiments, the presence of the antisense compound hybridized with the target nucleic acid (occupancy) results in a modulation of antisense activity. In certain embodiments, antisense compounds having a particular chemical motif or pattern of chemical modifications are particularly suited to exploit one or more mechanisms. In certain embodiments, antisense compounds function through more than one mechanism and/or through mechanisms that have not been elucidated. Accordingly, the antisense compounds described herein are not limited by particular mechanism.

Antisense mechanisms include, without limitation, RNase H mediated antisense; RNAi mechanisms, which utilize the RISC pathway and include, without limitation, siRNA, ssRNA and microRNA mechanisms; and occupancy based mechanisms. Certain antisense compounds may act through more than one such mechanism and/or through additional mechanisms.

RNase H-Mediated Antisense

In certain embodiments, antisense activity results at least in part from degradation of target RNA by RNase H. RNase H is a cellular endonuclease that 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. Accordingly, antisense compounds comprising at least a portion of DNA or DNA-like nucleosides may activate RNase H, resulting in cleavage of the target nucleic acid. In certain embodiments, antisense compounds that utilize RNase H comprise one or more modified nucleosides. In certain embodiments, such antisense compounds comprise at least one block of 1-8 modified nucleosides. In certain such embodiments, the modified nucleosides do not support RNase H activity. In certain embodiments, such antisense compounds are gapmers, as described herein. In certain such embodiments, the gap of the gapmer comprises DNA nucleosides. In certain such embodiments, the gap of the gapmer comprises DNA-like nucleosides. In certain such embodiments, the gap of the gapmer comprises DNA nucleosides and DNA-like nucleosides.

Certain antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal region having a plurality of nucleotides that supports RNaseH cleavage is positioned between external regions having a plurality of nucleotides that are chemically distinct from the nucleosides of the internal region. In the case of an antisense oligonucleotide having a gapmer motif, the gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified

nucleosides. In certain embodiments, the regions of a gapmer are differentiated by the types of sugar moieties comprising each distinct region. The types of sugar moieties that are used to differentiate the regions of a gapmer may in some embodiments include β-D-ribonucleosides, β-D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides may include 2'-MOE and 2'-O-CH_3, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides may include those having a constrained ethyl). In certain embodiments, nucleosides in the wings may include several modified sugar moieties, including, for example 2'-MOE and bicyclic sugar moieties such as constrained ethyl or LNA. In certain embodiments, wings may include several modified and unmodified sugar moieties. In certain embodiments, wings may include various combinations of 2'-MOE nucleosides, bicyclic sugar moieties such as constrained ethyl nucleosides or LNA nucleosides, and 2'-deoxynucleosides.

Each distinct region may comprise uniform sugar moieties, variant, or alternating sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5'-wing, "Y" represents the length of the gap, and "Z" represents the length of the 3'-wing. "X" and "Z" may comprise uniform, variant, or alternating sugar moieties. In certain embodiments, "X" and "Y" may include one or more 2'-deoxynucleosides."Y" may comprise 2'-deoxynucleosides. As used herein, a gapmer described as "X-Y-Z" has a configuration such that the gap is positioned immediately adjacent to each of the 5'-wing and the 3' wing. Thus, no intervening nucleotides exist between the 5'-wing and gap, or the gap and the 3'-wing. Any of the antisense compounds described herein can have a gapmer motif. In certain embodiments, "X" and "Z" are the same; in other embodiments they are different. In certain embodiments, "Y" is between 8 and 15 nucleosides. X, Y, or Z can be any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or more nucleosides.

In certain embodiments, the antisense compound targeted to a GHR nucleic acid has a gapmer motif in which the gap consists of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 linked nucleosides.

In certain embodiments, the antisense oligonucleotide has a sugar motif described by Formula A as follows: $(J)_m$-$(B)_n$-$(J)_p$-$(B)_r$-$(A)_t$-$(D)_g$-$(A)_v$-$(B)_w$-$(J)_x$-$(B)_y$-$(J)_z$

wherein:

each A is independently a 2'-substituted nucleoside;

each B is independently a bicyclic nucleoside;

each J is independently either a 2'-substituted nucleoside or a 2'-deoxynucleoside;

each D is a 2'-deoxynucleoside;

m is 0-4; n is 0-2; p is 0-2; r is 0-2; t is 0-2; v is 0-2; w is 0-4; x is 0-2; y is 0-2; z is 0-4; g is 6-14;

provided that:

at least one of m, n, and r is other than 0;

at least one of w and y is other than 0;

the sum of m, n, p, r, and t is from 2 to 5; and

the sum of v, w, x, y, and z is from 2 to 5.

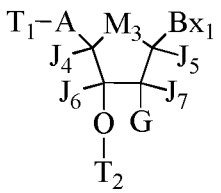
RNAi Compounds

In certain embodiments, antisense compounds are interfering RNA compounds (RNAi), which include double-stranded RNA compounds (also referred to as short-interfering RNA or siRNA) and single-stranded RNAi compounds (or ssRNA). Such compounds work at least in part through the RISC pathway to degrade and/or sequester a target nucleic acid (thus, include microRNA/microRNA-mimic compounds). In certain embodiments, antisense compounds comprise modifications that make them particularly suited for such mechanisms.

i. ssRNA compounds

In certain embodiments, antisense compounds including those particularly suited for use as single-stranded RNAi compounds (ssRNA) comprise a modified 5'-terminal end. In certain such embodiments, the 5'-terminal end comprises a modified phosphate moiety. In certain embodiments, such modified phosphate is stabilized (e.g., resistant to degradation/cleavage compared to unmodified 5'-phosphate). In certain embodiments, such 5'-terminal nucleosides stabilize the 5'-phosphorous moiety. Certain modified 5'-terminal nucleosides may be found in the art, for example in WO/2011/139702.

In certain embodiments, the 5'-nucleoside of an ssRNA compound has Formula IIc:



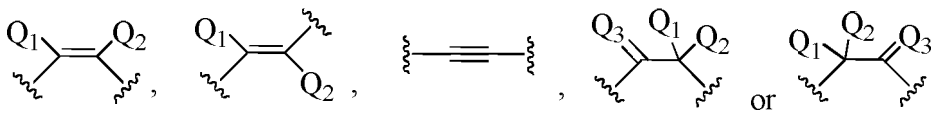
IIc

wherein:

T_1 is an optionally protected phosphorus moiety;

T_2 is an internucleoside linking group linking the compound of Formula IIc to the oligomeric compound;

A has one of the formulas:



Q_1 and Q_2 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl, substituted C_2-C_6 alkynyl or $N(R_3)(R_4)$;

Q_3 is O, S, $N(R_5)$ or $C(R_6)(R_7)$;

each R_3, R_4 R_5, R_6 and R_7 is, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl or C_1-C_6 alkoxy;

M_3 is O, S, NR_{14}, $C(R_{15})(R_{16})$, $C(R_{15})(R_{16})C(R_{17})(R_{18})$, $C(R_{15})=C(R_{17})$, $OC(R_{15})(R_{16})$ or $OC(R_{15})(Bx_2)$;

R_{14} is H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

R_{15}, R_{16}, R_{17} and R_{18} are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

Bx_1 is a heterocyclic base moiety;

or if Bx_2 is present then Bx_2 is a heterocyclic base moiety and Bx_1 is H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

J_4, J_5, J_6 and J_7 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

or J_4 forms a bridge with one of J_5 or J_7 wherein said bridge comprises from 1 to 3 linked biradical groups selected from O, S, NR_{19}, $C(R_{20})(R_{21})$, $C(R_{20})=C(R_{21})$, $C[=C(R_{20})(R_{21})]$ and C(=O) and the other two of J_5, J_6 and J_7 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

each R_{19}, R_{20} and R_{21} is, independently, H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_2-C_6 alkynyl or substituted C_2-C_6 alkynyl;

G is H, OH, halogen or $O\text{-}[C(R_8)(R_9)]_n\text{-}[(C=O)_m\text{-}X_1]_j\text{-}Z$;

each R_8 and R_9 is, independently, H, halogen, C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

X_1 is O, S or $N(E_1)$;

Z is H, halogen, 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, substituted C_2-C_6 alkynyl or $N(E_2)(E_3)$;

E_1, E_2 and E_3 are each, independently, H, C_1-C_6 alkyl or substituted C_1-C_6 alkyl;

n is from 1 to about 6;

m is 0 or 1;

j is 0 or 1;

each substituted group comprises one or more optionally protected substituent groups independently selected from halogen, OJ_1, $N(J_1)(J_2)$, $=NJ_1$, SJ_1, N_3, CN, $OC(=X_2)J_1$, $OC(=X_2)N(J_1)(J_2)$ and $C(=X_2)N(J_1)(J_2)$;

X_2 is O, S or NJ_3;

each J_1, J_2 and J_3 is, independently, H or C_1-C_6 alkyl;

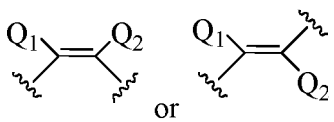
when j is 1 then Z is other than halogen or $N(E_2)(E_3)$; and

wherein said oligomeric compound comprises from 8 to 40 monomeric subunits and is hybridizable to at least a portion of a target nucleic acid.

In certain embodiments, M_3 is O, CH=CH, OCH_2 or $OC(H)(Bx_2)$. In certain embodiments, M_3 is O.

In certain embodiments, J_4, J_5, J_6 and J_7 are each H. In certain embodiments, J_4 forms a bridge with one of J_5 or J_7.

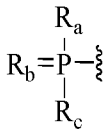
In certain embodiments, A has one of the formulas:



wherein:

Q_1 and Q_2 are each, independently, H, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy or substituted C_1-C_6 alkoxy. In certain embodiments, Q_1 and Q_2 are each H. In certain embodiments, Q_1 and Q_2 are each, independently, H or halogen. In certain embodiments, Q_1 and Q_2 is H and the other of Q_1 and Q_2 is F, CH_3 or OCH_3.

In certain embodiments, T_1 has the formula:



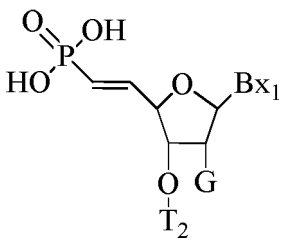
wherein:

R_a and R_c are each, independently, protected hydroxyl, protected thiol, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, substituted C_1-C_6 alkoxy, protected amino or substituted amino; and

R_b is O or S. In certain embodiments, R_b is O and R_a and R_c are each, independently, OCH_3, OCH_2CH_3 or $CH(CH_3)_2$.

In certain embodiments, G is 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, $O(CH_2)_3$-$N(R_{10})(R_{11})$, $O(CH_2)_2$-$ON(R_{10})(R_{11})$, $O(CH_2)_2$-$O(CH_2)_2$-$N(R_{10})(R_{11})$, $OCH_2C(=O)$-$N(R_{10})(R_{11})$, $OCH_2C(=O)$-$N(R_{12})$-$(CH_2)_2$-$N(R_{10})(R_{11})$ or $O(CH_2)_2$-$N(R_{12})$-$C(=NR_{13})[N(R_{10})(R_{11})]$ wherein R_{10}, R_{11}, R_{12} and R_{13} are each, independently, H or C_1-C_6 alkyl. In certain embodiments, G is halogen, OCH_3, OCF_3, OCH_2CH_3, OCH_2CF_3, OCH_2-$CH=CH_2$, $O(CH_2)_2$-OCH_3, $O(CH_2)_2$-$O(CH_2)_2$-$N(CH_3)_2$, $OCH_2C(=O)$-$N(H)CH_3$, $OCH_2C(=O)$-$N(H)$-$(CH_2)_2$-$N(CH_3)_2$ or OCH_2-$N(H)$-$C(=NH)NH_2$. In certain embodiments, G is F, OCH_3 or $O(CH_2)_2$-OCH_3. In certain embodiments, G is $O(CH_2)_2$-OCH_3.

In certain embodiments, the 5'-terminal nucleoside has Formula IIe:



IIe

In certain embodiments, antisense compounds, including those particularly suitable for ssRNA 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 uniform sugar modifications. In certain such embodiments, each nucleoside of the region comprises the same RNA-like sugar modification. In certain embodiments, each nucleoside of the region is a 2'-F nucleoside. In certain embodiments, each nucleoside of the region is a 2'-OMe nucleoside. In certain embodiments, each nucleoside of the region is a 2'-MOE nucleoside. In certain embodiments, each nucleoside of the region is a

cEt nucleoside. In certain embodiments, each nucleoside of the region is an LNA nucleoside. In certain embodiments, the uniform region constitutes all or essentially all of the oligonucleotide. In certain embodiments, the region constitutes the entire oligonucleotide except for 1-4 terminal nucleosides.

In certain embodiments, oligonucleotides comprise one or more regions of alternating sugar modifications, wherein the nucleosides alternate between nucleotides having a sugar modification of a first type and nucleotides having a sugar modification of a second type. In certain embodiments, nucleosides of both types are RNA-like nucleosides. In certain embodiments the alternating nucleosides are selected from: 2'-OMe, 2'-F, 2'-MOE, LNA, and cEt. In certain embodiments, the alternating modificatios are 2'-F and 2'-OMe. Such regions may be contiguous or may be interupted by differently modified nucleosides or conjugated nucleosides.

In certain embodiments, the alternating region of alternating modifications each consist of a single nucleoside (i.e., the patern is $(AB)_xA_y$ wheren A is a nucleoside having a sugar modification of a first type and B is a nucleoside having a sugar modification of a second type; x is 1-20 and y is 0 or 1). In certan embodiments, one or more alternating regions in an alternating motif includes more than a single nucleoside of a type. For example, oligonucleotides may include one or more regions of any of the following nucleoside motifs:

AABBAA;

ABBABB;

AABAAB;

ABBABAABB;

ABABAA;

AABABAB;

ABABAA;

ABBAABBABABAA;

BABBAABBABABAA; or

ABABBAABBABABAA;

wherein A is a nucleoside of a first type and B is a nucleoside of a second type. In certain embodiments, A and B are each selected from 2'-F, 2'-OMe, BNA, and MOE.

In certain embodiments, oligonucleotides having such an alternating motif also comprise a modified 5' terminal nucleoside, such as those of formula IIc or IIe.

In certain embodiments, oligonucleotides comprise a region having a 2-2-3 motif. Such regions comprises the following motif:

$-(A)_2-(B)_x-(A)_2-(C)_y-(A)_3-$

wherein: A is a first type of modifed nucleosde;

B and C, are nucleosides that are differently modified than A, however, B and C may have the same or different modifications as one another;

x and y are from 1 to 15.

In certain embodiments, A is a 2'-OMe modified nucleoside. In certain embodiments, B and C are both 2'-F modified nucleosides. In certain embodiments, A is a 2'-OMe modified nucleoside and B and C are both 2'-F modified nucleosides.

In certain embodiments, oligonucleosides have the following sugar motif:

$5'- (Q)- (AB)_xA_y-(D)_z$

wherein:

Q is a nucleoside comprising a stabilized phosphate moiety. In certain embodiments, Q is a nucleoside having Formula IIc or IIe;

A is a first type of modifed nucleoside;

B is a second type of modified nucleoside;

D is a modified nucleoside comprising a modification different from the nucleoside adjacent to it. Thus, if y is 0, then D must be differently modified than B and if y is 1, then D must be differently modified than A. In certain embodiments, D differs from both A and B.

X is 5-15;

Y is 0 or 1;

Z is 0-4.

In certain embodiments, oligonucleosides have the following sugar motif:

$5'- (Q)- (A)_x-(D)_z$

wherein:

Q is a nucleoside comprising a stabilized phosphate moiety. In certain embodiments, Q is a nucleoside having Formula IIc or IIe;

A is a first type of modifed nucleoside;

D is a modified nucleoside comprising a modification different from A.

X is 11-30;

Z is 0-4.

In certain embodiments A, B, C, and D in the above motifs are selected from: 2'-OMe, 2'-F, 2'-MOE, LNA, and cEt. In certain embodiments, D represents terminal nucleosides. In certain embodiments, such terminal nucleosides are not designed to hybridize to the target nucleic acid (though one or more might hybridize by chance). In certiain embodiments, the nucleobase of each D nucleoside is adenine, regardless of the identity of the nucleobase at the corresponding position of the target nucleic acid. In certain embodiments the nucleobase of each D nucleoside is thymine.

In certain embodiments, antisense compounds, including those particularly suited for use as ssRNA 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 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 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 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 8 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 one 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.

Oligonucleotides having any of the various sugar motifs described herein, may have any linkage motif. For example, the oligonucleotides, including but not limited to those described above, may have a

linkage motif selected from non-limiting the table below:

5' most linkage	Central region	3'-region
PS	Alternating PO/PS	6 PS
PS	Alternating PO/PS	7 PS
PS	Alternating PO/PS	8 PS

ii. siRNA compounds

In certain embodiments, antisense compounds are double-stranded RNAi compounds (siRNA). In such embodiments, one or both strands may comprise any modification motif described above for ssRNA. In certain embodiments, ssRNA compounds may be unmodified RNA. In certain embodiments, siRNA compounds may comprise unmodified RNA nucleosides, but modified internucleoside linkages.

Several embodiments relate to double-stranded compositions wherein each strand comprises a motif defined by the location of one or more modified or unmodified nucleosides. In certain embodiments, compositions are provided comprising a first and a second oligomeric compound that are fully or at least partially hybridized to form a duplex region and further comprising a region that is complementary to and hybridizes to a nucleic acid target. It is suitable that such a composition comprise a first oligomeric compound that is an antisense strand having full or partial complementarity to a nucleic acid target and a second oligomeric compound that is a sense strand having one or more regions of complementarity to and forming at least one duplex region with the first oligomeric compound.

The compositions of several embodiments modulate gene expression by hybridizing to a nucleic acid target resulting in loss of its normal function. In some embodiments, the target nucleic acid is GHR. In certain embodiment, the degradation of the targeted GHR is facilitated by an activated RISC complex that is formed with compositions of the invention.

Several embodiments are directed to double-stranded compositions wherein one of the strands is useful in, for example, influencing the preferential loading of the opposite strand into the RISC (or cleavage) complex. The compositions are useful for targeting selected nucleic acid molecules and modulating the expression of one or more genes. In some embodiments, the compositions of the present invention hybridize to a portion of a target RNA resulting in loss of normal function of the target RNA.

Certain embodiments are drawn to double-stranded compositions wherein both the strands comprises a hemimer motif, a fully modified motif, a positionally modified motif or an alternating motif. Each strand of the compositions of the present invention can be modified to fulfil a particular role in for example the siRNA pathway. Using a different motif in each strand or the same motif with different

chemical modifications in each strand permits targeting the antisense strand for the RISC complex while inhibiting the incorporation of the sense strand. Within this model, each strand can be independently modified such that it is enhanced for its particular role. The antisense strand can be modified at the 5'-end to enhance its role in one region of the RISC while the 3'-end can be modified differentially to enhance its role in a different region of the RISC.

The double-stranded oligonucleotide molecules can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The double-stranded oligonucleotide molecules can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double-stranded structure, for example wherein the double-stranded region is about 15 to about 30, e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs; the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof (e.g., about 15 to about 25 or more nucleotides of the double-stranded oligonucleotide molecule are complementary to the target nucleic acid or a portion thereof). Alternatively, the double-stranded oligonucleotide is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siRNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s).

The double-stranded oligonucleotide can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The double-stranded oligonucleotide can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide can be processed either in vivo or in vitro to generate an active siRNA molecule capable of mediating RNAi.

In certain embodiments, the double-stranded oligonucleotide comprises separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the double-stranded oligonucleotide comprises nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the double-stranded oligonucleotide interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene.

As used herein, double-stranded oligonucleotides need not be limited to those molecules containing only RNA, but further encompasses chemically modified nucleotides and non-nucleotides. In certain embodiments, the short interfering nucleic acid molecules lack 2'-hydroxy (2'-OH) containing nucleotides. In certain embodiments short interfering nucleic acids optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such double-stranded oligonucleotides that do not require the presence of ribonucleotides within the molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, double-stranded oligonucleotides can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. As used herein, the term siRNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, double-stranded oligonucleotides can be used to epigenetically silence genes at both the post-transcriptional level and the pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siRNA molecules of the invention can result from siRNA mediated modification of chromatin structure or methylation pattern to alter gene expression (see, for example, Verdel et al., 2004, Science, 303, 672-676; Pal-Bhadra et al., 2004, Science, 303, 669-672; Allshire, 2002, Science, 297, 1818-1819; Volpe et al., 2002, Science, 297, 1833-1837; Jenuwein, 2002, Science, 297, 2215-2218; and Hall et al., 2002, Science, 297, 2232-2237).

It is contemplated that compounds and compositions of several embodiments provided herein can target GHR by a dsRNA-mediated gene silencing or RNAi mechanism, including, e.g., "hairpin" or stem-loop double-stranded RNA effector molecules in which a single RNA strand with self-complementary sequences is capable of assuming a double-stranded conformation, or duplex dsRNA effector molecules comprising two separate strands of RNA. In various embodiments, the dsRNA consists entirely of

ribonucleotides or consists of a mixture of ribonucleotides and deoxynucleotides, such as the RNA/DNA hybrids disclosed, for example, by WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999. The dsRNA or dsRNA effector molecule may be a single molecule with a region of self-complementarity such that nucleotides in one segment of the molecule base pair with nucleotides in another segment of the molecule. In various embodiments, a dsRNA that consists of a single molecule consists entirely of ribonucleotides or includes a region of ribonucleotides that is complementary to a region of deoxyribonucleotides. Alternatively, the dsRNA may include two different strands that have a region of complementarity to each other.

In various embodiments, both strands consist entirely of ribonucleotides, one strand consists entirely of ribonucleotides and one strand consists entirely of deoxyribonucleotides, or one or both strands contain a mixture of ribonucleotides and deoxyribonucleotides. In certain embodiments, the regions of complementarity are at least 70, 80, 90, 95, 98, or 100% complementary to each other and to a target nucleic acid sequence. In certain embodiments, the region of the dsRNA that is present in a double-stranded conformation includes at least 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 50, 75,100, 200, 500, 1000, 2000 or 5000 nucleotides or includes all of the nucleotides in a cDNA or other target nucleic acid sequence being represented in the dsRNA. In some embodiments, the dsRNA does not contain any single stranded regions, such as single stranded ends, or the dsRNA is a hairpin. In other embodiments, the dsRNA has one or more single stranded regions or overhangs. In certain embodiments, RNA/DNA hybrids include a DNA strand or region that is an antisense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% complementarity to a target nucleic acid) and an RNA strand or region that is a sense strand or region (e.g, has at least 70, 80, 90, 95, 98, or 100% identity to a target nucleic acid), and vice versa.

In various embodiments, the RNA/DNA hybrid is made in vitro using enzymatic or chemical synthetic methods such as those described herein or those described in WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999. In other embodiments, a DNA strand synthesized in vitro is complexed with an RNA strand made in vivo or in vitro before, after, or concurrent with the transformation of the DNA strand into the cell. In yet other embodiments, the dsRNA is a single circular nucleic acid containing a sense and an antisense region, or the dsRNA includes a circular nucleic acid and either a second circular nucleic acid or a linear nucleic acid (see, for example, WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999.) Exemplary circular nucleic acids include lariat structures in which the free 5' phosphoryl group of a nucleotide becomes linked to the 2' hydroxyl group of another nucleotide in a loop back fashion.

In other embodiments, the dsRNA includes one or more modified nucleotides in which the 2' position in the sugar contains a halogen (such as fluorine group) or contains an alkoxy group (such as a methoxy group) which increases the half-life of the dsRNA in vitro or in vivo compared to the corresponding

dsRNA in which the corresponding 2' position contains a hydrogen or an hydroxyl group. In yet other embodiments, the dsRNA includes one or more linkages between adjacent nucleotides other than a naturally-occurring phosphodiester linkage. Examples of such linkages include phosphoramide, phosphorothioate, and phosphorodithioate linkages. The dsRNAs may also be chemically modified nucleic acid molecules as taught in U.S. Pat. No. 6,673,661. In other embodiments, the dsRNA contains one or two capped strands, as disclosed, for example, by WO 00/63364, filed Apr. 19, 2000, or U.S. Ser. No. 60/130,377, filed Apr. 21, 1999.

In other embodiments, the dsRNA can be any of the at least partially dsRNA molecules disclosed in WO 00/63364, as well as any of the dsRNA molecules described in U.S. Provisional Application 60/399,998; and U.S. Provisional Application 60/419,532, and PCT/US2003/033466, published on April 29, 2004 as WO 2004/035765, the teaching of which is hereby incorporated by reference. Any of the dsRNAs may be expressed in vitro or in vivo using the methods described herein or standard methods, such as those described in WO 00/63364.

Occupancy

In certain embodiments, antisense compounds are not expected to result in cleavage or the target nucleic acid via RNase H or to result in cleavage or sequestration through the RISC pathway. In certain such embodiments, antisense activity may result from occupancy, wherein the presence of the hybridized antisense compound disrupts the activity of the target nucleic acid. In certain such embodiments, the antisense compound may be uniformly modified or may comprise a mix of modifications and/or modified and unmodified nucleosides.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

Nucleotide sequences that encode growth hormone receptor (GHR) targetable with the compounds provided herein include, without limitation, the following: GENBANK Accession No. NM_000163.4 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No X06562.1 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. DR006395.1 (incorporated herein as SEQ ID NO: 4), GENBANK Accession No. DB052048.1 (incorporated herein as SEQ ID NO: 5), GENBANK Accession No. AF230800.1 (incorporated herein as SEQ ID NO: 6), the complement of GENBANK Accession No. AA398260.1 (incorporated herein as SEQ ID NO: 7), GENBANK Accession No. BC136496.1 (incorporated herein as SEQ ID NO: 8), GENBANK Accession No. NM_001242399.2 (incorporated herein as SEQ ID NO: 9), GENBANK Accession No. NM_001242400.2 (incorporated herein as SEQ ID NO: 10), GENBANK Accession No. NM_001242401.3 (incorporated herein as SEQ ID NO: 11), GENBANK Accession No. NM_001242402.2 (incorporated herein as SEQ ID NO: 12), GENBANK Accession No. NM_001242403.2 (incorporated herein as SEQ ID NO: 13), GENBANK Accession No.

NM_001242404.2 (incorporated herein as SEQ ID NO: 14), GENBANK Accession No. NM_001242405.2 (incorporated herein as SEQ ID NO: 15), GENBANK Accession No. NM_001242406.2 (incorporated herein as SEQ ID NO: 16), GENBANK Accession No. NM_001242460.1 (incorporated herein as SEQ ID NO: 17), GENBANK Accession NM_001242461.1 (incorporated herein as SEQ ID NO: 18), GENBANK Accession No. NM_001242462.1 (incorporated herein as SEQ ID NO: 19), or GENBANK Accession No NW_001120958.1 truncated from nucleotides 4410000 to 4720000 (incorporated herein as SEQ ID NO: 2332).

Hybridization

In some embodiments, hybridization occurs between an antisense compound disclosed herein and a GHR nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary nucleobases of the nucleic acid molecules.

Hybridization can occur under varying conditions. Stringent conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art. In certain embodiments, the antisense compounds provided herein are specifically hybridizable with a GHR nucleic acid.

Complementarity

An antisense compound and a target nucleic acid are complementary to each other when a sufficient number of nucleobases of the antisense compound can hydrogen bond with the corresponding nucleobases of the target nucleic acid, such that a desired effect will occur (e.g., antisense inhibition of a target nucleic acid, such as a GHR nucleic acid).

Non-complementary nucleobases between an antisense compound and a GHR nucleic acid may be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound may hybridize over one or more segments of a GHR nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

In certain embodiments, the antisense compounds provided herein, or a specified portion thereof, are, or are at least, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a GHR nucleic acid, a target region, target segment, or specified portion thereof. Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods.

For example, an antisense compound in which 18 of 20 nucleobases of the antisense compound are complementary to a target region, and would therefore specifically hybridize, would represent 90 percent complementarity. In this example, the remaining noncomplementary nucleobases may be clustered or interspersed with complementary nucleobases and need not be contiguous to each other or to complementary nucleobases. As such, an antisense compound which is 18 nucleobases in length having four noncomplementary nucleobases which are flanked by two regions of complete complementarity with the target nucleic acid would have 77.8% overall complementarity with the target nucleic acid and would thus fall within the scope of the present invention. Percent complementarity of an antisense compound with a region of a target nucleic acid can be determined routinely using BLAST programs (basic local alignment search tools) and PowerBLAST programs known in the art (Altschul *et al.*, *J. Mol. Biol.*, 1990, 215, 403 410; Zhang and Madden, Genome Res., 1997, 7, 649 656). Percent homology, sequence identity or complementarity, can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.), using default settings, which uses the algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2, 482 489).

In certain embodiments, the antisense compounds provided herein, or specified portions thereof, are fully complementary (i.e. 100% complementary) to a target nucleic acid, or specified portion thereof. For example, an antisense compound may be fully complementary to a GHR nucleic acid, or a target region, or a target segment or target sequence thereof. As used herein, "fully complementary" means each nucleobase of an antisense compound is capable of precise base pairing with the corresponding nucleobases of a target nucleic acid. For example, a 20 nucleobase antisense compound is fully complementary to a target sequence that is 400 nucleobases long, so long as there is a corresponding 20 nucleobase portion of the target nucleic acid that is fully complementary to the antisense compound. Fully complementary can also be used in reference to a specified portion of the first and /or the second nucleic acid. For example, a 20 nucleobase portion of a 30 nucleobase antisense compound can be "fully complementary" to a target sequence that is 400 nucleobases long. The 20 nucleobase portion of the 30 nucleobase oligonucleotide is fully complementary to the target sequence if the target sequence has a corresponding 20 nucleobase portion wherein each nucleobase is complementary to the 20 nucleobase portion of the antisense compound. At the same time, the entire 30 nucleobase antisense compound may or may not be fully complementary to the target sequence, depending on whether the remaining 10 nucleobases of the antisense compound are also complementary to the target sequence.

The location of a non-complementary nucleobase may be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they may be contiguous (i.e. linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer antisense oligonucleotide.

In certain embodiments, antisense compounds that are, or are up to 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a GHR nucleic acid, or specified portion thereof.

In certain embodiments, antisense compounds that are, or are up to 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2, or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a GHR nucleic acid, or specified portion thereof.

The antisense compounds provided also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an antisense compound. In certain embodiments, the antisense compounds, are complementary to at least an 8 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 9 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 10 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least an 11 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 12 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 13 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 14 nucleobase portion of a target segment. In certain embodiments, the antisense compounds are complementary to at least a 15 nucleobase portion of a target segment. Also contemplated are antisense compounds that are complementary to at least a 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more nucleobase portion of a target segment, or a range defined by any two of these values.

Identity

The antisense compounds provided herein may also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific Isis number, or portion thereof. As used herein, an antisense compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the antisense compounds described herein as well as compounds having non-identical bases relative to the antisense compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the antisense

compound. Percent identity of an antisense compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

In certain embodiments, the antisense compounds, or portions thereof, are at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to one or more of the antisense compounds or SEQ ID NOs, or a portion thereof, disclosed herein.

In certain embodiments, a portion of the antisense compound is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

In certain embodiments, a portion of the antisense oligonucleotide is compared to an equal length portion of the target nucleic acid. In certain embodiments, an 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobase portion is compared to an equal length portion of the target nucleic acid.

Modifications

A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

Modified Internucleoside Linkages

The naturally occuring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

In certain embodiments, antisense compounds targeted to a GHR nucleic acid comprise one or more modified internucleoside linkages. In certain embodiments, the modified internucleoside linkages are phosphorothioate linkages. In certain embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

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, internucleoside linkages are arranged in a gapped motif. In such embodiments, the internucleoside linkages in each of two wing regions are different from the internucleoside linkages in the gap region. In certain embodiments the internucleoside linkages in the wings are phosphodiester and the internucleoside linkages in the gap are phosphorothioate. The nucleoside motif is independently selected, so such oligonucleotides having a gapped internucleoside linkage motif may or may not have a gapped nucleoside motif and if it does have a gapped nucleoside motif, the wing and gap lengths may or may not be the same.

In certain embodiments, oligonucleotides comprise a region having an alternating internucleoside linkage motif. In certain embodiments, oligonucleotides of the present invention 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. 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 8 phosphorothioate internucleoside linkages. In certain embodiments, the oligonucleotide comprises at least 10 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 8 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, oligonucleotides comprise one or more methylphosponate linkages. In certain embodiments, oligonucleotides having a gapmer nucleoside motif comprise a linkage motif comprising all phosphorothioate linkages except for one or two methylphosponate linkages. In certain embodiments, one methylphosponate linkage is in the central gap of an oligonucleotide having a gapmer nucleoside motif.

In certain embodiments, it is desirable to arrange the number of phosphorothioate internucleoside linkages and phosphodiester internucleoside linkages to maintain nuclease resistance. In certain embodiments, it is desirable to arrange the number and position of phosphorothioate internucleoside linkages and the number and position of phosphodiester internucleoside linkages to maintain nuclease resistance. In certain embodiments, the number of phosphorothioate internucleoside linkages may be decreased and the number of phosphodiester internucleoside linkages may be increased. In certain embodiments, the number of phosphorothioate internucleoside linkages may be decreased and the number of phosphodiester internucleoside linkages may be increased while still maintaining nuclease resistance. In certain embodiments it is desirable to decrease the number of phosphorothioate internucleoside linkages while retaining nuclease resistance. In certain embodiments it is desirable to increase the number of phosphodiester internucleoside linkages while retaining nuclease resistance.

Modified Sugar Moieties

Antisense compounds can optionally contain one or more nucleosides wherein the sugar group has been modified. Such sugar modified nucleosides may impart enhanced nuclease stability, increased binding affinity, or some other beneficial biological property to the antisense compounds. In certain embodiments, nucleosides comprise chemically modified ribofuranose ring moieties. Examples of chemically modified ribofuranose rings include without limitation, addition of substitutent groups (including 5' and 2' substituent groups, bridging of non-geminal ring atoms to form bicyclic nucleic acids (BNA), replacement of the ribosyl ring oxygen atom with S, N(R), or $C(R_1)(R_2)$ (R, R_1 and R_2 are each independently H, C_1-C_{12} alkyl or a protecting group) and combinations thereof. Examples of chemically modified sugars include 2'-F-5'-methyl substituted nucleoside (see PCT International Application WO 2008/101157 Published on 8/21/08 for other disclosed 5',2'-bis substituted nucleosides) or replacement of the ribosyl ring oxygen atom with S with 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 BNA (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).

Examples of nucleosides having modified sugar moieties include without limitation nucleosides comprising 5'-vinyl, 5'-methyl (*R* or *S*), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F and 2'-

$O(CH_2)_2OCH_3$ substituent groups. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, OCF_3, OCH_2F, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-$N(R_m)(R_n)$, O-CH_2-C(=O)-$N(R_m)(R_n)$, and O-CH_2-C(=O)-$N(R_l)$-$(CH_2)_2$-$N(R_m)(R_n)$, where each R_l, R_m and R_n is, independently, H or substituted or unsubstituted C_1-C_{10} alkyl.

As used herein, "bicyclic nucleosides" refer to modified nucleosides comprising a bicyclic sugar moiety. Examples of bicyclic nucleosides include without limitation nucleosides comprising a bridge between the 4' and the 2' ribosyl ring atoms. In certain embodiments, antisense compounds provided herein include one or more bicyclic nucleosides comprising a 4' to 2' bridge. Examples of such 4' to 2' bridged bicyclic nucleosides, include but are not limited to one of the formulae: 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)-S-2'; 4'-$(CH_2)_2$-O-2' (ENA); 4'-$CH(CH_3)$-O-2' (also referred to as constrained ethyl or cEt) and 4'-$CH(CH_2OCH_3)$-O-2' (and analogs thereof see U.S. Patent 7,399,845, issued on July 15, 2008); 4'-$C(CH_3)(CH_3)$-O-2' (and analogs thereof see published International Application WO/2009/006478, published January 8, 2009); 4'-CH_2-$N(OCH_3)$-2' (and analogs thereof see published International Application WO/2008/150729, published December 11, 2008); 4'-CH_2-O-$N(CH_3)$-2' (see published U.S. Patent Application US2004-0171570, published September 2, 2004); 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 Zhou *et al., J. Org. Chem.,* 2009, *74*, 118-134); and 4'-CH_2-C(=CH_2)-2' (and analogs thereof see published International Application WO 2008/154401, published on December 8, 2008).

Further reports related to bicyclic nucleosides can also be found in published literature (see 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.*, 2007, *129(26)* 8362-8379; Elayadi *et al., Curr. Opinion Invest. Drugs,* 2001, *2*, 558-561; Braasch *et al., Chem. Biol.,* 2001, *8*, 1-7; and Orum *et al., Curr. Opinion Mol. Ther.,* 2001, *3*, 239-243; U.S. Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; and 7,696,345; U.S. Patent Publication No. US2008-0039618; US2009-0012281; U.S. Patent Serial Nos. 61/026,995 and 61/097,787; Published PCT International applications WO 1999/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; WO 2009/006478; WO 2010/036698; WO 2011/017521; WO 2009/067647; WO 20009/100320. Each of the foregoing bicyclic nucleosides can be prepared having one or more stereochemical sugar configurations including for example α-L-ribofuranose and β-D-ribofuranose (see PCT international application PCT/DK98/00393, published on March 25, 1999 as WO 99/14226).

In certain embodiments, bicyclic sugar moieties of BNA nucleosides include, but are not limited to, compounds having at least one bridge between the 4' and the 2' position of the pentofuranosyl sugar moiety

wherein such bridges independently comprises 1 or from 2 to 4 linked groups independently selected from -$[C(R_a)(R_b)]_n$-, -$C(R_a)$=$C(R_b)$-, -$C(R_a)$=N-, -C(=O)-, -C(=NR_a)-, -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;

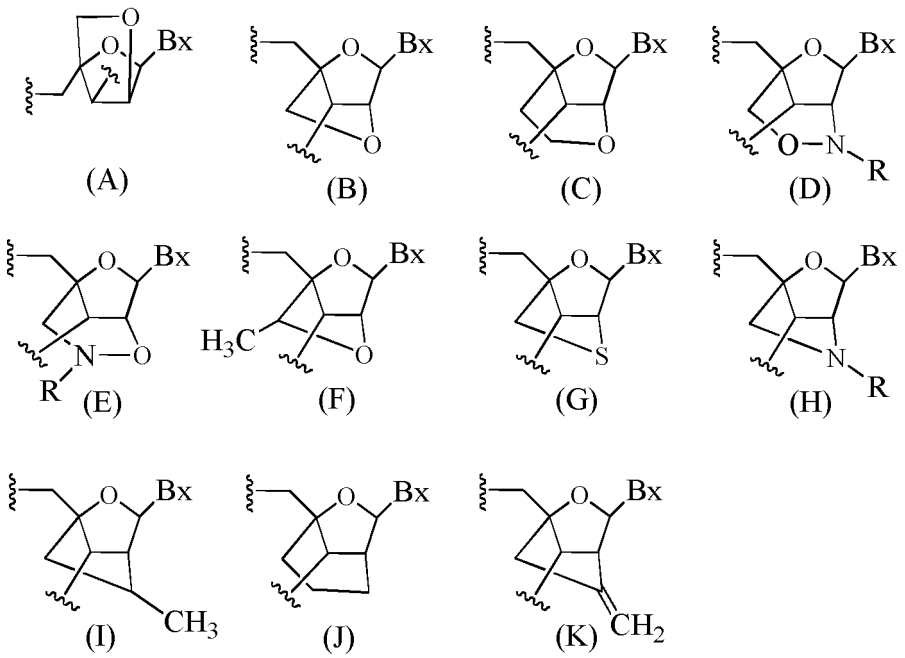
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle 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.

In certain embodiments, the bridge of a bicyclic sugar moiety is -$[C(R_a)(R_b)]_n$-, -$[C(R_a)(R_b)]_n$-O-, -$C(R_aR_b)$-N(R)-O- or –$C(R_aR_b)$-O-N(R)-. In certain embodiments, the bridge is 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 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.

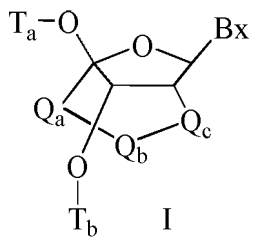
In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2-O-2') BNA's have been incorporated into antisense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

In certain embodiments, 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 , (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, and (F) methyl(methyleneoxy) (4'-$CH(CH_3)$-O-2') BNA, (G) methylene-thio (4'-CH_2-S-2') BNA, (H) methylene-amino (4'-CH_2-N(R)-2') BNA, (I) methyl carbocyclic (4'-CH_2-$CH(CH_3)$-2') BNA, (J) propylene carbocyclic (4'-$(CH_2)_3$-2') BNA and (K) vinyl BNA as depicted below:



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

In certain embodiments, bicyclic nucleosides are provided having Formula I:



I

wherein:

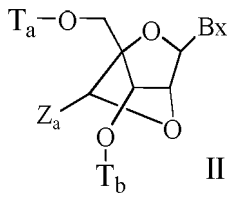
Bx is a heterocyclic base moiety;

$-Q_a-Q_b-Q_c-$ is $-CH_2-N(R_c)-CH_2-$, $-C(=O)-N(R_c)-CH_2-$, $-CH_2-O-N(R_c)-$, $-CH_2-N(R_c)-O-$ or $-N(R_c)-O-CH_2$;

R_c is C_1-C_{12} alkyl or an amino protecting group; and

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium.

In certain embodiments, bicyclic nucleosides are provided having Formula II:



II

wherein:

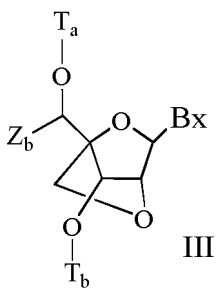
Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

Z_a 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.

In one embodiment, each of the substituted groups is, independently, mono or poly substituted with substituent groups independently selected from halogen, oxo, hydroxyl, OJ_c, NJ_cJ_d, SJ_c, N_3, $OC(=X)J_c$, and $NJ_eC(=X)NJ_cJ_d$, wherein each J_c, J_d and J_e is, independently, H, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl and X is O or NJ_c.

In certain embodiments, bicyclic nucleosides are provided having Formula III:



III

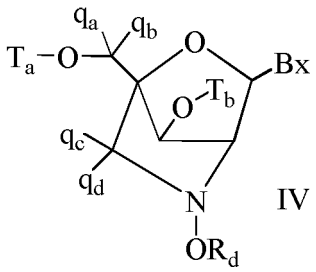
wherein:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

Z_b 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 or substituted acyl (C(=O)-).

In certain embodiments, bicyclic nucleosides are provided having Formula IV:



IV

wherein:

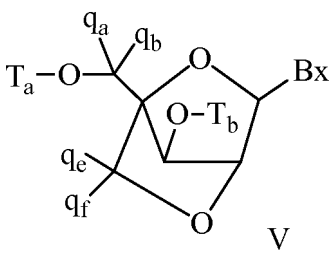
Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

R_d is 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;

each q_a, q_b, q_c and q_d is, independently, H, halogen, 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, C_1-C_6 alkoxyl, substituted C_1-C_6 alkoxyl, acyl, substituted acyl, C_1-C_6 aminoalkyl or substituted C_1-C_6 aminoalkyl;

In certain embodiments, bicyclic nucleosides are provided having Formula V:



V

wherein:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

q_a, q_b, q_e and q_f are each, independently, hydrogen, halogen, 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_1-C_{12} alkoxy, substituted C_1-C_{12} alkoxy, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O\text{-}C(=O)NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)NJ_jJ_k$ or $N(H)C(=S)NJ_jJ_k$;

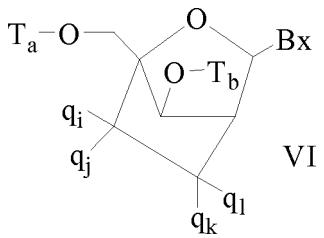
or q_e and q_f together are $=C(q_g)(q_h)$;

q_g and q_h are each, independently, H, halogen, C_1-C_{12} alkyl or substituted C_1-C_{12} alkyl.

The synthesis and preparation of the methyleneoxy (4'-CH_2-O-2') BNA monomers adenine, cytosine, guanine, 5-methyl-cytosine, thymine and uracil, along with their oligomerization, and nucleic acid recognition properties have been described (Koshkin *et al.*, *Tetrahedron*, 1998, *54*, 3607-3630). BNAs and preparation thereof are also described in WO 98/39352 and WO 99/14226.

Analogs of methyleneoxy (4'-CH_2-O-2') BNA and 2'-thio-BNAs, have also been prepared (Kumar *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222). Preparation of locked nucleoside analogs comprising oligodeoxyribonucleotide duplexes as substrates for nucleic acid polymerases has also been described (Wengel *et al.*, WO 99/14226). Furthermore, synthesis of 2'-amino-BNA, a novel comformationally restricted high-affinity oligonucleotide analog has been described in the art (Singh *et al.*, *J. Org. Chem.*, 1998, *63*, 10035-10039). In addition, 2'-amino- and 2'-methylamino-BNA's have been prepared and the thermal stability of their duplexes with complementary RNA and DNA strands has been previously reported.

In certain embodiments, bicyclic nucleosides are provided having Formula VI:



VI

wherein:

Bx is a heterocyclic base moiety;

T_a and T_b are each, independently H, a hydroxyl protecting group, a conjugate group, a reactive phosphorus group, a phosphorus moiety or a covalent attachment to a support medium;

each q_i, q_j, q_k and q_l is, independently, H, halogen, 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_1-C_{12} alkoxyl, substituted C_1-C_{12} alkoxyl, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O\text{-}C(=O)NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)NJ_jJ_k$ or $N(H)C(=S)NJ_jJ_k$; and

q_i and q_j or q_l and q_k together are $=C(q_g)(q_h)$, wherein q_g and q_h are each, independently, H, halogen, C_1-C_{12} alkyl or substituted C_1-C_{12} alkyl.

One carbocyclic bicyclic nucleoside having a 4'-$(CH_2)_3$-2' bridge and the alkenyl analog bridge 4'-CH=CH-CH_2-2' have been described (Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443 and Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740). The synthesis and preparation of carbocyclic bicyclic nucleosides along with their oligomerization and biochemical studies have also been described (Srivastava *et al., J. Am. Chem. Soc.*, 2007, *129(26)*, 8362-8379).

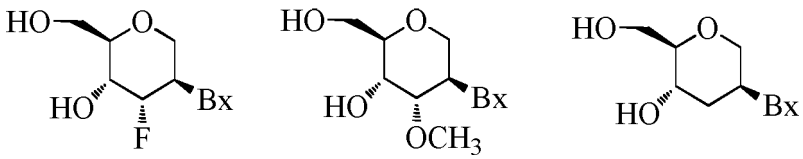
As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2' carbon atom and the 4' carbon atom of the sugar ring.

As used herein, "monocylic nucleosides" refer to nucleosides comprising modified sugar moieties that are not bicyclic sugar moieties. In certain embodiments, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position.

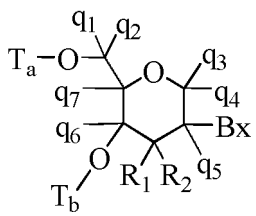
As used herein, "2'-modified sugar" means a furanosyl sugar modified at the 2' position. In certain embodiments, such modifications include substituents selected from: a halide, including, but not limited to substituted and unsubstituted alkoxy, substituted and unsubstituted thioalkyl, substituted and unsubstituted amino alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted allyl, and substituted and unsubstituted alkynyl. In certain embodiments, 2' modifications are selected from substituents including, but not limited to: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nF$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other 2'-substituent groups can also be selected from: C_1-C_{12} alkyl, substituted alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, F, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving pharmacokinetic properties, or a group for improving the pharmacodynamic properties of an antisense compound, and other substituents having similar

properties. In certain embodiments, modifed nucleosides comprise a 2'-MOE side chain (Baker *et al.*, *J. Biol. Chem.*, 1997, *272*, 11944-12000). Such 2'-MOE substitution have been described as having improved binding affinity compared to unmodified nucleosides and to other modified nucleosides, such as 2'- *O*-methyl, *O*-propyl, and *O*-aminopropyl. Oligonucleotides having the 2'-MOE substituent also have been shown to be antisense inhibitors of gene expression with promising features for *in vivo* use (Martin, *Helv. Chim. Acta*, 1995, *78*, 486-504; Altmann *et al.*, *Chimia*, 1996, *50*, 168-176; Altmann *et al.*, *Biochem. Soc. Trans.*, 1996, *24*, 630-637; and Altmann *et al.*, *Nucleosides Nucleotides*, 1997, *16*, 917-926).

As used herein, a "modified tetrahydropyran nucleoside" or "modified THP nucleoside" means a nucleoside having a six-membered tetrahydropyran "sugar" substituted in for the pentofuranosyl residue in normal nucleosides (a sugar surrogate). Modified THP nucleosides include, but are not limited to, what is referred to in the art as hexitol nucleic acid (HNA), anitol nucleic acid (ANA), manitol nucleic acid (MNA) (see Leumann, *Bioorg. Med. Chem.*, 2002, *10*, 841-854) or fluoro HNA (F-HNA) having a tetrahydropyran ring system as illustrated below:



In certain embodiments, sugar surrogates are selected having Formula VII:



VII

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

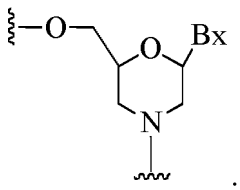
Bx is a heterocyclic base moiety;

T_a and T_b are each, independently, an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound or one of T_a and T_b is an internucleoside linking group linking the tetrahydropyran nucleoside analog to the antisense compound and the other of T_a and T_b 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 selected from hydrogen, hydroxyl, halogen, subsitituted 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 VII 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 VII are provided wherein one of R_1 and R_2 is fluoro. 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.

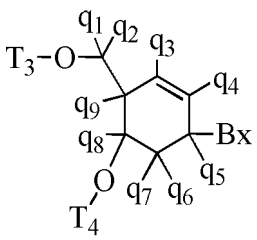
In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example nucleosides comprising morpholino sugar moieties and their use in oligomeric compounds has been reported (see for example: Braasch *et al.*, *Biochemistry*, 2002, *41*, 4503-4510; 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 formula:



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 referred to herein as "modifed morpholinos."

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, antisense compounds comprise one or more modified cyclohexenyl nucleosides, which is a nucleoside having a six-membered cyclohexenyl in place of the pentofuranosyl residue in naturally occurring nucleosides. Modified cyclohexenyl nucleosides include, but are not limited to those described in the art (see for example commonly owned, published PCT Application WO 2010/036696, published on April 10, 2010, Robeyns *et al., J. Am. Chem. Soc.,* 2008, *130(6)*, 1979-1984; Horváth *et al., Tetrahedron Letters,* 2007, *48*, 3621-3623; Nauwelaerts *et al., J. Am. Chem. Soc.*, 2007, *129(30)*, 9340-9348; Gu *et al.,, Nucleosides, Nucleotides & Nucleic Acids*, 2005, *24(5-7)*, 993-998; Nauwelaerts *et al., Nucleic Acids Research,* 2005, *33(8)*, 2452-2463; Robeyns et al., *Acta Crystallographica, Section F: Structural Biology and Crystallization Communications,* 2005, *F61(6)*, 585-586; Gu *et al., Tetrahedron*, 2004, *60(9)*, 2111-2123; Gu *et al., Oligonucleotides*, 2003, *13(6)*, 479-489; Wang *et al., J. Org. Chem.,* 2003, *68*, 4499-4505; Verbeure *et al., Nucleic Acids Research*, 2001, *29(24)*, 4941-4947; Wang *et al., J. Org. Chem.,* 2001, *66*, 8478-82; Wang *et al., Nucleosides, Nucleotides & Nucleic Acids*, 2001, *20(4-7)*, 785-788; Wang *et al., J. Am. Chem.,* 2000, *122*, 8595-8602; Published PCT application, WO 06/047842; and Published PCT Application WO 01/049687; the text of each is incorporated by reference herein, in their entirety). Certain modified cyclohexenyl nucleosides have Formula X.



X

wherein independently for each of said at least one cyclohexenyl nucleoside analog of Formula X:

Bx is a heterocyclic base moiety;

T_3 and T_4 are each, independently, an internucleoside linking group linking the cyclohexenyl nucleoside analog to an antisense compound or one of T_3 and T_4 is an internucleoside linking group linking the tetrahydropyran nucleoside analog to an 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; and

q_1, q_2, q_3, q_4, q_5, q_6, q_7, q_8 and q_9 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, substituted C_2-C_6 alkynyl or other sugar substituent group.

As used herein, "2'-modified" or "2'-substituted" refers to a nucleoside comprising a sugar comprising a substituent at the 2' position other than H or OH. 2'-modified nucleosides, include, but are not

limited to, bicyclic nucleosides wherein the bridge connecting two carbon atoms of the sugar ring connects the 2' carbon and another carbon of the sugar ring; and nucleosides with non-bridging 2'substituents, such as allyl, amino, azido, thio, O-allyl, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-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 or substituted or unsubstituted C_1-C_{10} alkyl. 2'-modifed nucleosides may further comprise other modifications, for example at other positions of the sugar and/or at the nucleobase.

As used herein, "2'-F" refers to a nucleoside comprising a sugar comprising a fluoro group at the 2' position of the sugar ring.

As used herein, "2'-OMe" or "2'-OCH_3" or "2'-O-methyl" each refers to a nucleoside comprising a sugar comprising an -OCH_3 group at the 2' position of the sugar ring.

As used herein, "MOE" or "2'-MOE" or "2'-$OCH_2CH_2OCH_3$" or "2'-O-methoxyethyl" each refers to a nucleoside comprising a sugar comprising a -$OCH_2CH_2OCH_3$ group at the 2' position of the sugar ring.

As used herein, "oligonucleotide" refers to a compound comprising a plurality of linked nucleosides. In certain embodiments, one or more of the plurality of nucleosides is modified. In certain embodiments, an oligonucleotide comprises one or more ribonucleosides (RNA) and/or deoxyribonucleosides (DNA).

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 for example review article: Leumann, *Bioorg. Med. Chem.*, 2002, *10*, 841-854). Such ring systems can undergo various additional substitutions to enhance activity.

Methods for the preparations of modified sugars are well known to those skilled in the art. Some representative U.S. patents that teach the preparation of such modified sugars include without limitation, U.S.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,670,633; 5,700,920; 5,792,847 and 6,600,032 and International Application PCT/US2005/019219, filed June 2, 2005 and published as WO 2005/121371 on December 22, 2005, and each of which is herein incorporated by reference in its entirety.

In nucleotides having modified sugar moieties, the nucleobase moieties (natural, modified or a combination thereof) are maintained for hybridization with an appropriate nucleic acid target.

In certain embodiments, antisense compounds comprise one or more nucleosides having modified sugar moieties. In certain embodiments, the modified sugar moiety is 2'-MOE. In certain embodiments, the 2'-MOE modified nucleosides are arranged in a gapmer motif. In certain embodiments, the modified sugar

moiety is a bicyclic nucleoside having a (4'-$CH(CH_3)$-O-2') bridging group. In certain embodiments, the (4'-$CH(CH_3)$-O-2') modified nucleosides are arranged throughout the wings of a gapmer motif.

Modified Nucleobases

Nucleobase (or base) modifications or substitutions are structurally distinguishable from, yet functionally interchangeable with, naturally occurring or synthetic unmodified nucleobases. Both natural and modified nucleobases are capable of participating in hydrogen bonding. Such nucleobase modifications can impart nuclease stability, binding affinity or some other beneficial biological property to antisense compounds. Modified nucleobases include synthetic and natural nucleobases such as, for example, 5-methylcytosine (5-me-C). Certain nucleobase substitutions, including 5-methylcytosine substitutions, are particularly useful for increasing the binding affinity of an antisense compound for a target nucleic acid. For example, 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y.S., Crooke, S.T. and Lebleu, B., eds., Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278).

Additional modified nucleobases include 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-CH3) 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 and 3-deazaguanine and 3-deazaadenine.

Heterocyclic base moieties can 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. Nucleobases that are particularly useful for increasing the binding affinity of antisense compounds include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2 aminopropyladenine, 5-propynyluracil and 5-propynylcytosine.

In certain embodiments, antisense compounds targeted to a GHR nucleic acid comprise one or more modified nucleobases. In certain embodiments, shortened or gap-widened antisense oligonucleotides targeted to a GHR nucleic acid comprise one or more modified nucleobases. In certain embodiments, the modified nucleobase is 5-methylcytosine. In certain embodiments, each cytosine is a 5-methylcytosine.

Conjugated Antisense compounds

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.

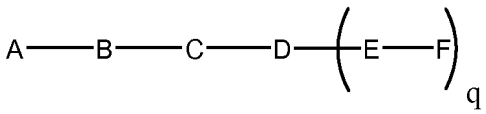
In certain embodiments, conjugation allows one to alter antisense compounds in ways that have less attractive consequences in the absence of conjugation. For example, in certain embodiments, replacing one or more phosphorothioate linkages of a fully phosphorothioate antisense compound with phosphodiester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

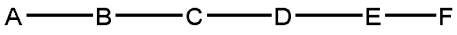
D is the branching group

each E is a tether;

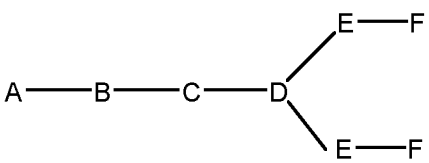
each F is a ligand; and

q is an integer between 1 and 5.

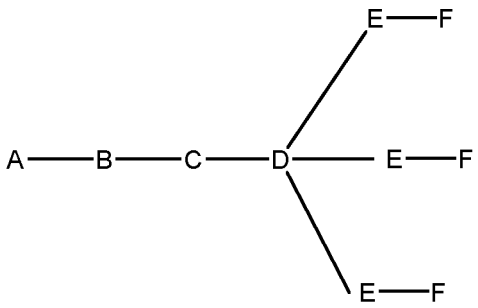
In the above diagram and in similar diagrams herein, the branching group "D" branches as many times as is necessary to accommodate the number of (E-F) groups as indicated by "q". Thus, where q = 1, the formula is:



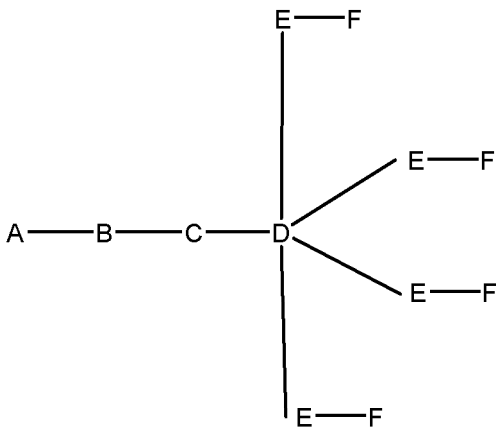
where q = 2, the formula is:



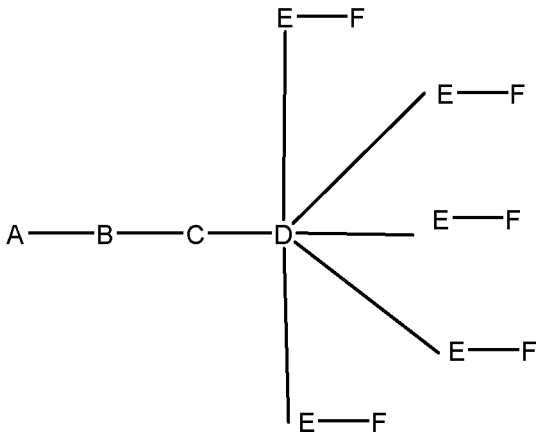
where q = 3, the formula is:



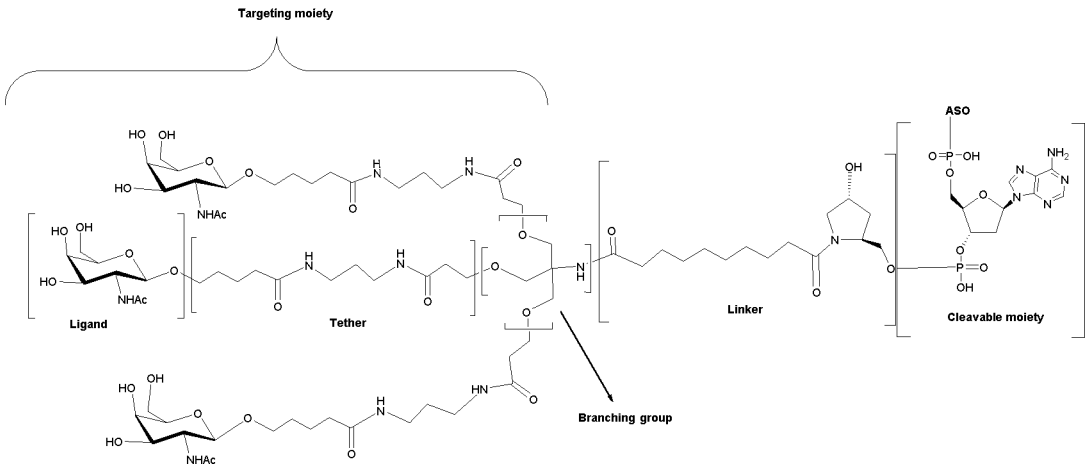
where q = 4, the formula is:



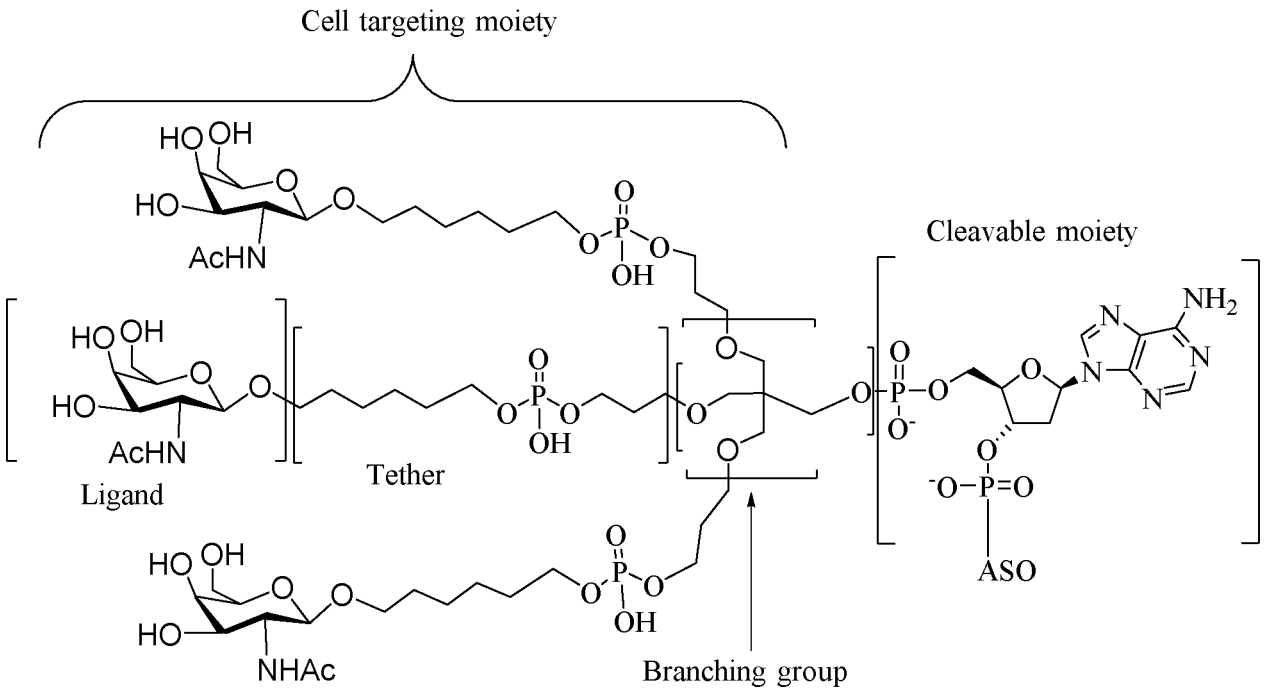
where q = 5, the formula is:



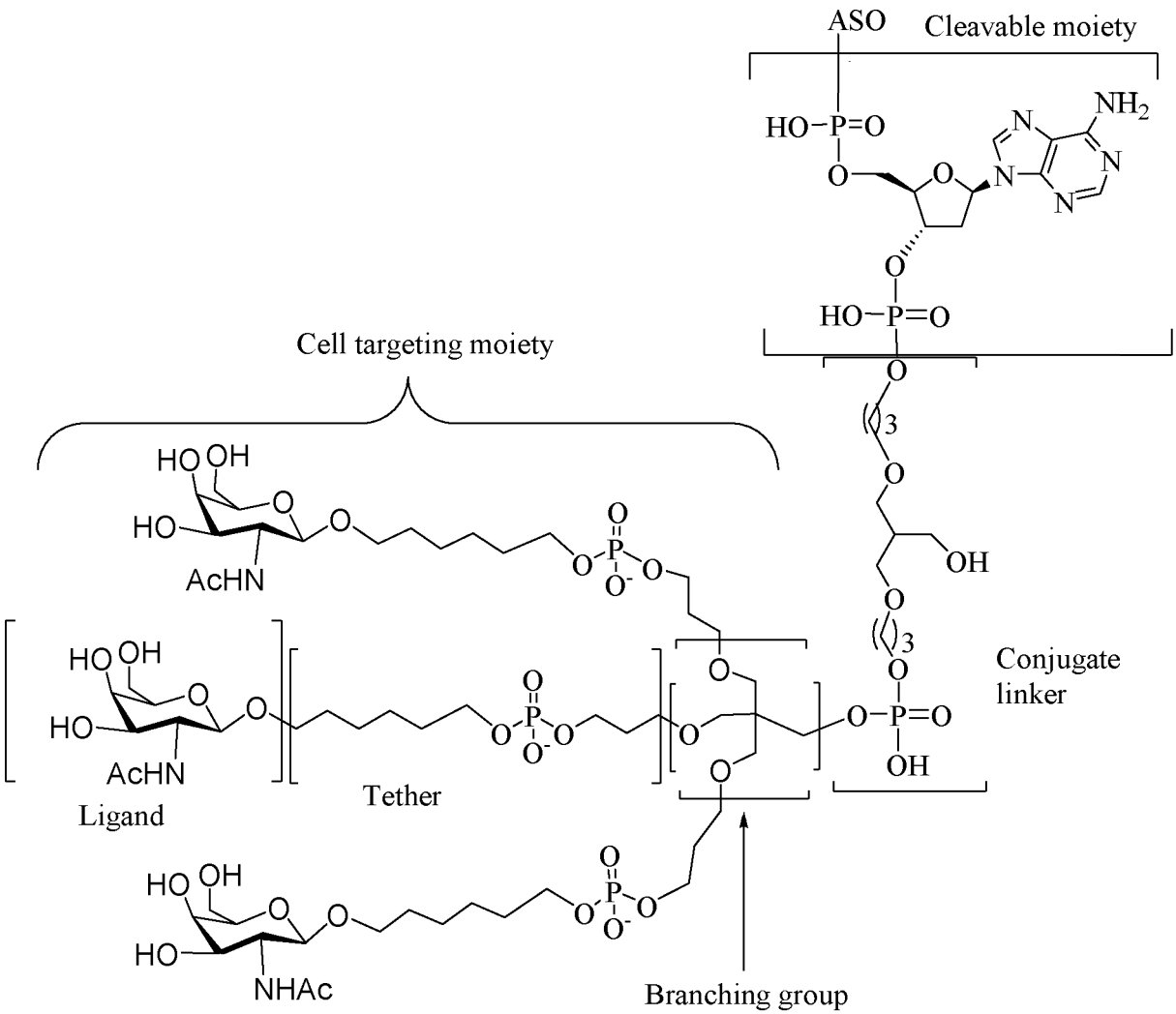
In certain embodiments, conjugated antisense compounds are provided having the structure:



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

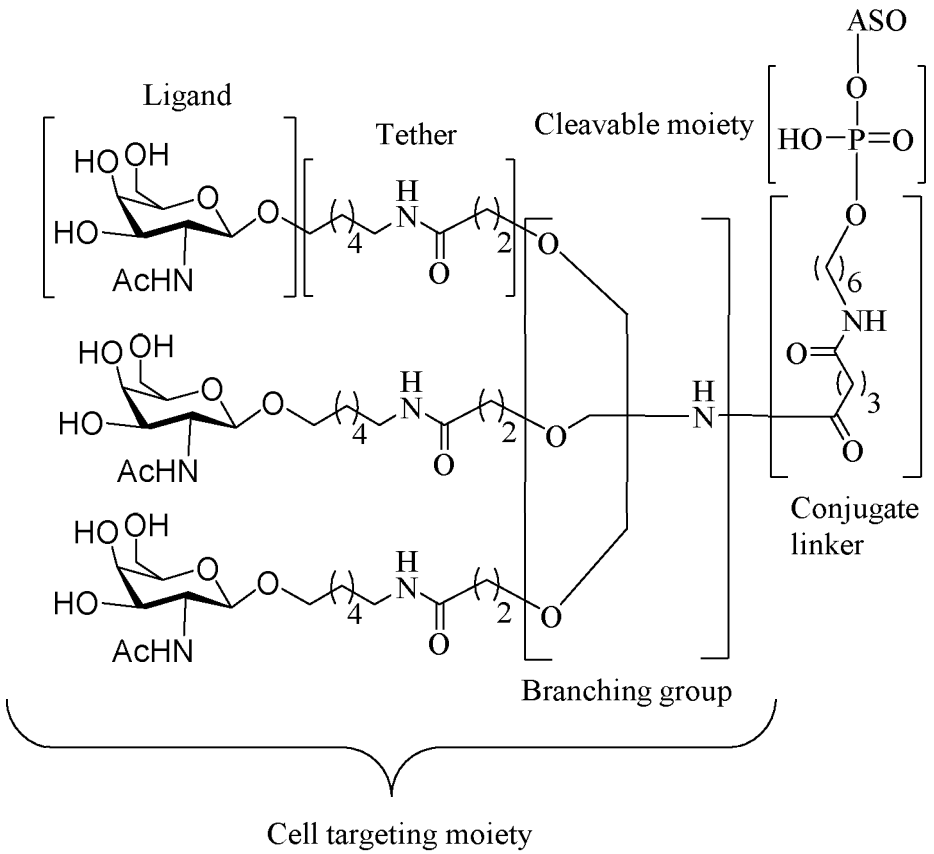


In certain embodiments, conjugated antisense compounds are provided having the structure:



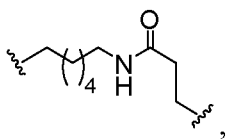
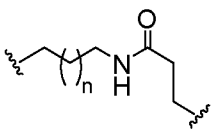
.

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

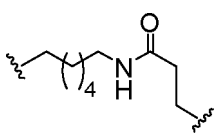


The present disclosure provides the following non-limiting numbered embodiments:

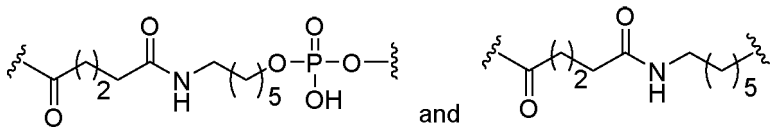
Embodiment 1. The conjugated antisense compound of any of embodiments 1179 to 1182, wherein the tether has a structure selected from among:

 , or  ; wherein each n is independently, 0, 1, 2, 3, 4, 5, 6, or 7.

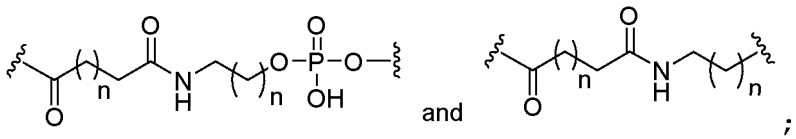
Embodiment 2. The conjugated antisense compound of any of embodiments 1179 to 1182, wherein the tether has the structure:

 .

Embodiment 3. The conjugated antisense compound of any of embodiments 1179 to 1182 or 1688 to 1689, wherein the linker has a structure selected from among:

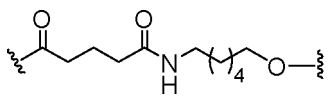


Embodiment 4. The conjugated antisense compound of any of embodiments 1179 to 1182 or 1688 to 1689, wherein the linker has a structure selected from among:



wherein each n is independently, 0, 1, 2, 3, 4, 5, 6, or 7.

Embodiment 5. The conjugated antisense compound of any of embodiments 1179 to 1182 or 1688 to 1689, wherein the linker has the structure:



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.

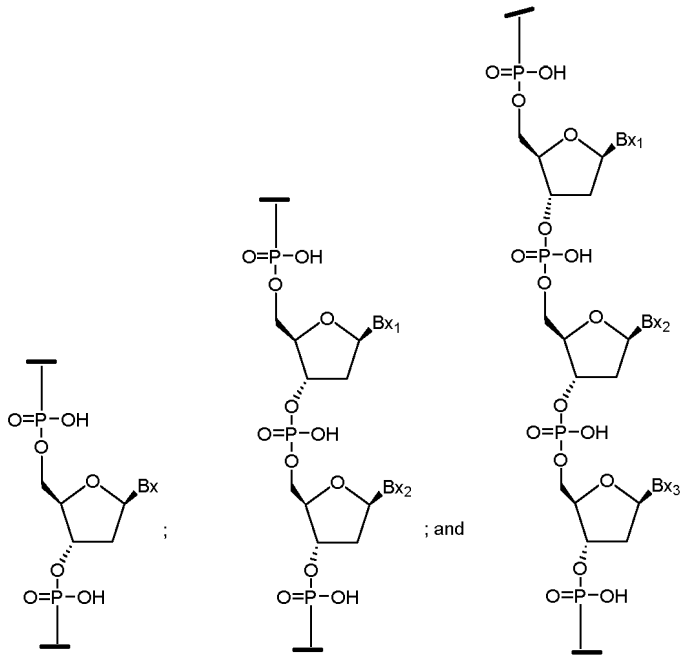
i. Certain Cleavable Moieties

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

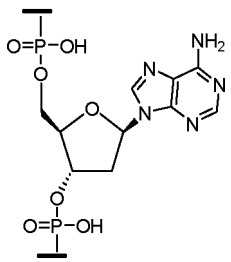
comprising an optionally protected heterocyclic base selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methylcytosine, 4-N-benzoyl-5-methylcytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. In certain embodiments, the cleavable moiety is 2'-deoxy nucleoside that is 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:



ii. **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.

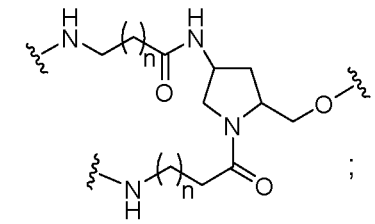
In certain embodiments, the linker includes at least a linear group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether (-S-) and hydroxylamino (-O-N(H)-) groups. In certain embodiments, the linear group comprises groups selected from alkyl, amide and ether 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.

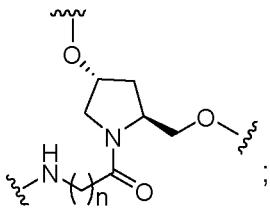
In certain embodiments, the linker includes the linear group covalently attached to a scaffold group. In certain embodiments, the scaffold includes a branched aliphatic group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain 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.

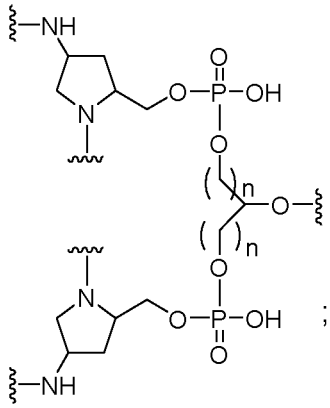
In certain embodiments, the linker includes a protein binding moiety. In certain embodiments, the protein binding moiety is a lipid such as for example including but not limited to cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, 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.,

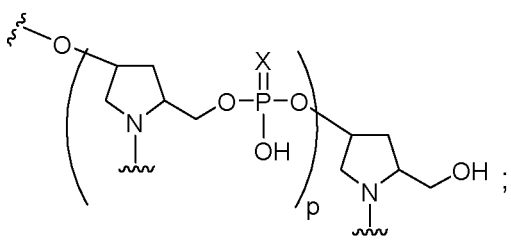
monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide, polysaccharide), an endosomolytic component, a steroid (e.g., uvaol, hecigenin, diosgenin), a terpene (e.g., triterpene, e.g., sarsasapogenin, friedelin, epifriedelanol derivatized lithocholic acid), or a cationic lipid. In 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.

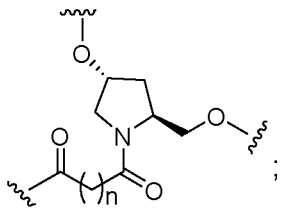
In certain embodiments, a linker has a structure selected from among:

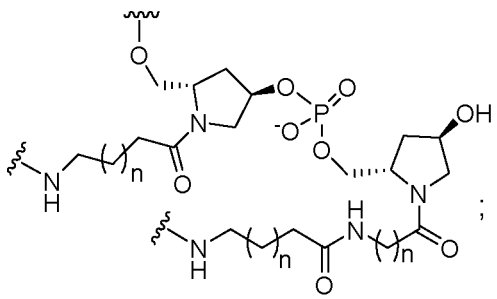

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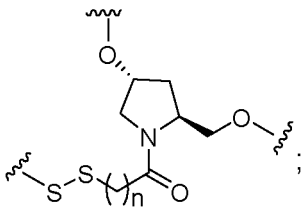

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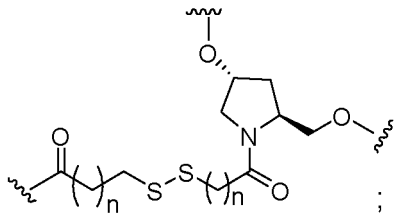

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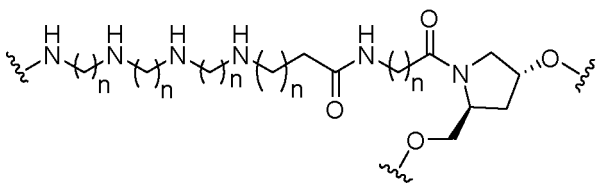

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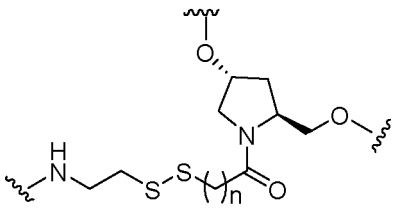

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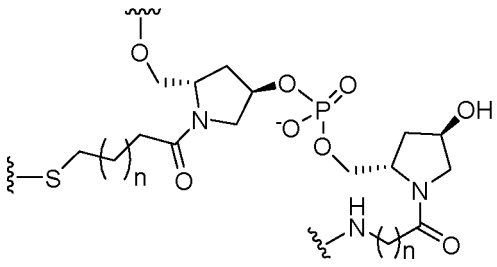

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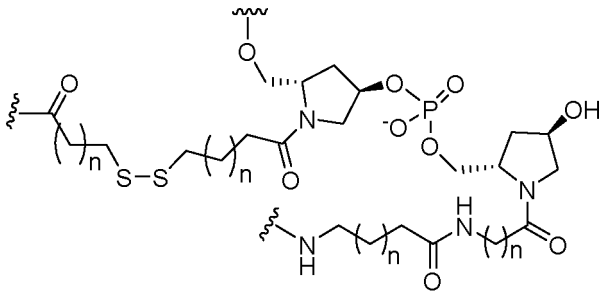

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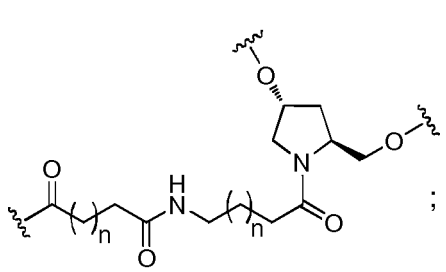

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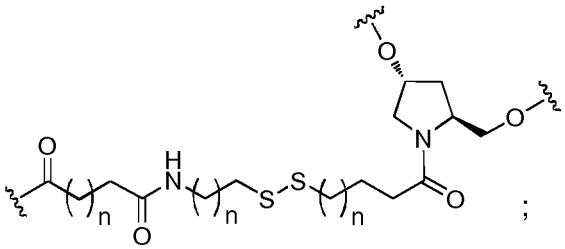

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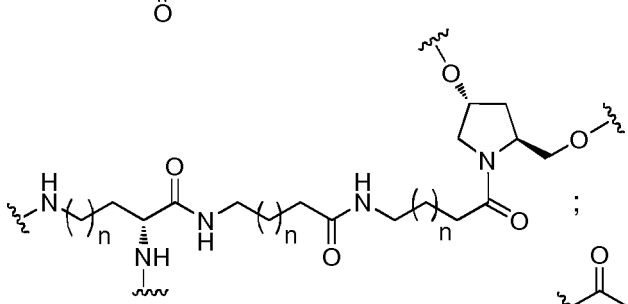


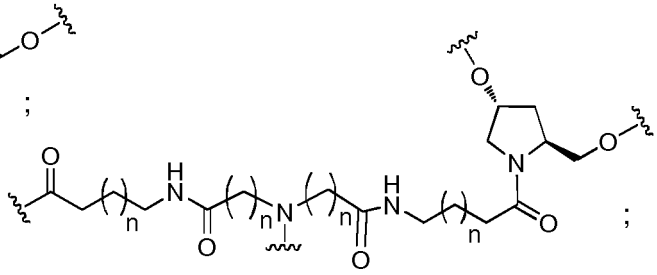
wherein each n is, independently, from 1 to 20; and p is from 1 to 6.

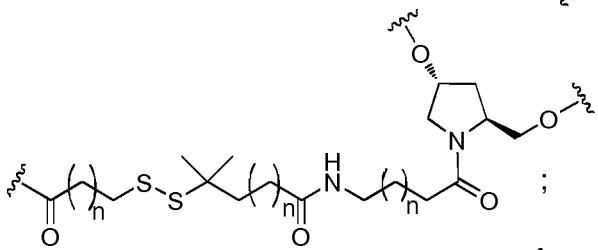
In certain embodiments, a linker has a structure selected from among:

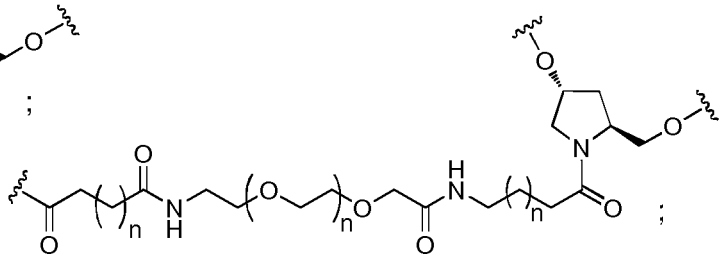

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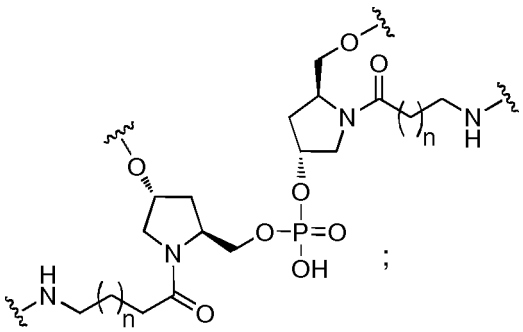

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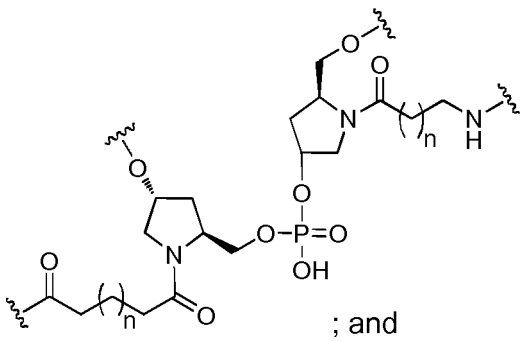

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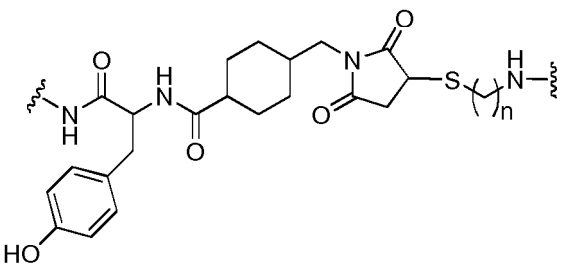

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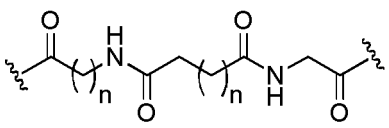
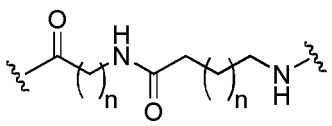
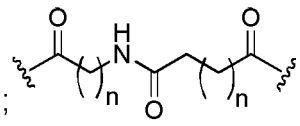
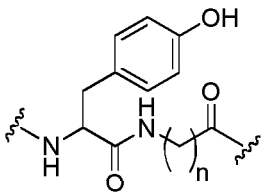
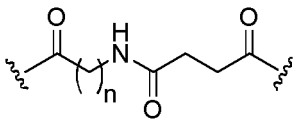
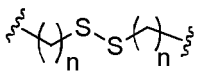
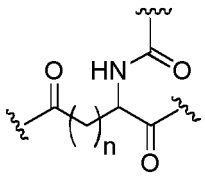
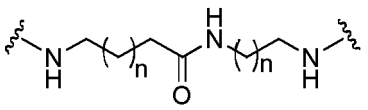
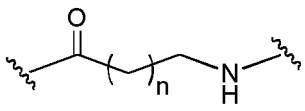
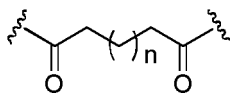
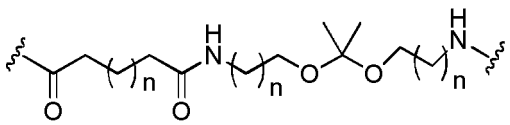
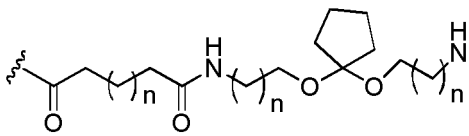
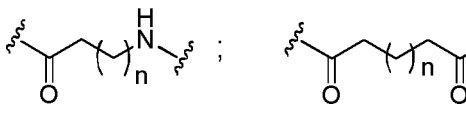

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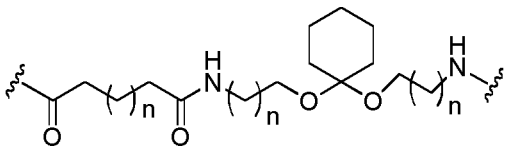
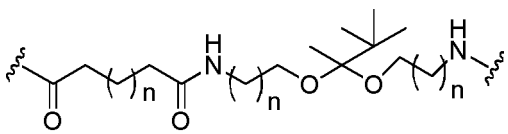

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wherein each n is, independently, from 1 to 20.

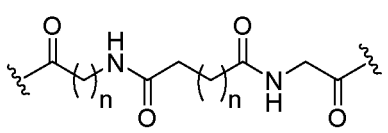
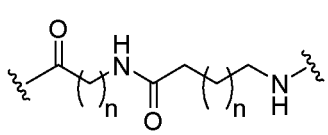
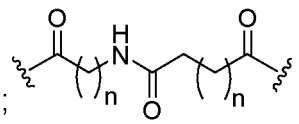
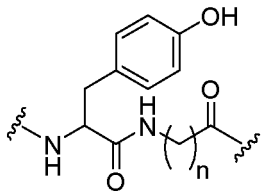
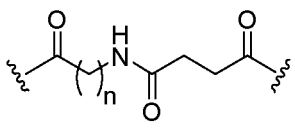
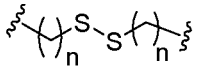
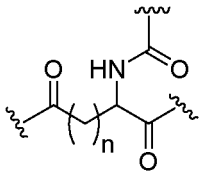
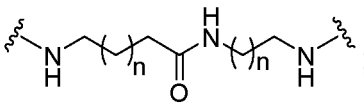
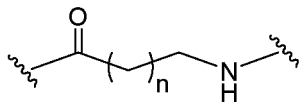
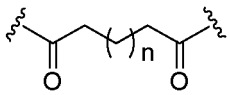
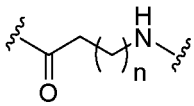
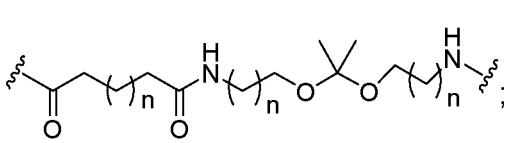
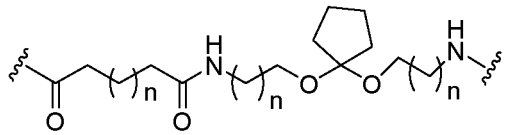
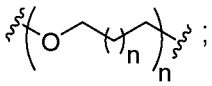
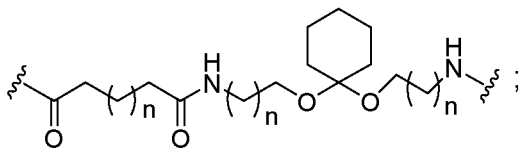
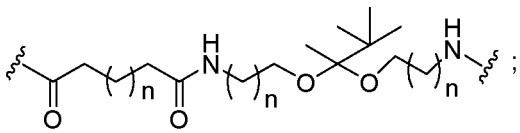
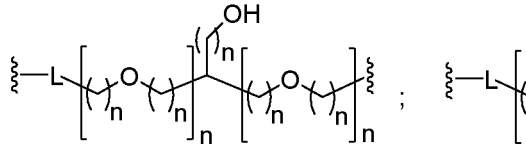
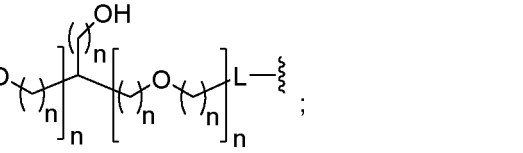
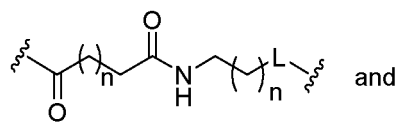
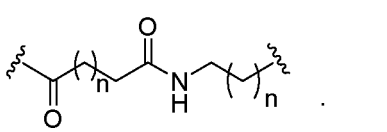
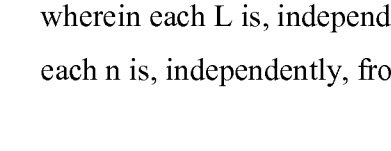
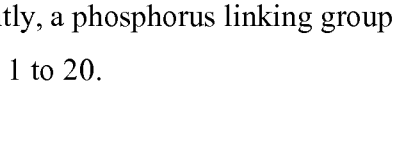
In certain embodiments, a linker has a structure selected from among:


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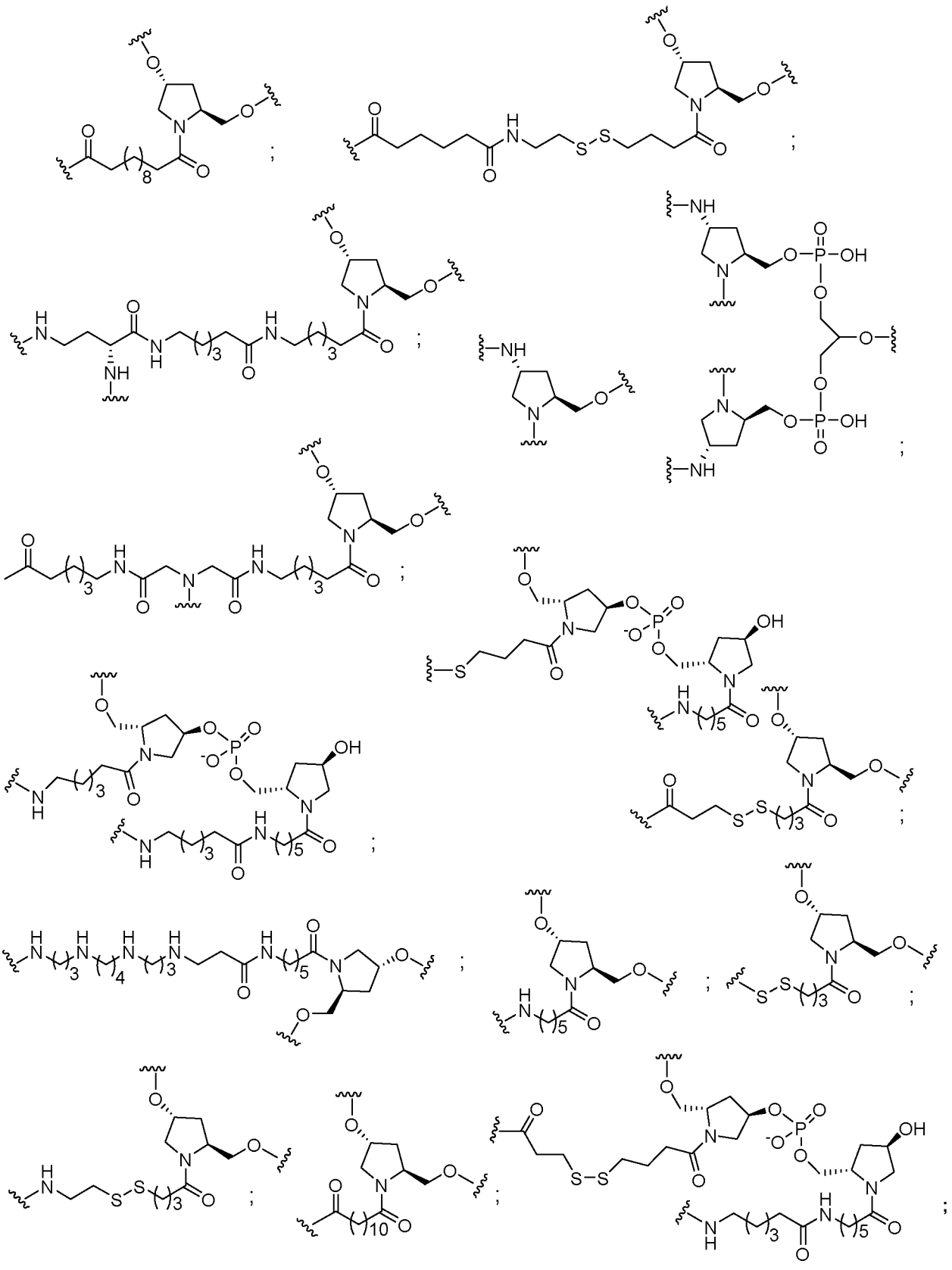
wherein n is from 1 to 20.

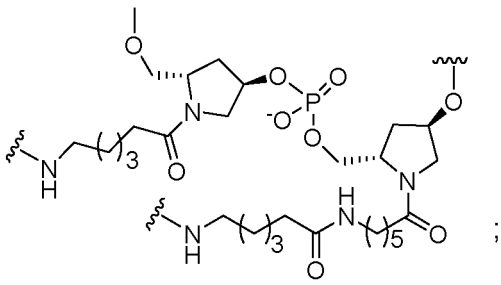
In certain embodiments, a linker has a structure selected from among:

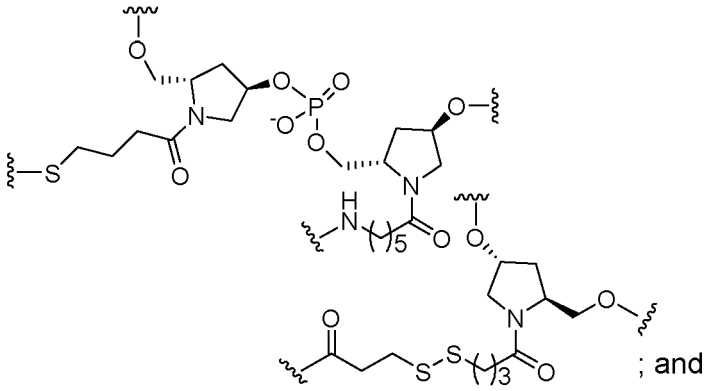

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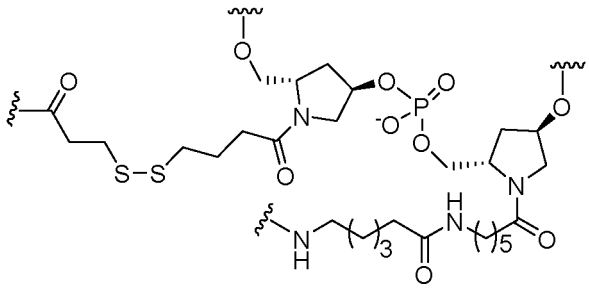
wherein each L is, independently, a phosphorus linking group or a neutral linking group; and each n is, independently, from 1 to 20.

In certain embodiments, a linker has a structure selected from among:

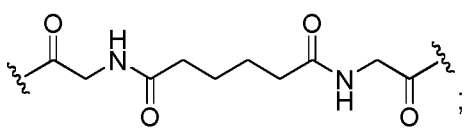
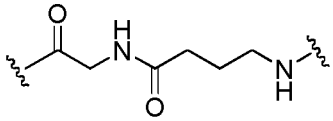
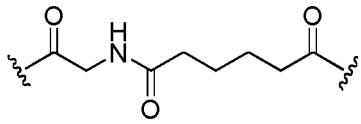


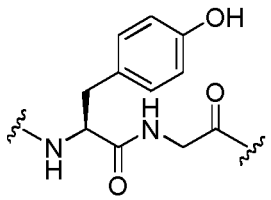
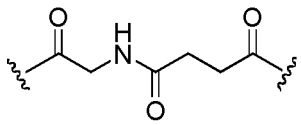
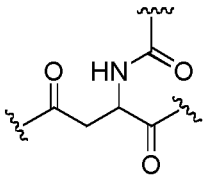

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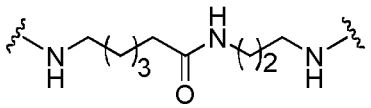
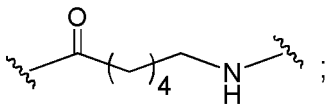
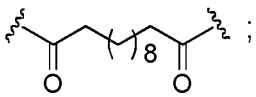

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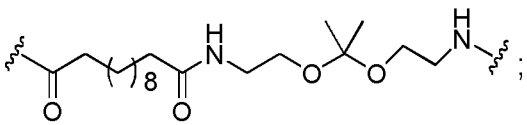
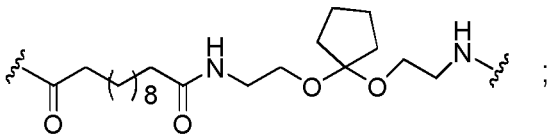

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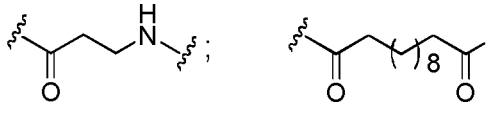
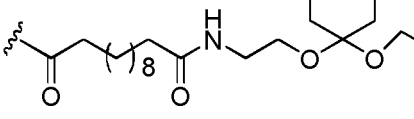
In certain embodiments, a linker has a structure selected from among:


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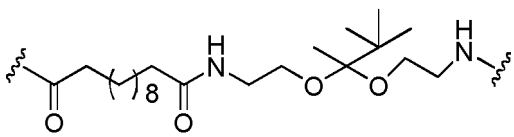

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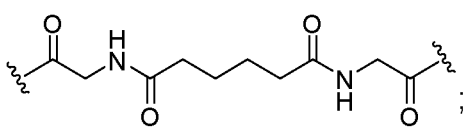
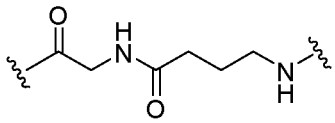
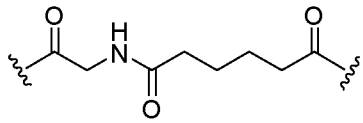

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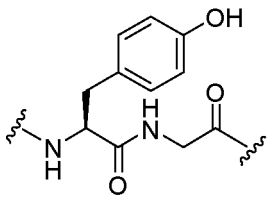
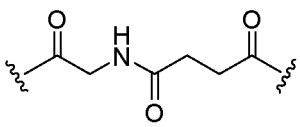
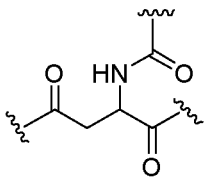
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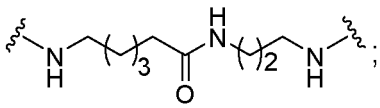
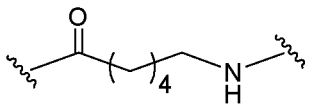
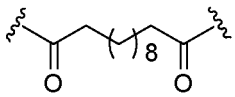
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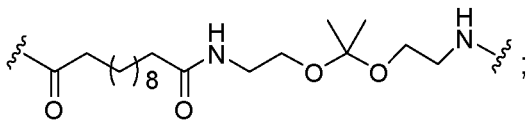
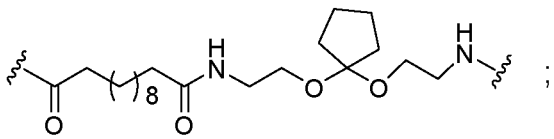

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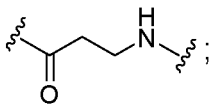
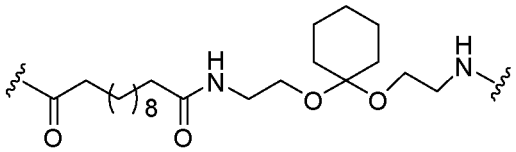
In certain embodiments, a linker has a structure selected from among:

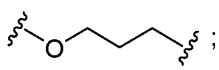
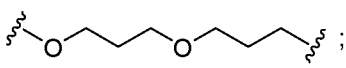
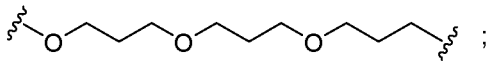

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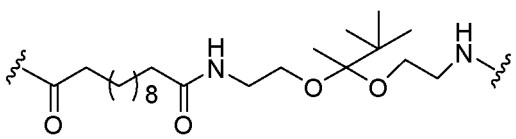
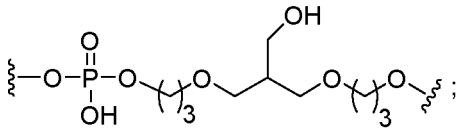

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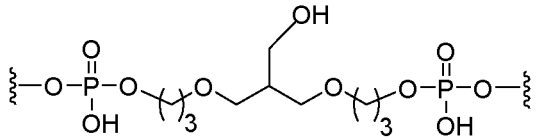
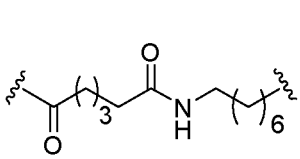

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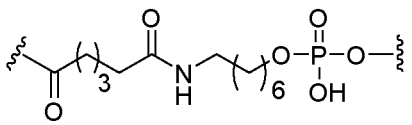

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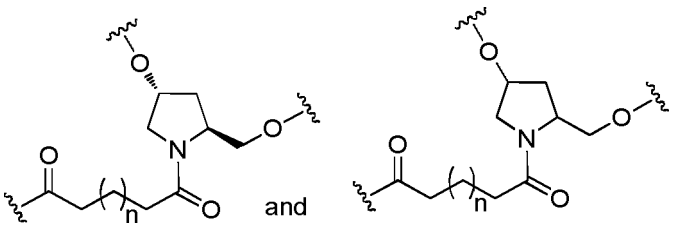

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and

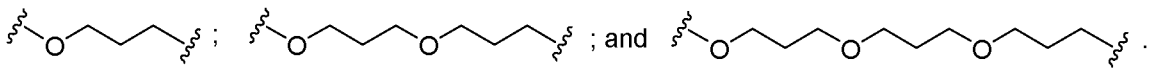

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In certain embodiments, a linker has a structure selected from among:

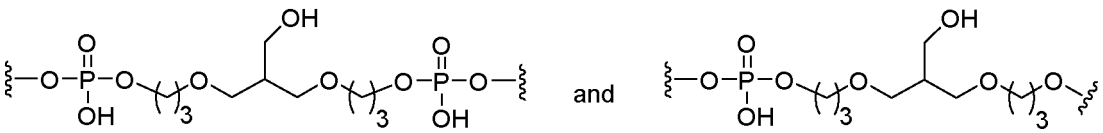


wherein n is from 1 to 20.

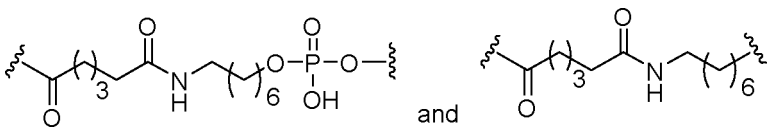
In certain embodiments, a linker has a structure selected from among:



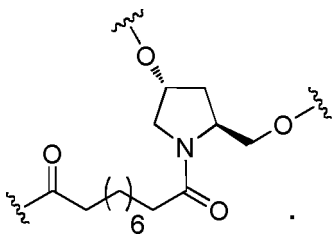
In certain embodiments, a linker has a structure selected from among:



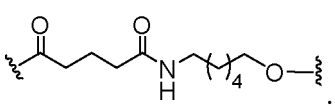
In certain embodiments, a linker has a structure selected from among:



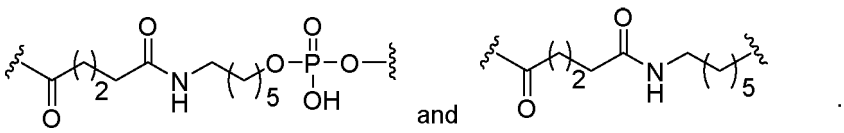
In certain embodiments, the conjugate linker has the structure:



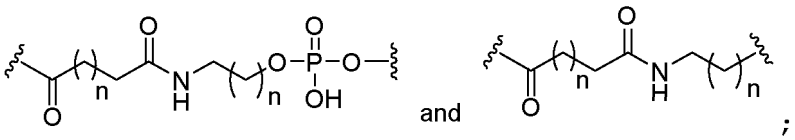
In certain embodiments, the conjugate linker has the structure:



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.

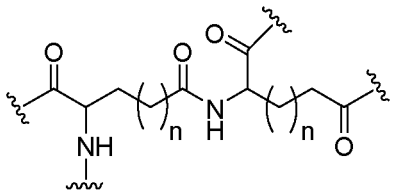
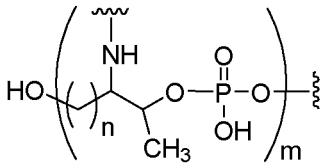
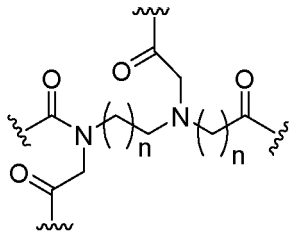
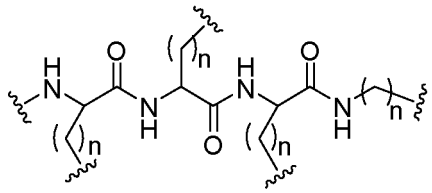
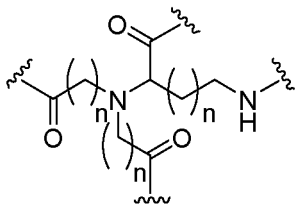
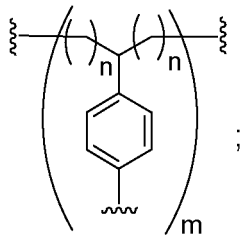
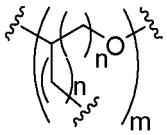
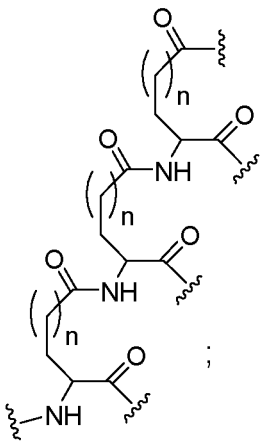
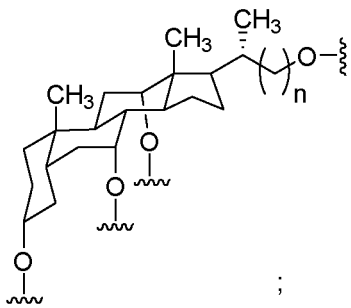
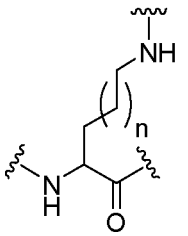
iii. Certain Cell-Targeting Moieties

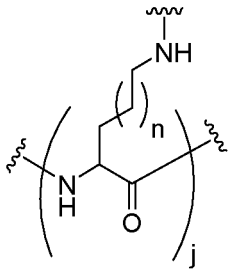
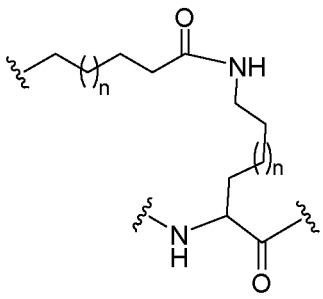
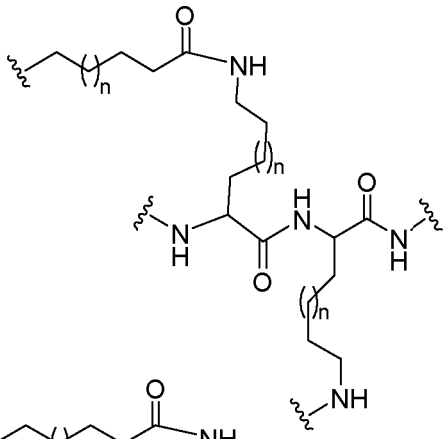
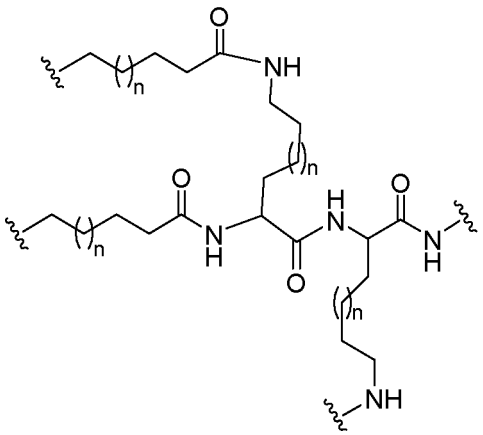
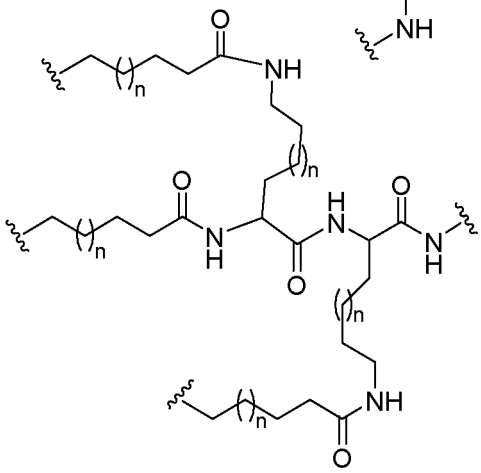
In certain embodiments, conjugate groups comprise cell-targeting moieties. Certain such cell-targeting moieties increase cellular uptake of antisense compounds. In certain embodiments, cell-targeting moieties comprise a branching group, one or more tether, and one or more ligand. In certain embodiments, 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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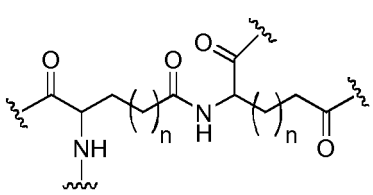
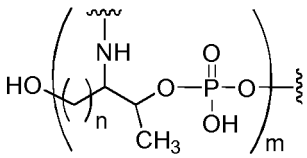
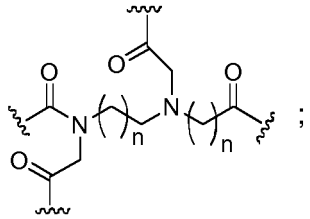
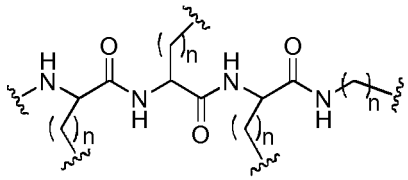
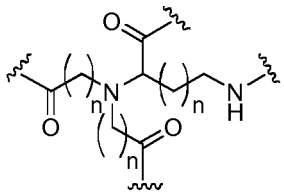
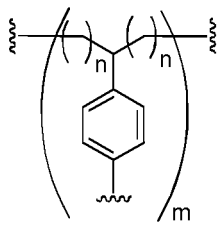
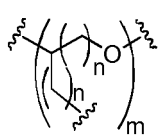
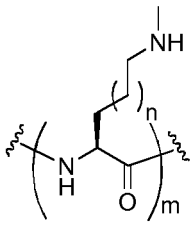
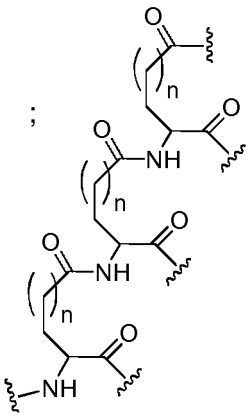
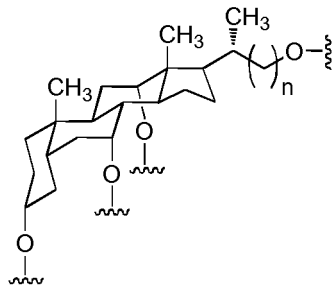
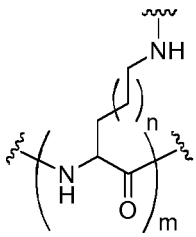

;

;

;

; and

.

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

j is from 1 to 3; and

m is from 2 to 6.

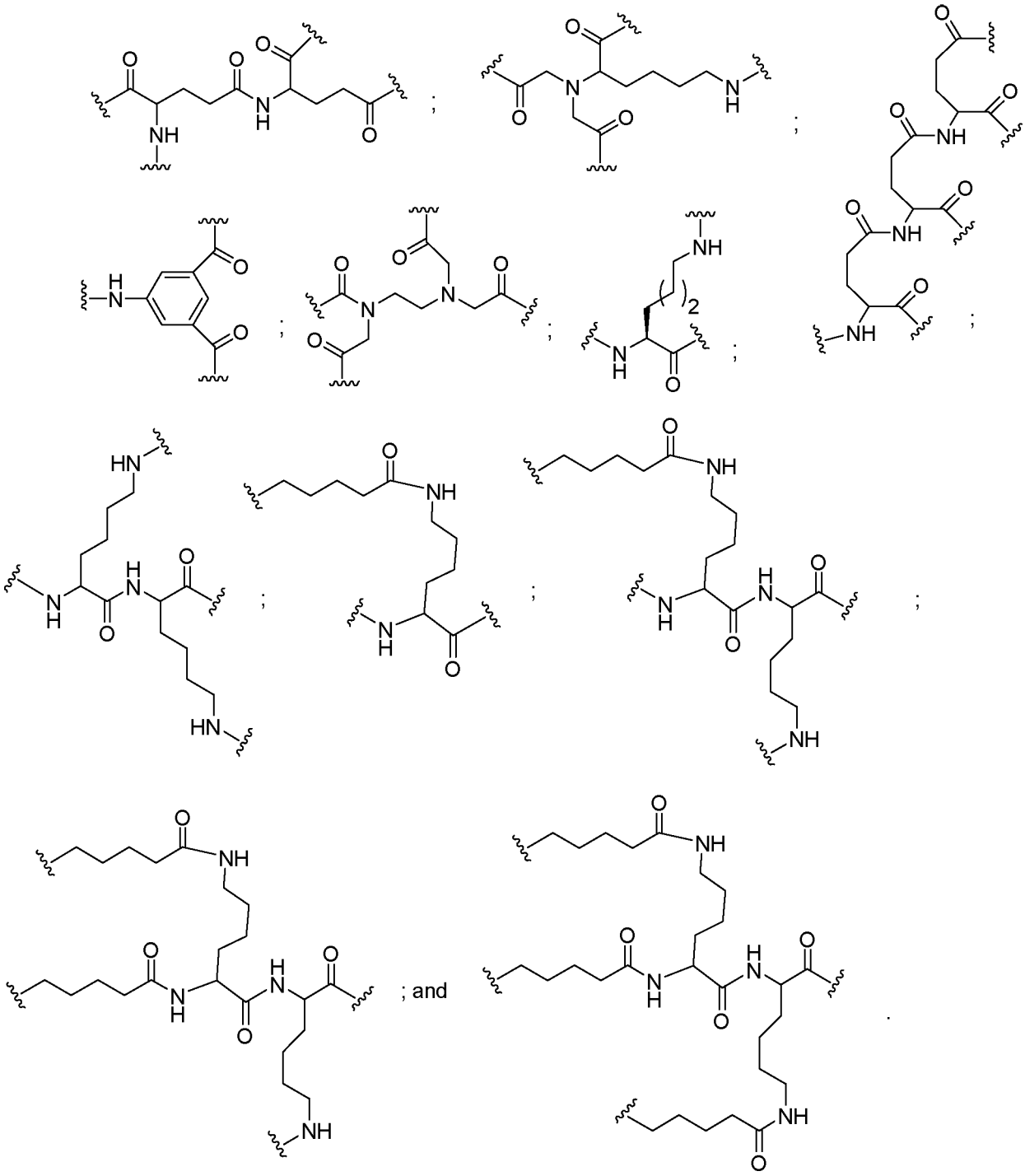
In certain embodiments, a branching group has a structure selected from among:


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;

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; and


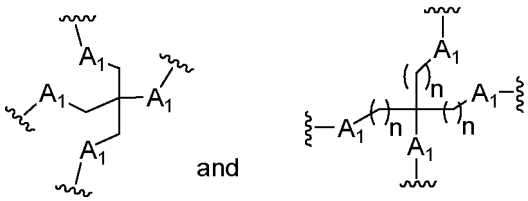
wherein each n is, independently, from 1 to 20; and

m is from 2 to 6.

In certain embodiments, a branching group has a structure selected from among:



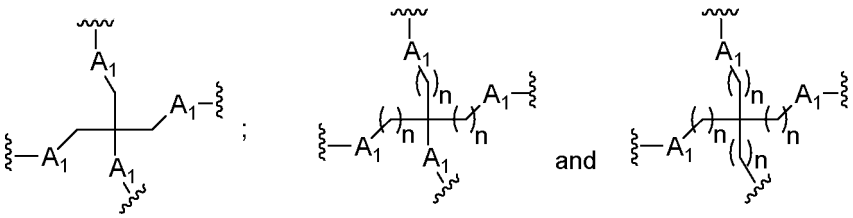
In certain embodiments, a branching group has a structure selected from among:



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

each n is, independently, from 1 to 20.

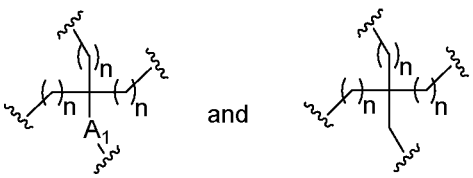
In certain embodiments, a branching group has a structure selected from among:



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

each n is, independently, from 1 to 20.

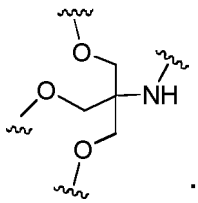
In certain embodiments, a branching group has a structure selected from among:



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

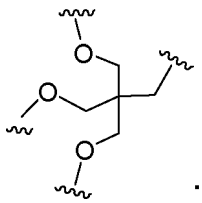
each n is, independently, from 1 to 20.

In certain embodiments, a branching group has a structure selected from among:



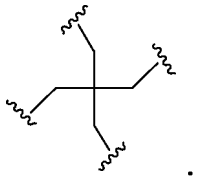
.

In certain embodiments, a branching group has a structure selected from among:



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In certain embodiments, a branching group has a structure selected from among:



.

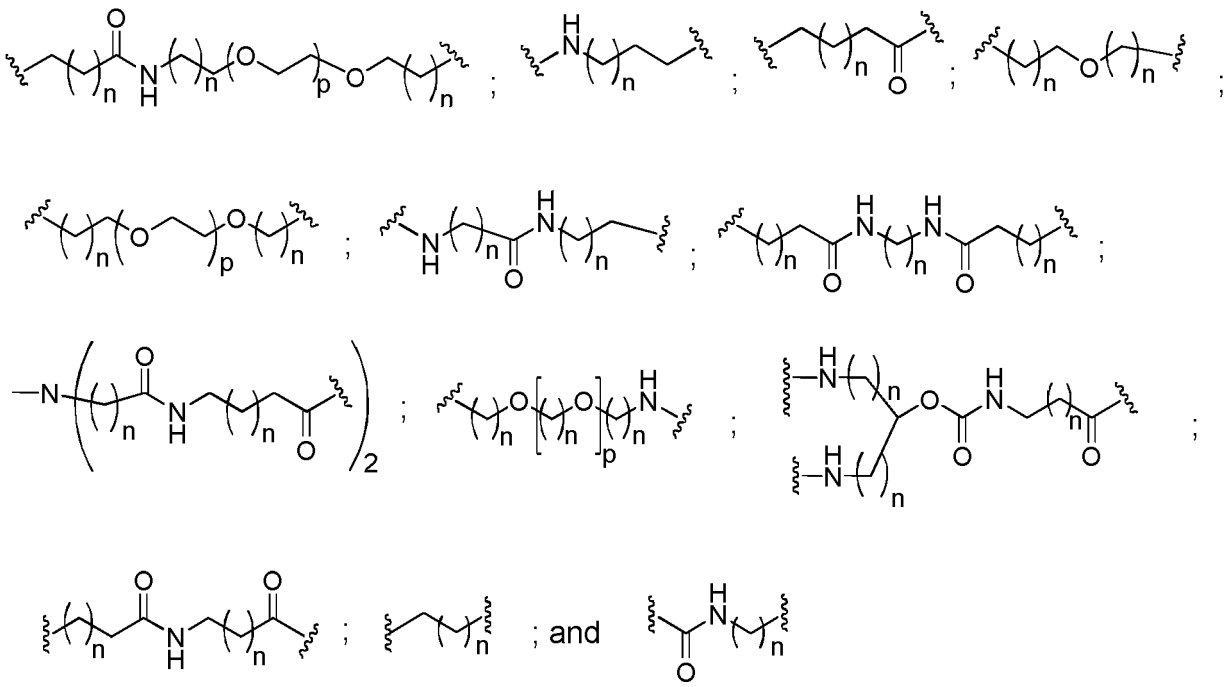
2. Certain Tethers

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.

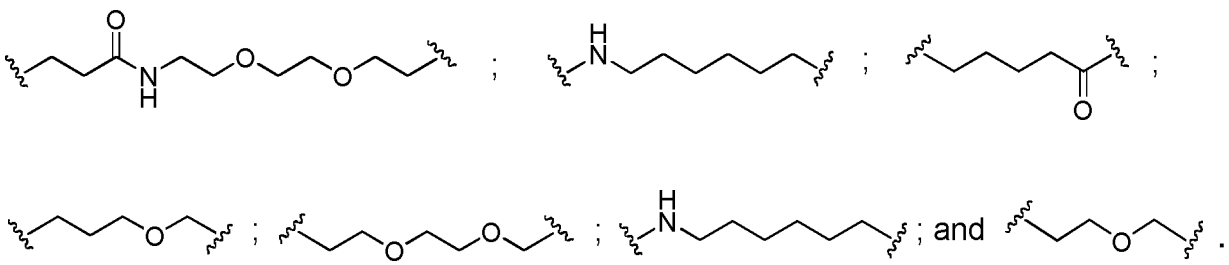
In certain embodiments, a tether has a structure selected from among:



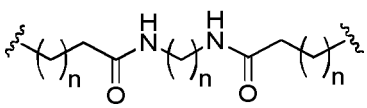
wherein each n is, independently, from 1 to 20; and

each p is from 1 to about 6.

In certain embodiments, a tether has a structure selected from among:

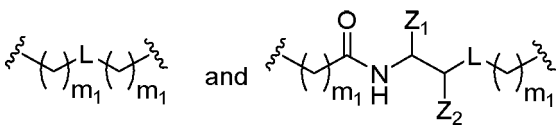


In certain embodiments, a tether has a structure selected from among:



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;

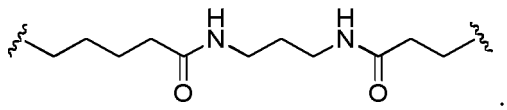
Z_1 is C(=O)O-R_2;

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

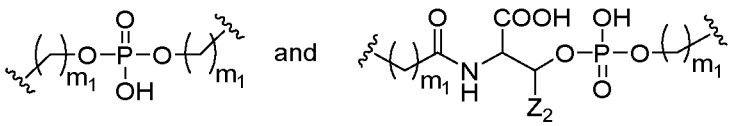
each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

In certain embodiments, a tether has a structure selected from among:



.

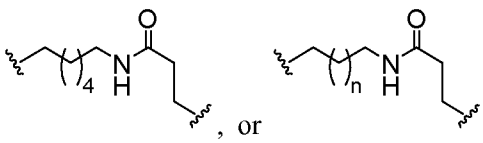
In certain embodiments, a tether has a structure selected from among:



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.

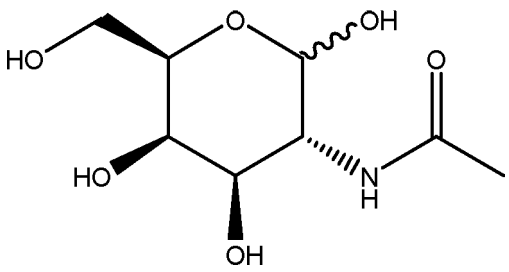
In certain embodiments, a tether comprises a phosphorus linking group. In certain embodiments, a tether does not comprise any amide bonds. In certain embodiments, a tether comprises a phosphorus linking group and does not comprise any amide bonds.

3. Certain Ligands

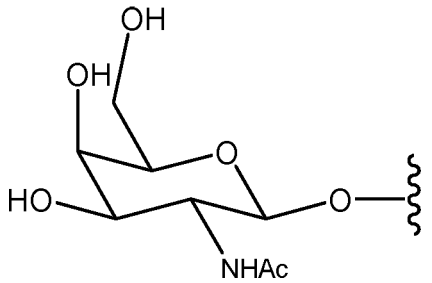
In certain embodiments, the present disclosure provides ligands wherein each ligand is covalently attached to a tether. In certain embodiments, each ligand is selected to have an affinity for at least one type of receptor on a target cell. In certain embodiments, ligands are selected that have an affinity 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.

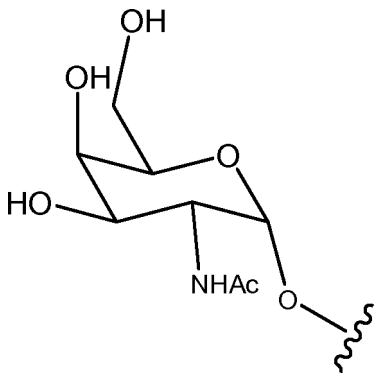
In certain embodiments, "GalNAc" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose, commonly referred to in the literature as N-acetyl galactosamine. In certain embodiments, "N-acetyl galactosamine" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose. In certain embodiments, "GalNAc" or "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

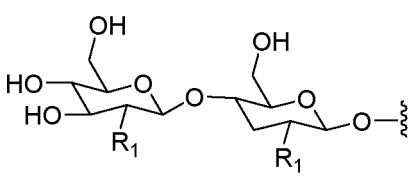


2-(Acetylamino)-2-deoxy-β-D-galactopyranose

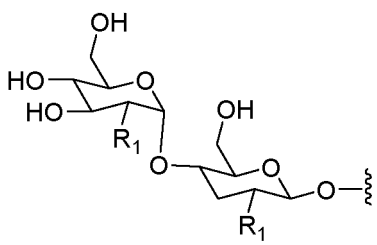


2-(Acetylamino)-2-deoxy-α-D-galactopyranose

In certain embodiments one or more ligand has a structure selected from among:

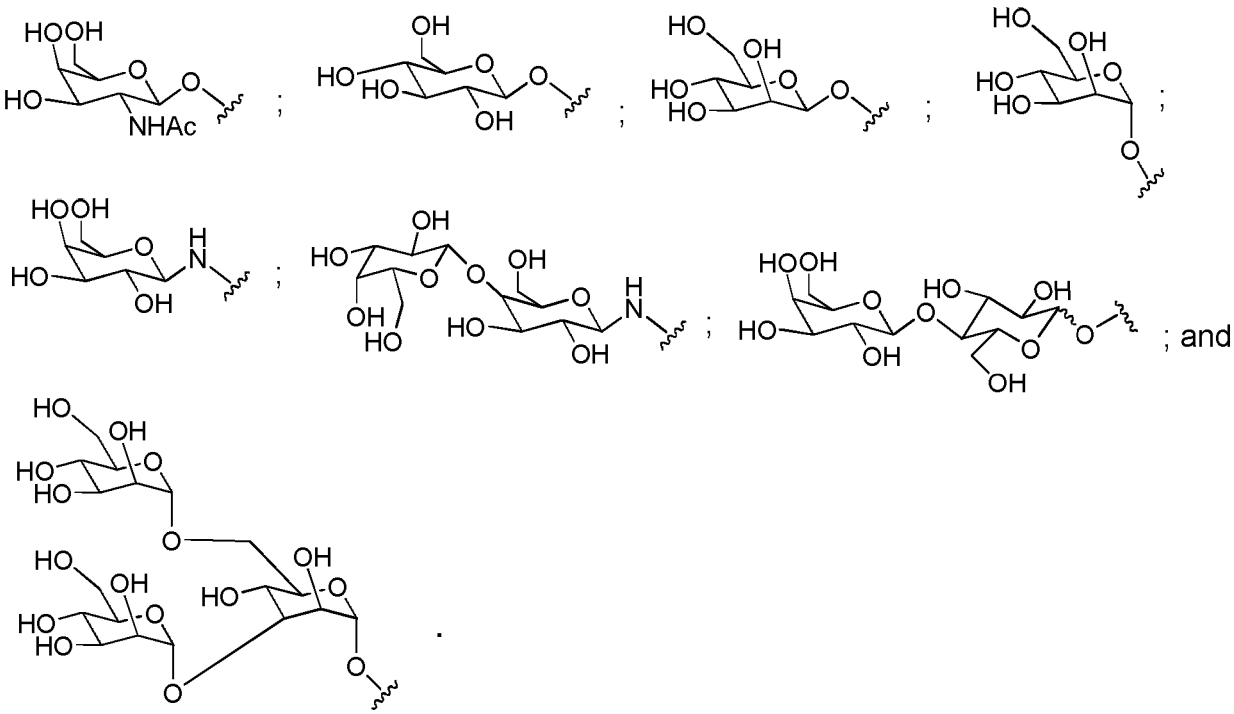


and

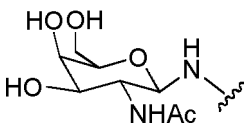


wherein each R_1 is selected from OH and NHCOOH.

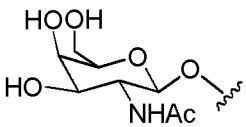
In certain embodiments one or more ligand has a structure selected from among:



In certain embodiments one or more ligand has a structure selected from among:

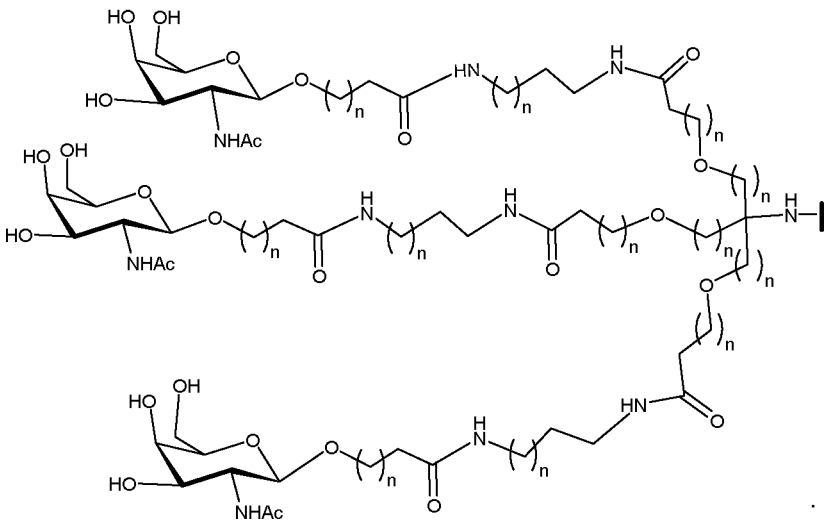


In certain embodiments one or more ligand has a structure selected from among:



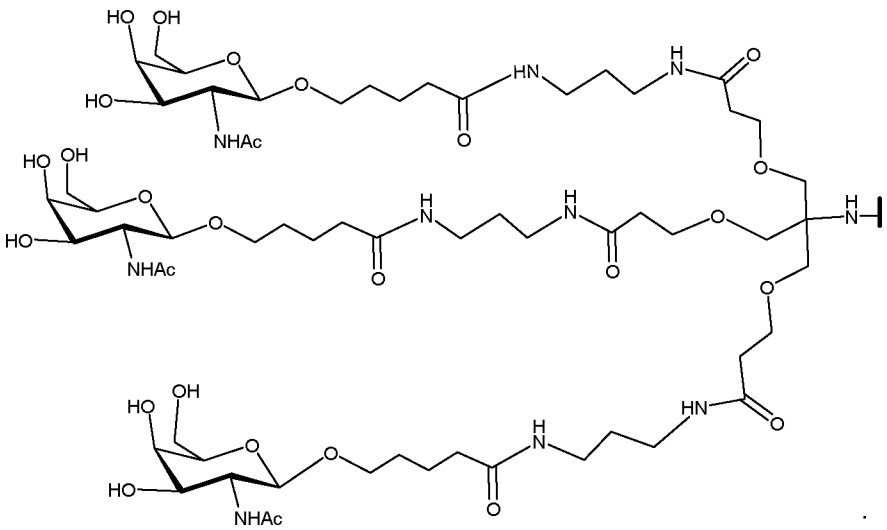
i. Certain Conjugates

In certain embodiments, conjugate groups comprise the structural features above. In certain such embodiments, conjugate groups have the following structure:

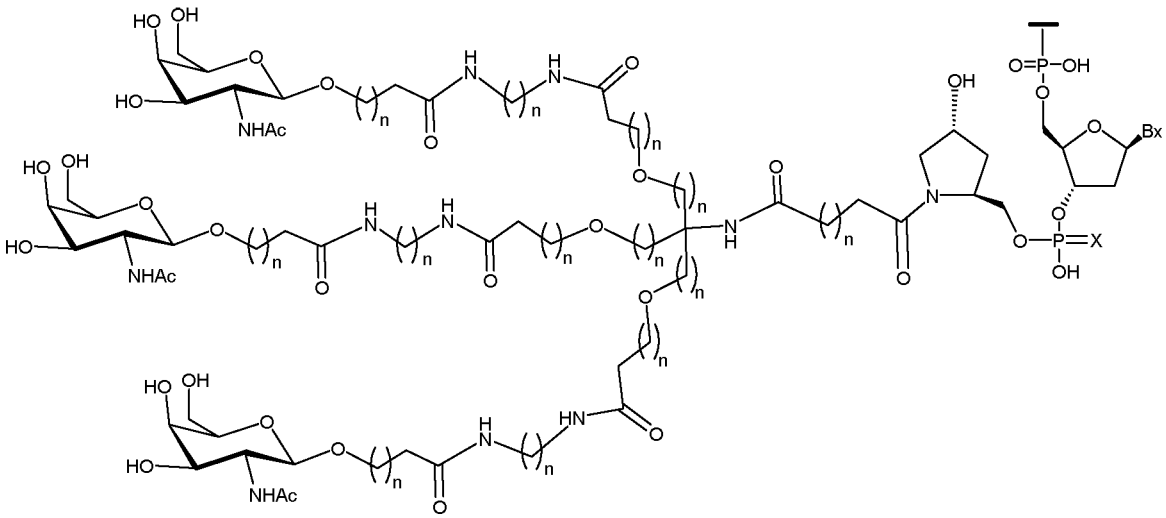


wherein each n is, independently, from 1 to 20.

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;

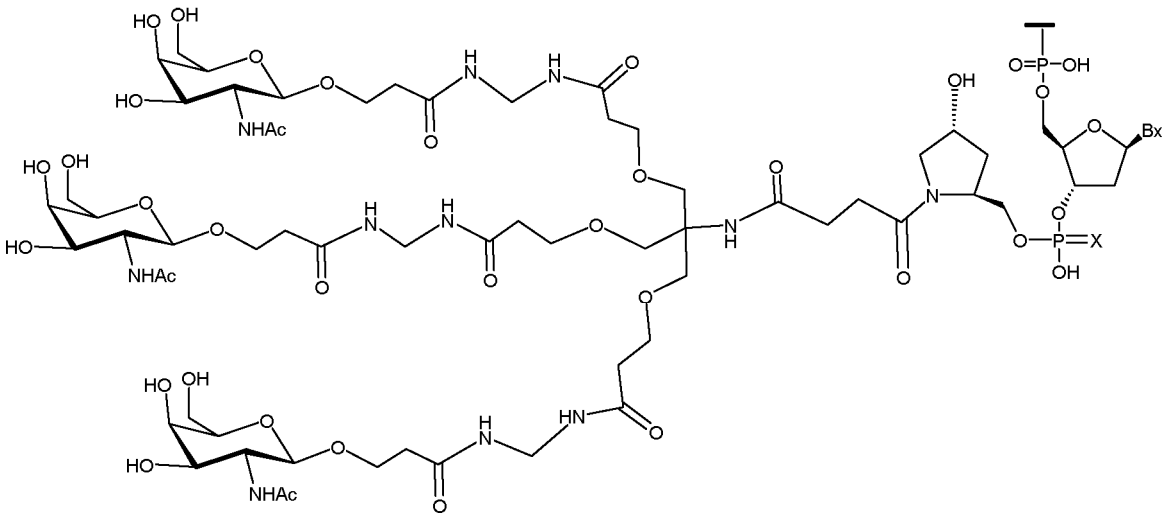
Z is H or a linked solid support;

Q is an antisense compound;

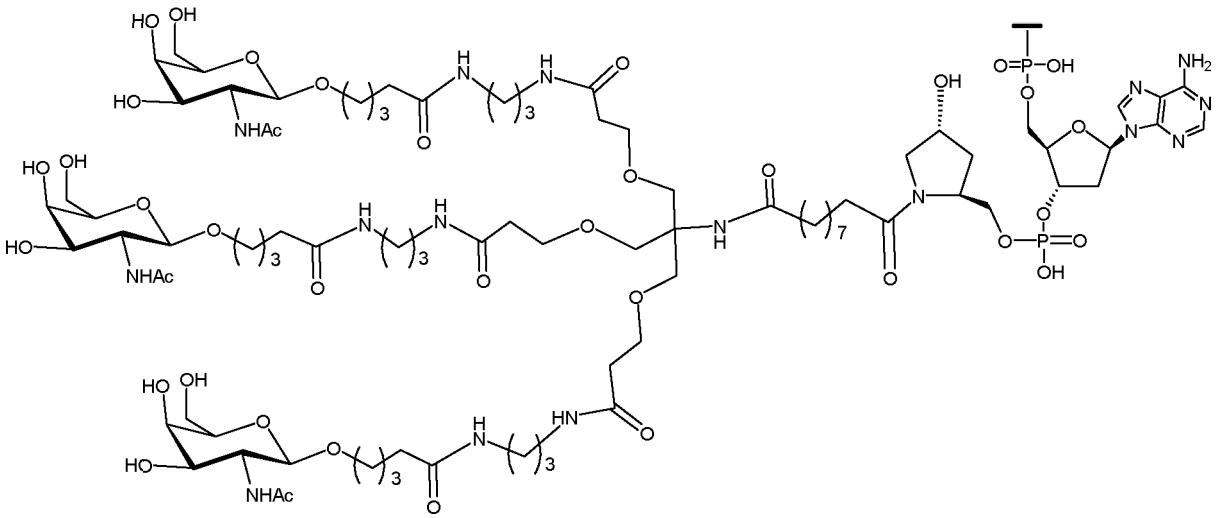
X is O or S; and

Bx is a heterocyclic base moiety.

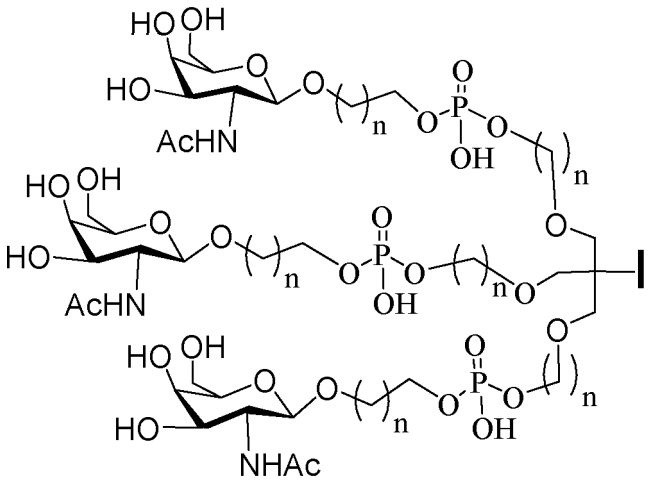
In certain such embodiments, conjugate groups have the following structure:



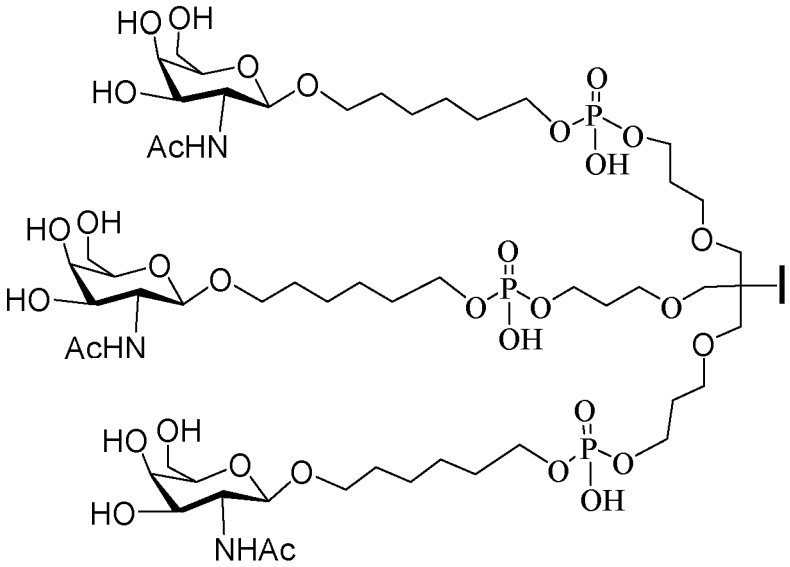
In certain such embodiments, conjugate groups have the following structure:



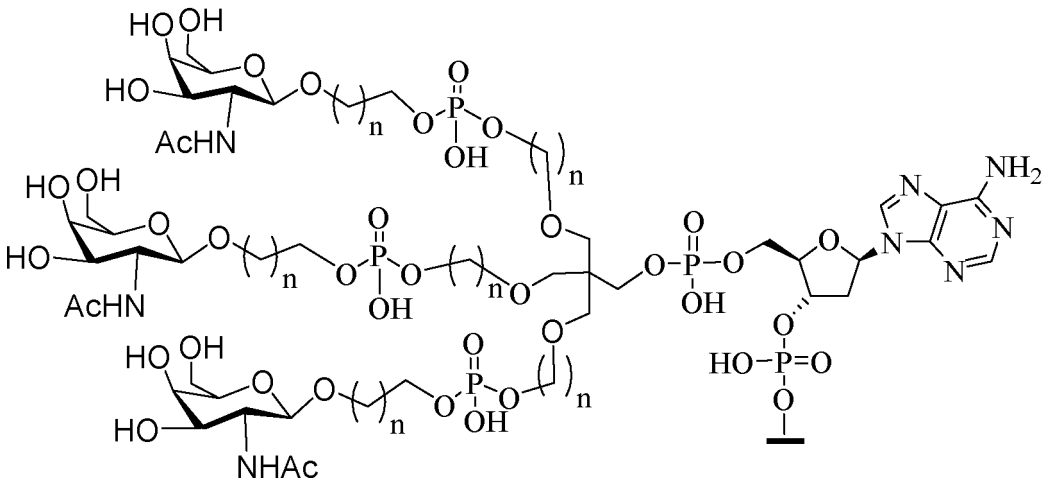
In certain such embodiments, conjugate groups have the following structure:



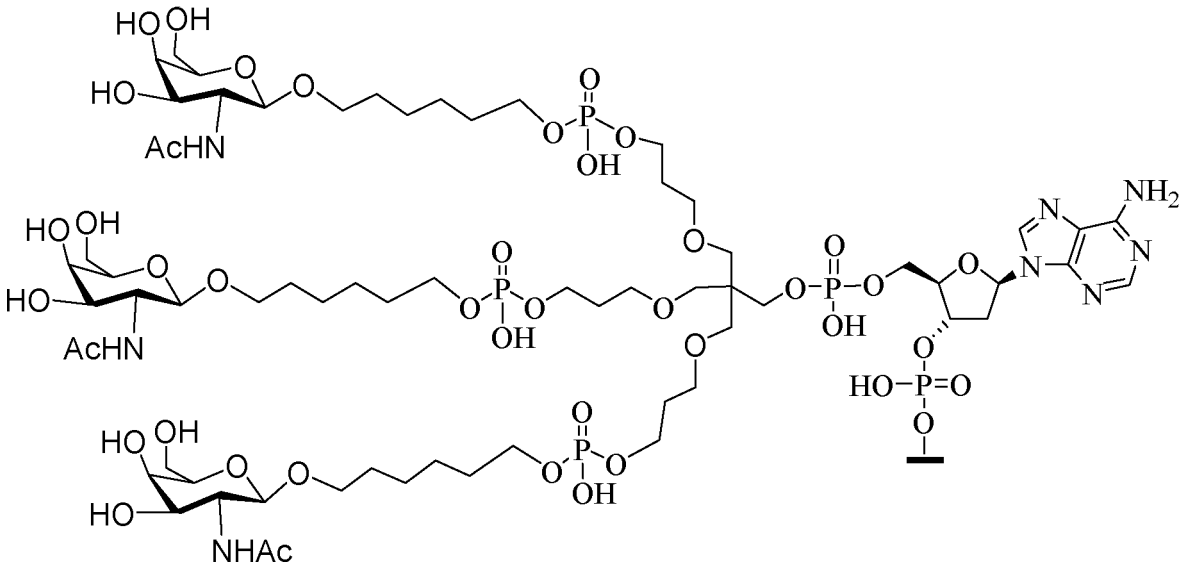
In certain such embodiments, conjugate groups have the following structure:



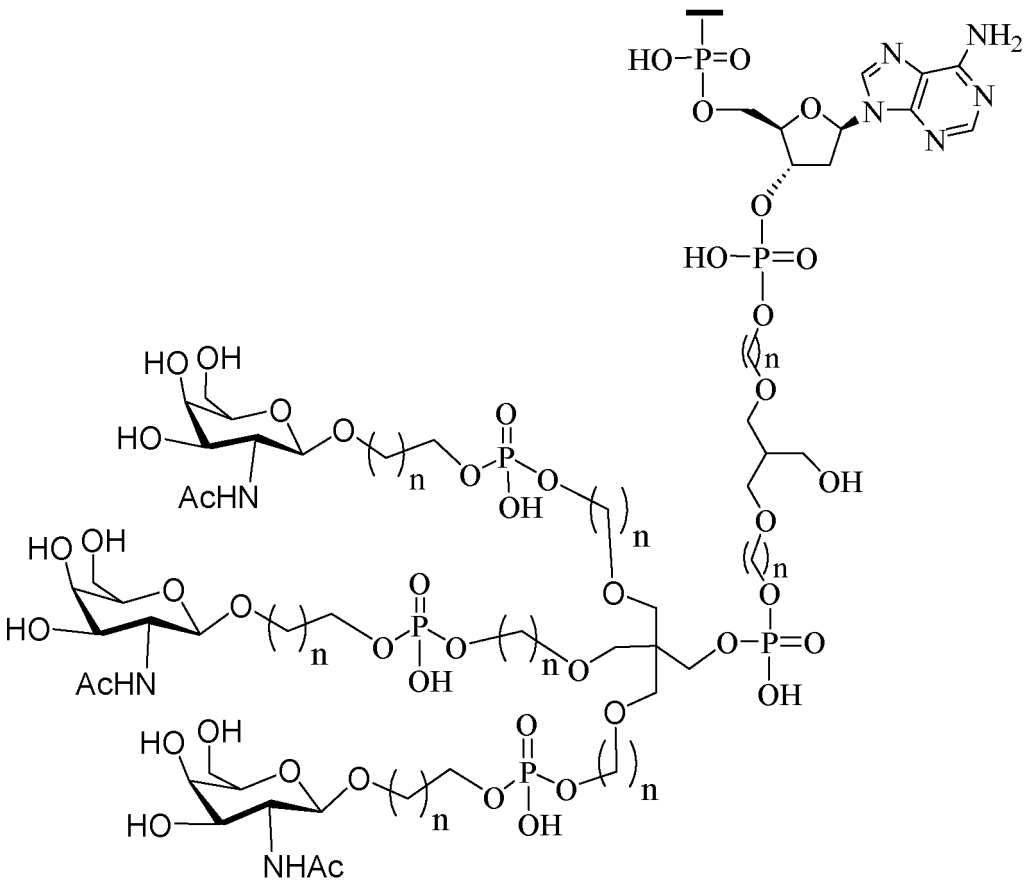
In certain such embodiments, conjugate groups have the following structure:



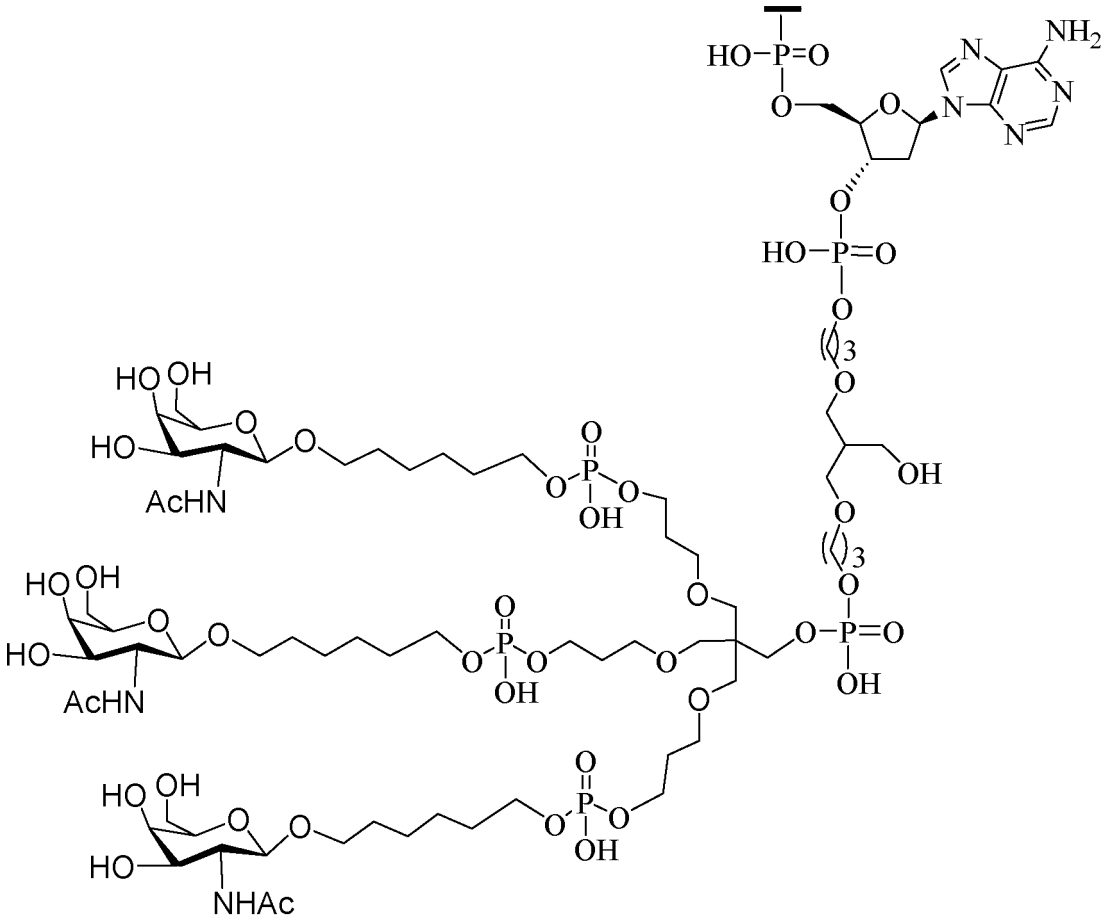
In certain such embodiments, conjugate groups have the following structure:



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

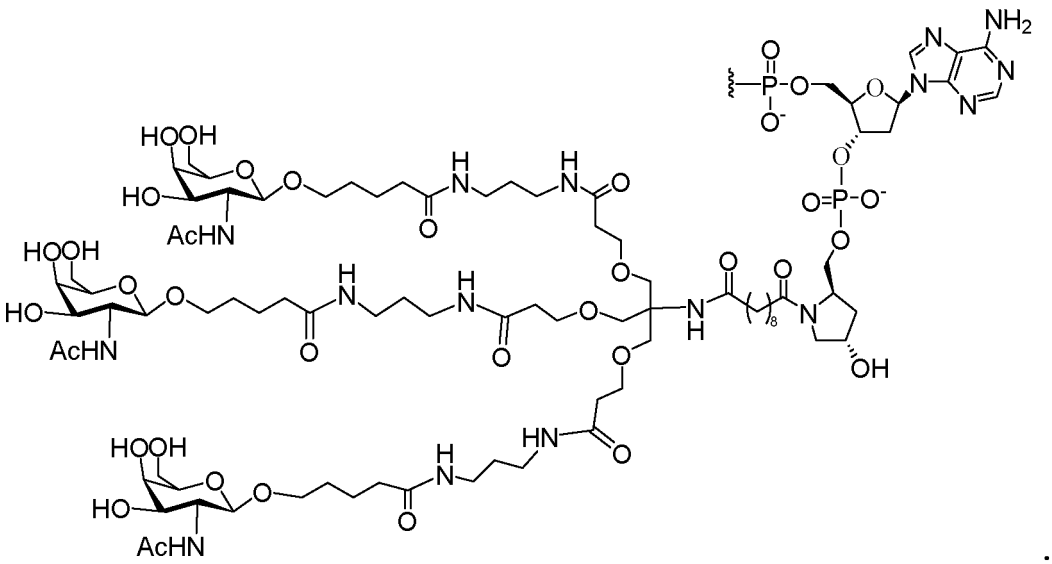


In certain such embodiments, conjugate groups have the following structure:

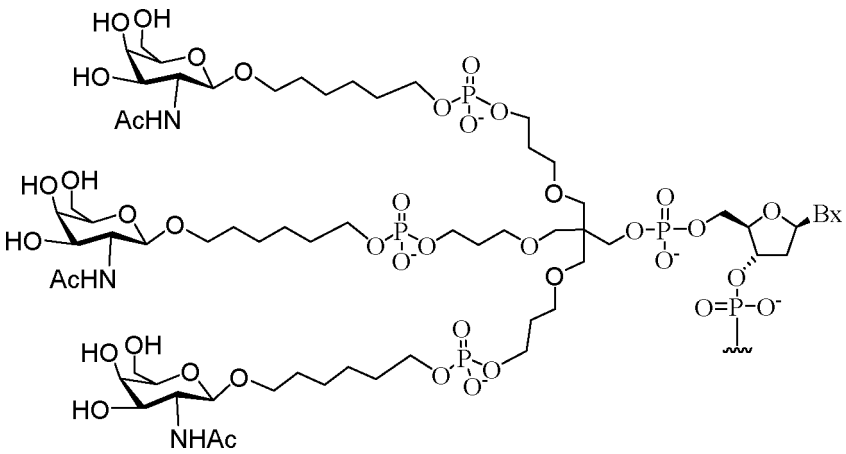


In certain embodiments, conjugates do not comprise a pyrrolidine.

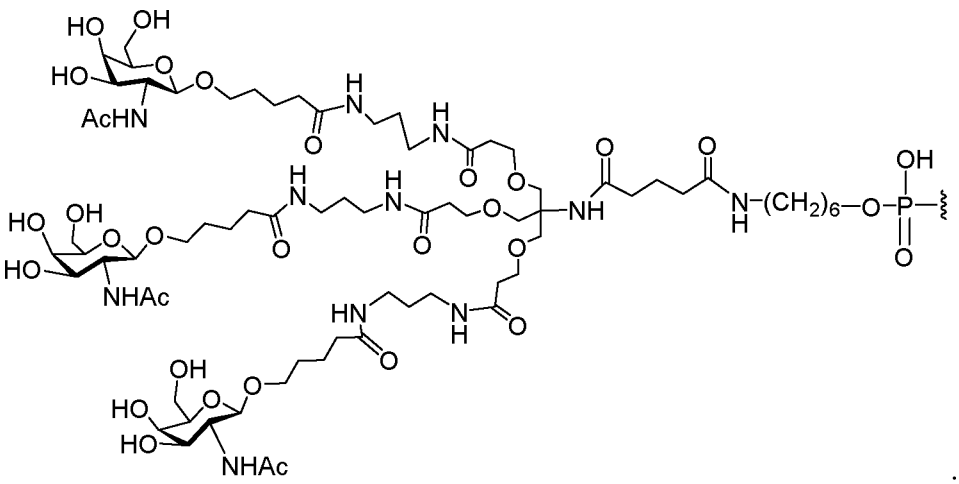
In certain such embodiments, conjugate groups have the following structure:



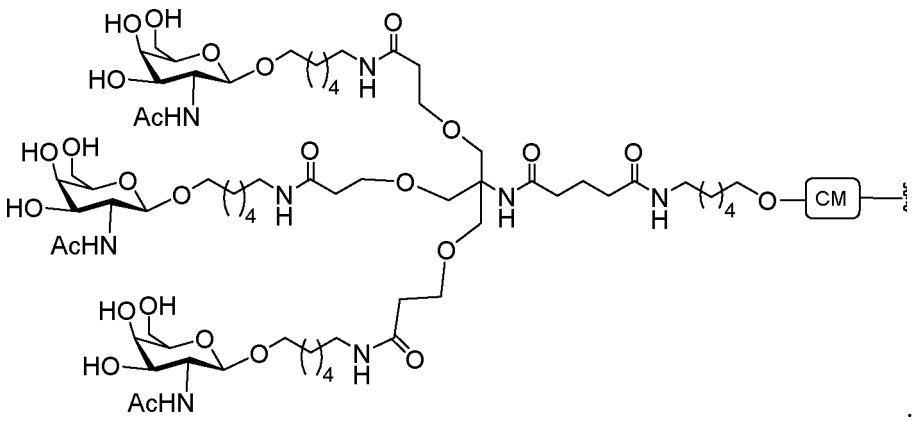
In certain such embodiments, conjugate groups have the following structure:



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

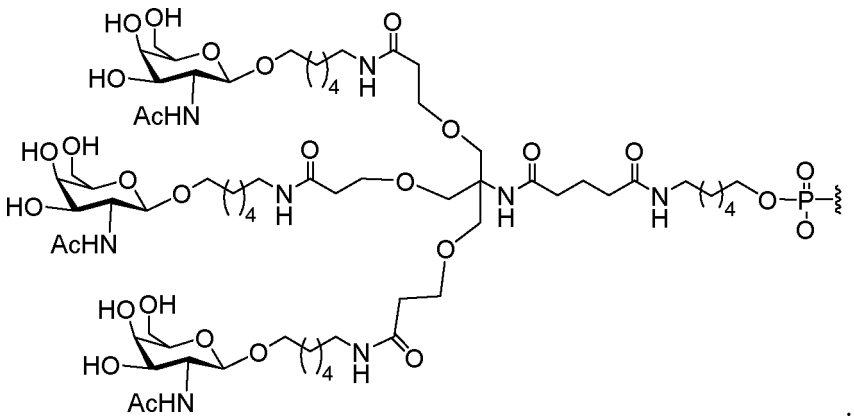


In certain such embodiments, conjugate groups have the following structure:



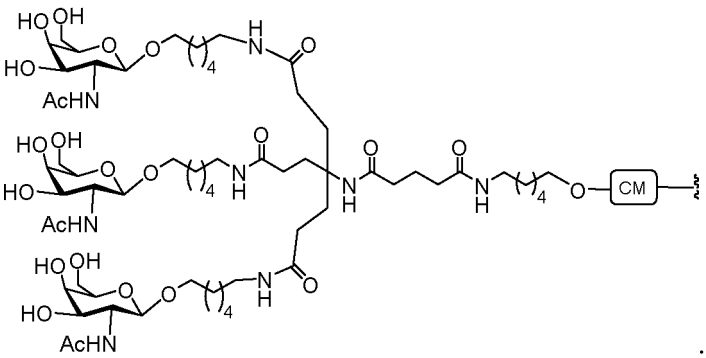
.

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



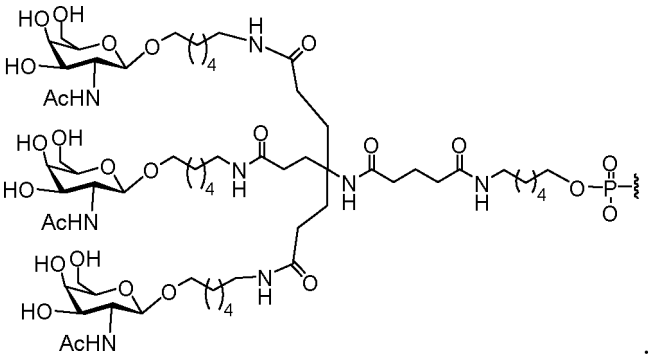
.

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

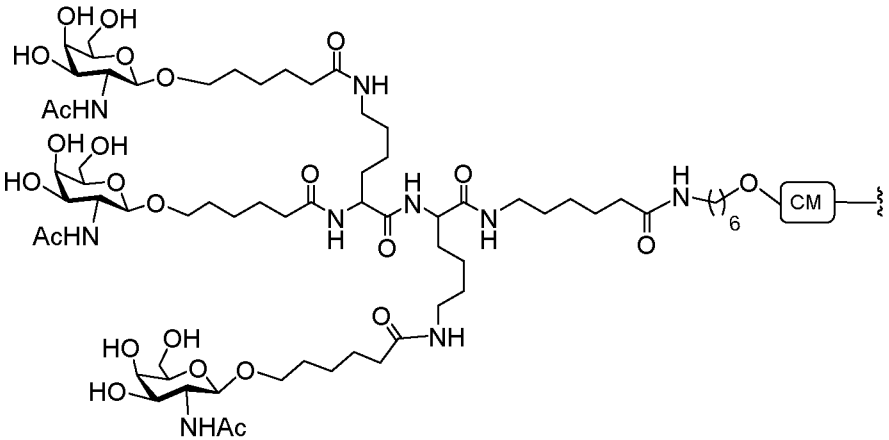


.

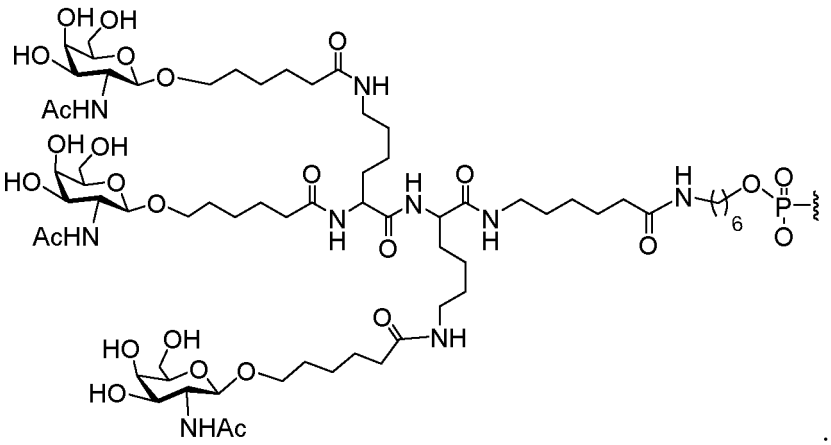
In certain such embodiments, conjugate groups have the following structure:



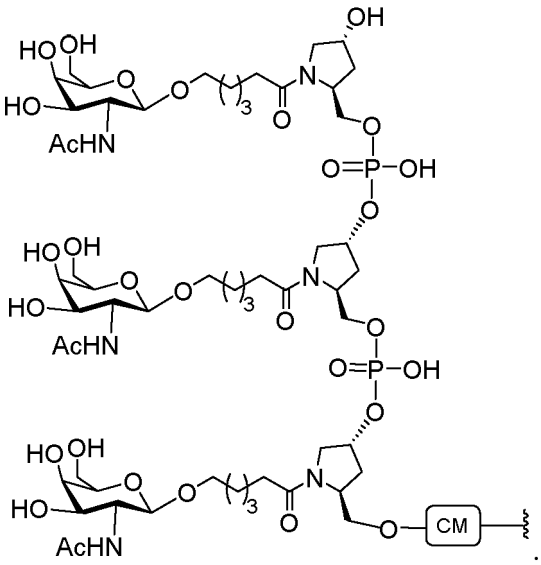
In certain such embodiments, conjugate groups have the following structure:



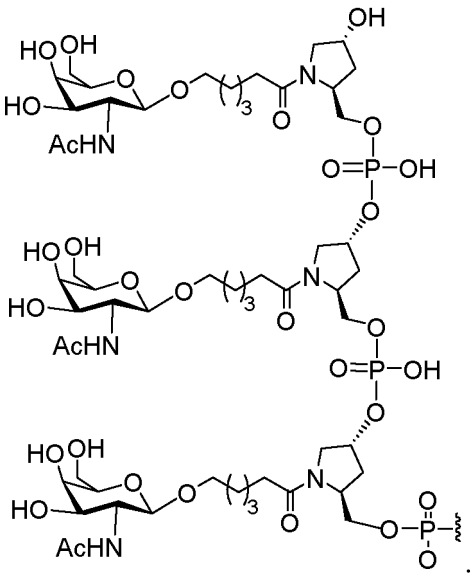
In certain such embodiments, conjugate groups have the following structure:



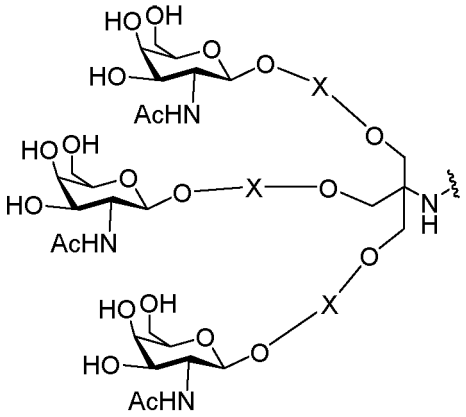
In certain such embodiments, conjugate groups have the following structure:



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

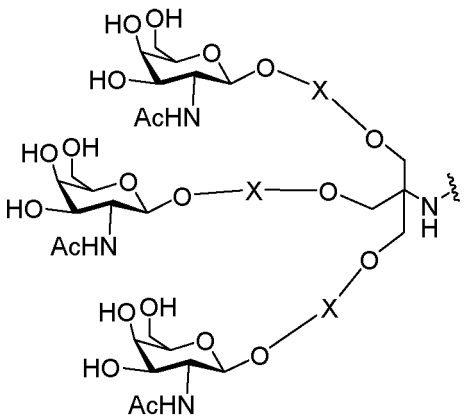


In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



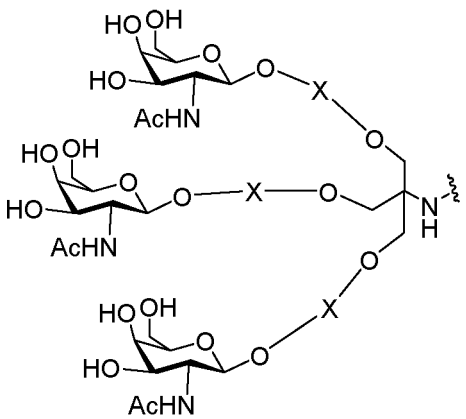
wherein X is a substituted or unsubstituted tether of six to eleven consecutively bonded atoms.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



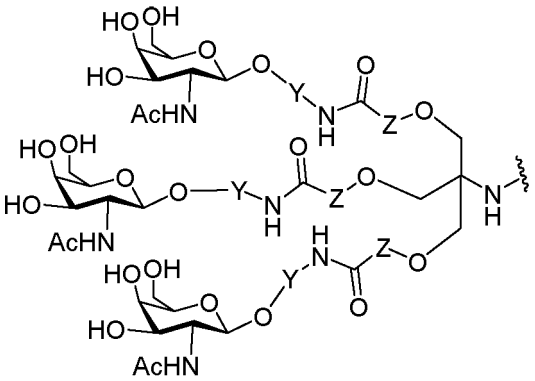
wherein X is a substituted or unsubstituted tether of ten consecutively bonded atoms.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



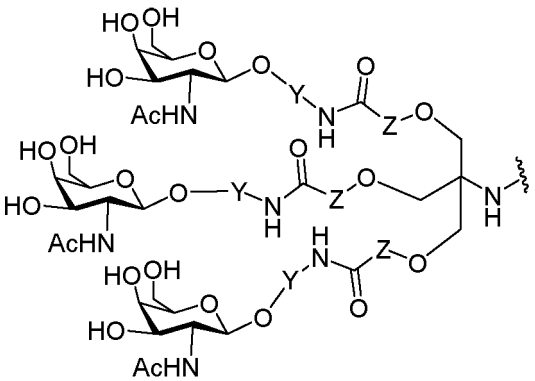
wherein X is a substituted or unsubstituted tether of four to eleven consecutively bonded atoms and wherein the tether comprises exactly one amide bond.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



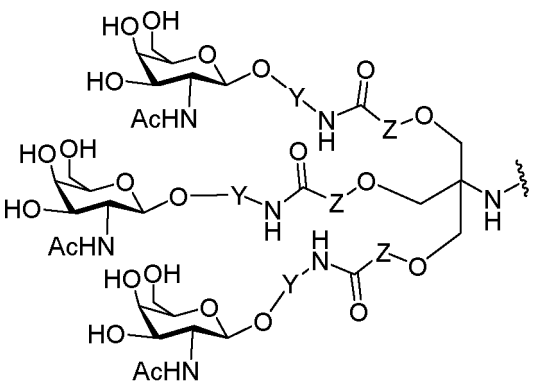
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



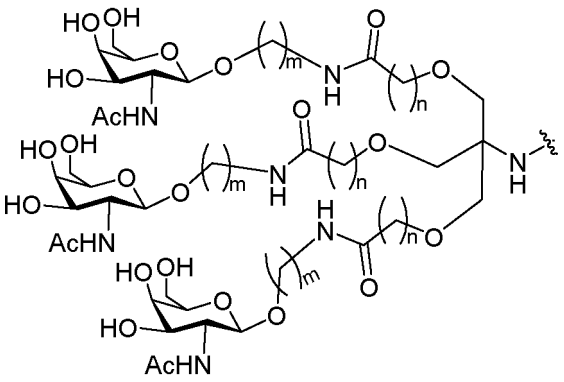
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising exactly one ether or exactly two ethers, an amide, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



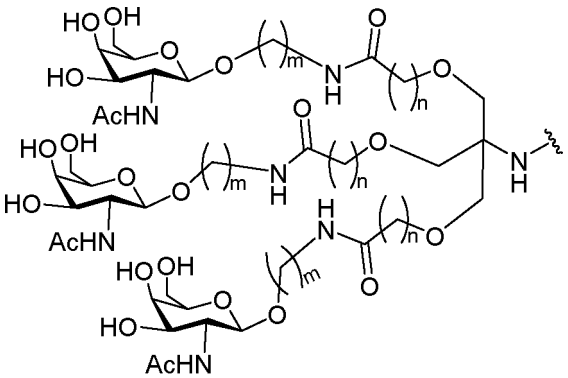
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



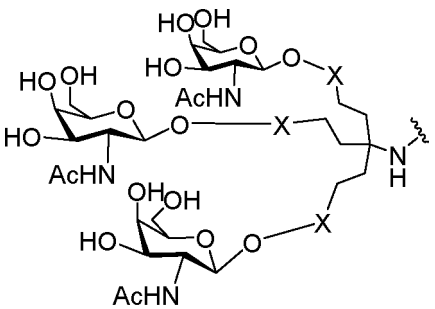
wherein m and n are independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



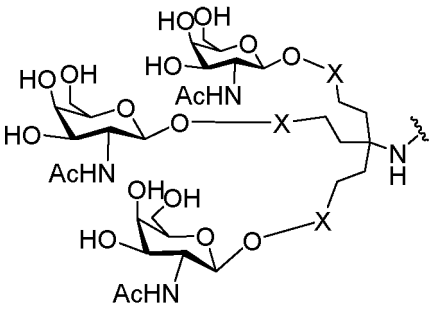
wherein m is 4, 5, 6, 7, or 8, and n is 1, 2, 3, or 4.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



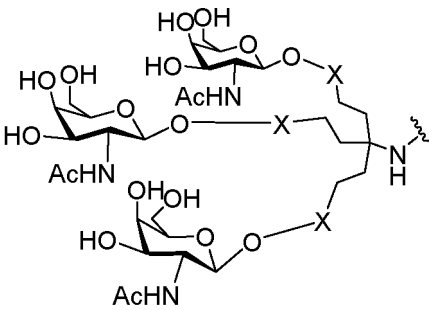
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein X does not comprise an ether group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



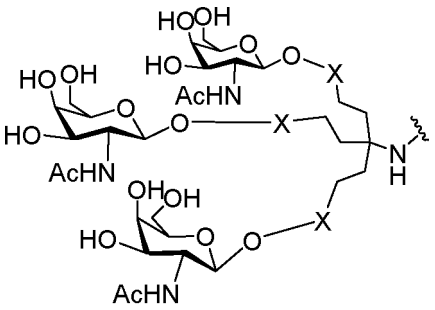
wherein X is a substituted or unsubstituted tether of eight consecutively bonded atoms, and wherein X does not comprise an ether group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



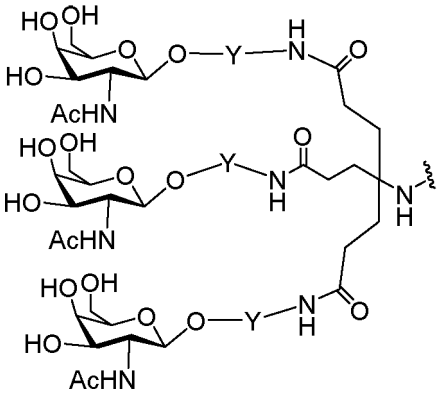
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein the tether comprises exactly one amide bond, and wherein X does not comprise an ether group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



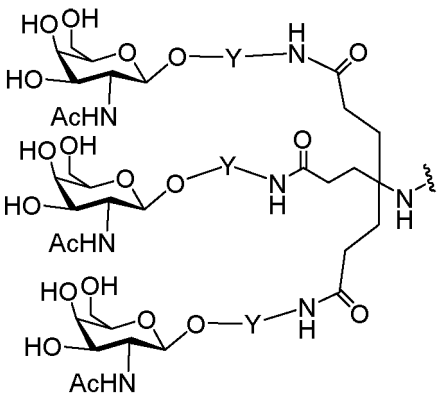
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms and wherein the tether consists of an amide bond and a substituted or unsubstituted C_2-C_{11} alkyl group.

In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



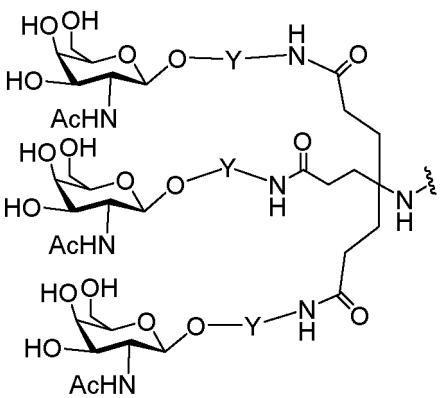
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



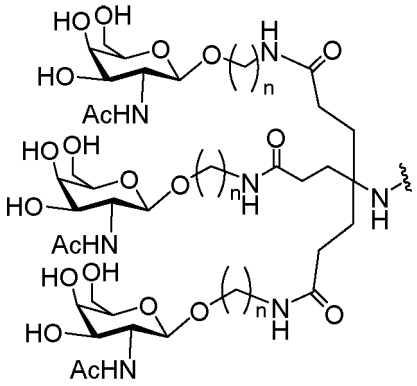
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising an ether, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



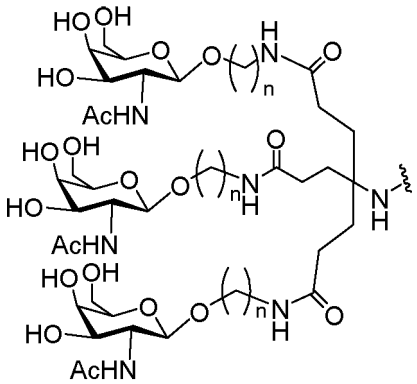
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

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:

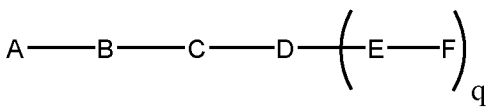


wherein n is 4, 5, 6, 7, or 8.

In certain embodiments, conjugates do not comprise a pyrrolidine.

a 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

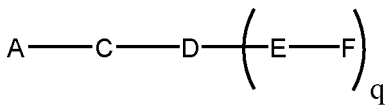
D is the branching group

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.

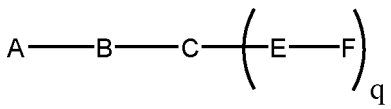
In certain such embodiments, the conjugate linker comprises at least one cleavable bond.

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

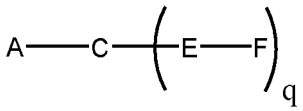
C is the conjugate linker

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;

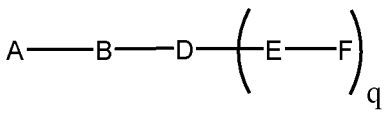
C is the conjugate linker

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

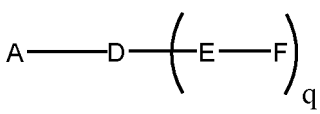
D is the branching group

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;

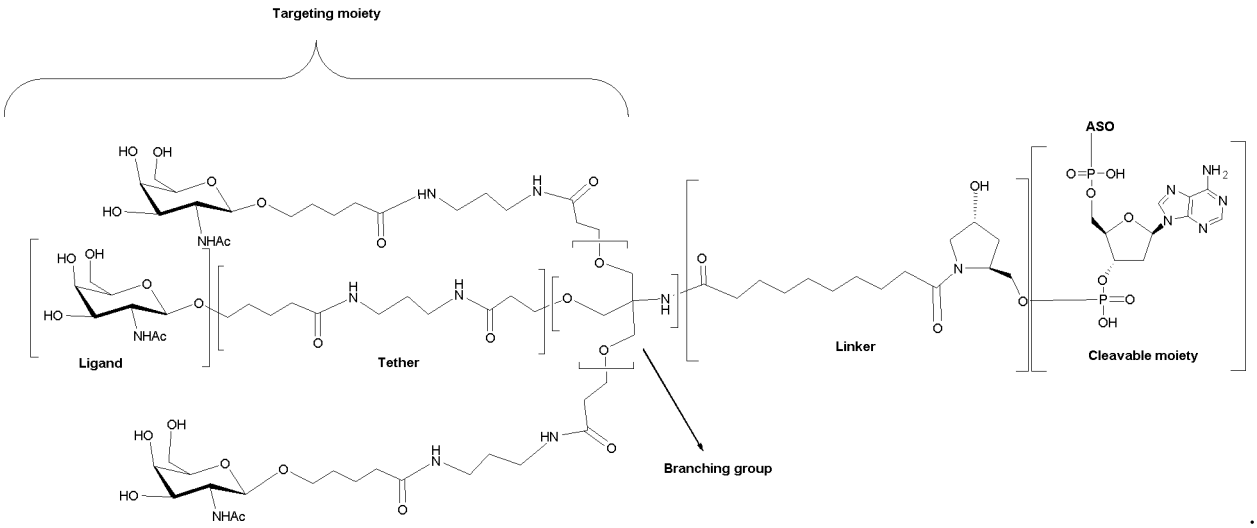
each F is a ligand; and

q is an integer between 1 and 5.

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

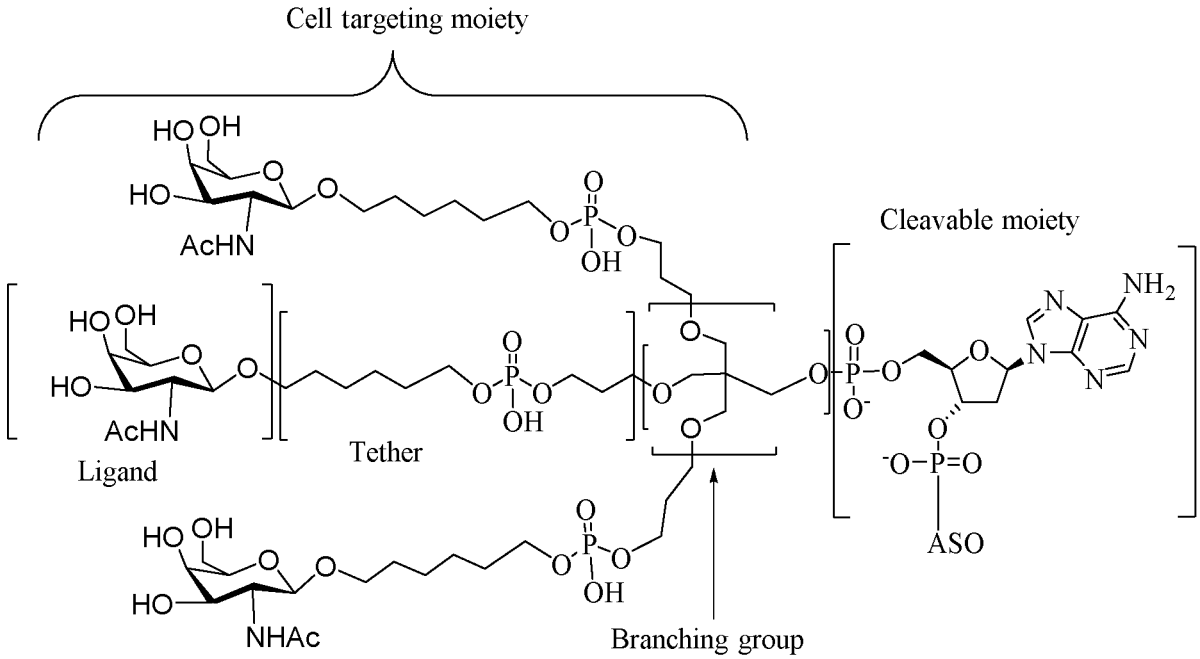
In certain embodiments each tether comprises at least one cleavable bond.

In certain embodiments, a conjugated antisense compound has a structure selected from among the following:

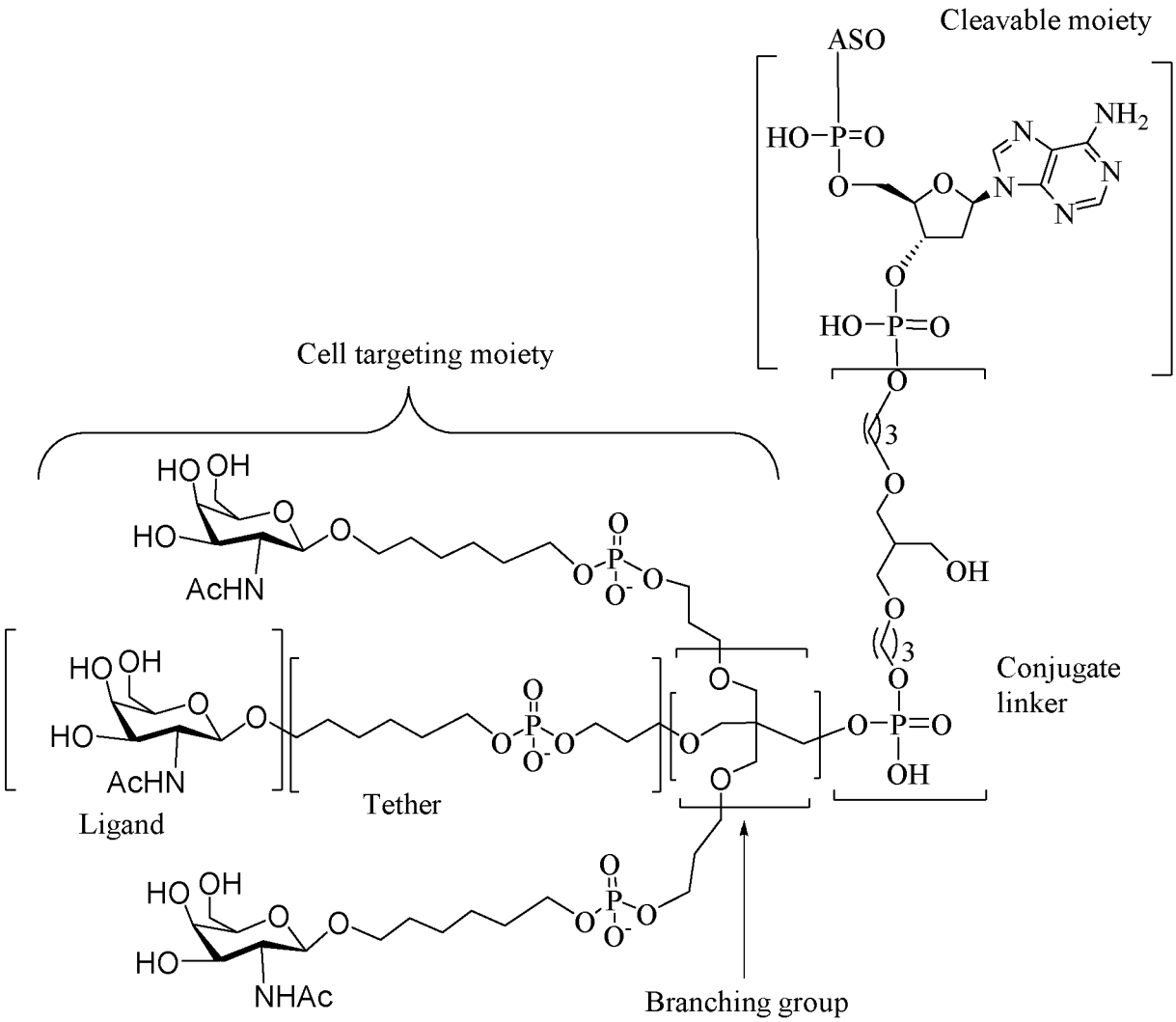


.

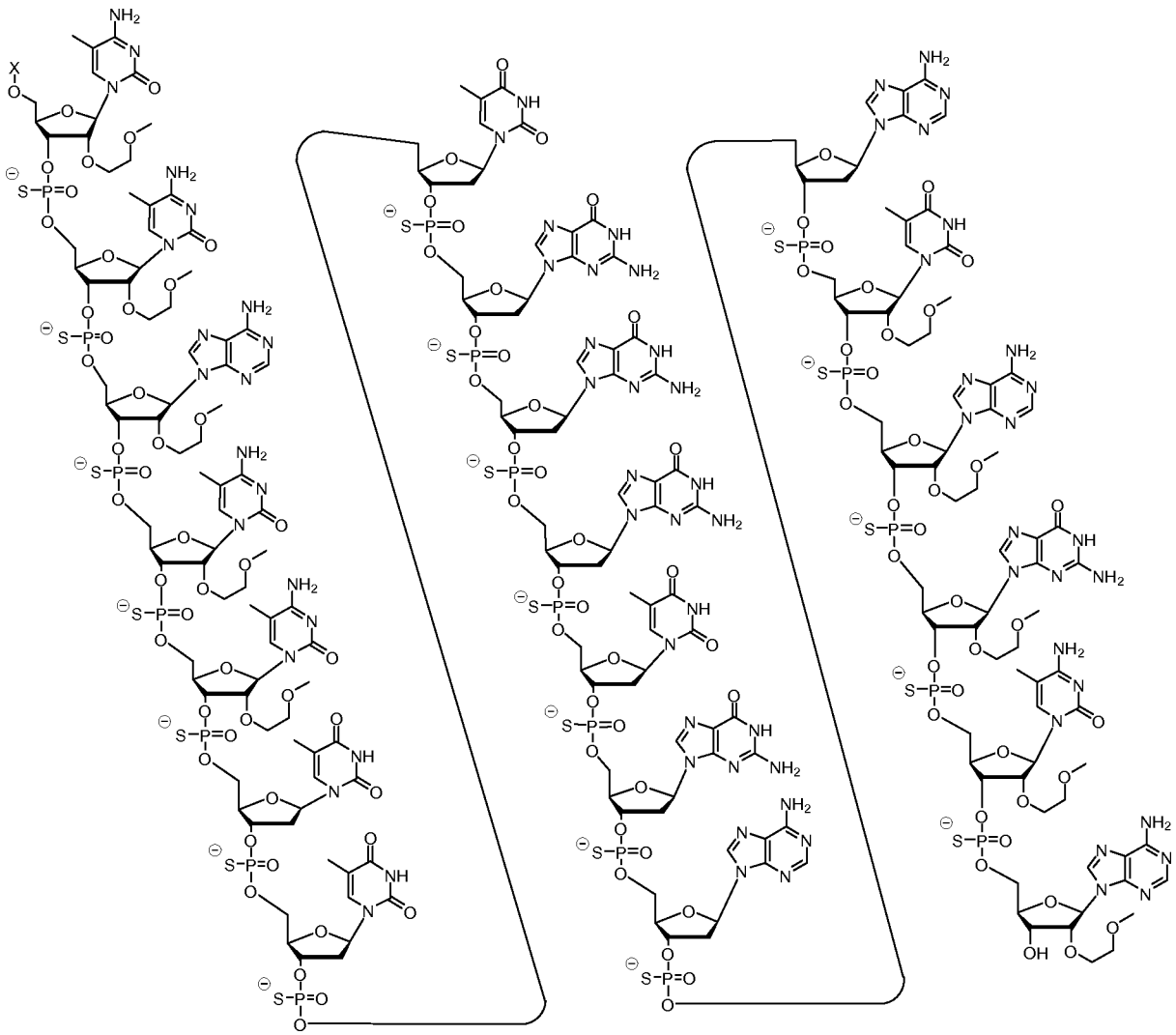
In certain embodiments, a conjugated antisense compound has a structure selected from among the following:



In certain embodiments, a conjugated antisense compound has a structure selected from among the following:

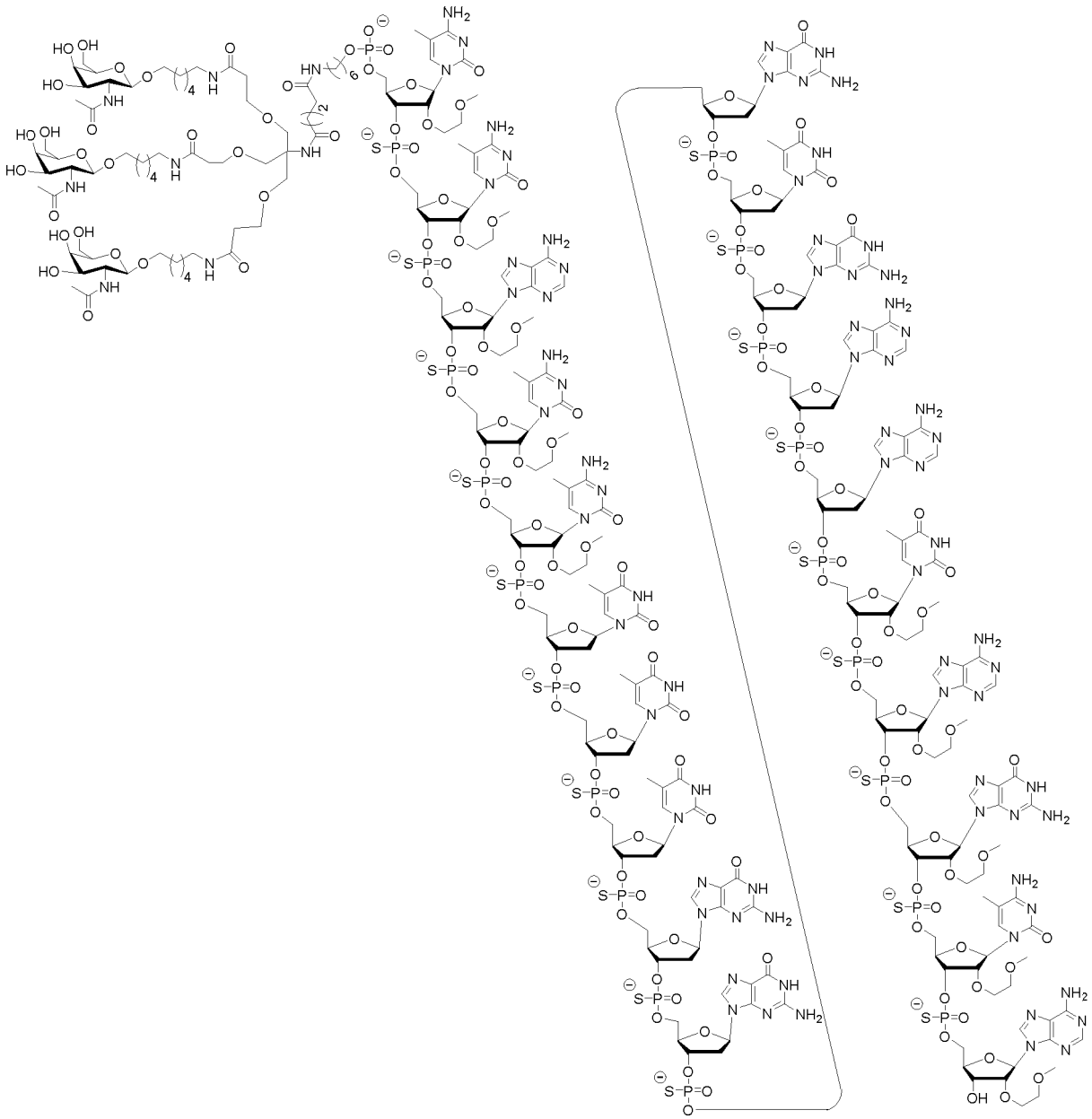


In certain embodiments, the conjugated antisense compound has the following structure: In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc on the 5' end. For instance, in certain embodiments, a compound comprises ISIS 532401 conjugated to GalNAc on the 5' end. . In further embodiments, the compound has the following chemical structure comprising or consisting of ISIS 532401 with 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:

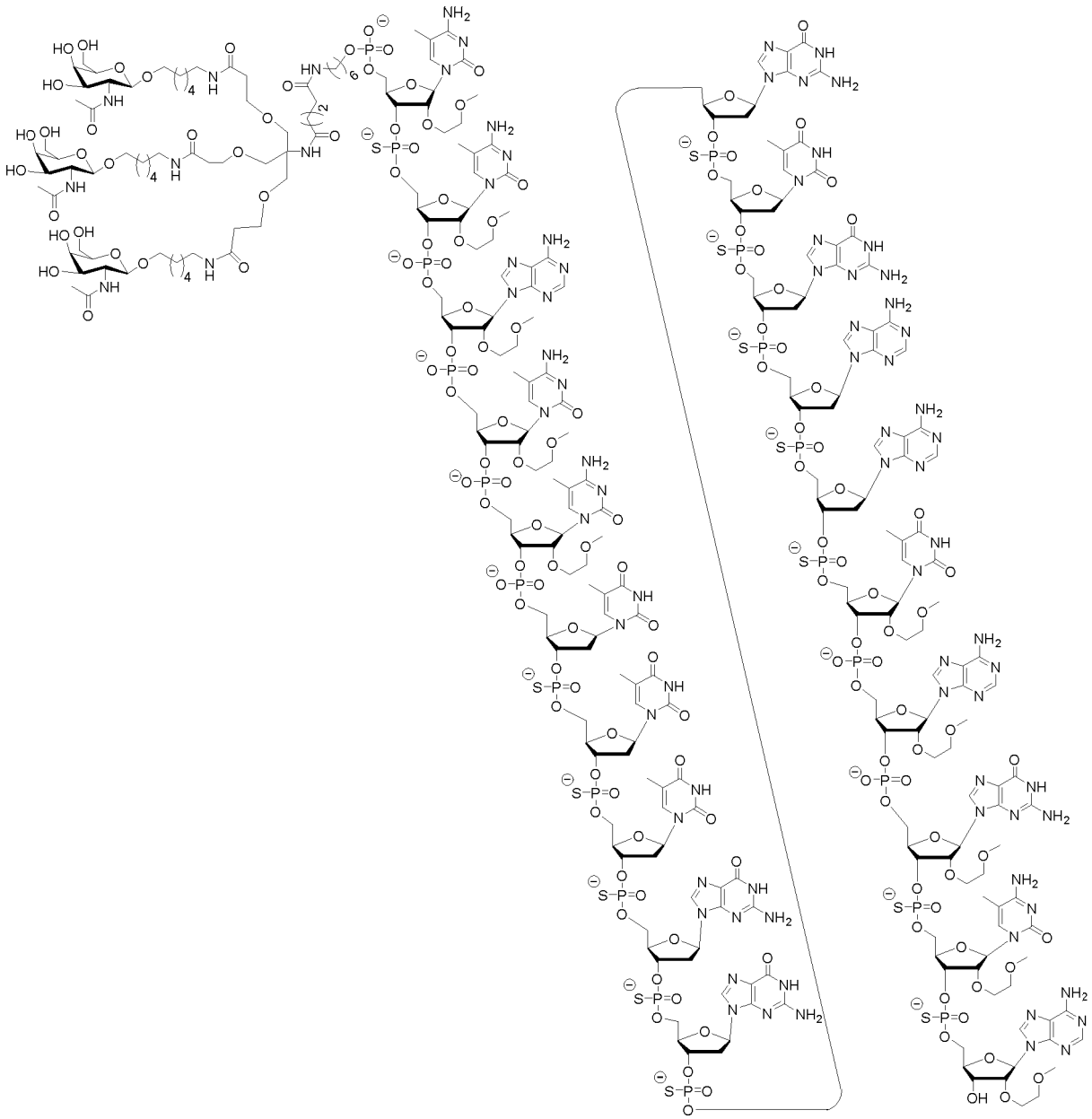


wherein X is a conjugate group comprising GalNAc.

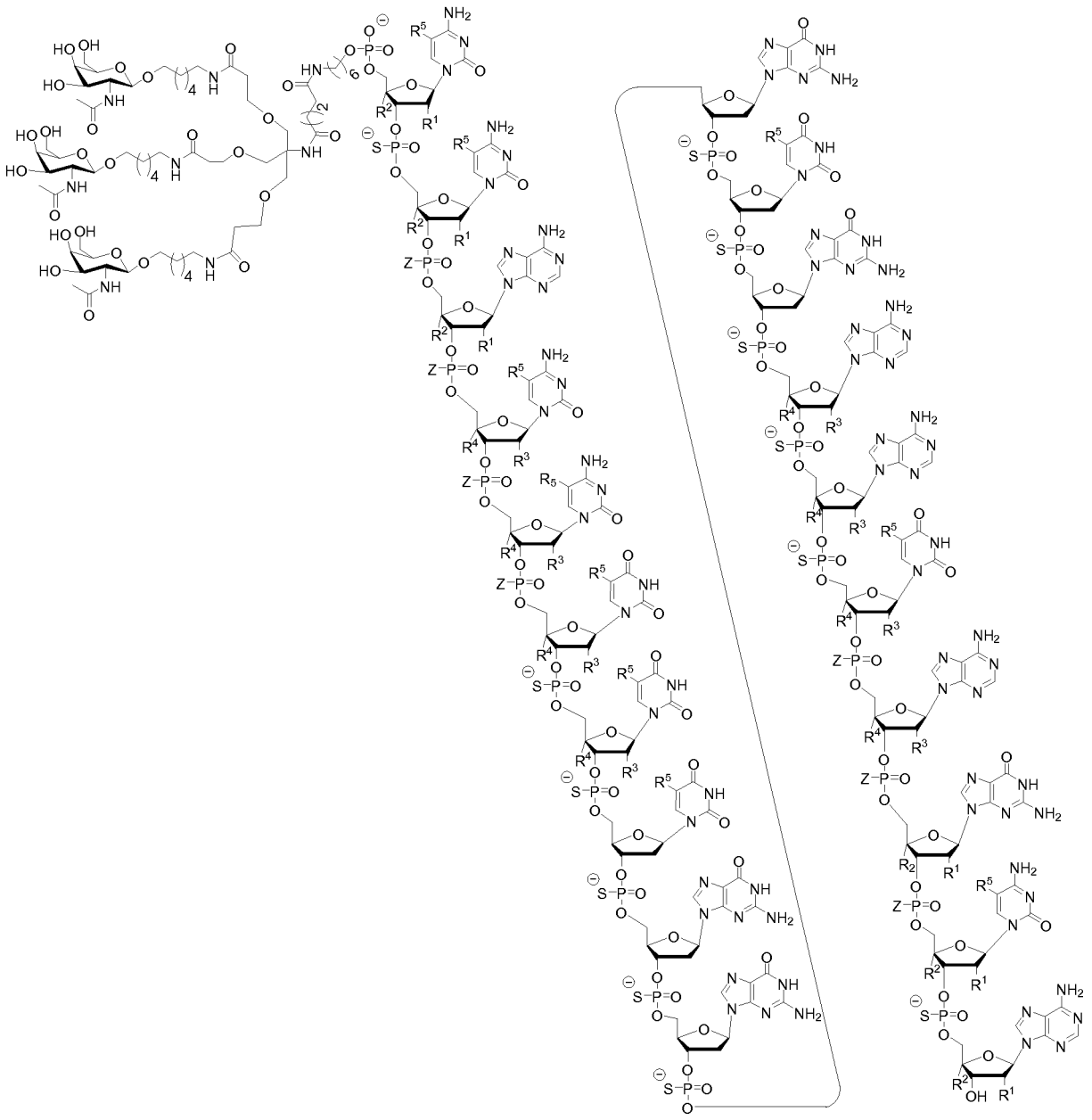
In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide com is a phosphorothioate linkage. In further embodiments, the compound comprises the sequence of ISIS 532401 conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide com is a phosphorothioate linkage. In such embodiments, the chemical structure is as follows:



In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide com is a phosphorothioate linkage or a phosphodiester linkage. In further embodiments, the compound comprises the sequence of ISIS 532401 conjugated to GalNAc, and wherein each internucleoside linkage of the oligonucleotide com is a phosphorothioate linkage or a phosphodiester linkage. In such embodiments, the chemical structure is as follows:



In certain embodiments, a compound comprises an ISIS oligonucleotide targeting GHR conjugated to GalNAc. In further such embodiments, the compound comprises the sequence of ISIS 532401 conjugated to GalNAc, and is represented by the following chemical structure:



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

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

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

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

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.

In vitro testing of antisense oligonucleotides

Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

Cells may be treated with antisense oligonucleotides when the cells reach approximately 60-80% confluency in culture.

One reagent commonly used to introduce antisense oligonucleotides into cultured cells includes the cationic lipid transfection reagent LIPOFECTIN (Invitrogen, Carlsbad, CA). Antisense oligonucleotides may be mixed with LIPOFECTIN in OPTI-MEM 1 (Invitrogen, Carlsbad, CA) to achieve the desired final concentration of antisense oligonucleotide and a LIPOFECTIN concentration that may range from 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE (Invitrogen, Carlsbad, CA). Antisense oligonucleotide is mixed with LIPOFECTAMINE in OPTI-MEM 1 reduced serum medium (Invitrogen, Carlsbad, CA) to achieve the desired concentration of antisense oligonucleotide and a LIPOFECTAMINE concentration that may range from 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another technique used to introduce antisense oligonucleotides into cultured cells includes electroporation.

Yet another technique used to introduce antisense oligonucleotides into cultured cells includes free uptake of the oligonucleotides by the cells.

Cells are treated with antisense oligonucleotides by routine methods. Cells may be harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein. In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

The concentration of antisense oligonucleotide used varies from cell line to cell line. Methods to determine the optimal antisense oligonucleotide concentration for a particular cell line are well known in the art. Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM when transfected with LIPOFECTAMINE. Antisense oligonucleotides are used at higher concentrations ranging from 625 to 20,000 nM when transfected using electroporation.

RNA Isolation

RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. RNA is prepared using methods well known in the art, for example, using the TRIZOL Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocols.

Certain Indications

Certain embodiments provided herein relate to methods of treating, preventing, or ameliorating a disease associated with excess growth hormone in a subject by administering a GHR specific inhibitor, such as an antisense compound or oligonucleotide targeted to GHR. In certain aspects, the disease associated with

excess growth hormone is acromegaly. In certain aspects, the disease associated with excess growth hormone is gigantism.

Certain embodiments provide a method of treating, preventing, or ameliorating acromegaly in a subject by administering a GHR specific inhibitor, such as an antisense compound or oligonucleotide targeted to GHR. Acromegaly is a disease associated with excess growth hormone (GH). In over 90 percent of acromegaly patients, the overproduction of growth hormones is caused by a benign tumor of the pituitary gland, called an adenoma, which produces excess growth hormone and compresses surrounding brain tissues. Expansion of the adenoma can cause headaches and visual impairment that often accompany acromegaly. In some instances, acromegaly is caused by tumors of the pancreas, lungs, or adrenal glands that lead to an excess of GH, either by producing GH or by producing Growth Hormone Releasing Hormone (GHRH), the hormone that stimulates the pituitary to make GH.

Acromegaly most commonly affects adults in middle age and can result in severe disfigurement, complicating conditions, and premature death. Because of its pathogenesis and slow progression, acromegaly often goes undiagnosed until changes in external features become noticeable, such as changes in the face. Acromegaly is often associated with gigantism.

Features of acromegaly include soft tissue swelling resulting in enlargement of the hands, feet, nose, lips and ears, and a general thickening of the skin; soft tissue swelling of internal organs, such as the heart and kidney; vocal cord swelling resulting in a low voice and slow speech; expansion of the skull; pronounced eyebrow protrusion, often with ocular distension; pronounced lower jaw protrusion and enlargement of the tongue; teeth gapping; and carpal tunnel syndrome. In certain embodiments, any one or combination of these features of acromegaly can be treated, prevented, or ameliorated by administering a compound or composition targeted to GHR provided herein.

EXAMPLES

Non-limiting 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 recited in the present application is incorporated herein by reference in its entirety.

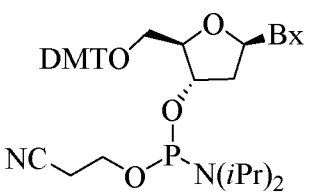
It is understood that the sequence set forth in each SEQ ID NO in the examples contained herein is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such,

antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

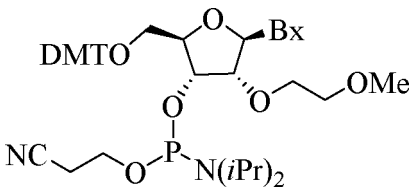
The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular 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

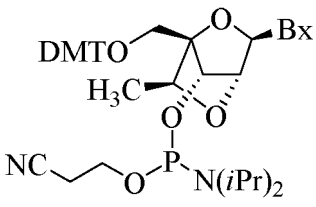
Compounds 1, 1a and 2 were prepared as per the procedures well known in the art as described in the specification herein (see Seth et al., Bioorg. Med. Chem., 2011, 21(4), 1122-1125, J. Org. Chem., 2010, 75(5), 1569-1581, Nucleic Acids Symposium Series, 2008, 52(1), 553-554); and also see published PCT 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).



1



1a

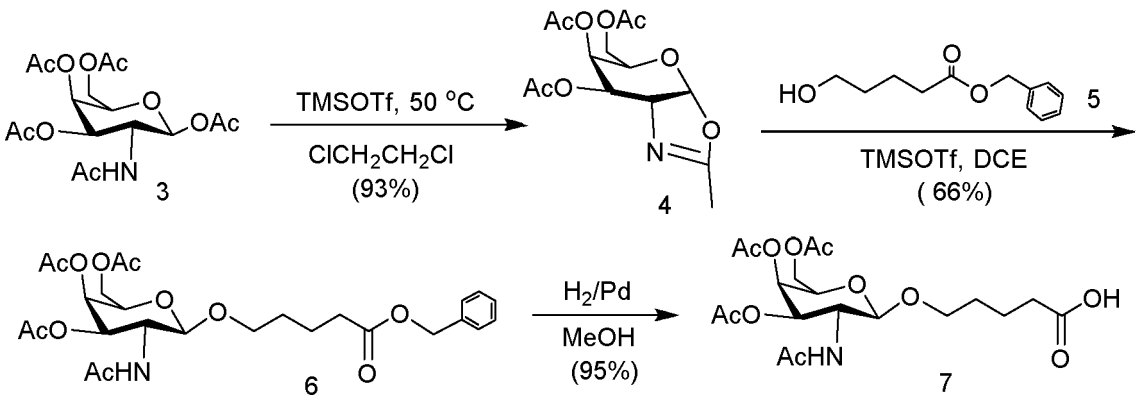


2

Bx is a heterocyclic base;

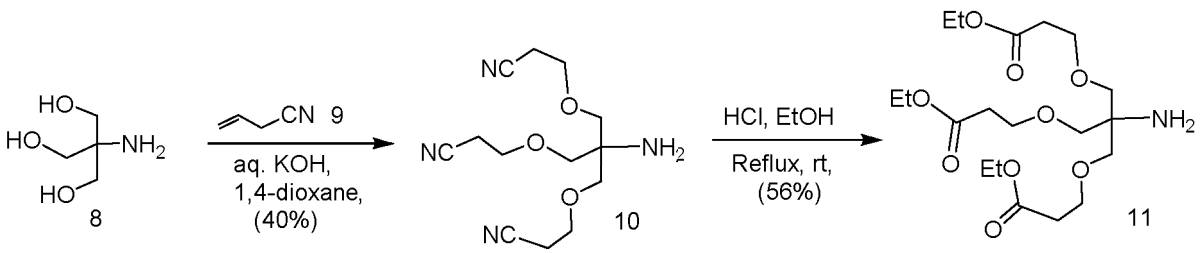
Example 2: Preparation of Compound 7

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).



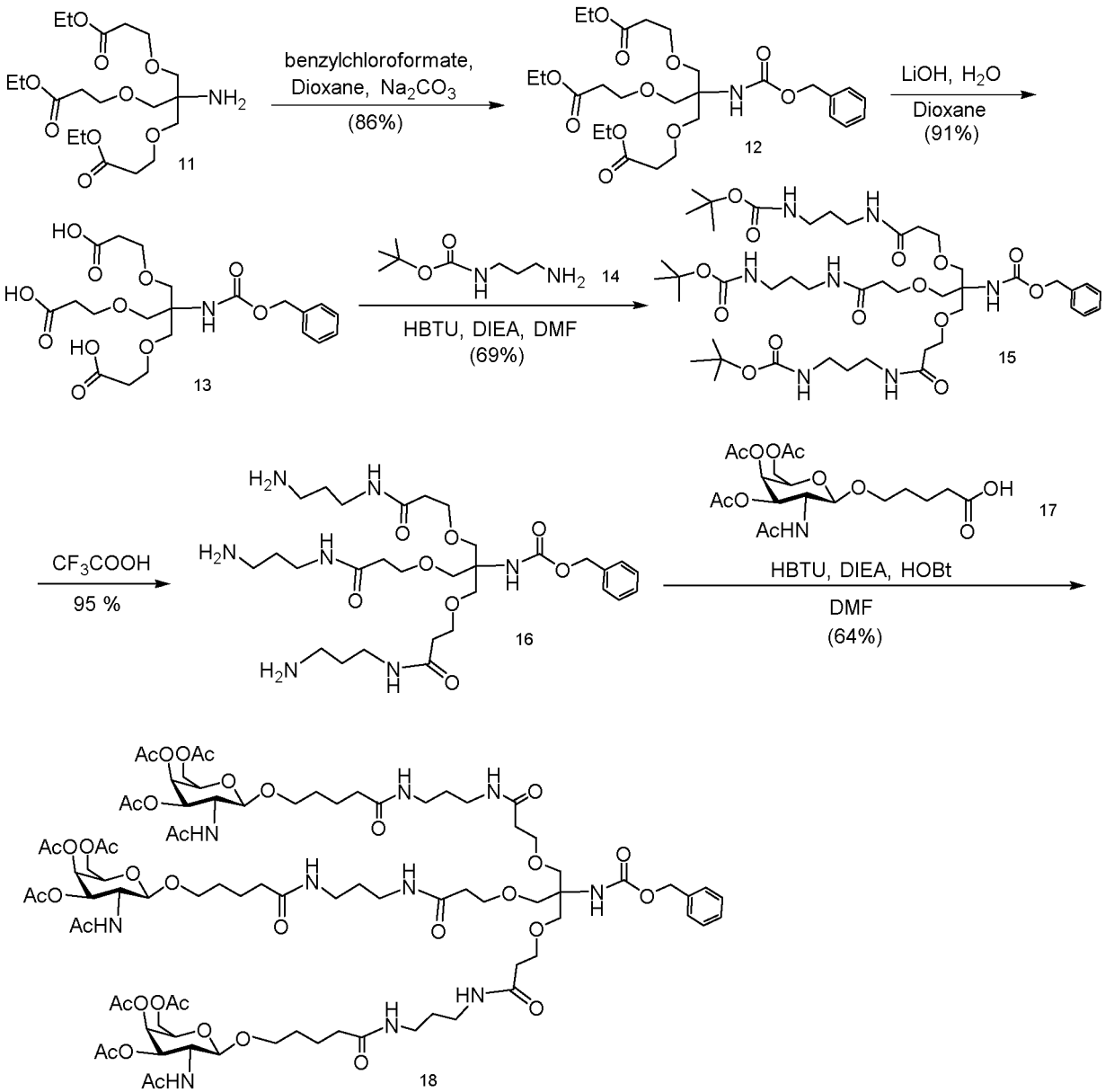
Example 3: Preparation of Compound 11

Compounds 8 and 9 are commercially available.



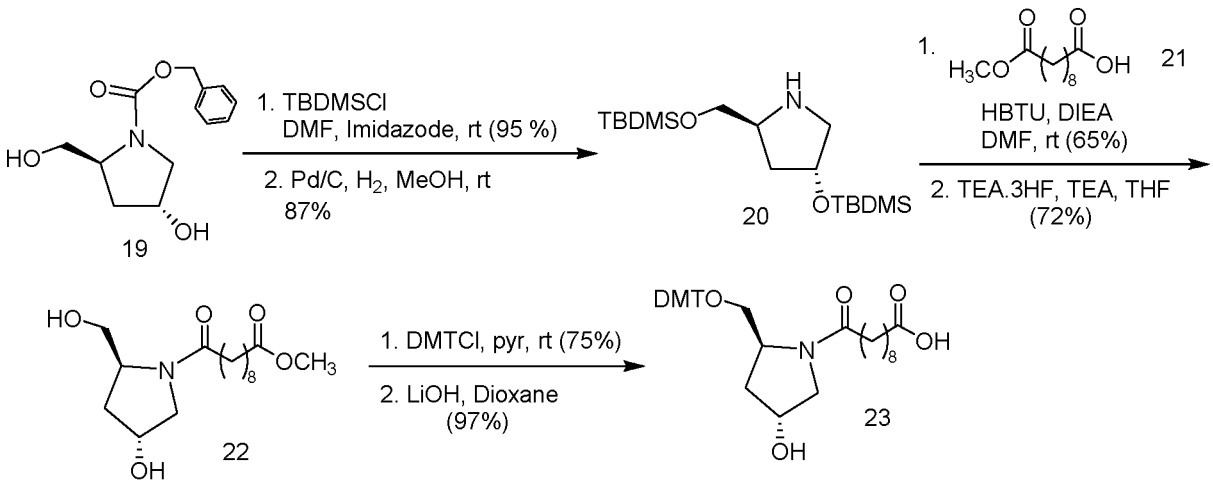
Example 4: Preparation of Compound 18

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.


benzylchloroformate,
Dioxane, Na2CO3
(86%)
LiOH, H2O
Dioxane
(91%)
HBTU, DIEA, DMF
(69%)
CF3COOH
95 %
HBTU, DIEA, HOBt
DMF
(64%)

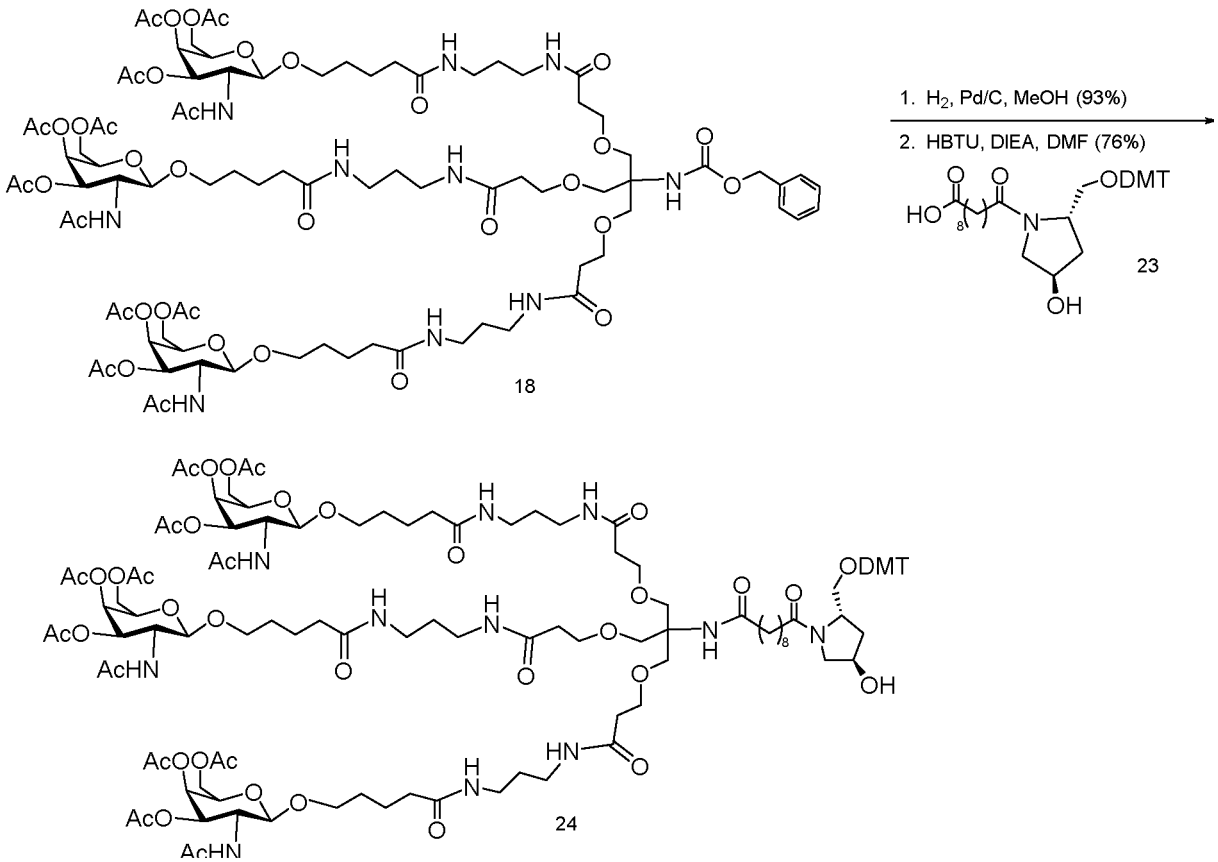
Example 5: Preparation of Compound 23

Compounds 19 and 21 are commercially available.



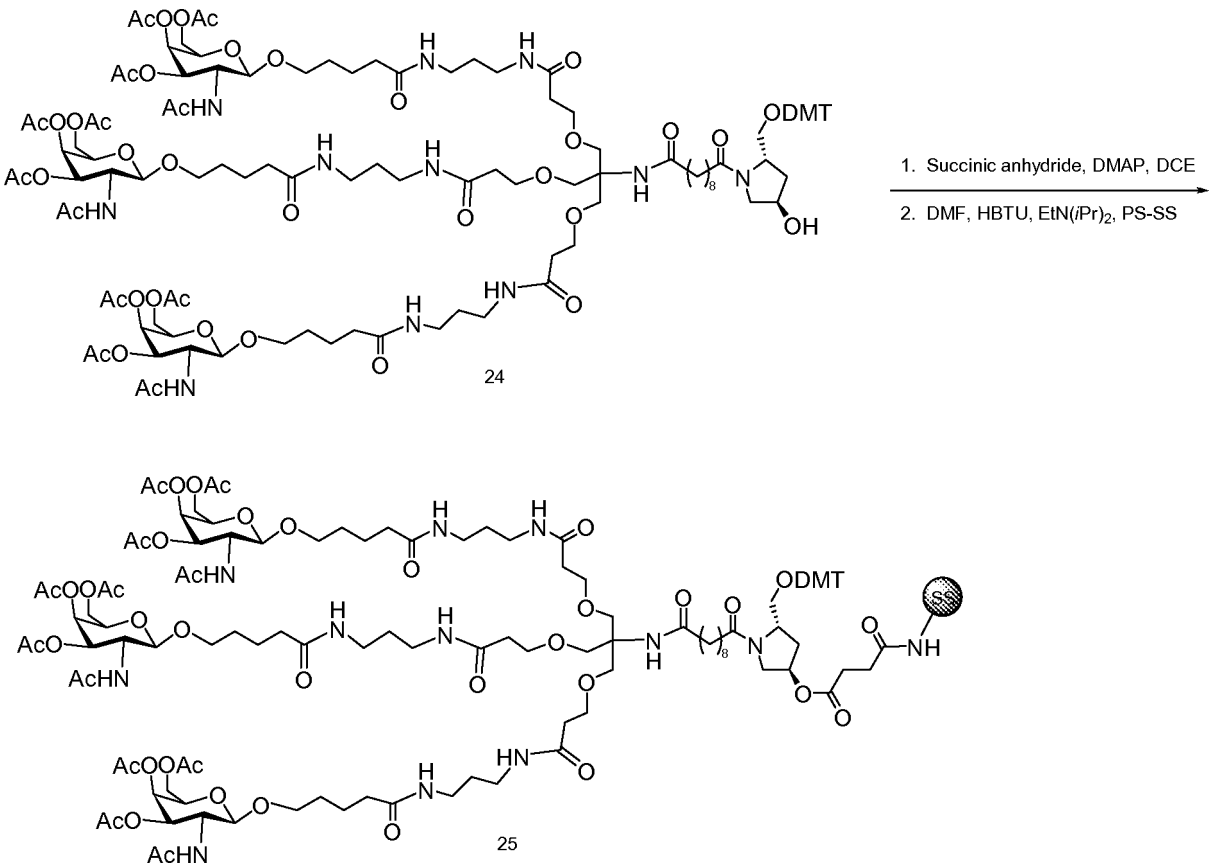
Example 6: Preparation of Compound 24

Compounds 18 and 23 were prepared as per the procedures illustrated in Examples 4 and 5.



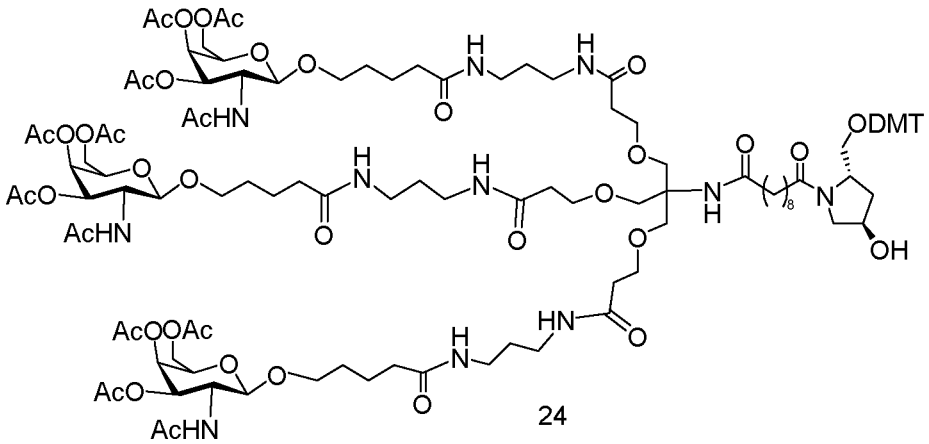
Example 7: Preparation of Compound 25

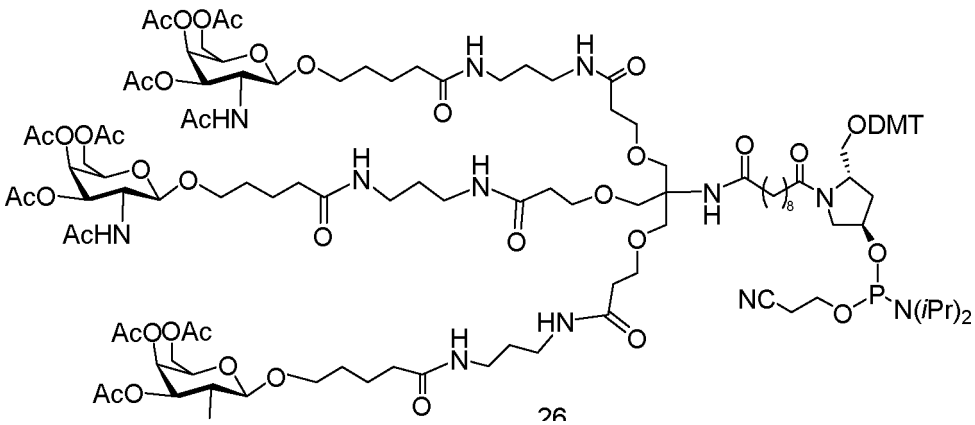
Compound 24 was prepared as per the procedures illustrated in Example 6.



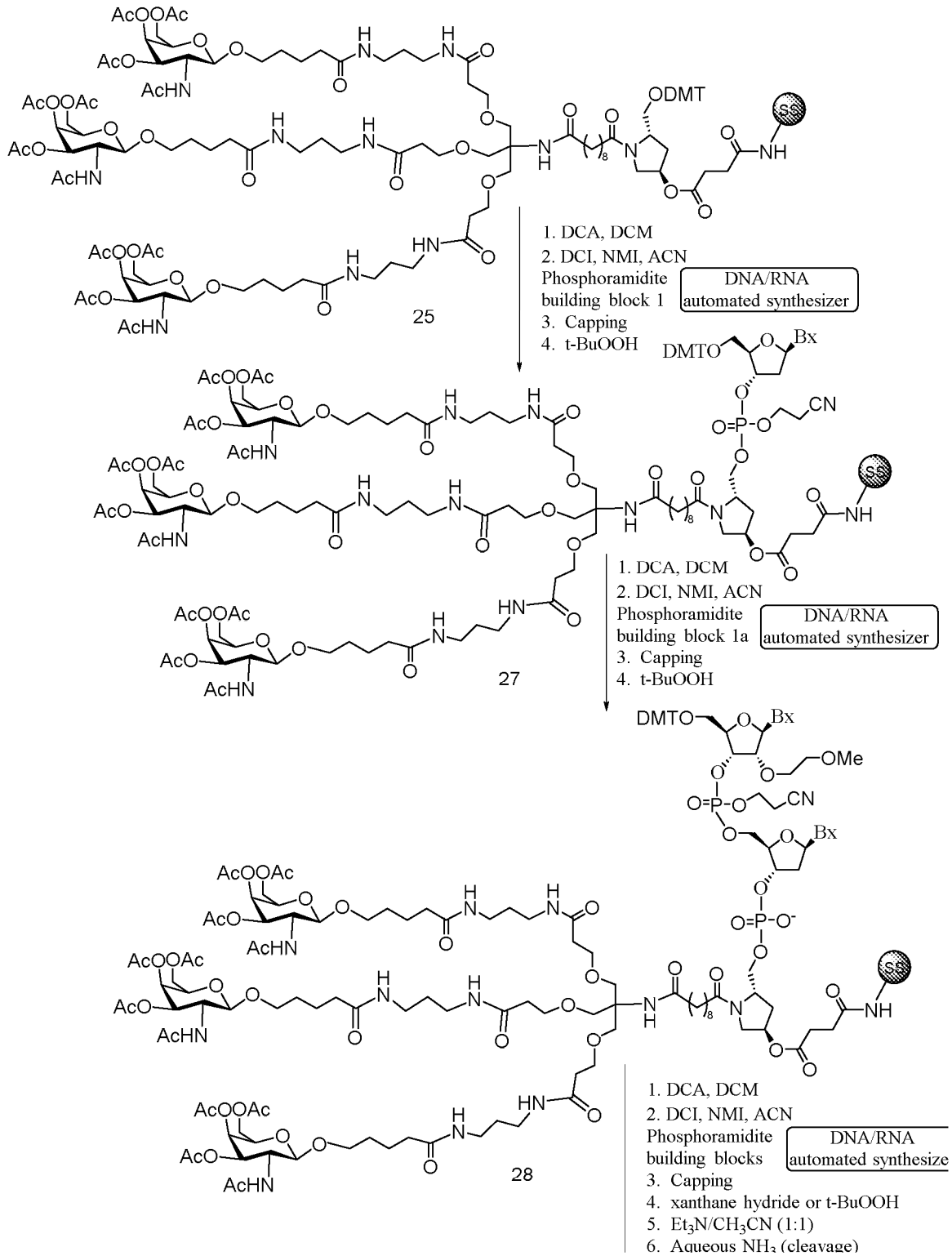
Example 8: Preparation of Compound 26

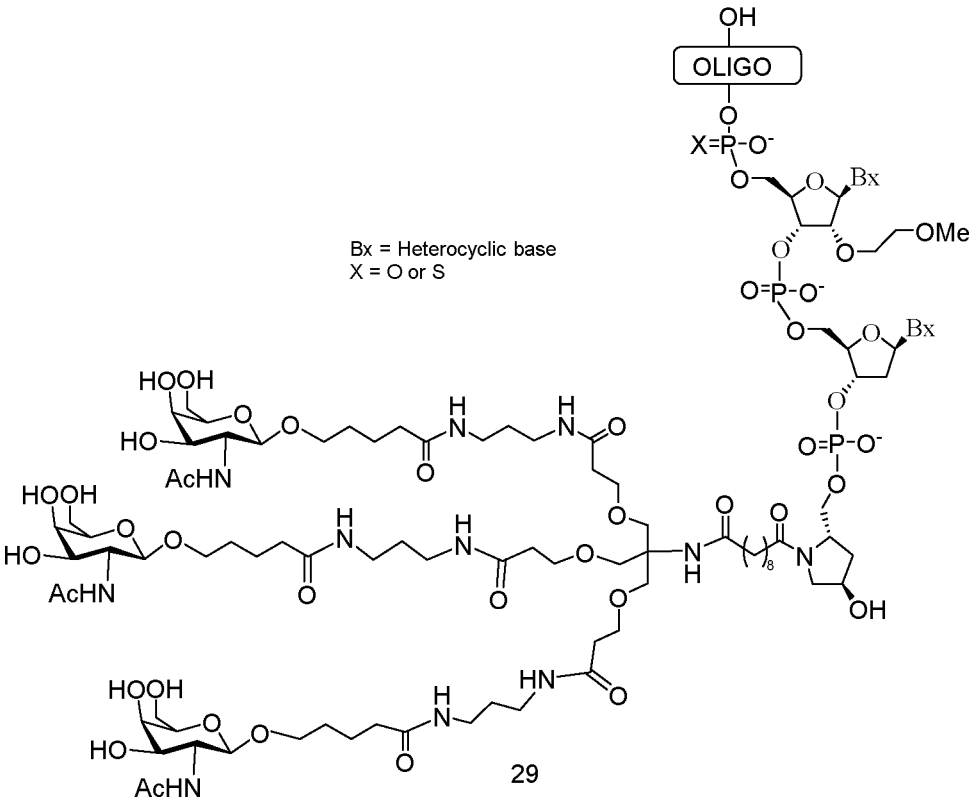
Compound 24 is prepared as per the procedures illustrated in Example 6.



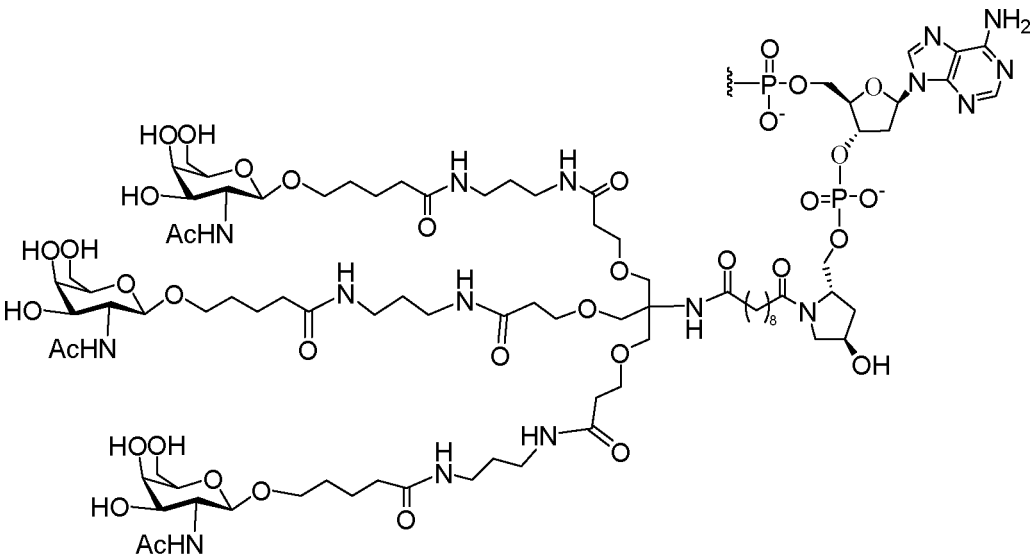


Example 9: General preparation of conjugated ASOs comprising GalNAc$_3$-1 at the 3' terminus, Compound 29

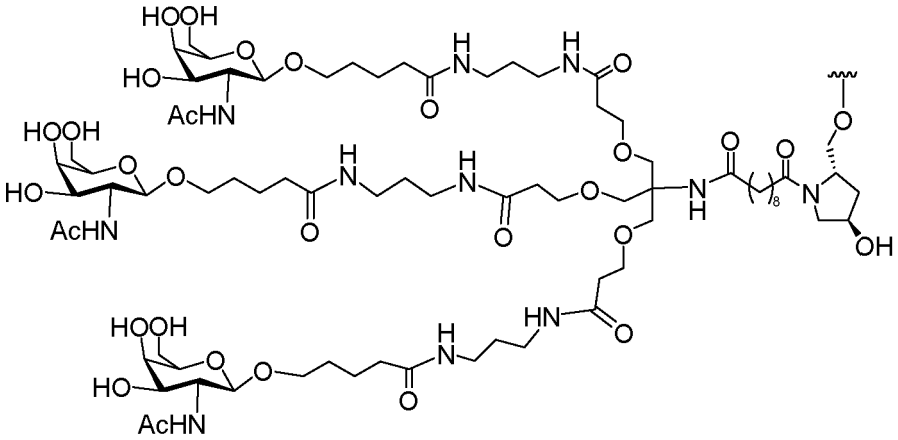




Wherein the protected **GalNAc$_3$-1** has the structure:

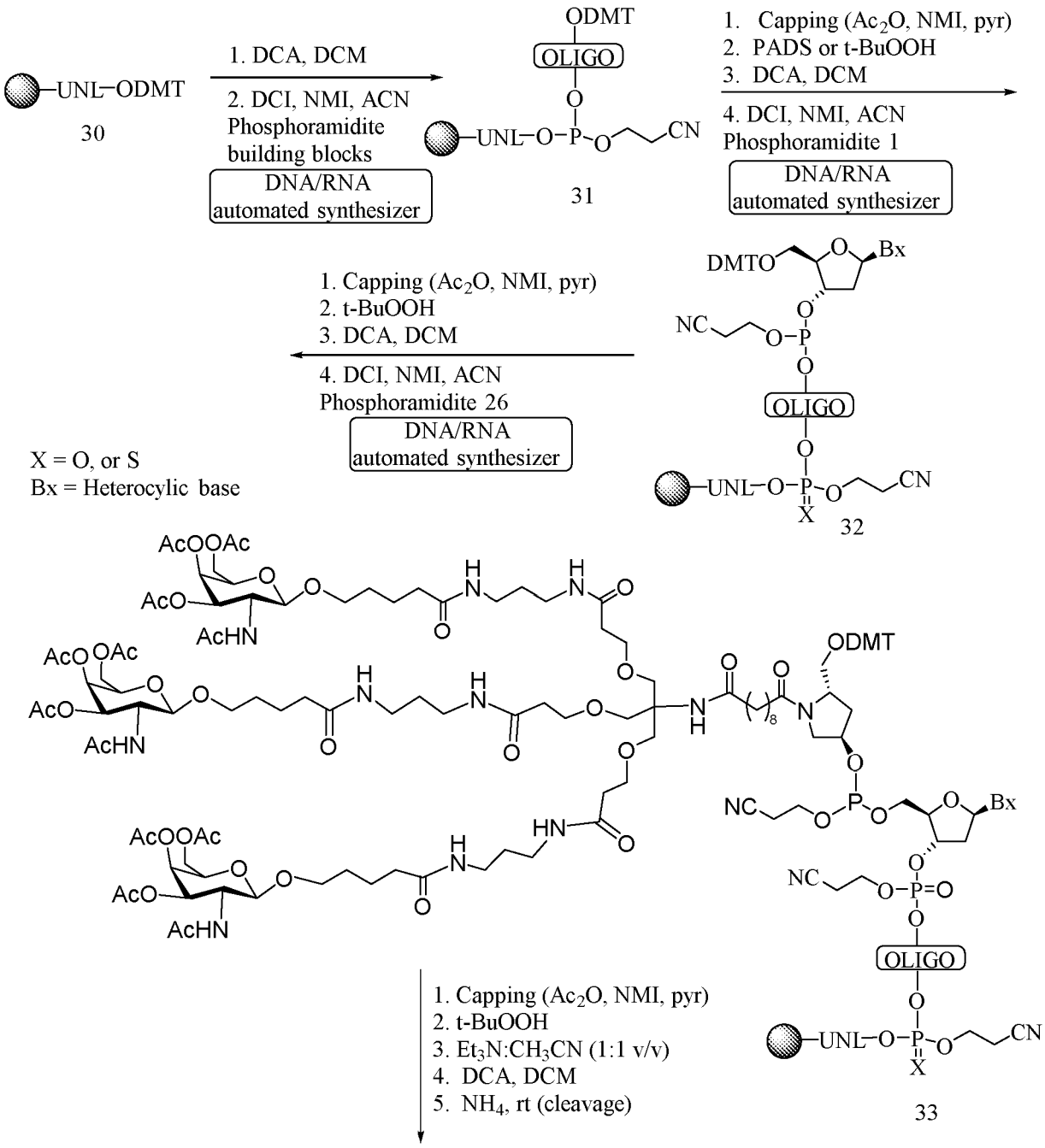


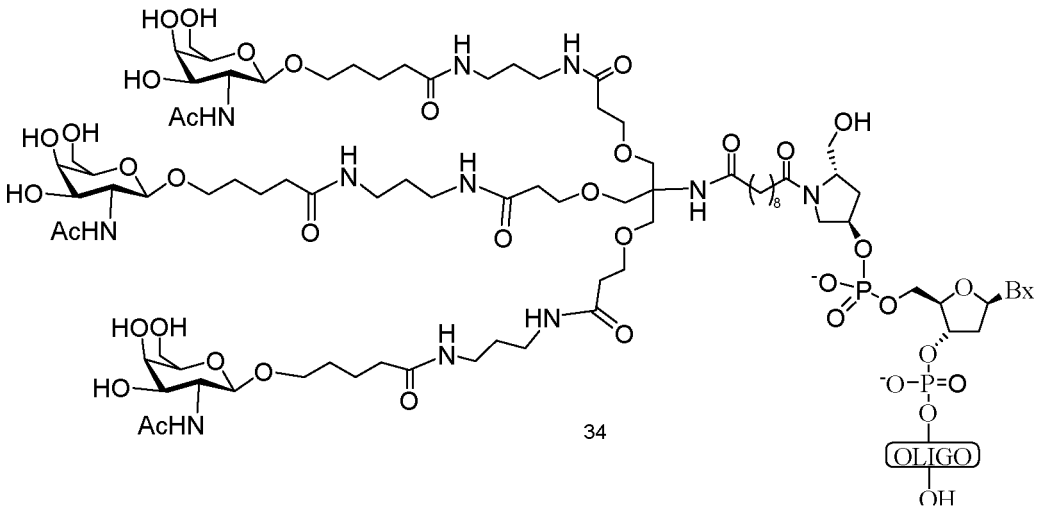
The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-1 (GalNAc$_3$-1$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-1$_a$ has the formula:



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

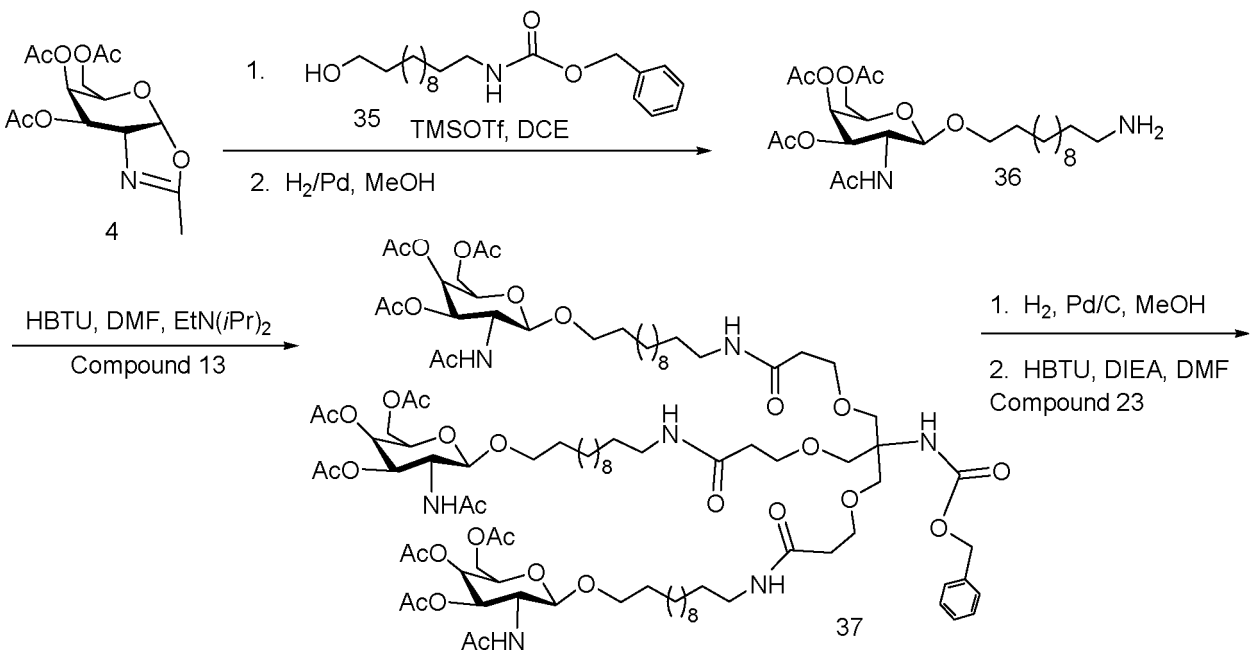


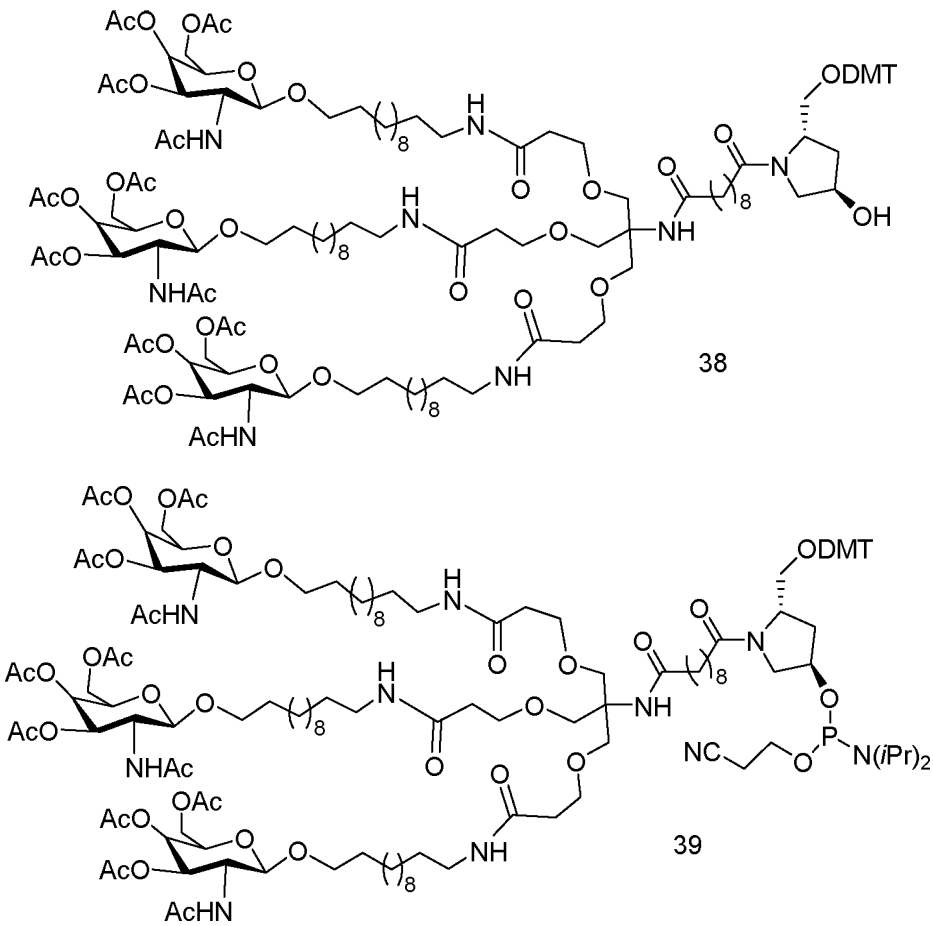


34

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

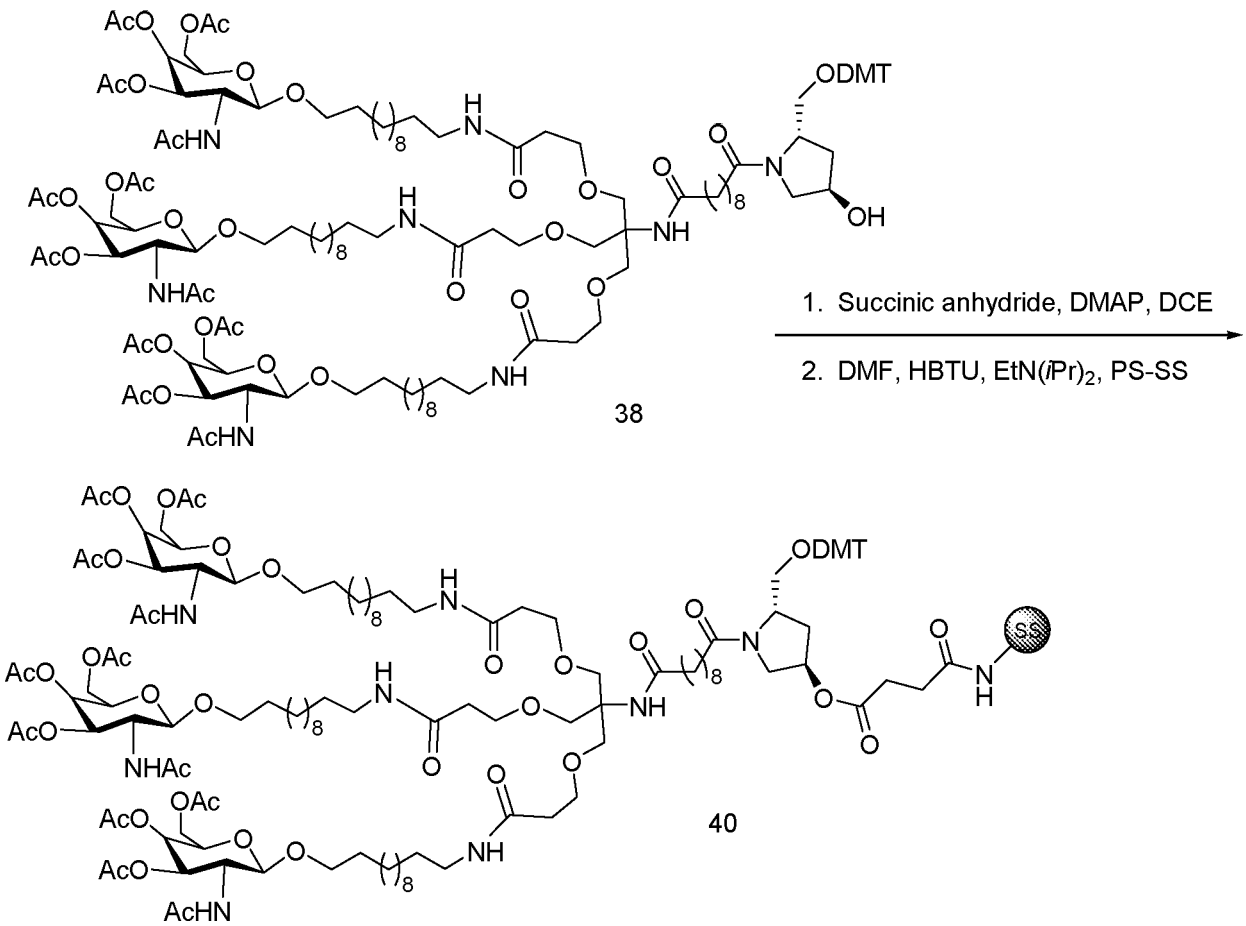




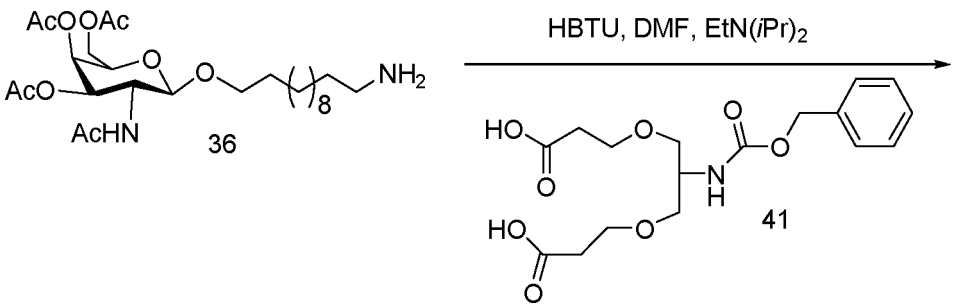
Compounds 4, 13 and 23 were prepared as per the procedures illustrated in Examples 2, 4, and 5. Compound 35 is prepared using similar procedures published in Rouchaud *et al., Eur. J. Org. Chem.,* 2011, *12*, 2346-2353.

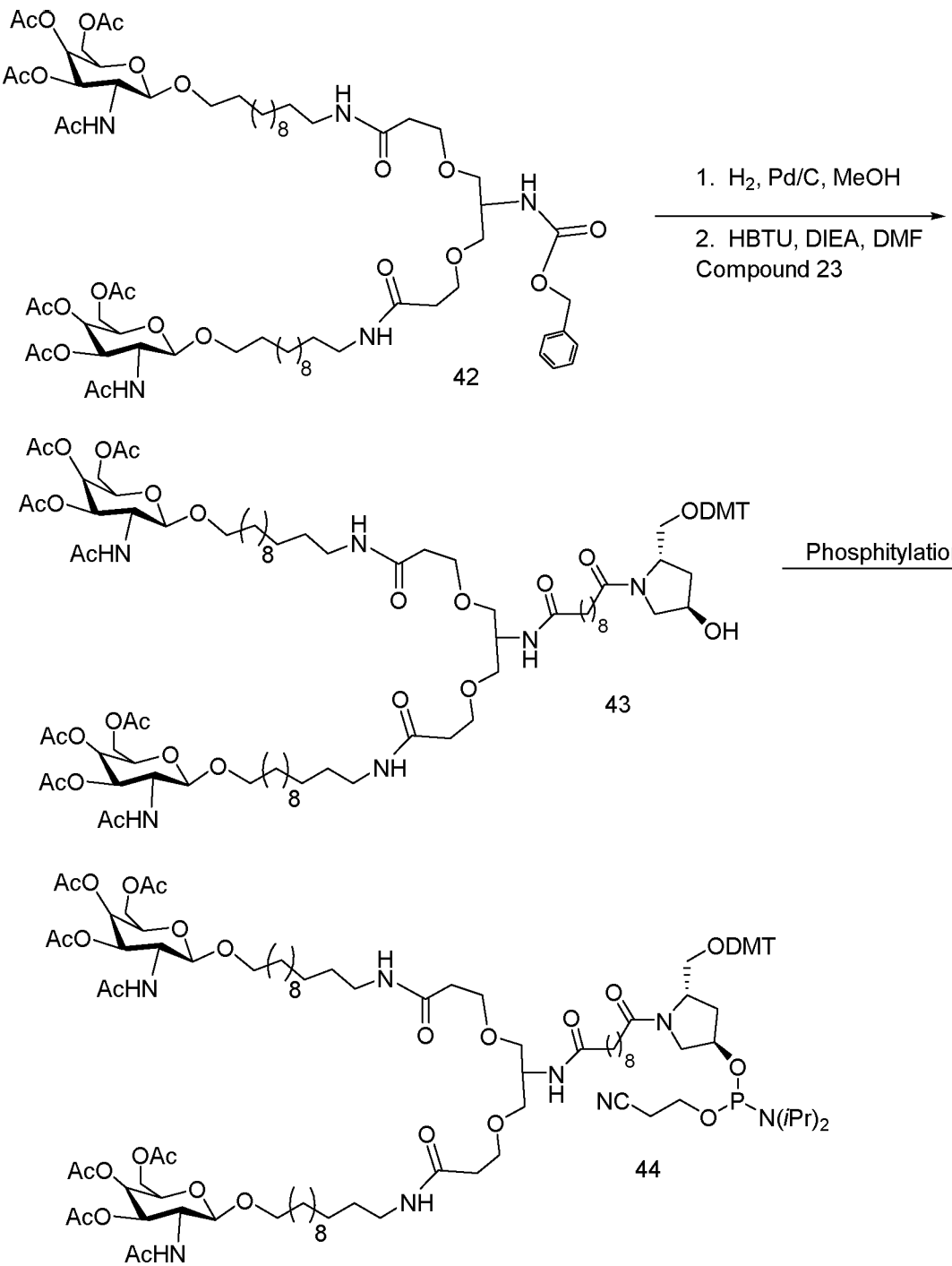
Example 12: Preparation of Compound 40

Compound 38 is prepared as per the procedures illustrated in Example 11.



Example 13: Preparation of Compound 44

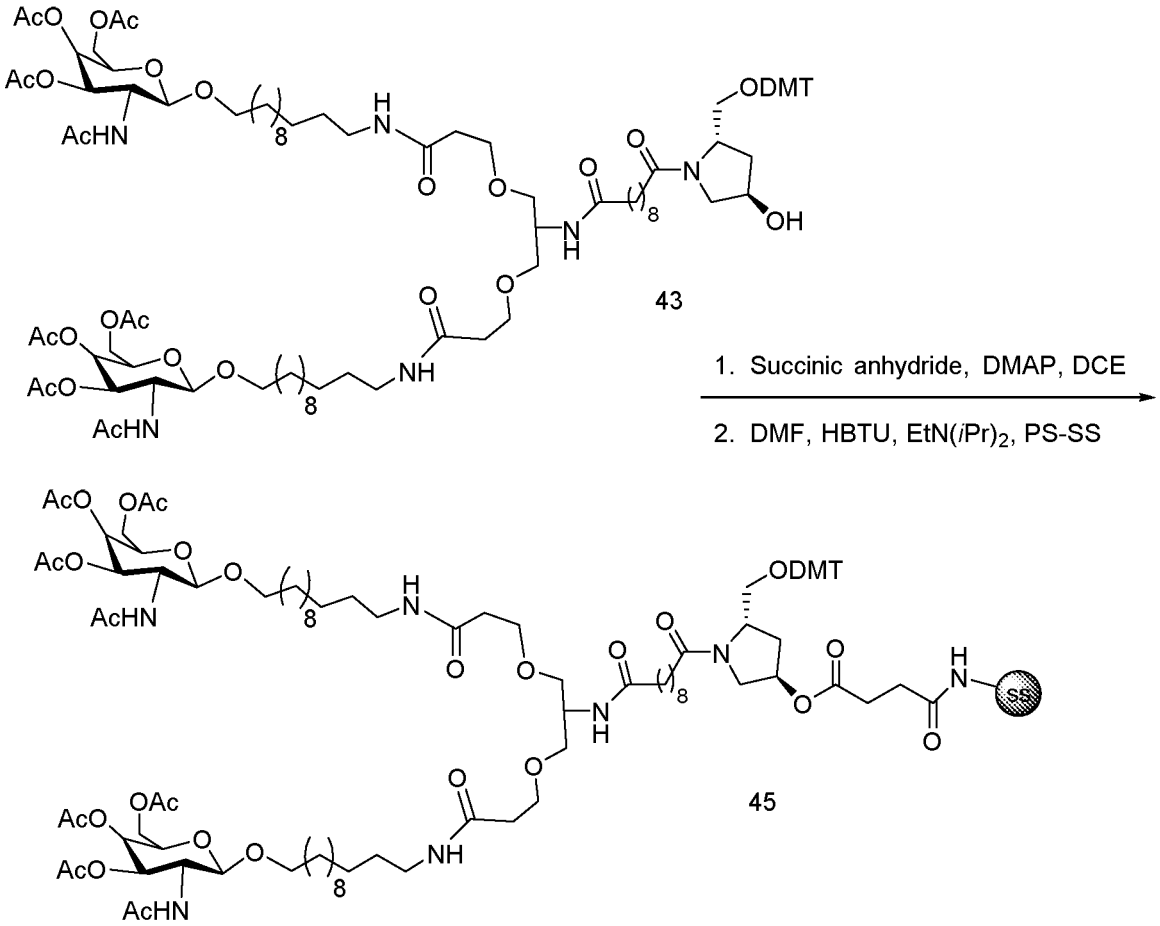




Compounds 23 and 36 are prepared as per the procedures illustrated in Examples 5 and 11. Compound 41 is prepared using similar procedures published in WO 2009082607.

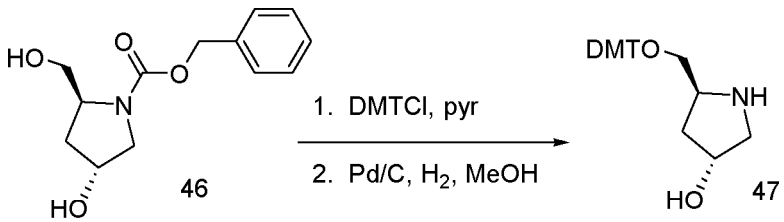
Example 14: Preparation of Compound 45

Compound 43 is prepared as per the procedures illustrated in Example 13.

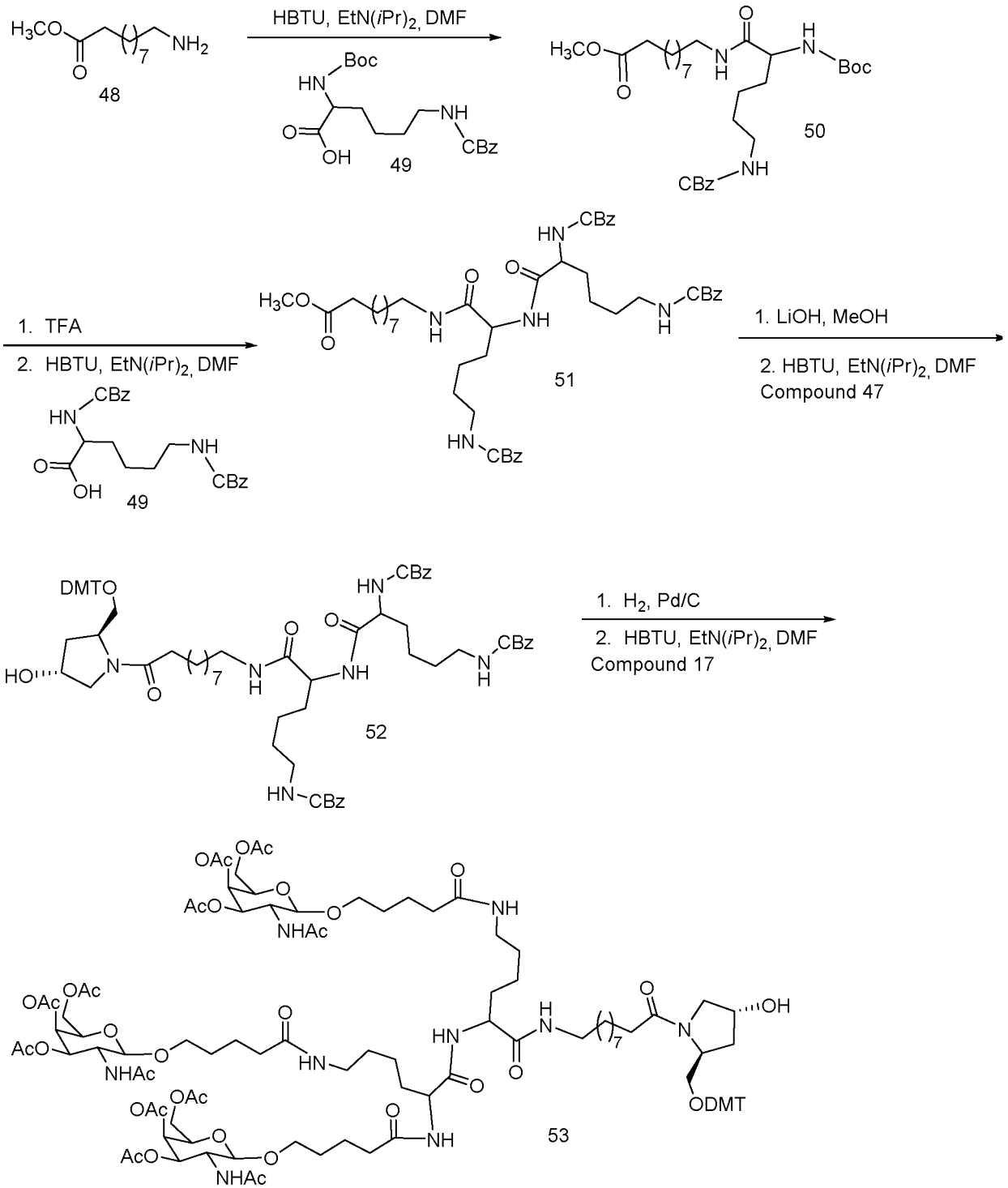


Example 15: Preparation of Compound 47

Compound 46 is commercially available.

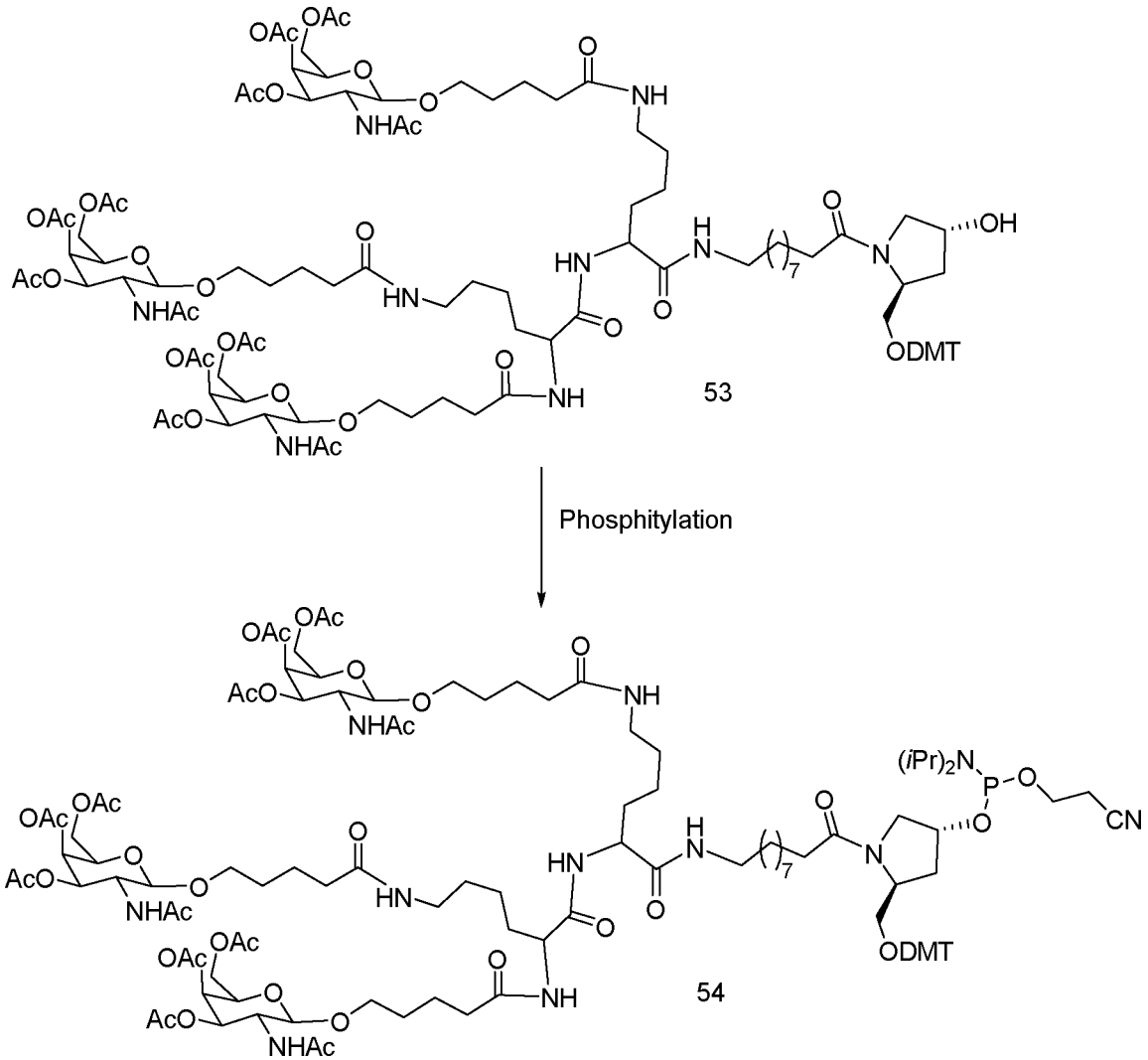


Example 16: Preparation of Compound 53



Compounds 48 and 49 are commercially available. Compounds 17 and 47 are prepared as per the procedures illustrated in Examples 4 and 15.

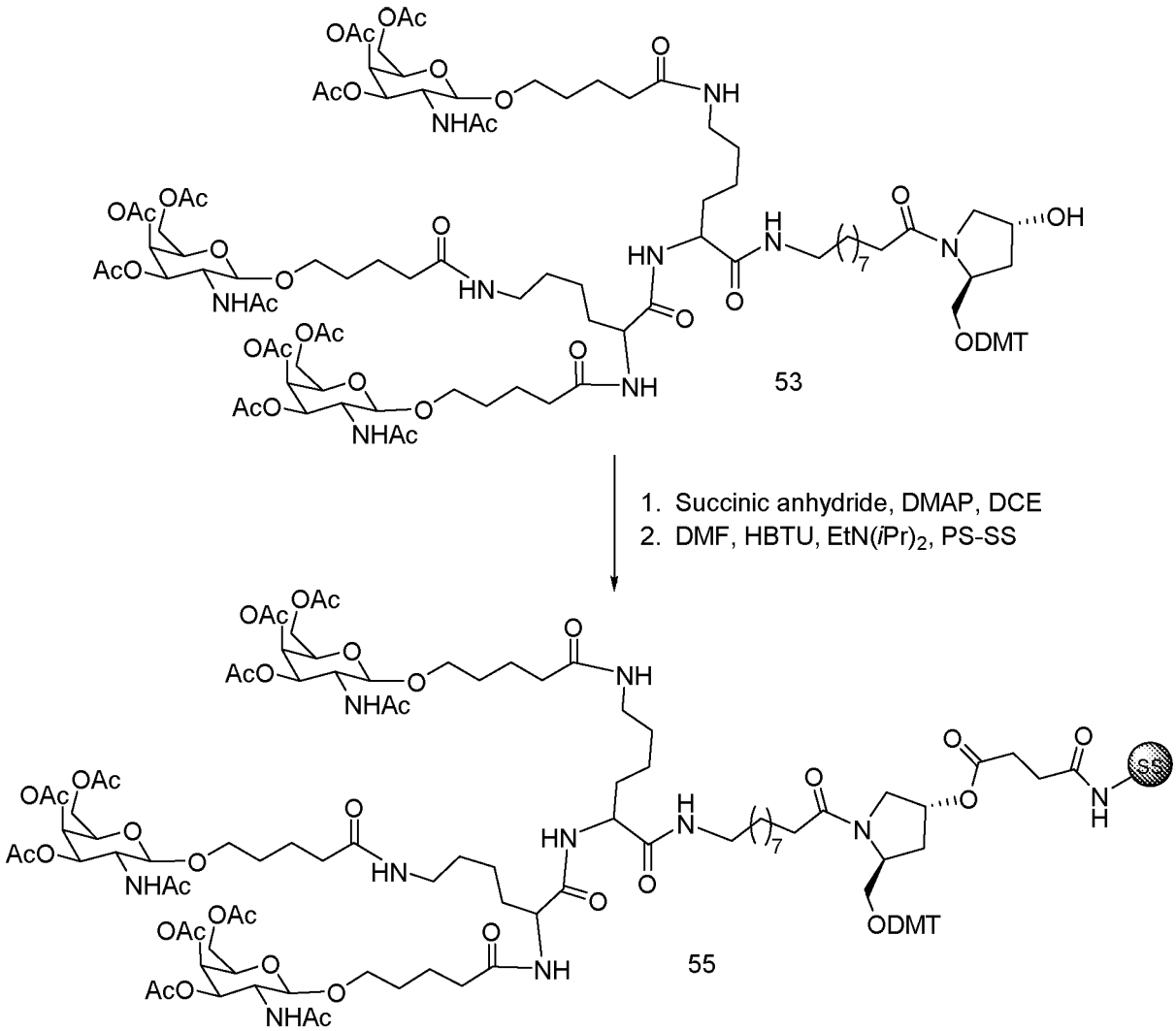
Example 17: Preparation of Compound 54



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	2296
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	2297

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	2297
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	2298
ISIS 651900	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do}}$-**GalNAc$_3-1_a$**	SRB-1	6721.1	6719.4	2299

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	2296
	0.75	42				
	2.25	32				
	6.75	19				
ISIS 647535	0.08	50	0.074	**GalNAc$_3$-1**	PS/20	2297
	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	2296
	0.75	51				
	2.25	23				
	6.75	13				

ISIS 647535	0.08	72	0.19	**GalNAc$_3$-1**	PS/20	2297
	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	2296
	0.75	46				
	2.25	21				
	6.75	12				
ISIS 647535	0.08	65	0.13	**GalNAc$_3$-1**	PS/20	2297
	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	2296
	0.75	164			
	2.25	110			
	6.75	82			
ISIS 647535	0.08	230	**GalNAc$_3$-1**	PS/20	2297
	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	2296
	0.75	27	12			
	2.25	50	4			
	6.75	45	2			
ISIS 647535	0.08	21	21	**GalNAc$_3$-1**	PS/20	2297
	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

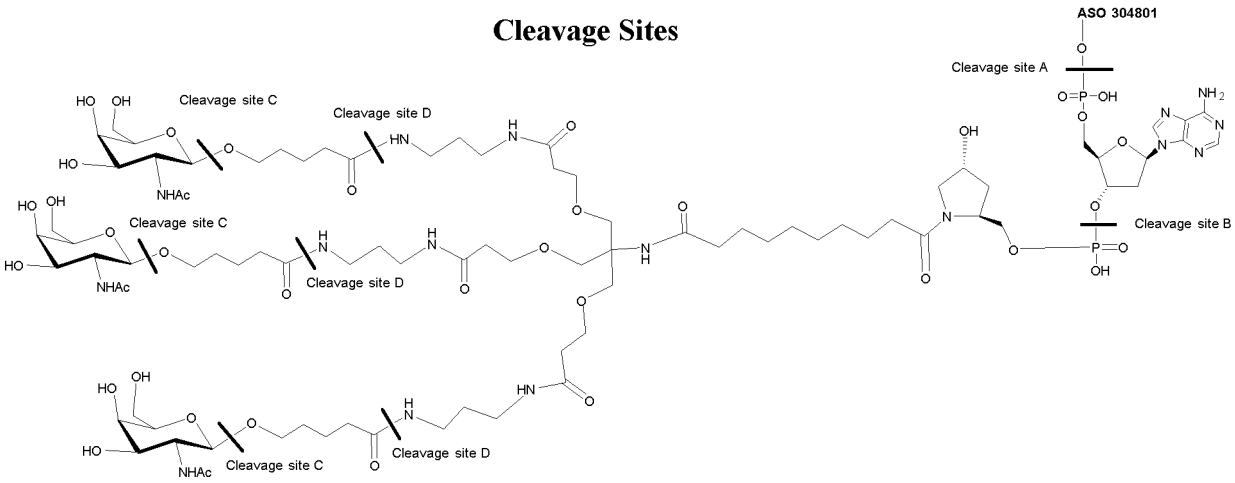
ASO	Dose (μmol/kg)	Liver (μg/g)	Kidney (μg/g)	Liver EC_{50} (μg/g)	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
ISIS 304801	0.1	5.2	2.1	53	None	PS/20	2296
	0.8	62.8	119.6				
	2.3	142.3	191.5				
	6.8	202.3	337.7				
ISIS 647535	0.1	3.8	0.7	3.8	**GalNAc$_3$-1**	PS/20	2297
	0.8	72.7	34.3				
	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.

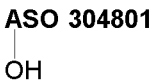
Table 23a
Observed full length metabolites of ISIS 647535

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

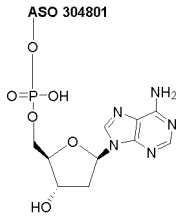
Cleavage Sites

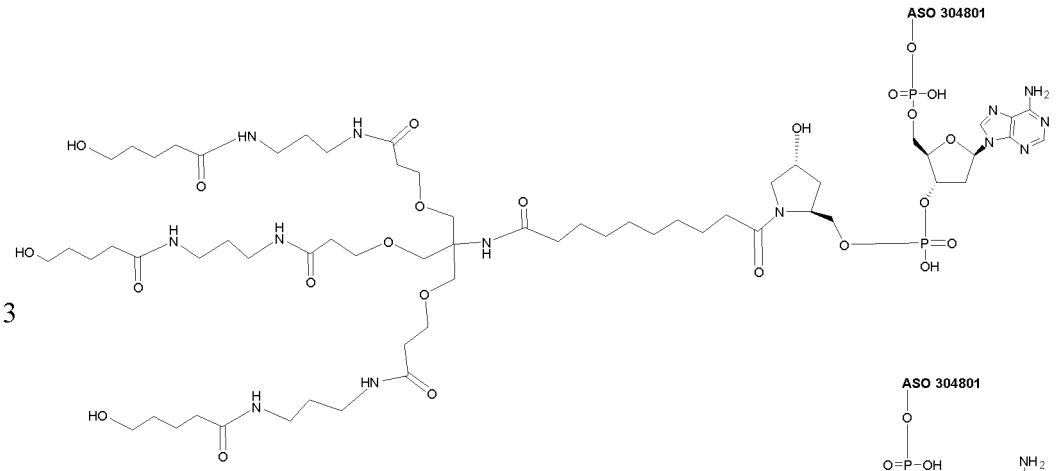


Metabolite 1

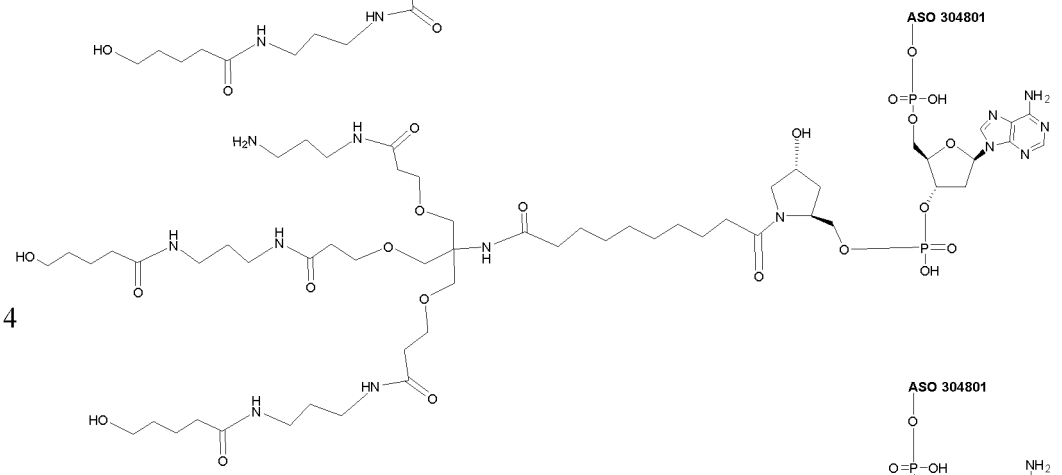


Metabolite 2

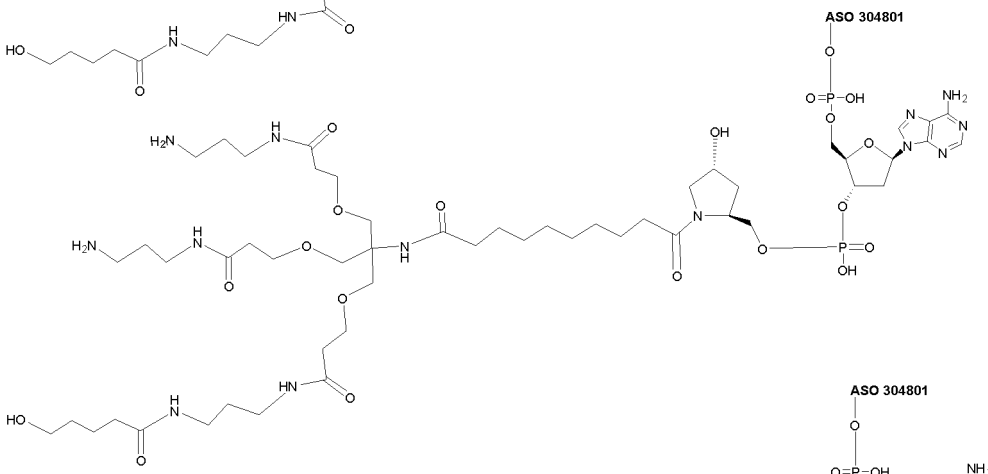




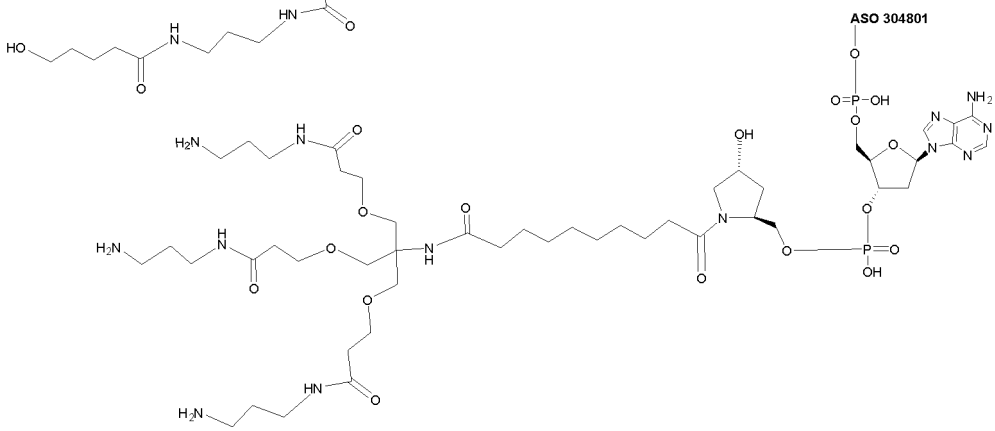
Metabolite 3



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 the 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	2296
	3	92				
	10	71				
	30	40				
ISIS 647535	0.3	98	1.9	**$GalNAc_3$-1**	PS/20	2297
	1	70				

	3	33				
	10	20				
ISIS 647536	0.3	103	1.7	**GalNAc$_3$-1**	PS/PO/20	2297
	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	2296
	3	92				
	10	71				
	30	40				
ISIS 647535	0.3	98	2.1	**GalNAc$_3$-1**	PS/20	2297
	1	70				
	3	33				
	10	20				
ISIS 647536	0.3	103	1.8	**GalNAc$_3$-1**	PS/PO/20	2297
	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	2296
	3	92				
	10	70				
	30	47				
ISIS 647535	0.3	100	2.2	**GalNAc$_3$-1**	PS/20	2297
	1	70				
	3	34				
	10	23				
ISIS 647536	0.3	95	1.9	**GalNAc$_3$-1**	PS/PO/20	2297
	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	1	104	None	PS/20	2296

304801	3	96			
	10	86			
	30	72			
ISIS 647535	0.3	93	**GalNAc$_3$-1**	PS/20	2297
	1	85			
	3	61			
	10	53			
ISIS 647536	0.3	115	**GalNAc$_3$-1**	PS/PO/20	2297
	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	2296
	3	186	79			
	10	226	63			
	30	240	46			
ISIS 647535	0.3	98	86	**GalNAc$_3$-1**	PS/20	2297
	1	214	67			
	3	212	39			
	10	218	35			
ISIS 647536	0.3	143	89	**GalNAc$_3$-1**	PS/PO/20	2297
	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	2298
	2	55					
	7	12					
	20	3					
ISIS 651900	0.07	98	0.3	**GalNAc$_3$-1**		PS/14	2299
	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	2300
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	2301
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	2296
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	2297
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	2296

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	2301
ISIS 304801	0.07	106.55	1,522	None	PS/20	2296
ISIS 647535	0.12	138	1,150	**GalNAc$_3$-1**	PS/20	2297
ISIS 616468	0.32	71.52	224	None	PS/PO/20	2296

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	2296
ISIS 647535	0.31	**GalNAc$_3$-1**	PS/20	2297

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 lack 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.

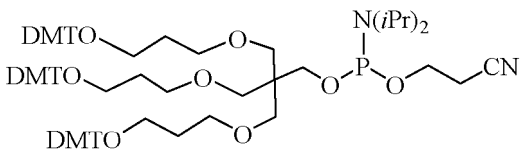
These results show reduction in potency for antisense compounds with PO/PS (ISIS 616468) in the wings relative to full PS (ISIS 304801).

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	2296
ISIS 616468	25 mg/kg/wk for 2 wks	40	None	14 PS/6 PO	2296

Example 27: Compound 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.

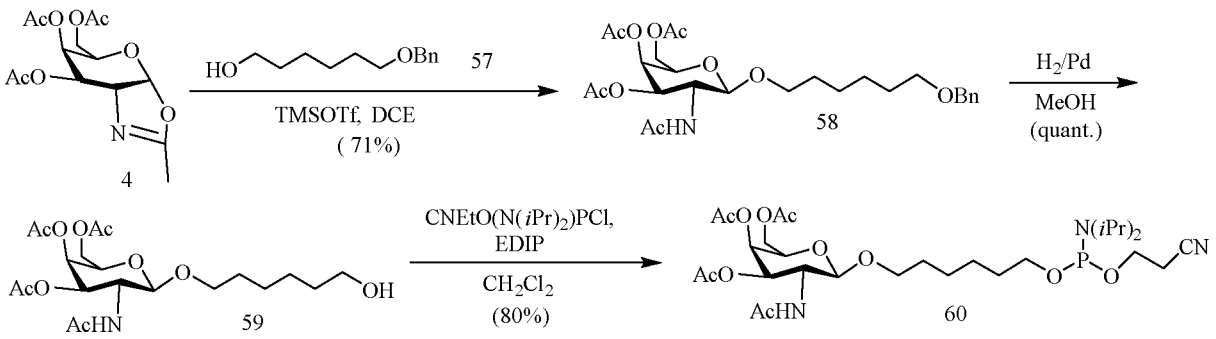


56

Example 28: Preparation of Compound 60

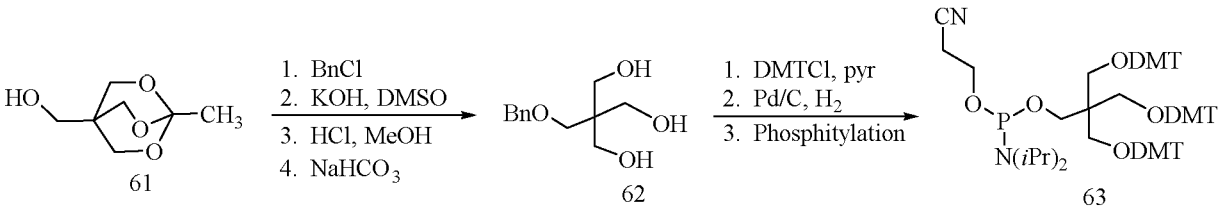
Compound 4 was prepared as per the procedures illustrated in Example 2. Compound 57 is commercially available. Compound 60 was confirmed by structural analysis.

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.

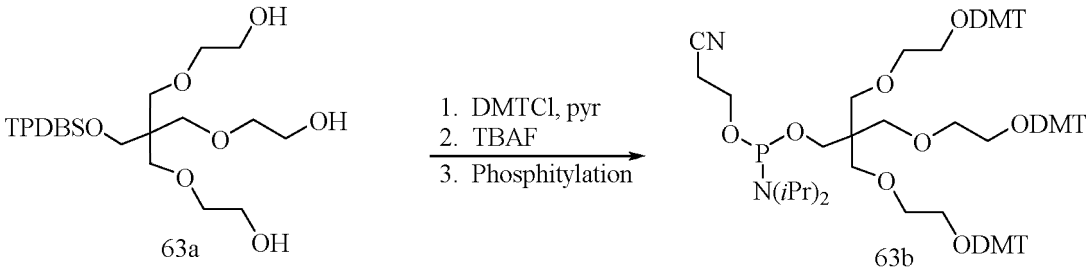


5

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.

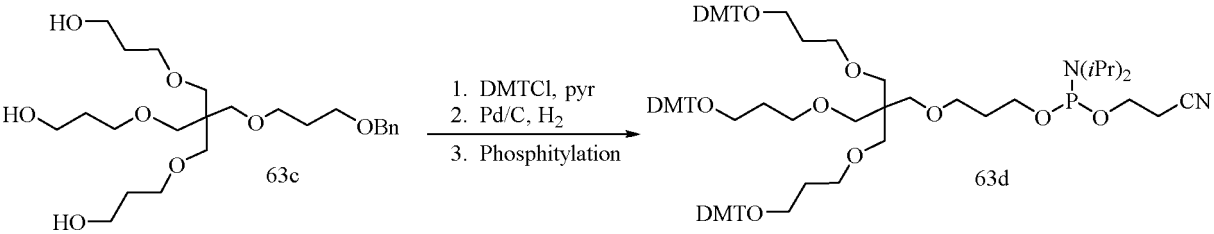
Example 30: Preparation of Compound 63b

Compound 63a is prepared using procedures similar to those reported by Hanessian *et al., Canadian Journal of Chemistry,* 1996, *74(9),* 1731-1737.



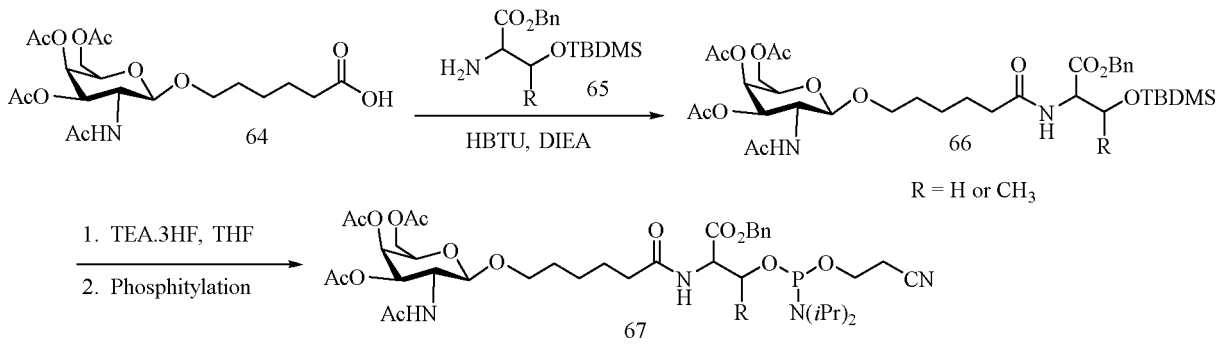
Example 31: Preparation of Compound 63d

Compound 63d is prepared using procedures similar to those reported by Chen *et al., Chinese Chemical Letters,* 1998, *9(5),* 451-453.



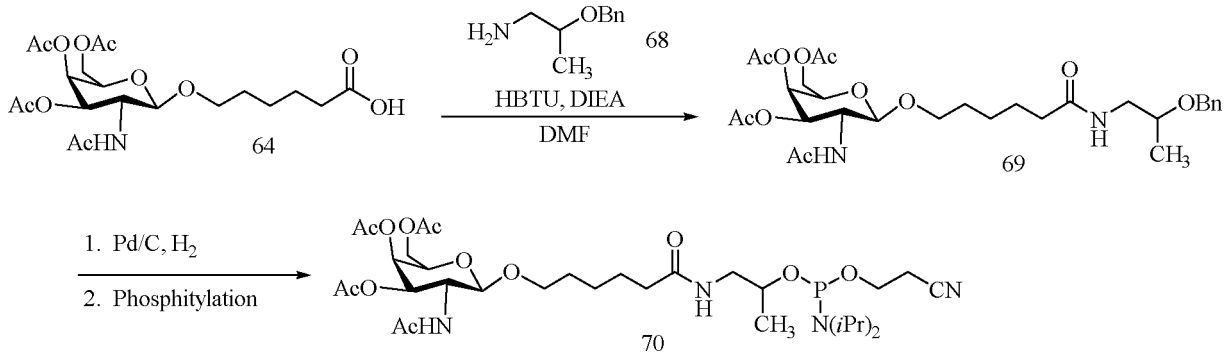
Example 32: Preparation of Compound 67

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.



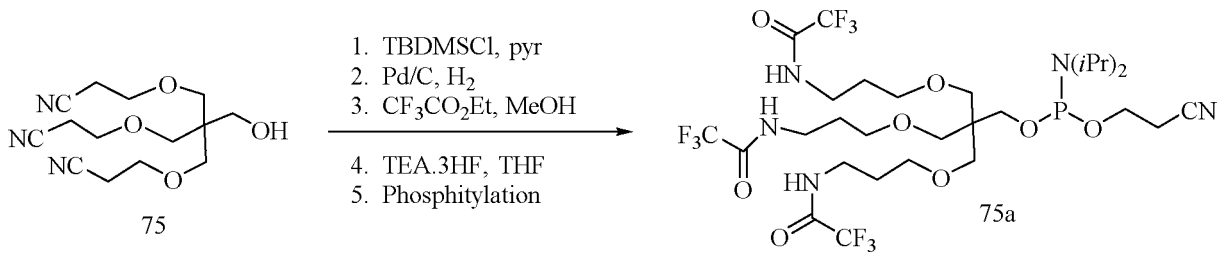
Example 33: Preparation of Compound 70

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.



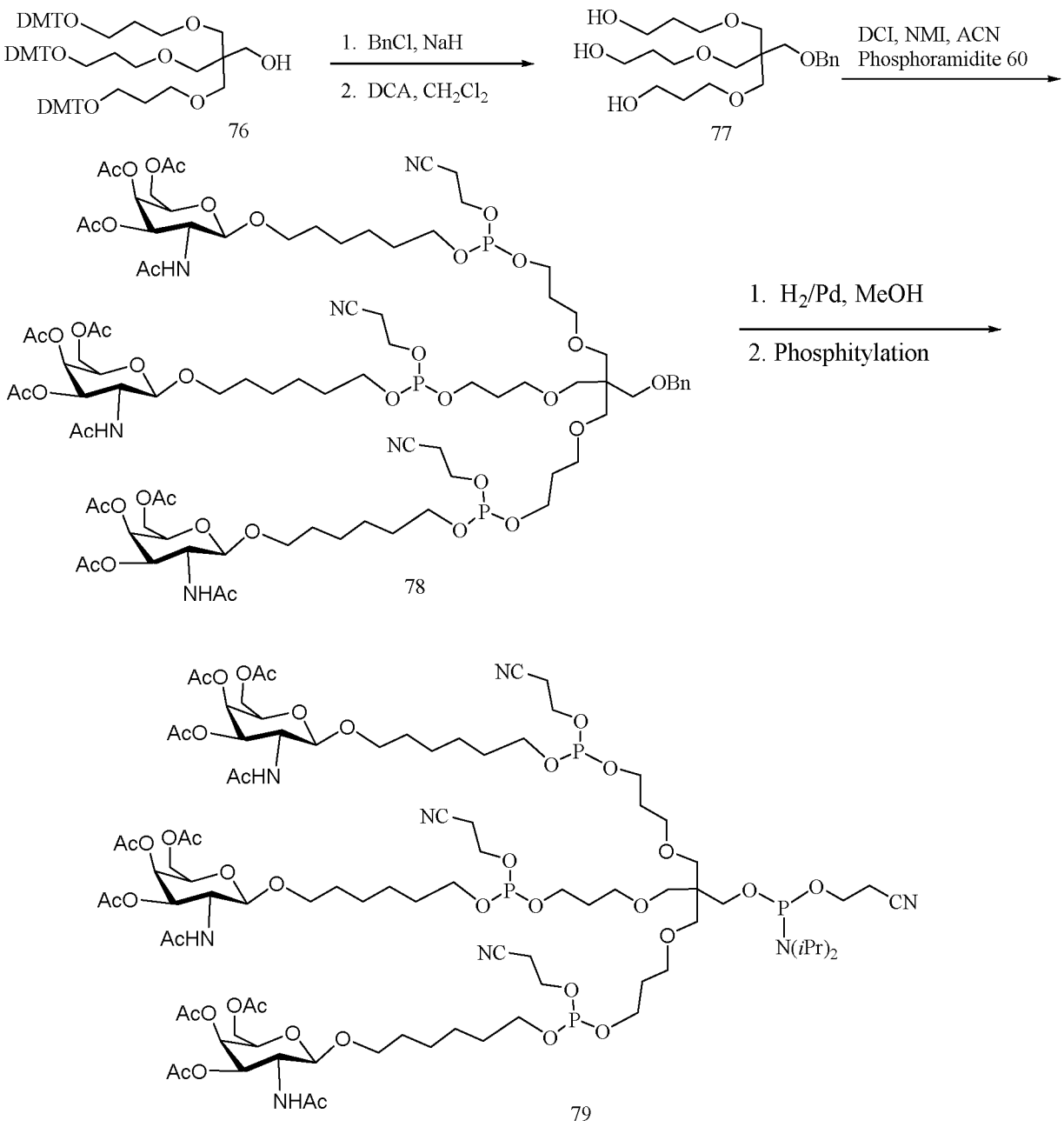
Example 34: Preparation of Compound 75a

Compound 75 is prepared according to published procedures reported by Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.



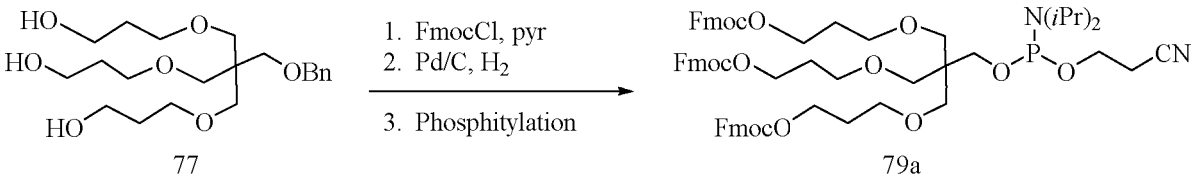
Example 35: Preparation of Compound 79

Compound 76 was prepared according to published procedures reported by Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

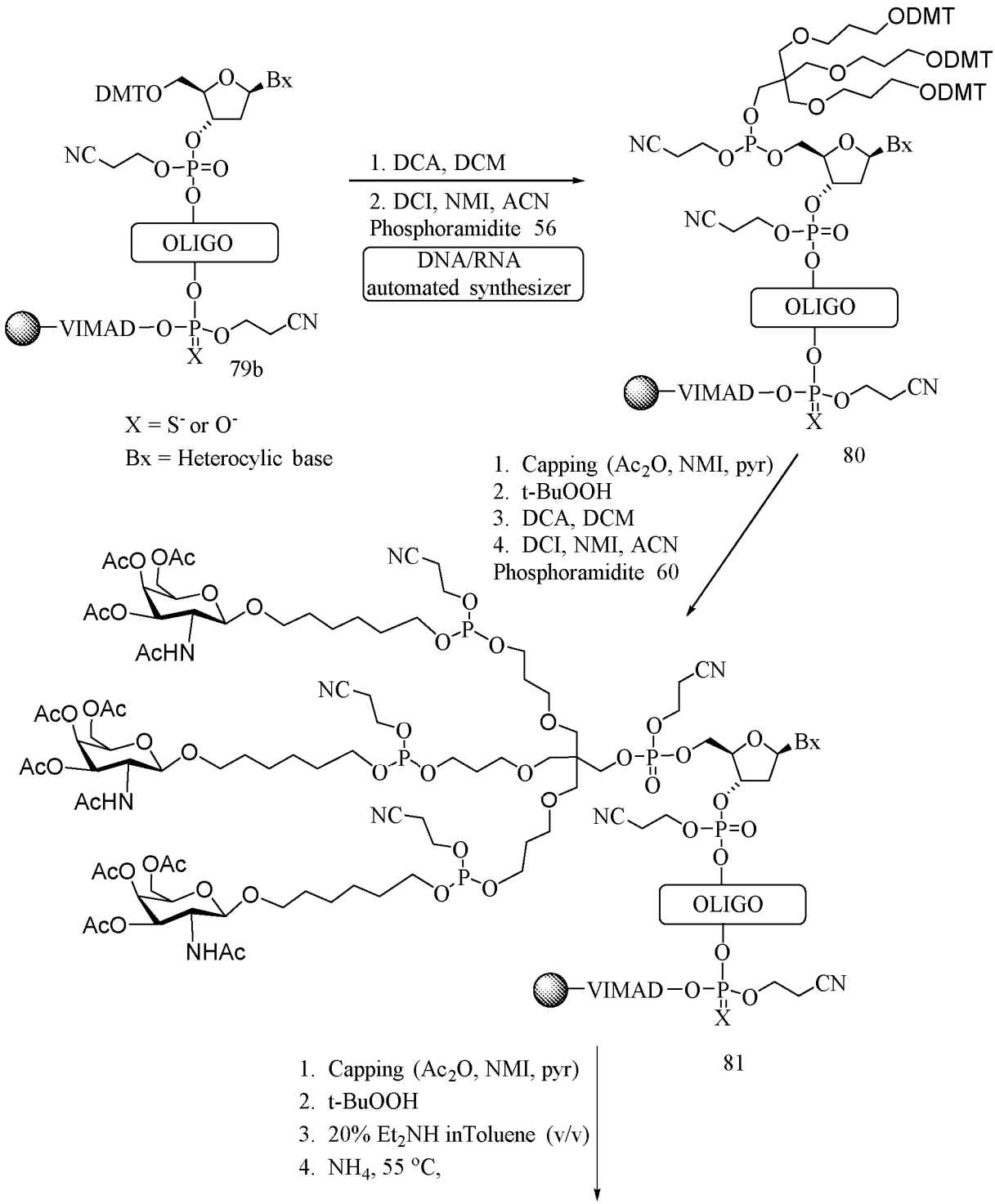


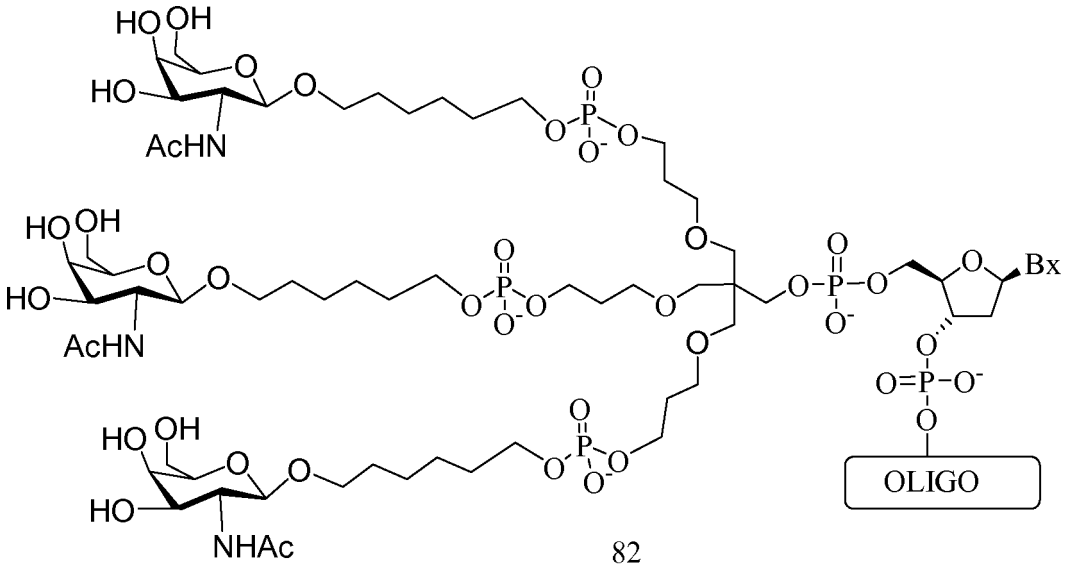
Example 36: Preparation of Compound 79a

Compound 77 is prepared as per the procedures illustrated in Example 35.



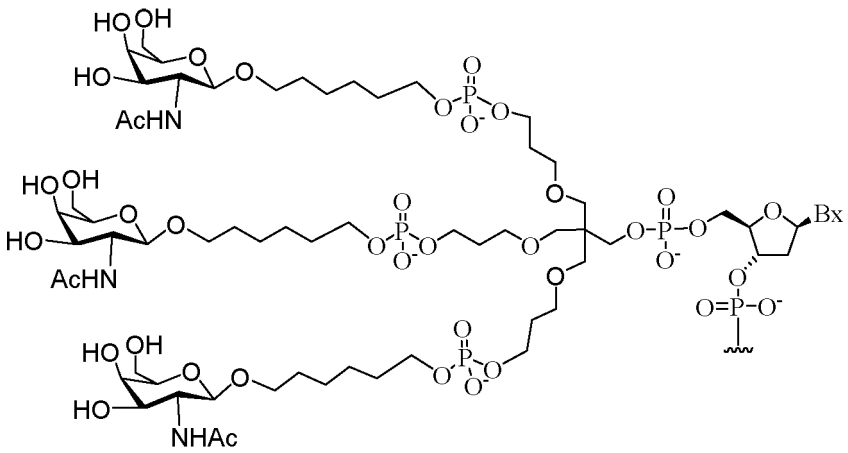
Example 37: General method for the preparation of conjugated oligomeric compound 82 comprising a phosphodiester linked GalNAc$_3$-2 conjugate at 5' terminus *via* solid support (Method I)



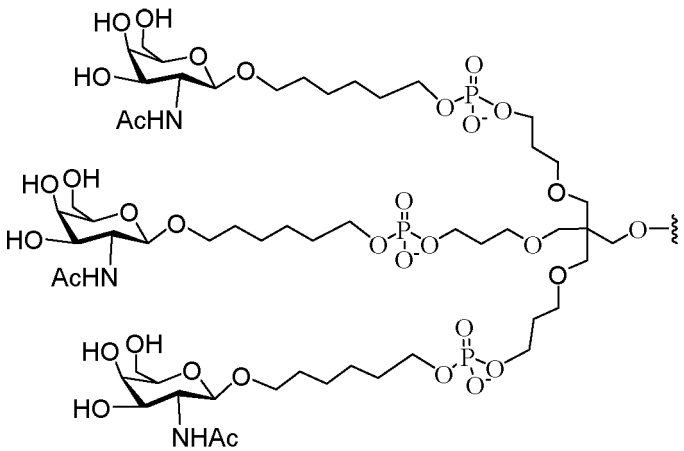


82

wherein $GalNAc_3$-2 has the structure:

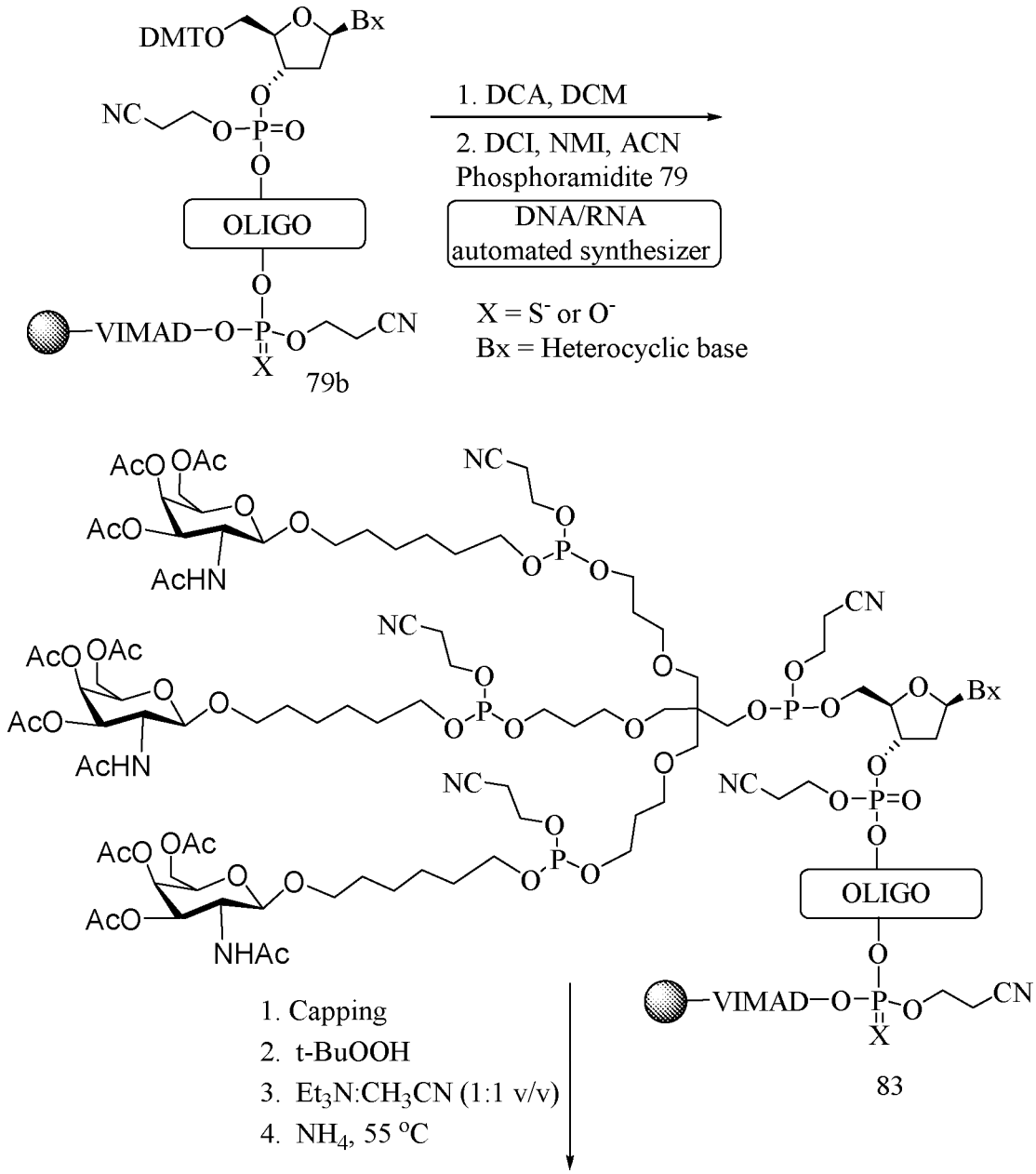


The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-2 ($GalNAc_3$-2_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein $GalNAc_3$-2_a has the formula:



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)

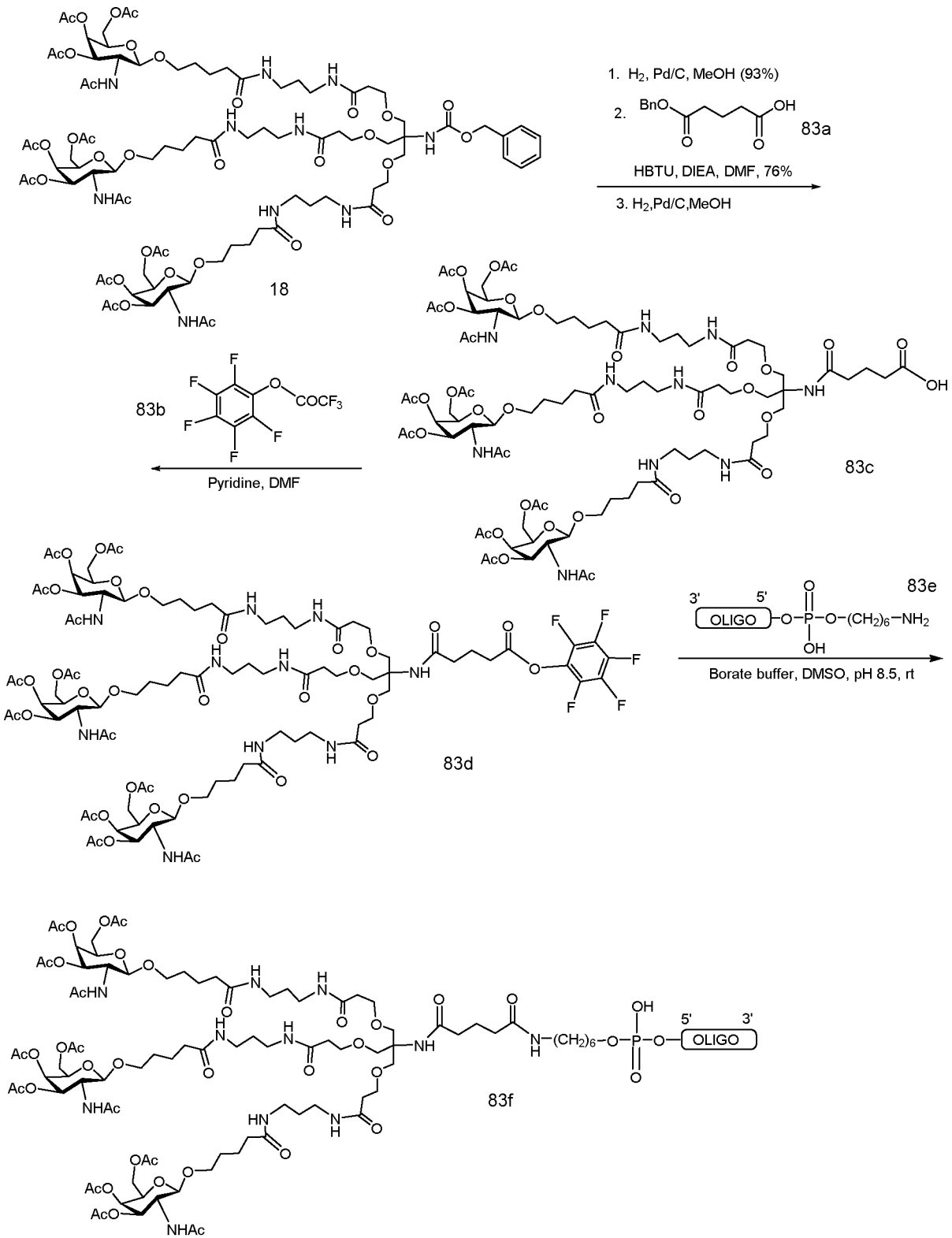


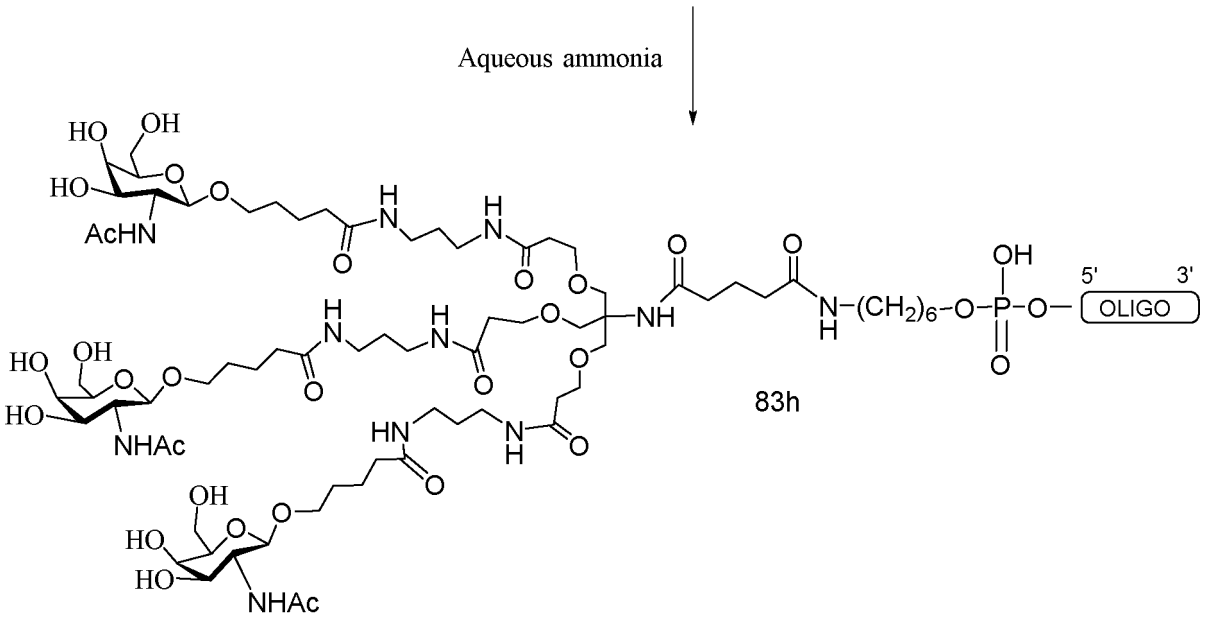
Oligomeric Compound 82

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.

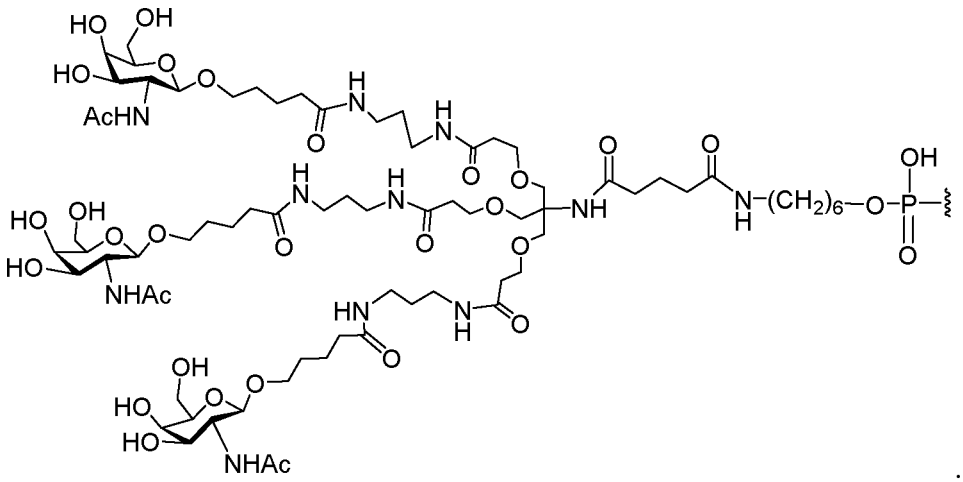
Example 39: General method for the preparation of oligomeric compound 83h comprising a $GalNAc_3$-3 Conjugate at the 5' Terminus ($GalNAc_3$-1 modified for 5' end attachment) *via* Solid Support


1. H2, Pd/C, MeOH (93%)
2.
83a
HBTU, DIEA, DMF, 76%
3. H2,Pd/C,MeOH
18
83b
Pyridine, DMF
83c
83d
83e
OLIGO
Borate buffer, DMSO, pH 8.5, rt
83f

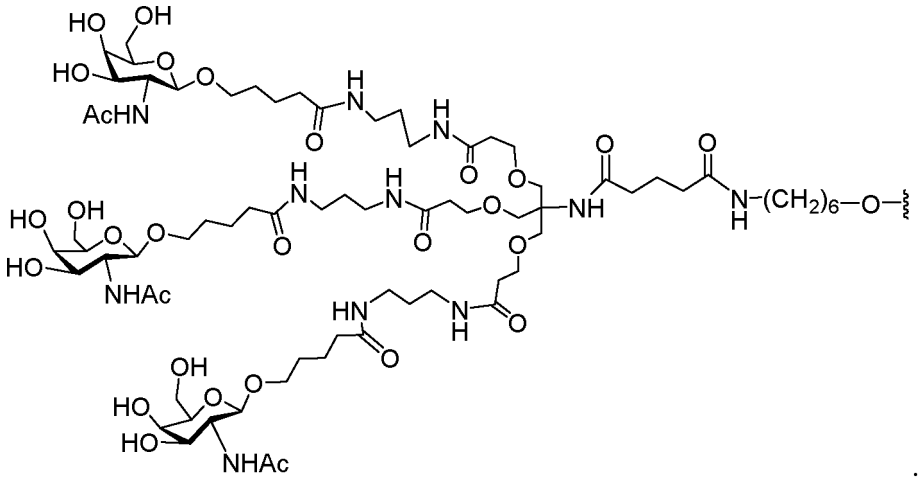


Compound 18 was prepared as per the procedures illustrated in Example 4. Compounds 83a and 83b are commercially available. Oligomeric Compound 83e comprising a phosphodiester linked hexylamine was prepared using standard oligonucleotide synthesis procedures. Treatment of the protected oligomeric compound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

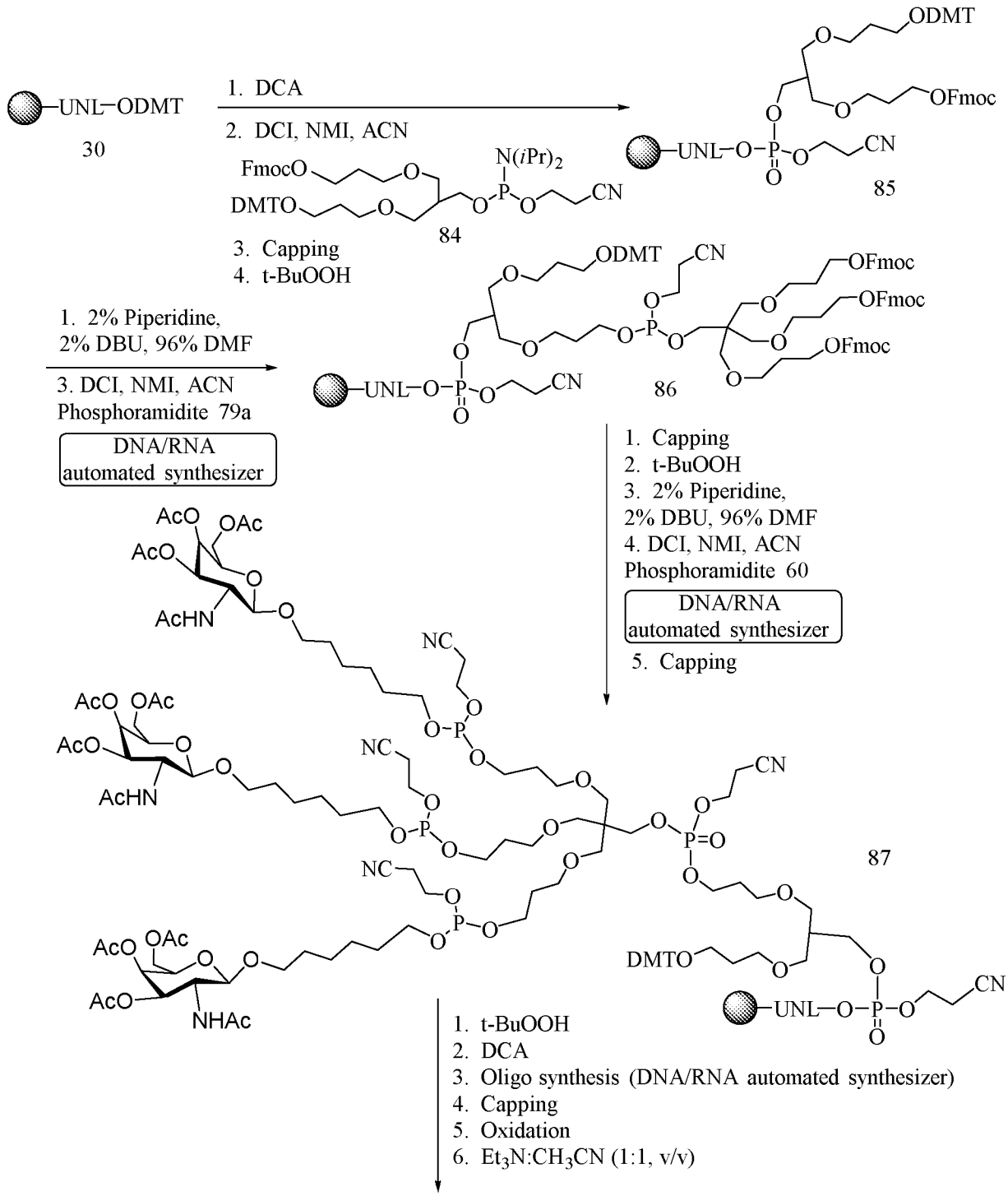
Wherein GalNAc$_3$-3 has the structure:

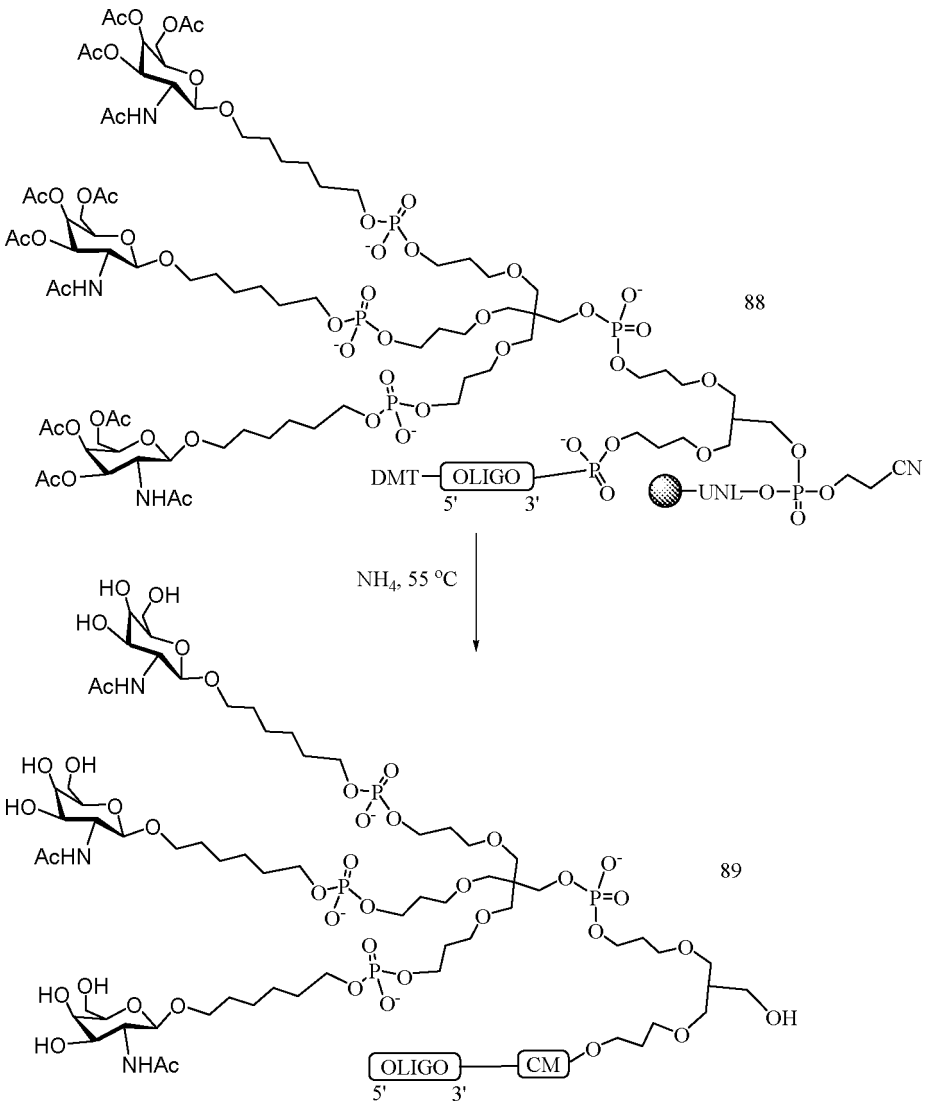


The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-3 (GalNAc$_3$-3$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-3$_a$ has the formula:

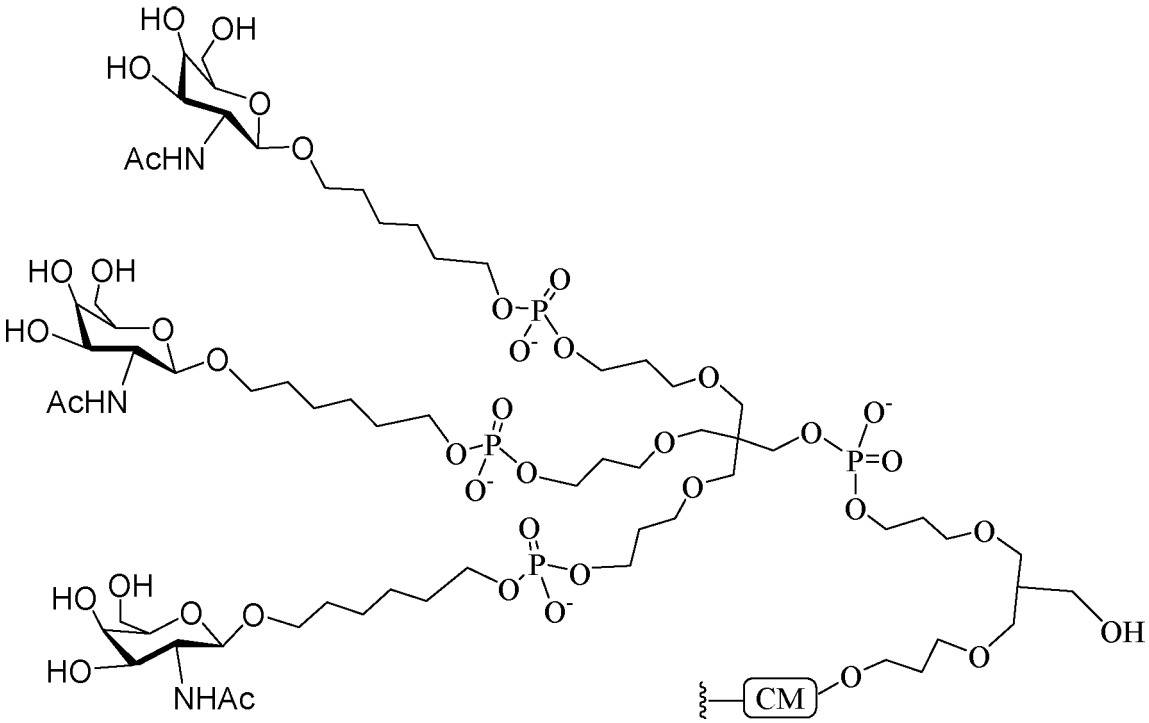


Example 40: General method for the preparation of oligomeric compound 89 comprising a phosphodiester linked GalNAc$_3$-4 conjugate at the 3' terminus *via* solid support

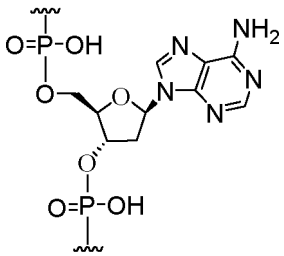



AcO
OAc
AcHN
DMT
OLIGO
5'
3'
UNL
CN
88
NH4, 55 °C
HO
OH
NHAc
CM
89

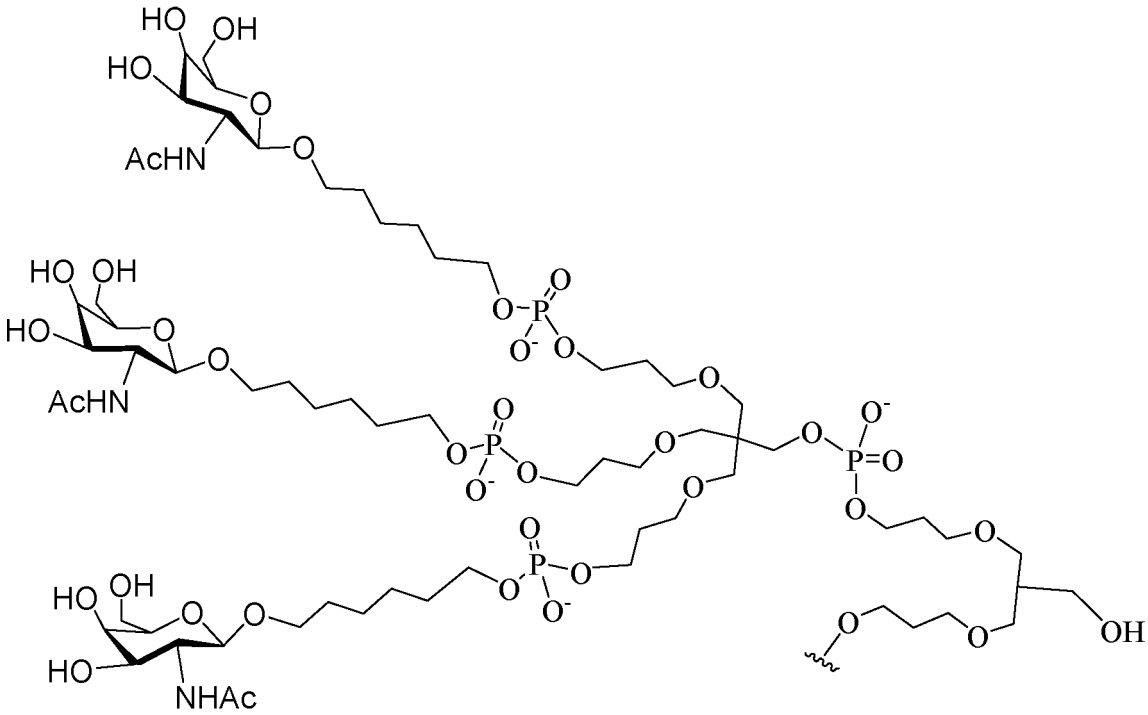
Wherein $GalNAc_3$-4 has the structure:



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	2302

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	2303

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	2298
	0.7	91			
	2	69			
	7	22			
	20	5			
651900	0.07	95	0.26	**3' $GalNAc_3$-1**	2299
	0.2	77			
	0.7	28			
	2	11			
	7	8			
661134	0.07	107	0.25	**5' $GalNAc_3$-2**	2302
	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	2304
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	2305
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	2305

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	2304
	10	52.40			
	30	24.95			
655861	0.5	81.22	2.2	Full PS with $GalNAc_3$-1 conjugate	2305
	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	2305
	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

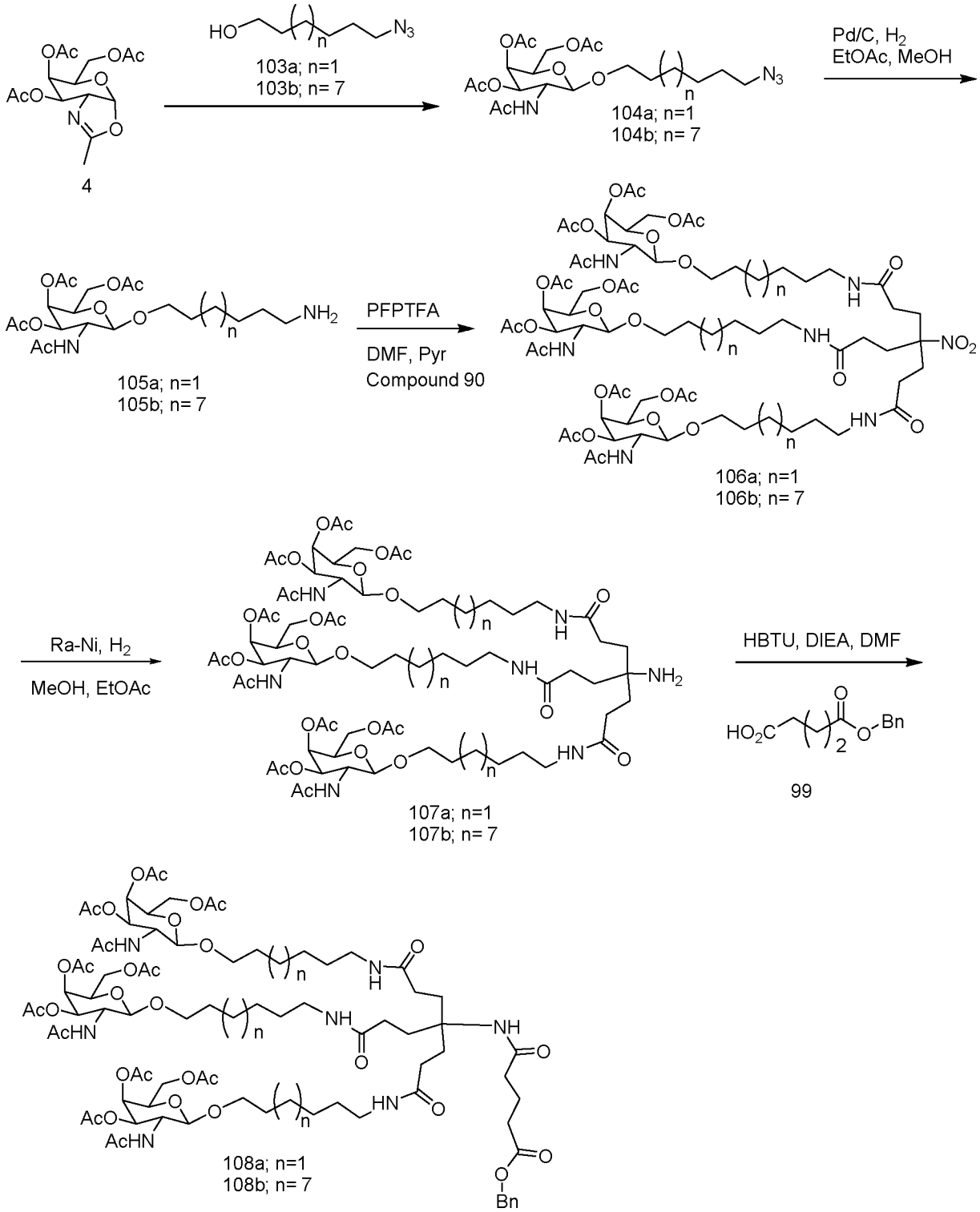
Effect of PO/PS linkages on transaminase levels of ASOs comprising $GalNAc_3$-1 conjugate at 3' terminus targeting SRB-1

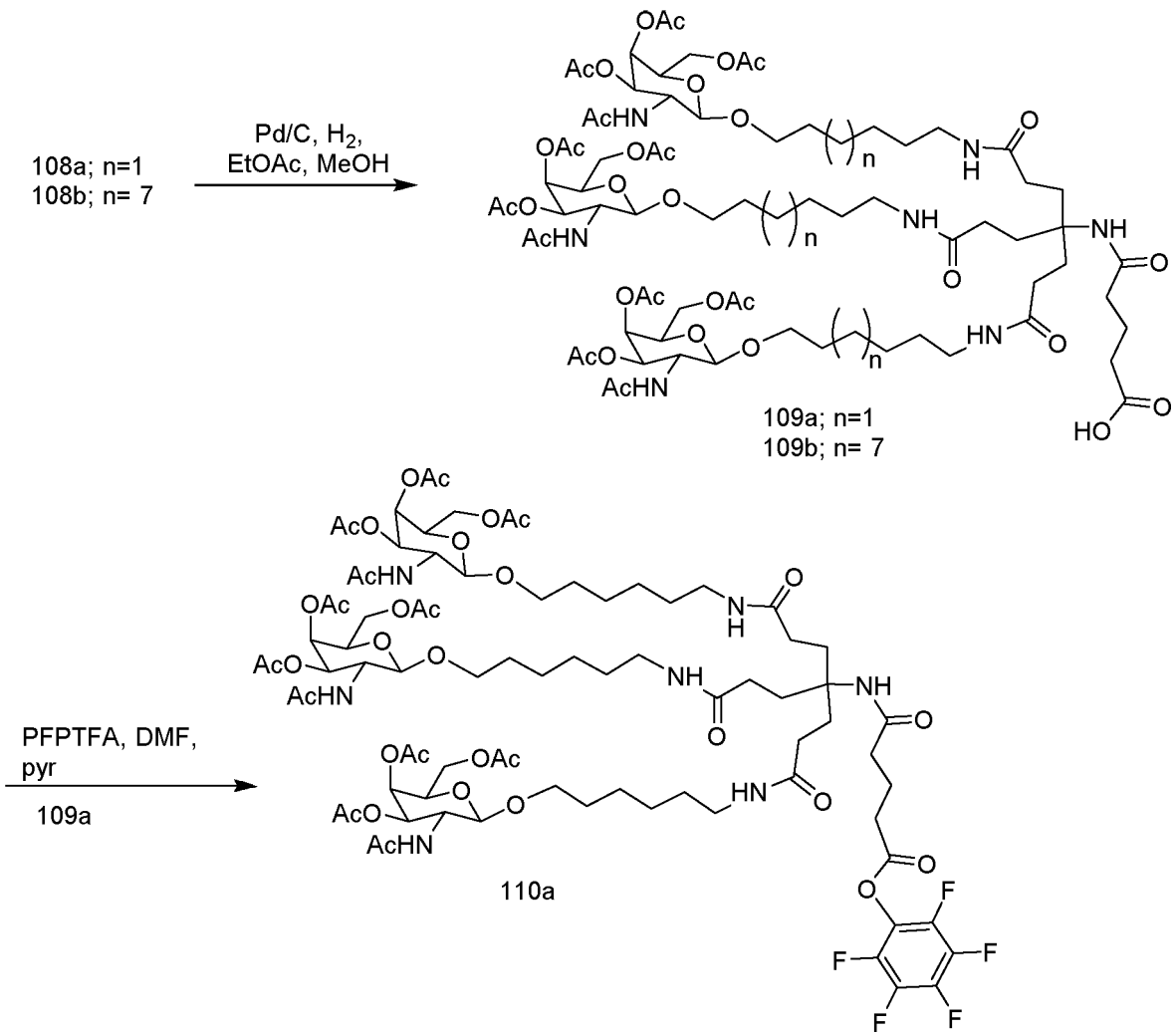
ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Chemistry	SEQ ID No.
PBS	0	28.5	65	--	
353382 (parent)	3	50.25	89	Full PS without conjugate	2304
	10	27.5	79.3		
	30	27.3	97		
655861	0.5	28	55.7	Full PS with **$GalNAc_3$-1**	2305
	1.5	30	78		
	5	29	63.5		
	15	28.8	67.8		
655862	0.5	50	75.5	Mixed PS/PO with	2305

	1.5	21.7	58.5	**GalNAc$_3$-1**	
	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.

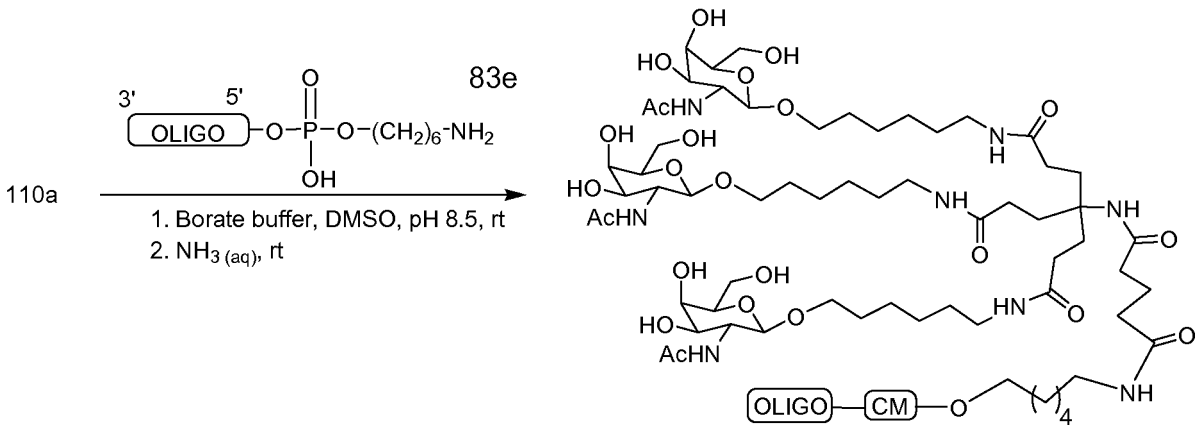
Compounds 107a and 107b were treated to the same conditions as for compounds 97a-d (Example 47), to give compounds 108a and 108b in 40-60% yield. LCMS and proton NMR was consistent with the structure.

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.

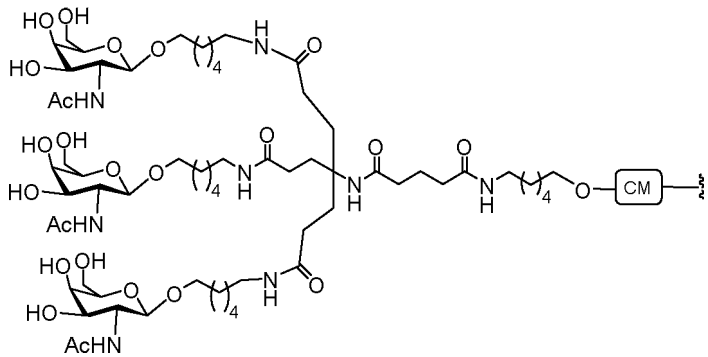
Example 46: General Procedure for Conjugation with PFP Esters (Oligonucleotide 111); Preparation of ISIS 666881 ($GalNAc_3$-10)

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).

Table 38a

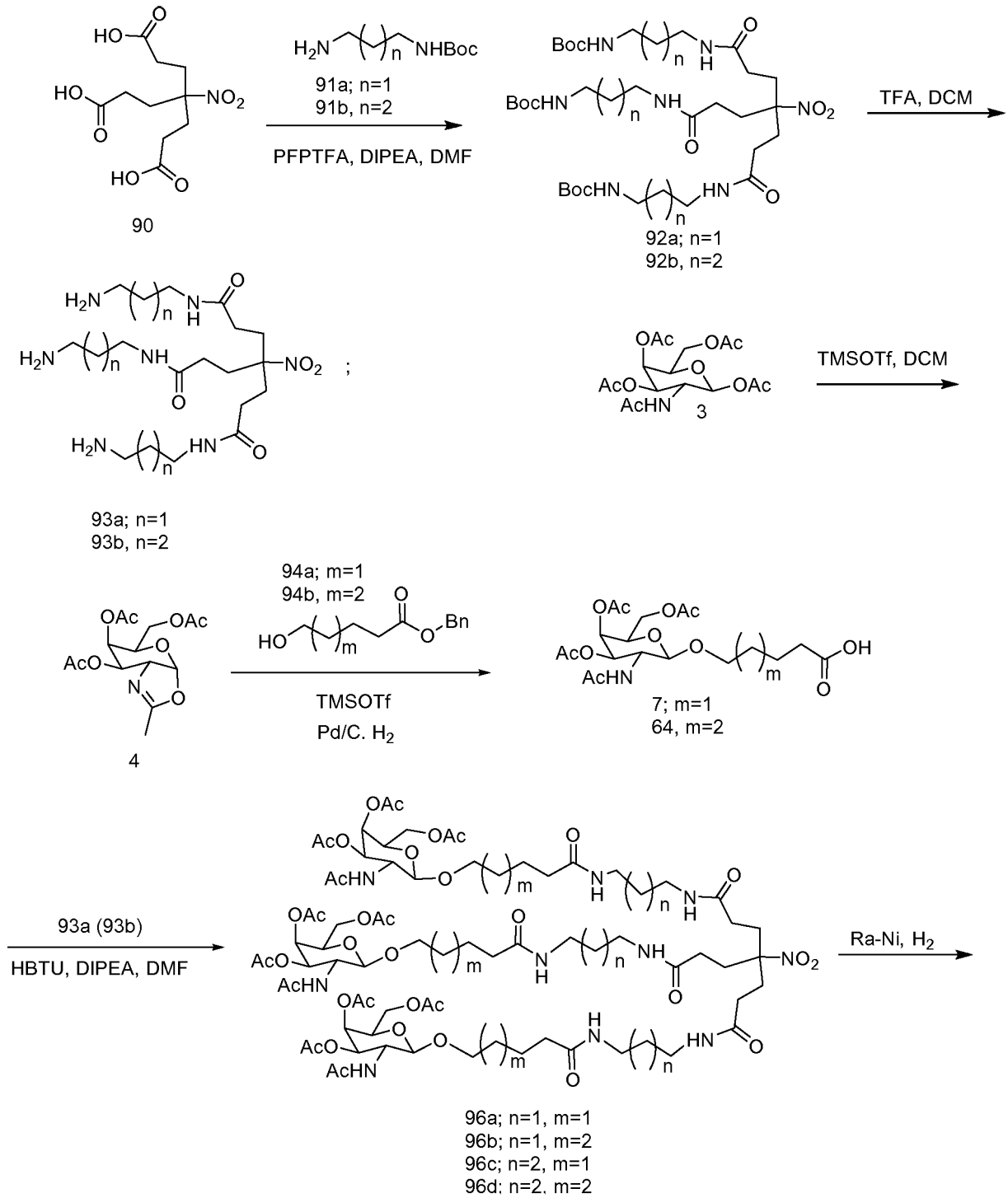
$GalNAc_3$-10 conjugated oligonucleotide

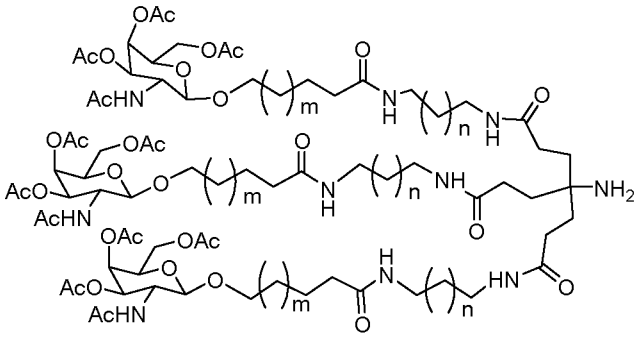
ASO	Sequence (5' to 3')	5' group	SEQ ID No.
ISIS 660254	$NH_2(CH_2)_{6}$-$_o$$A_{do}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	Hexylamine	2306
ISIS 666881	**$GalNAc_3$-10_a-$_o$-$A_{do}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$** $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	**$GalNAc_3$-10**	2306

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.

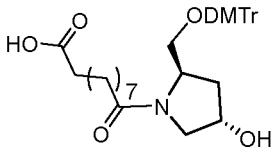
Example 47: Preparation of Oligonucleotide 102 Comprising GalNAc$_3$-8



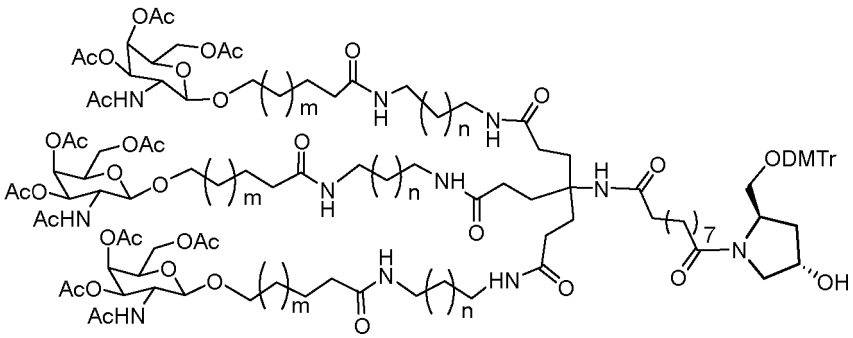


97a; n=1, m=1
97b; n=1, m=2
97c; n=2, m=1
97d; n=2, m=2

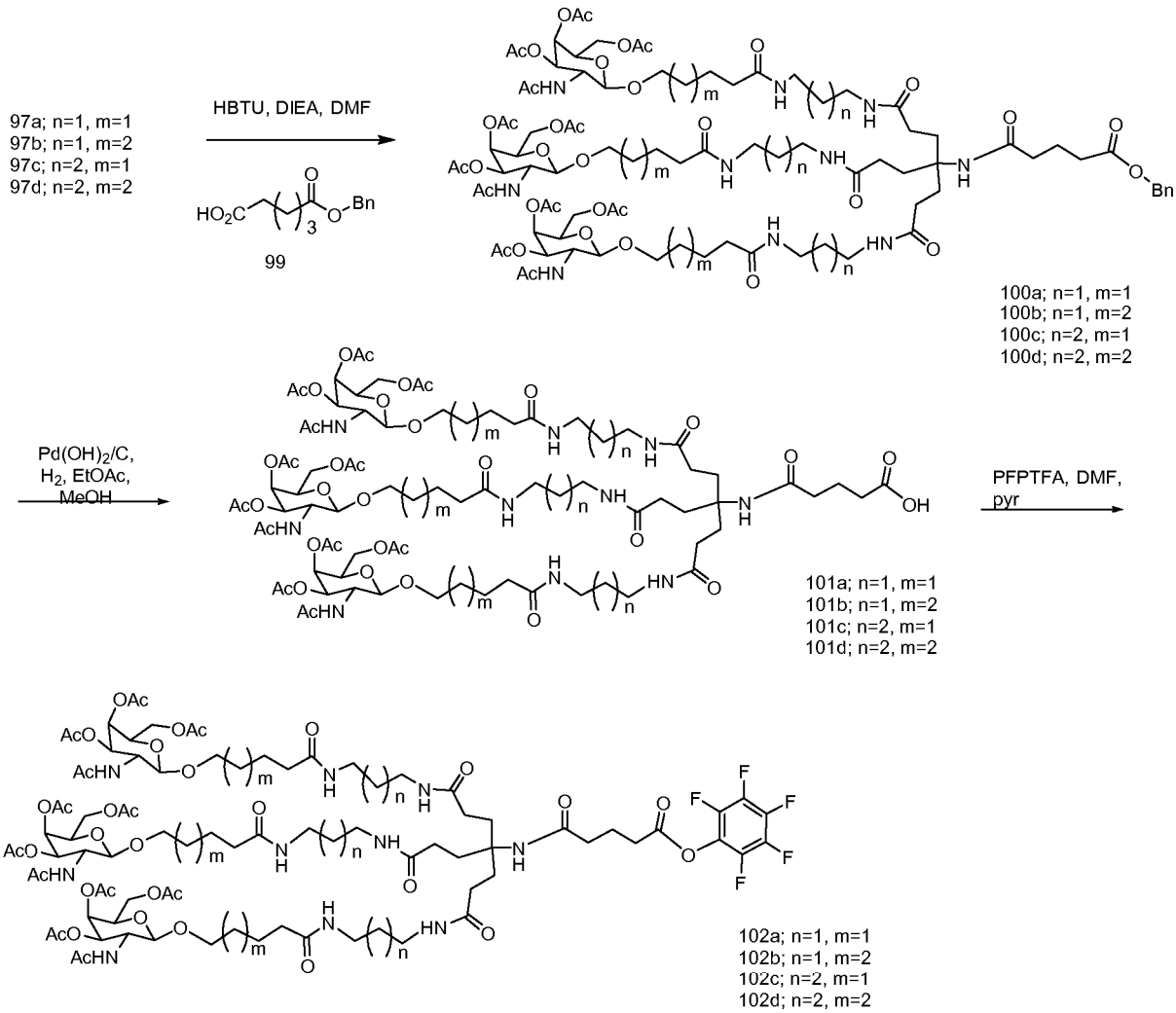
HBTU, DIEA, DMF



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.

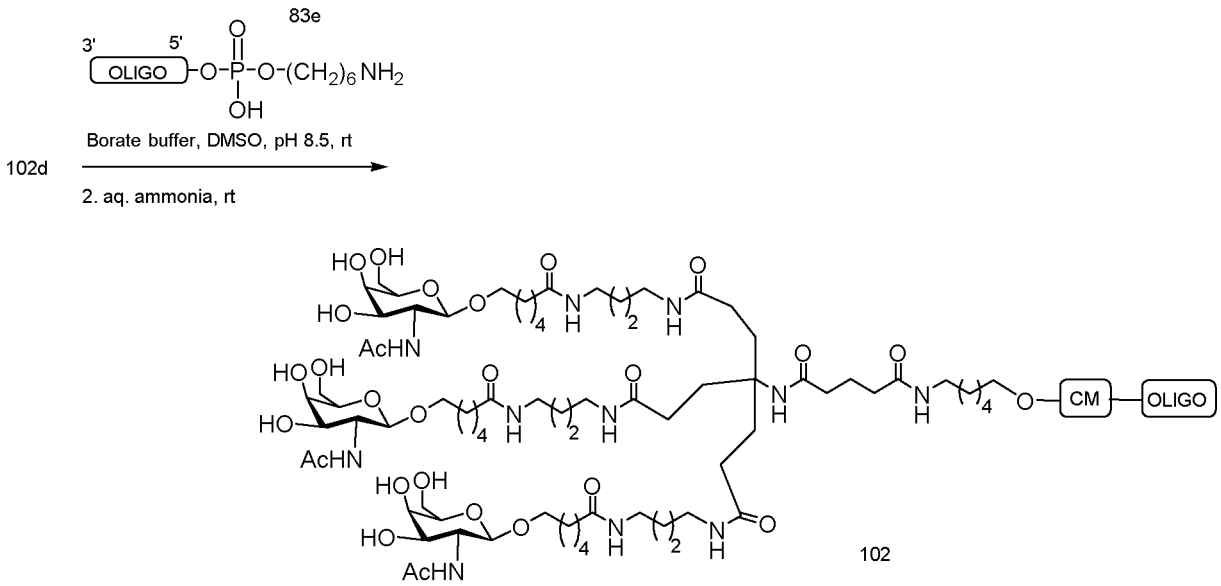
Compound 23 (0.32g, 0.53 mmoles) was treated with HBTU (0.2g, 0.53 mmoles) and *N*,*N*-Diisopropylethylamine (0.19 mL, 1.14 mmoles) in DMF (30mL) for 15 minutes. To this was added compounds 97a-d (0.38 mmoles), individually, and allowed to stir at room temperature for 16 hours. At that time, the DMF 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.

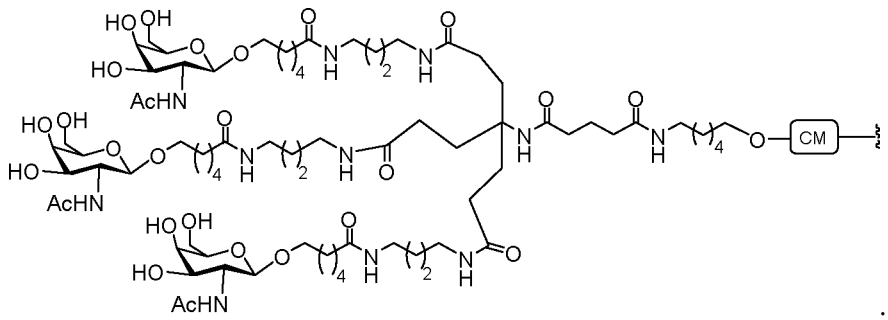
Compounds 101a-d (0.15 mmoles), individually, were dissolved in DMF (15 mL) and pyridine (0.016 mL, 0.2 mmoles). Pentafluorophenyl trifluoroacetate (0.034 mL, 0.2 mmoles) was added dropwise, under argon, and the reaction was allowed to stir at room temperature for 30 minutes. At that time, the DMF

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.

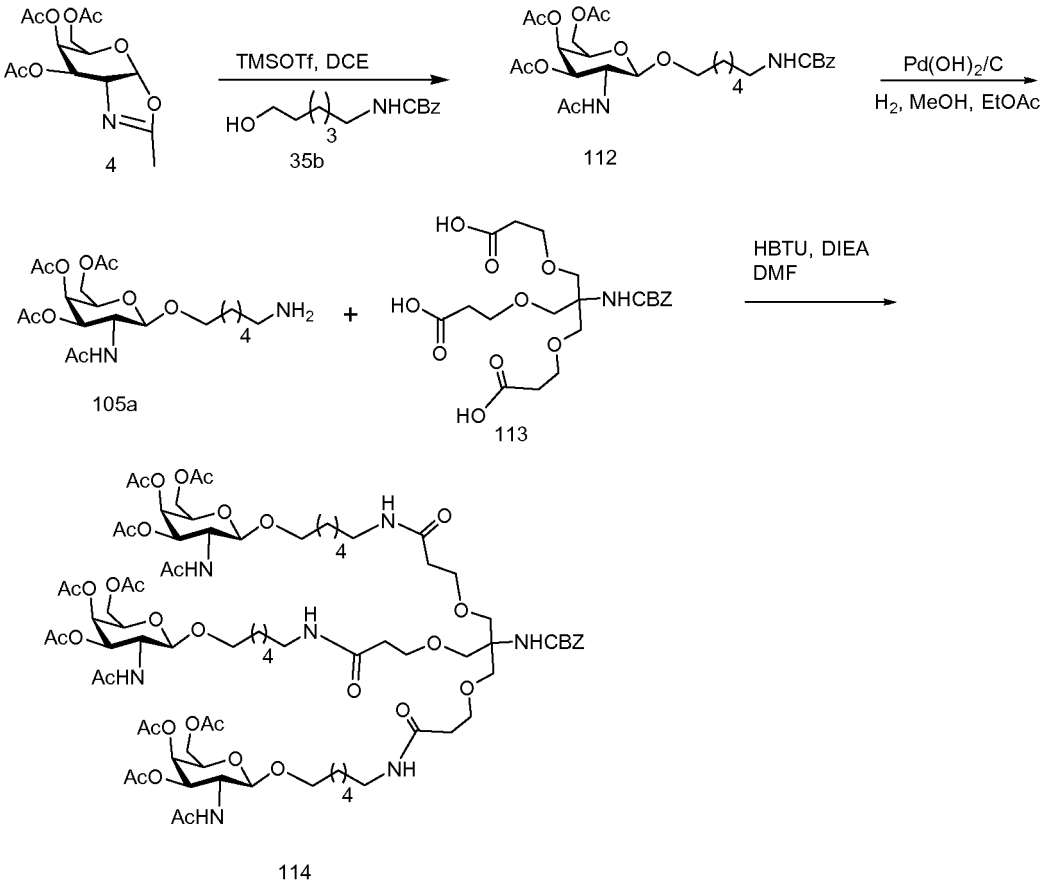


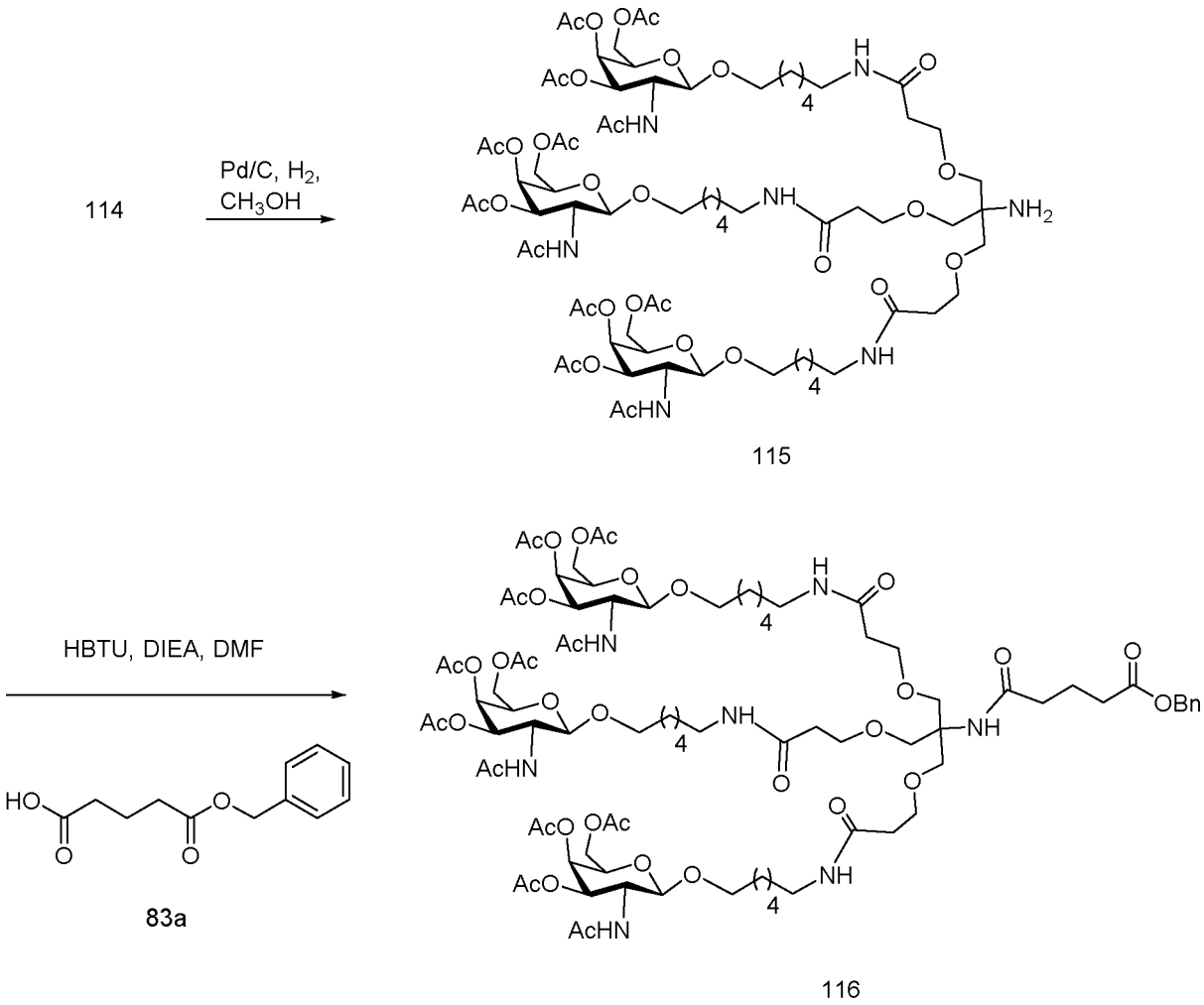
Oligomeric Compound 102, comprising a $GalNAc_3$-8 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-8 ($GalNAc_3$-8_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. 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).

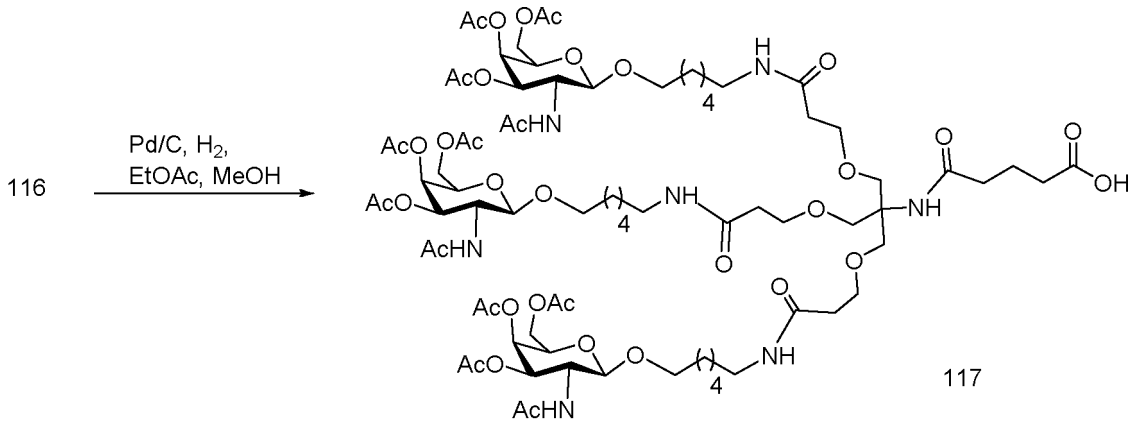
Compound 112 (5 g, 8.6 mmol) was dissolved in 1:1 methanol/ethyl acetate (22 mL/22 mL). Palladium hydroxide on carbon (0.5 g) was added. The reaction mixture was stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite and washed the pad with 1:1 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.

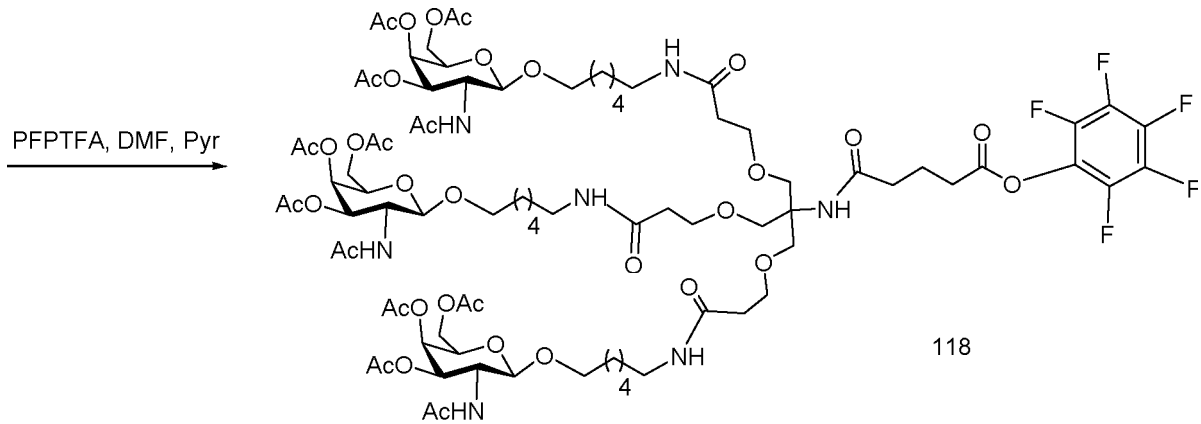
Compound 113 (1.25 g, 2.7 mmol), HBTU (3.2 g, 8.4 mmol) and DIEA (2.8 mL, 16.2 mmol) were dissolved in anhydrous DMF (17 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 105a (3.77 g, 8.4 mmol) in anhydrous DMF (20 mL) was added. The reaction was 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.

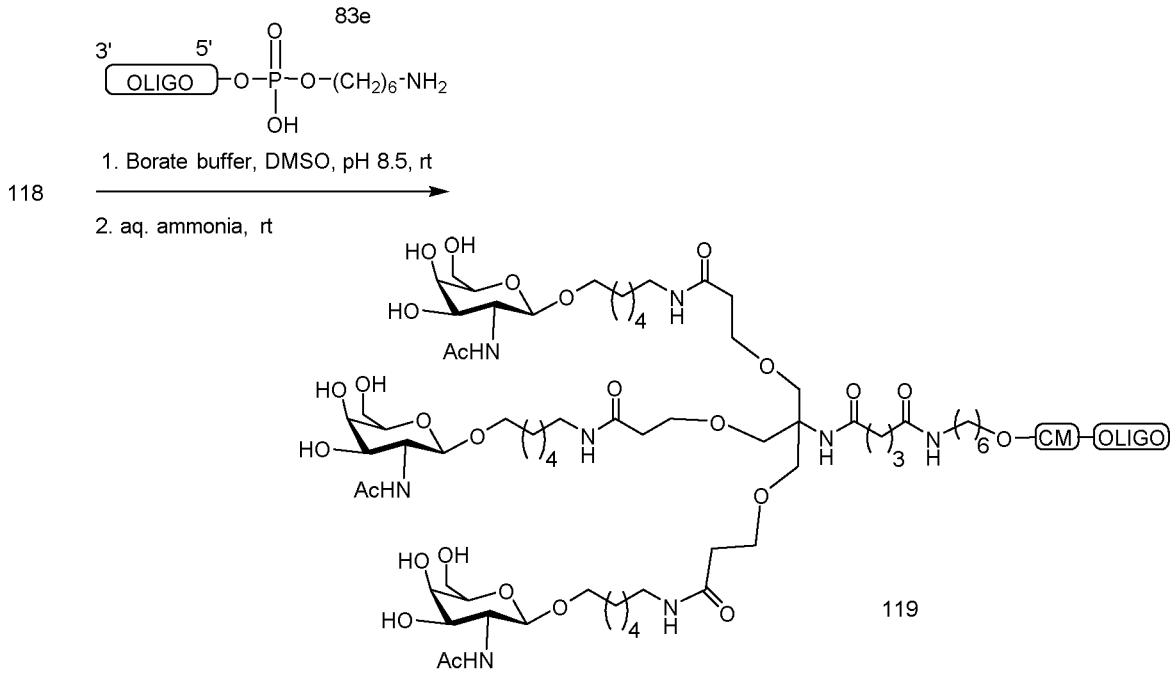
Compound 83a (0.17 g, 0.75 mmol), HBTU (0.31 g, 0.83 mmol) and DIEA (0.26 mL, 1.5 mmol) were dissolved in anhydrous DMF (5 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 115 (1.22 g, 0.75 mmol) in anhydrous DMF was added and the reaction was stirred 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.





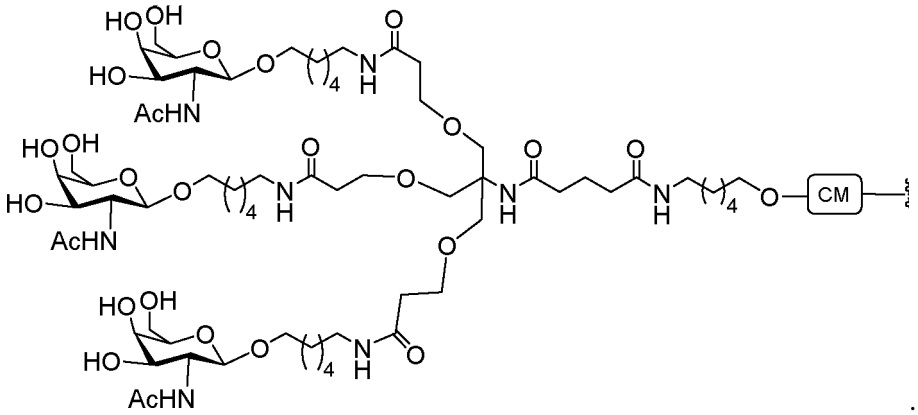
Compound 116 (0.74 g, 0.4 mmol) was dissolved in 1:1 methanol/ethyl acetate (5 mL/5 mL). Palladium on carbon (wet, 0.074 g) was added. The reaction mixture was flushed with hydrogen and stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite. The 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.

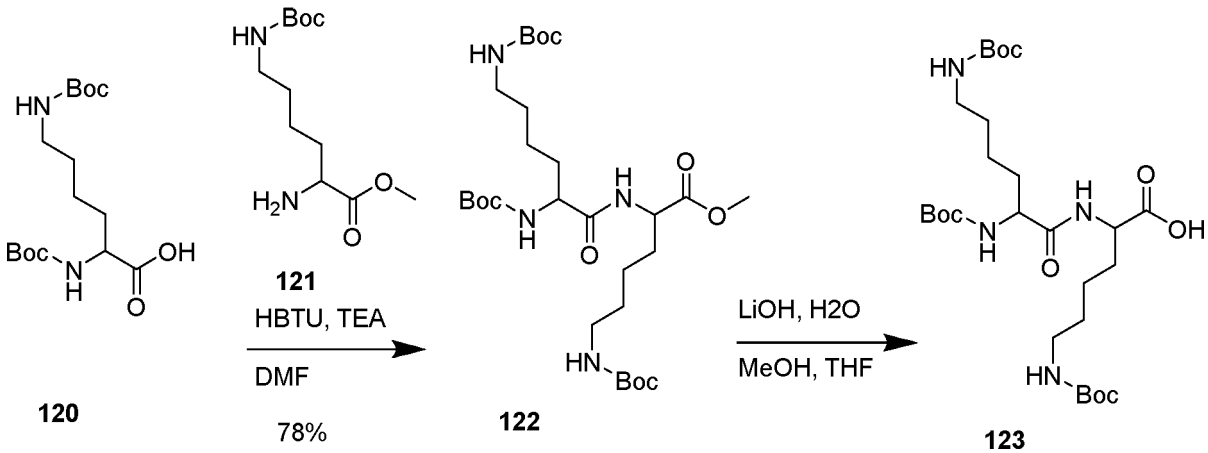


Oligomeric Compound 119, comprising a $GalNAc_3$-7 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-7 ($GalNAc_3$-7_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. 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:



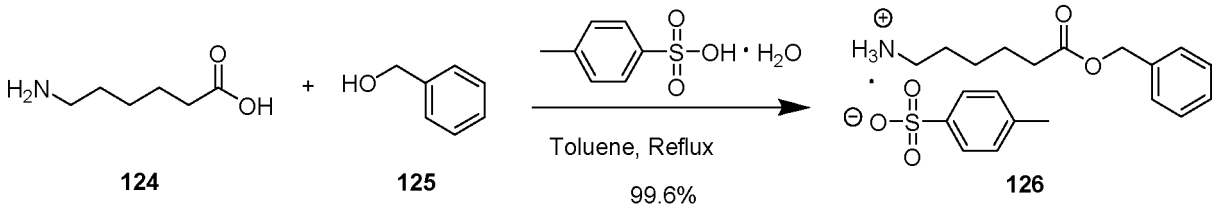
Example 49: Preparation of Oligonucleotide 132 Comprising GalNAc$_3$-5



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 $[M + H]^+$.

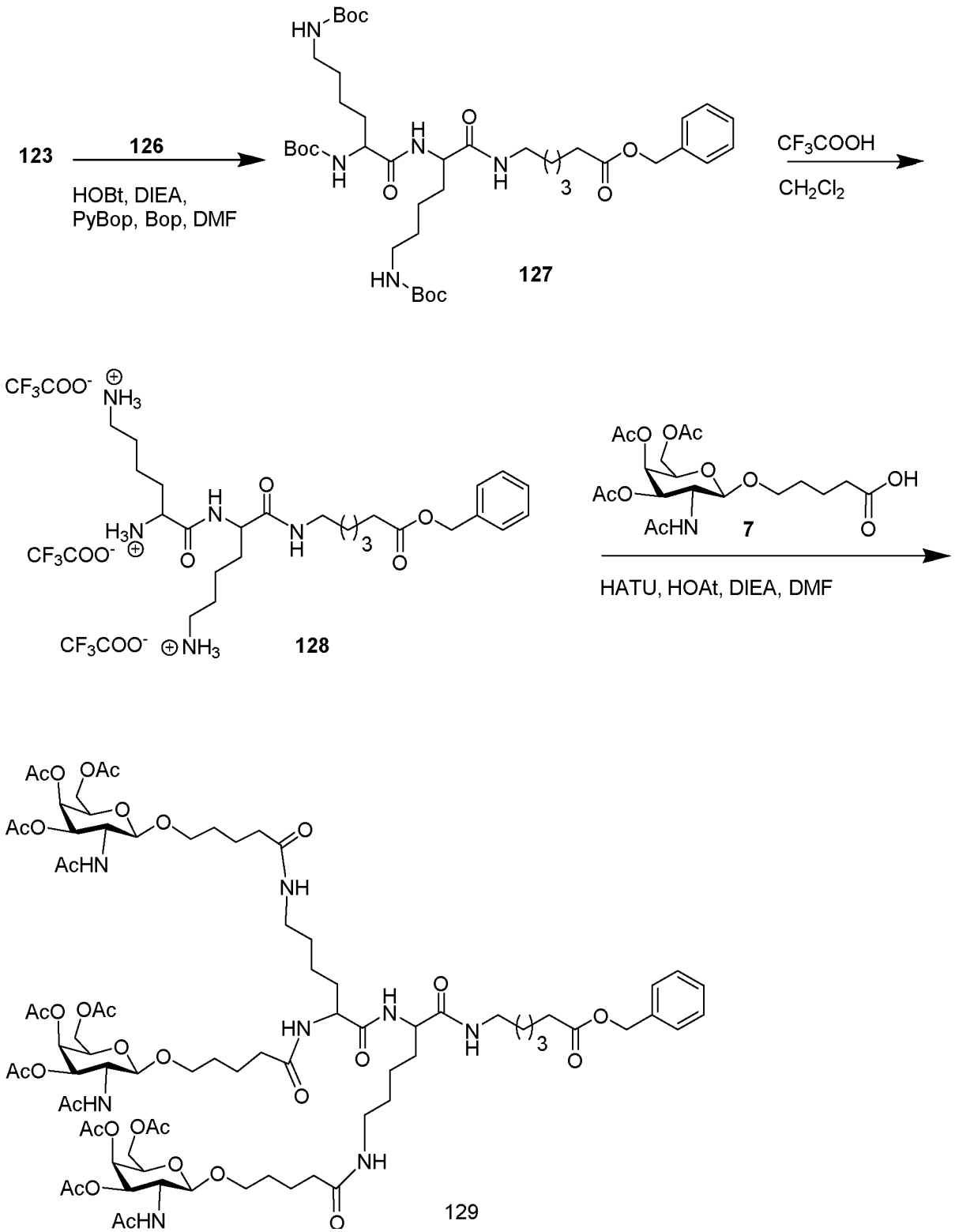
A solution of LiOH (92.15 mmol) in water (20 mL) and THF (10 mL) was added to a cooled solution of Compound 122 (7.75 g,13.16 mmol) dissolved in methanol (15 mL). The reaction mixture was stirred at

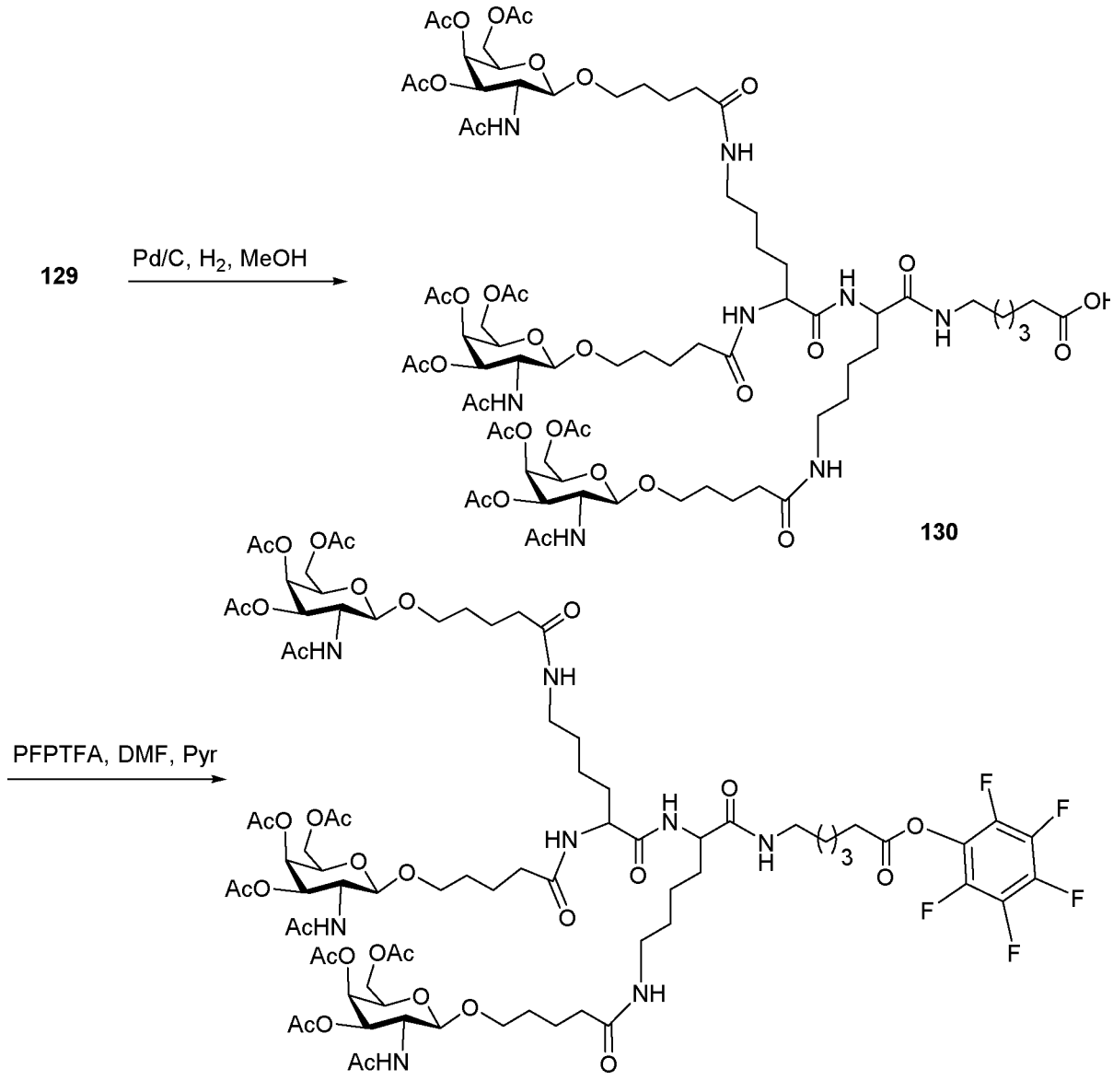
room temperature for 45 min. and monitored by TLC (EtOAc:hexane; 1:1). The reaction mixture was concentrated to half the volume under reduced pressure. The remaining solution was cooled an ice bath and neutralized by adding concentrated HCl. The reaction mixture was diluted, extracted with EtOAc (120 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).





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

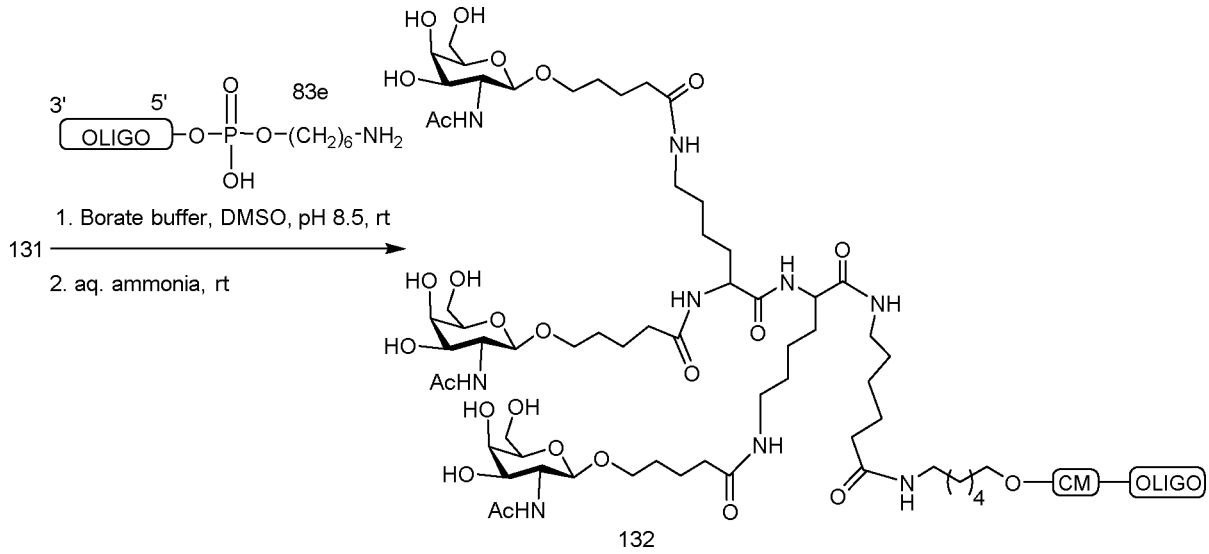
were consistent with structure. Mass *m/z* 778.4 $[M + H]^+$.

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 $[M + 2H]^+$.

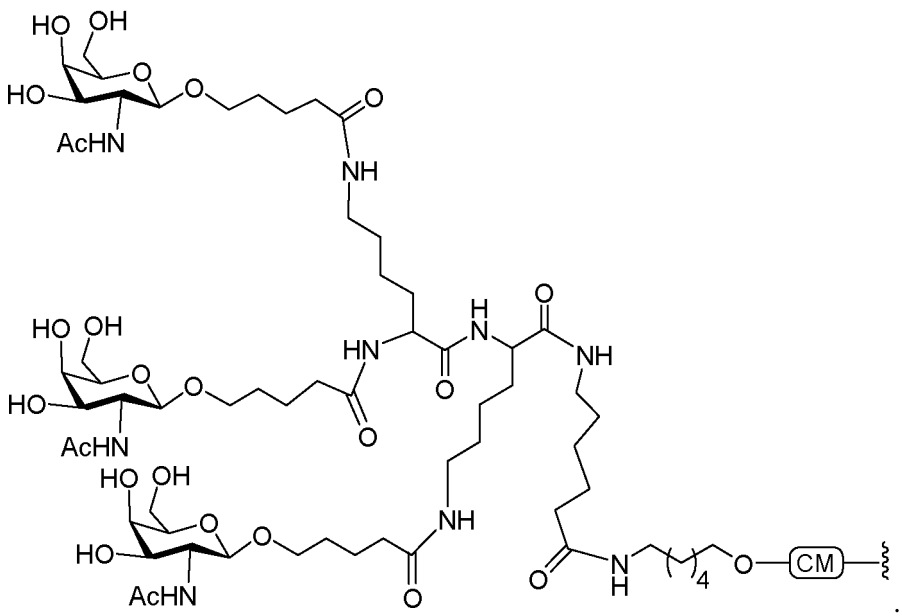
Compound 129 (0.09 g, 0.051 mmol) was dissolved in methanol (5 mL) in 20 mL scintillation vial. To this was added a small amount of 10% Pd/C (0.015 mg) and the reaction vessel was flushed with H_2 gas. The reaction mixture was stirred at room temperature under H_2 atmosphere for 18 h. The reaction mixture 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 $[M + 2H]^+$.



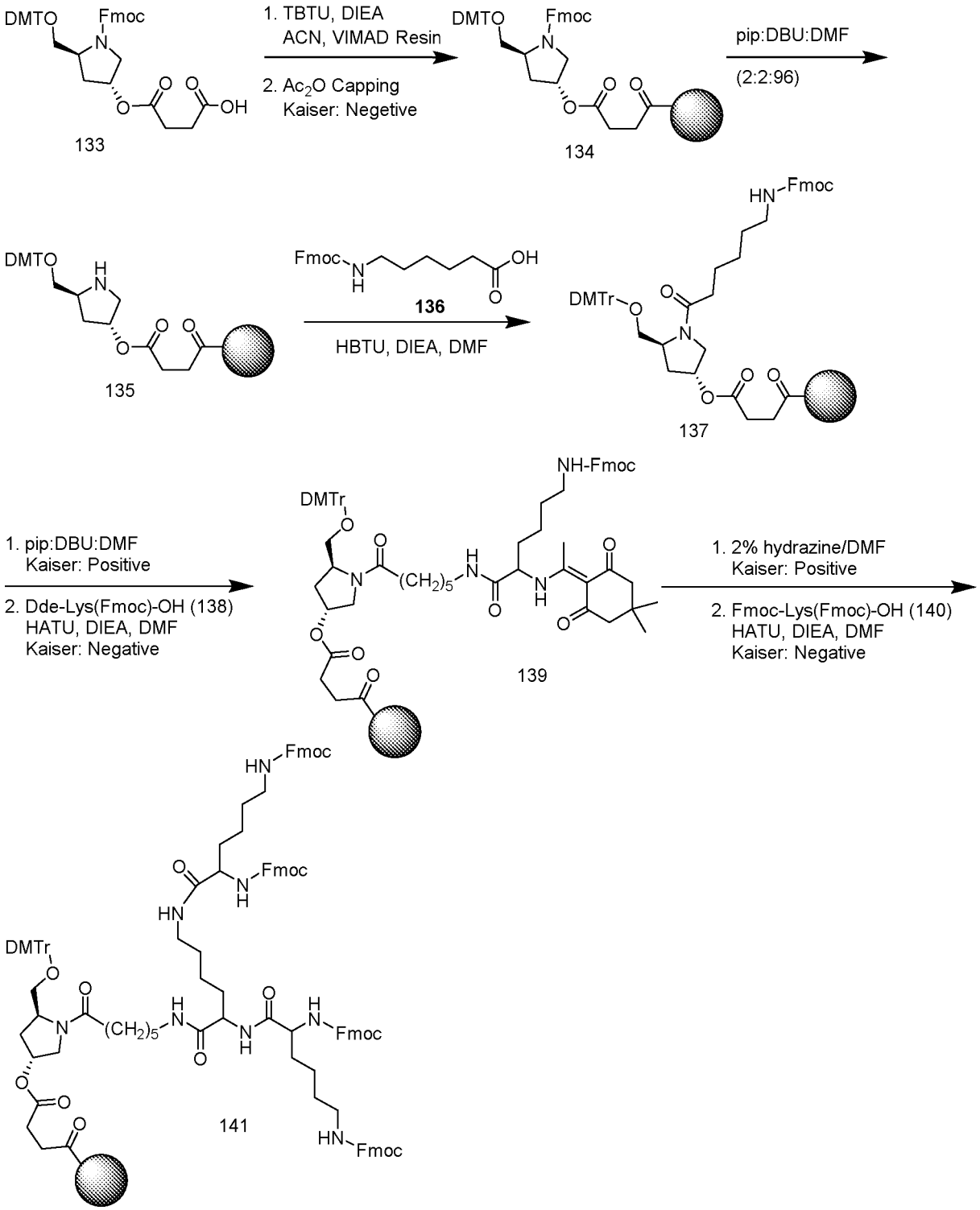
Oligomeric Compound 132, comprising a $GalNAc_3$-5 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-5 ($GalNAc_3$-5_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-.

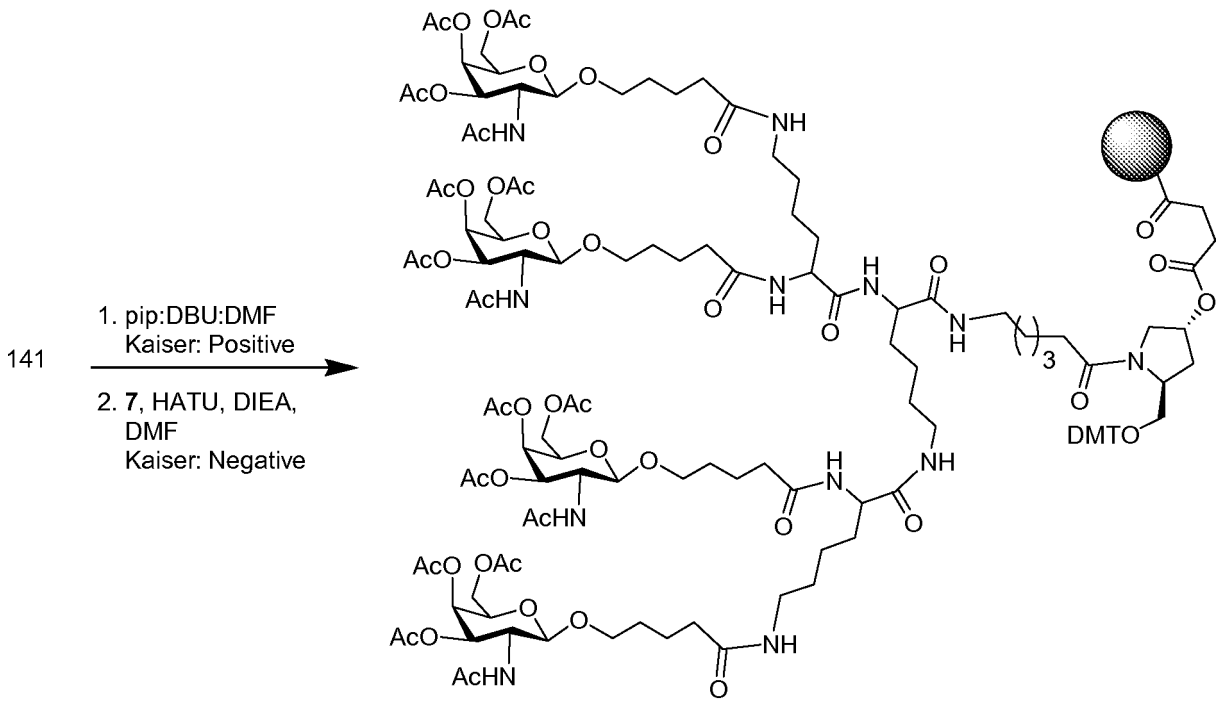
The structure of $GalNAc_3$-5 ($GalNAc_3$-5_a-CM-) is shown below:



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Example 50: Preparation of Oligonucleotide 144 Comprising GalNAc$_4$-11



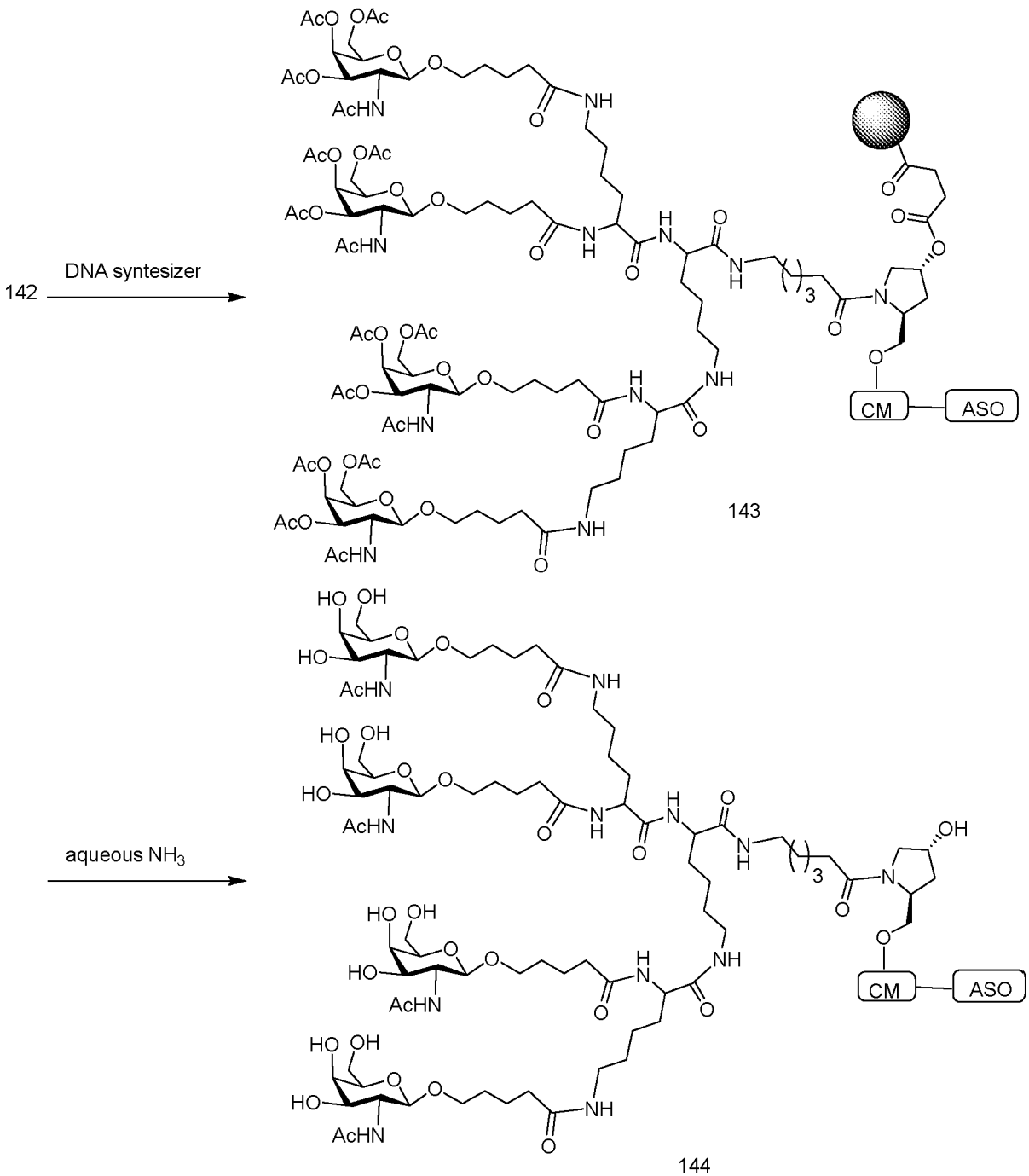


142

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.



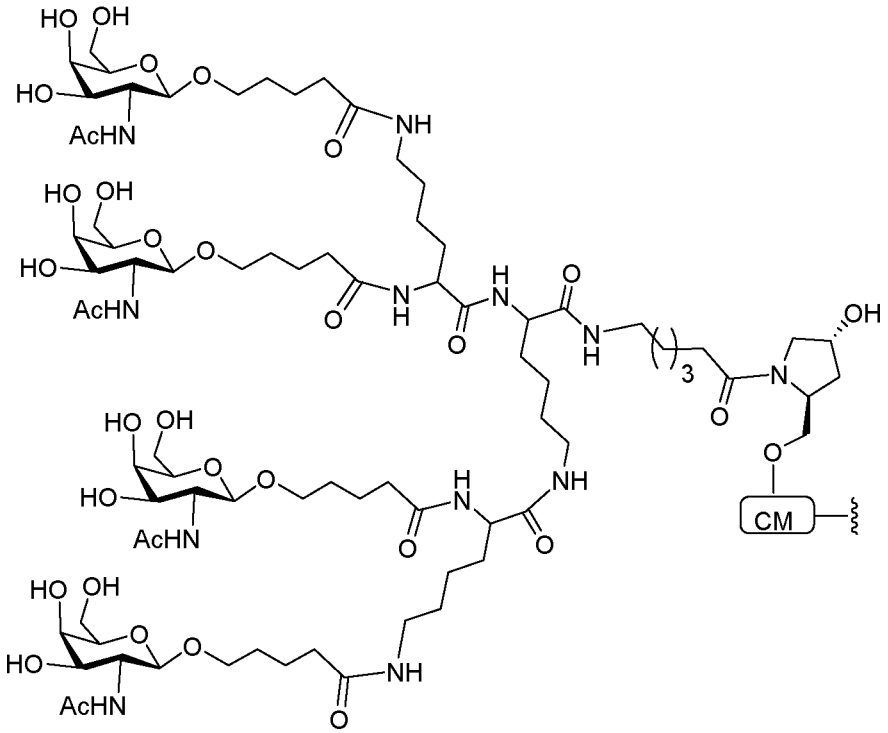
The solid support bound compound 143 was synthesized using standard solid phase synthesis on a DNA synthesizer.

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

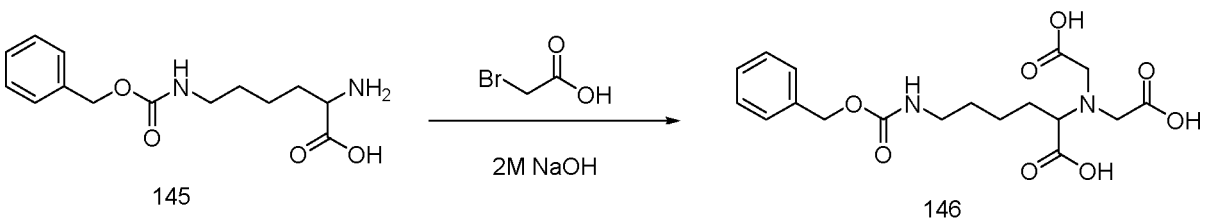
conjugated oligomeric compound was analyzed by LC-MS and the observed mass was consistent with structure.

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:

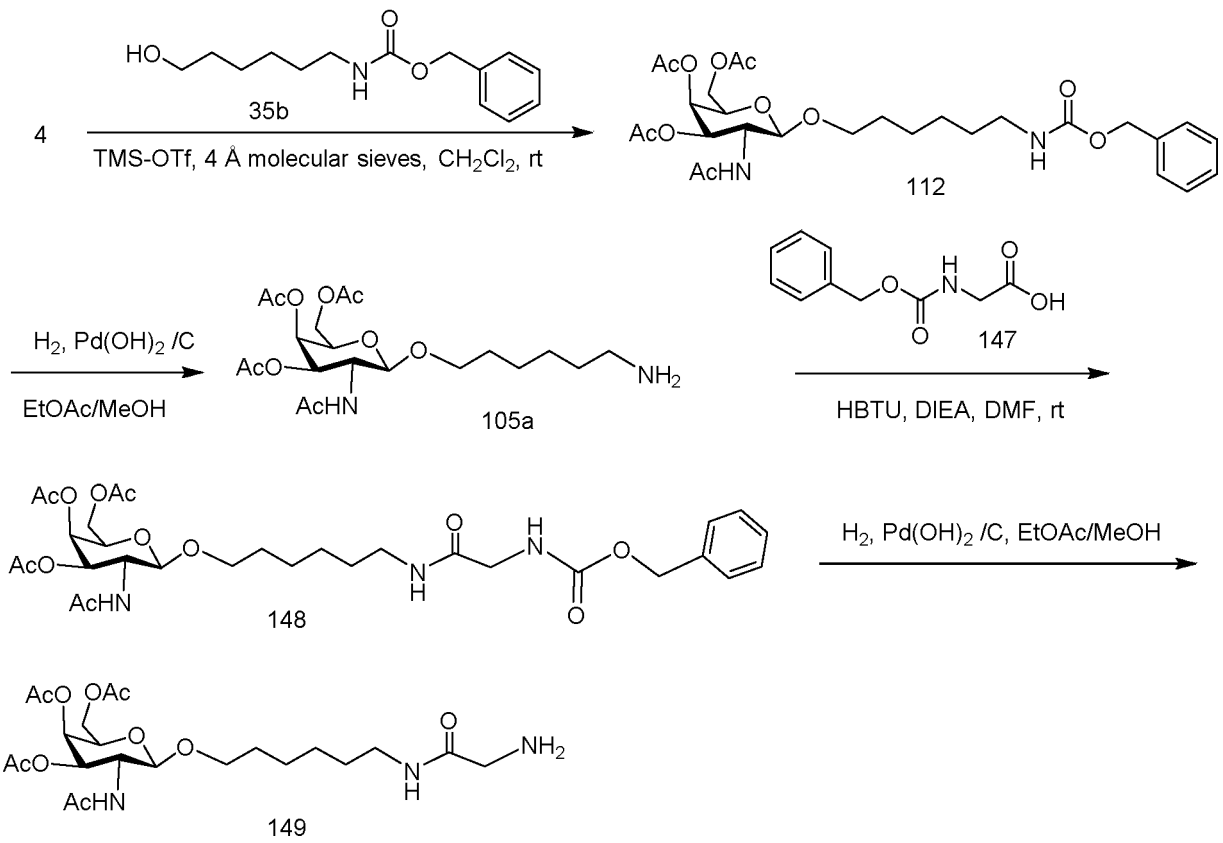


Example 51: Preparation of Oligonucleotide 155 Comprising $GalNAc_3$-6



145 146

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

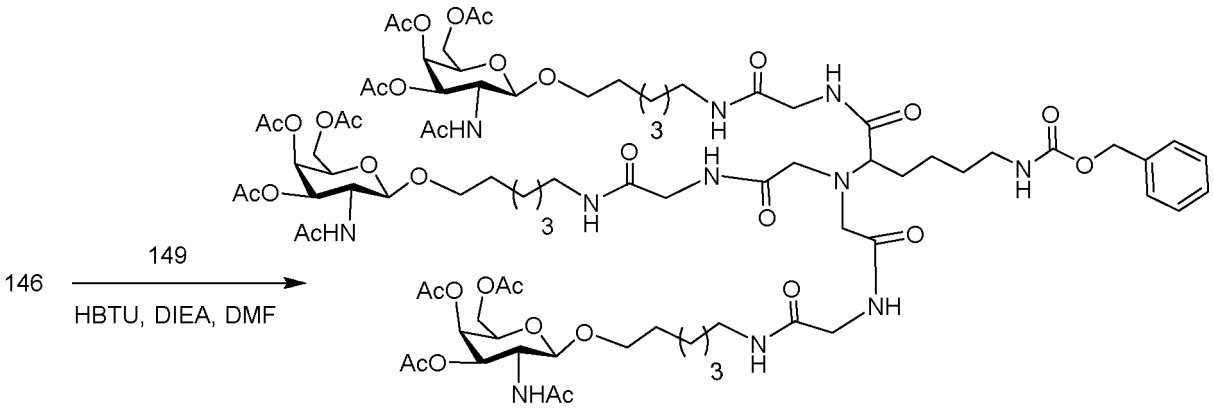


Compound 4 (15 g, 45.55 mmol) and compound 35b (14.3 grams, 57 mmol) were dissolved in CH_2Cl_2 (200 ml). Activated molecular sieves (4 Å. 2 g, powdered) were added, and the reaction was allowed to stir for 30 minutes under nitrogen atmosphere. TMS-OTf was added (4.1 ml, 22.77 mmol) and the reaction 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.

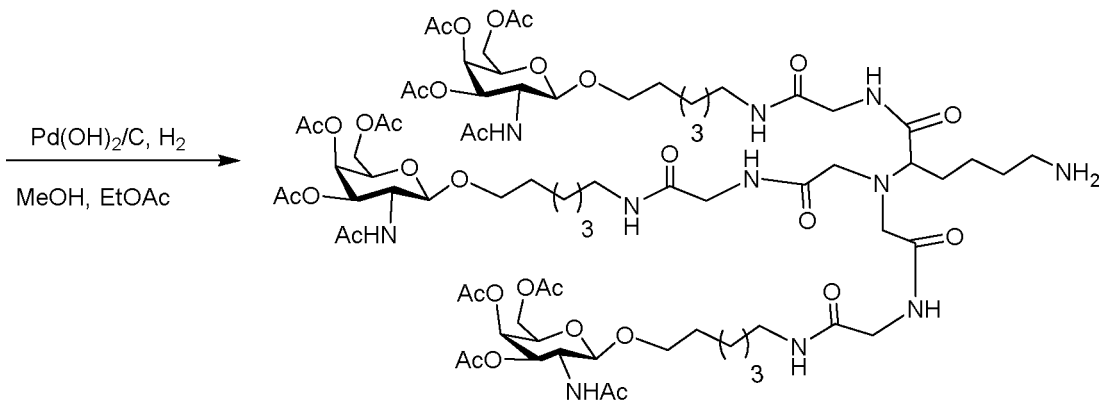
Compound 112 (4.27 g, 7.35 mmol) was dissolved in 1:1 MeOH/EtOAc (40 ml). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon, 400 mg) was added, and hydrogen gas was bubbled through the solution for 30 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.



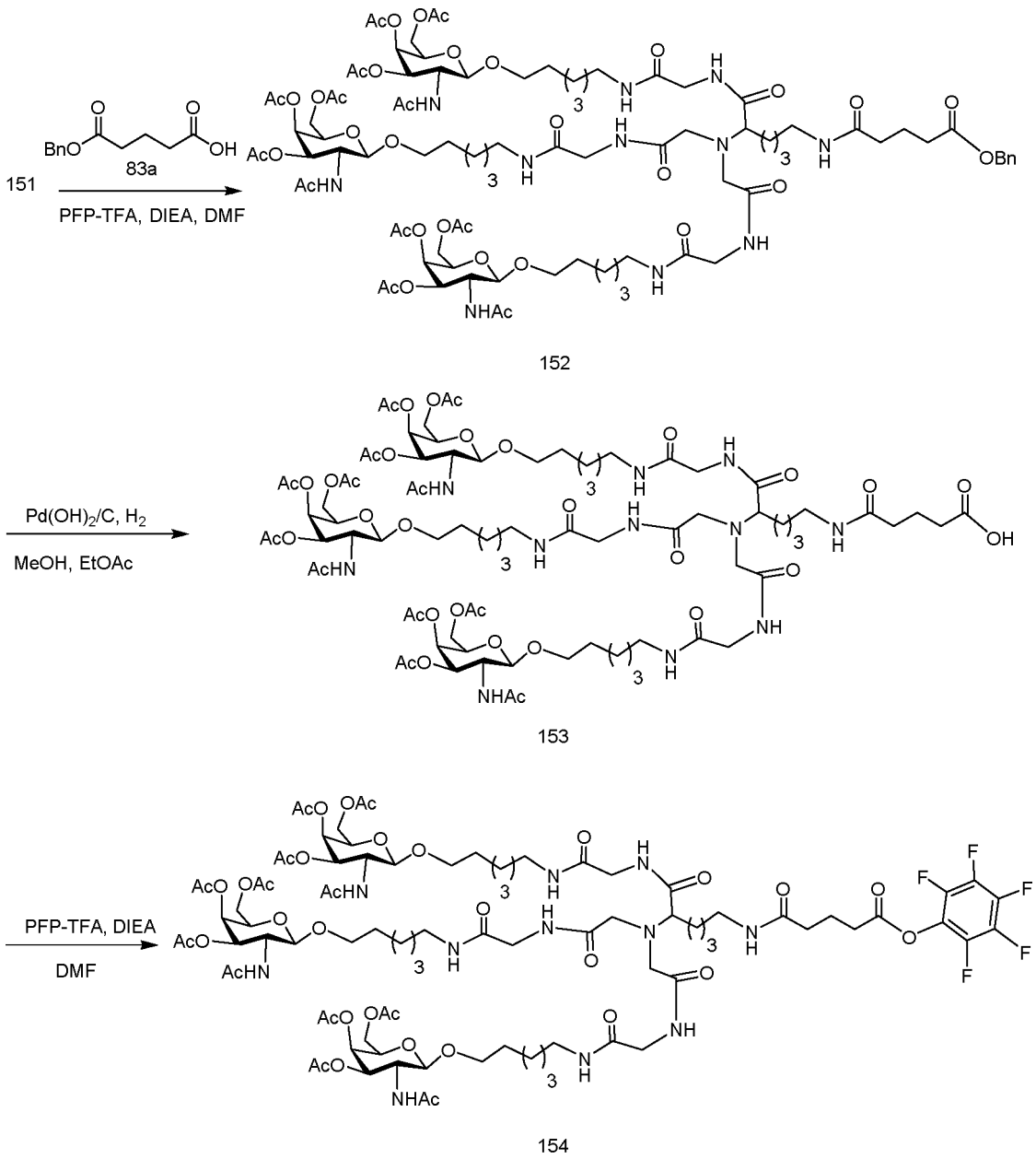
150



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.

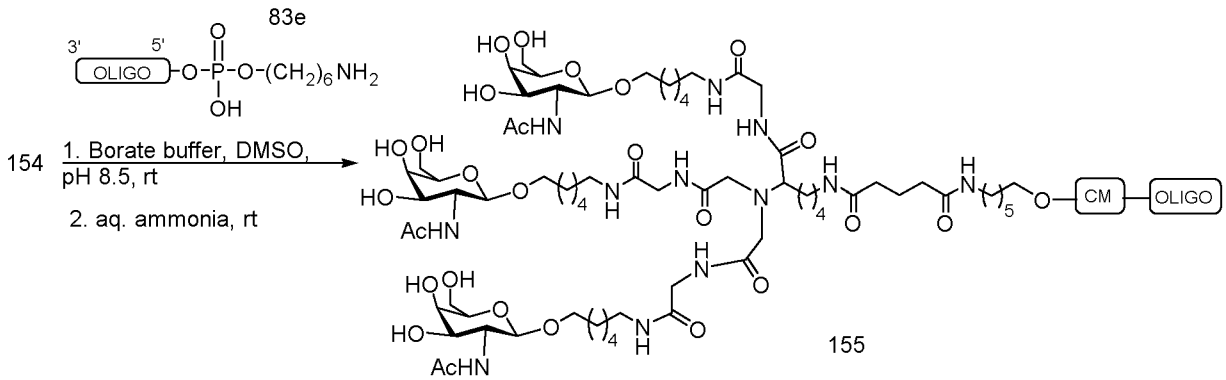


Compound 83a (0.11 g, 0.33 mmol) was dissolved in anhydrous DMF (5 mL) and *N,N*-Diisopropylethylamine (75 µL, 1 mmol) and PFP-TFA (90 µL, 0.76 mmol) were added. The reaction mixture turned magenta upon contact, and gradually turned orange over the next 30 minutes. Progress of reaction was monitored 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.

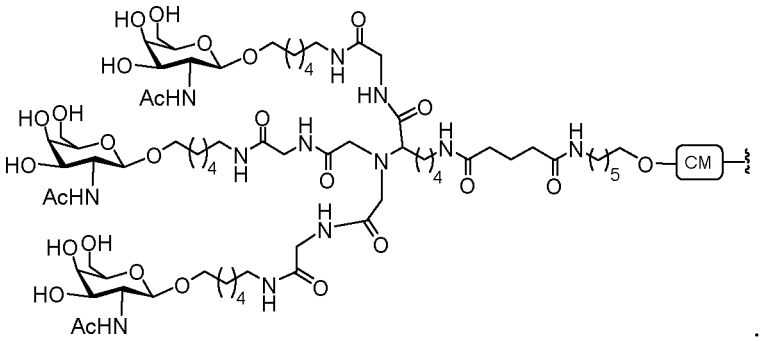
Compound 152 (0.35 g, 0.182 mmol) was dissolved in 1:1 MeOH/EtOAc (10 mL). The reaction mixture was purged by bubbling a stream of argon thru the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (35 mg). Hydrogen gas was bubbled thru the solution for 30 minutes. 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.

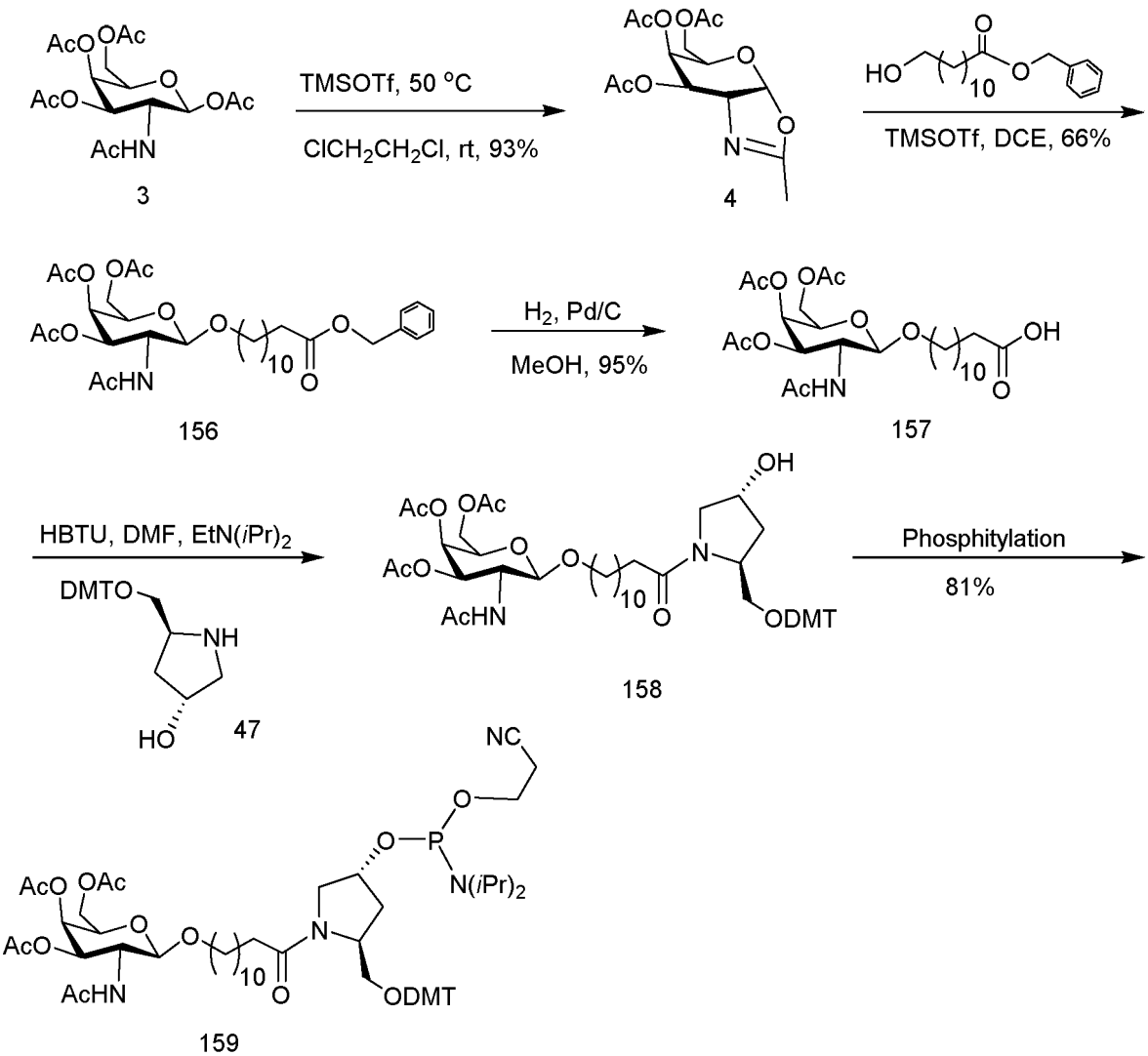


Oligomeric Compound 155, comprising a $GalNAc_3$-6 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-6 ($GalNAc_3$-6_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. 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

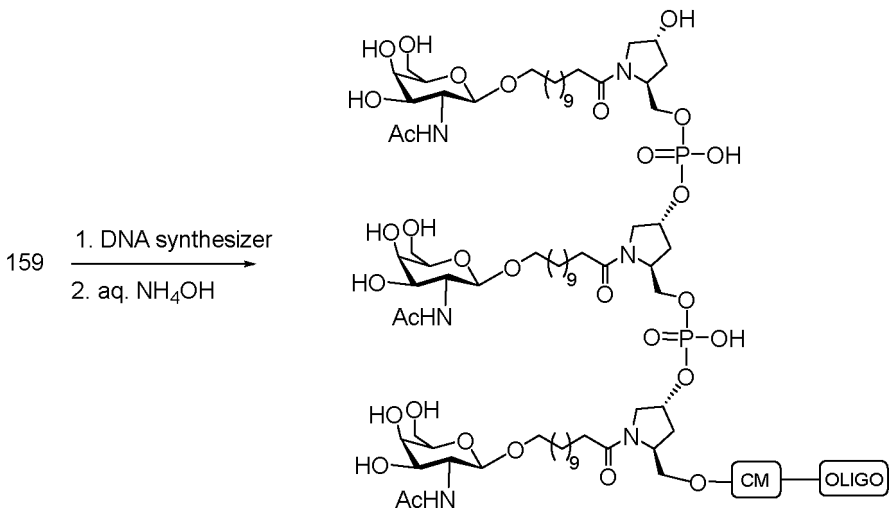


Compound 156 was synthesized following the procedure described in the literature (*J. Med. Chem.* 2004, *47*, 5798-5808).

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 $[M-H]^-$.

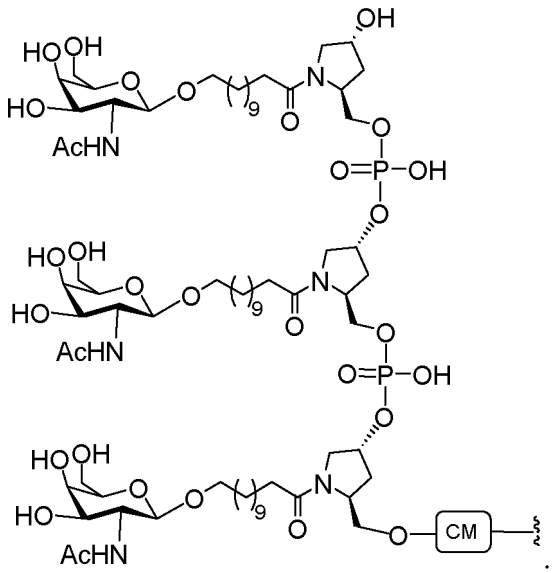
Compound 157 (5 g, 9.17 mmol) was dissolved in anhydrous DMF (30 mL). HBTU (3.65 g, 9.61 mmol) and *N*,*N*-Diisopropylethylamine (13.73 mL, 78.81 mmol) were added and the reaction mixture was stirred at room temperature for 5 minutes. To this a solution of compound 47 (2.96 g, 7.04 mmol) was added. The 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.



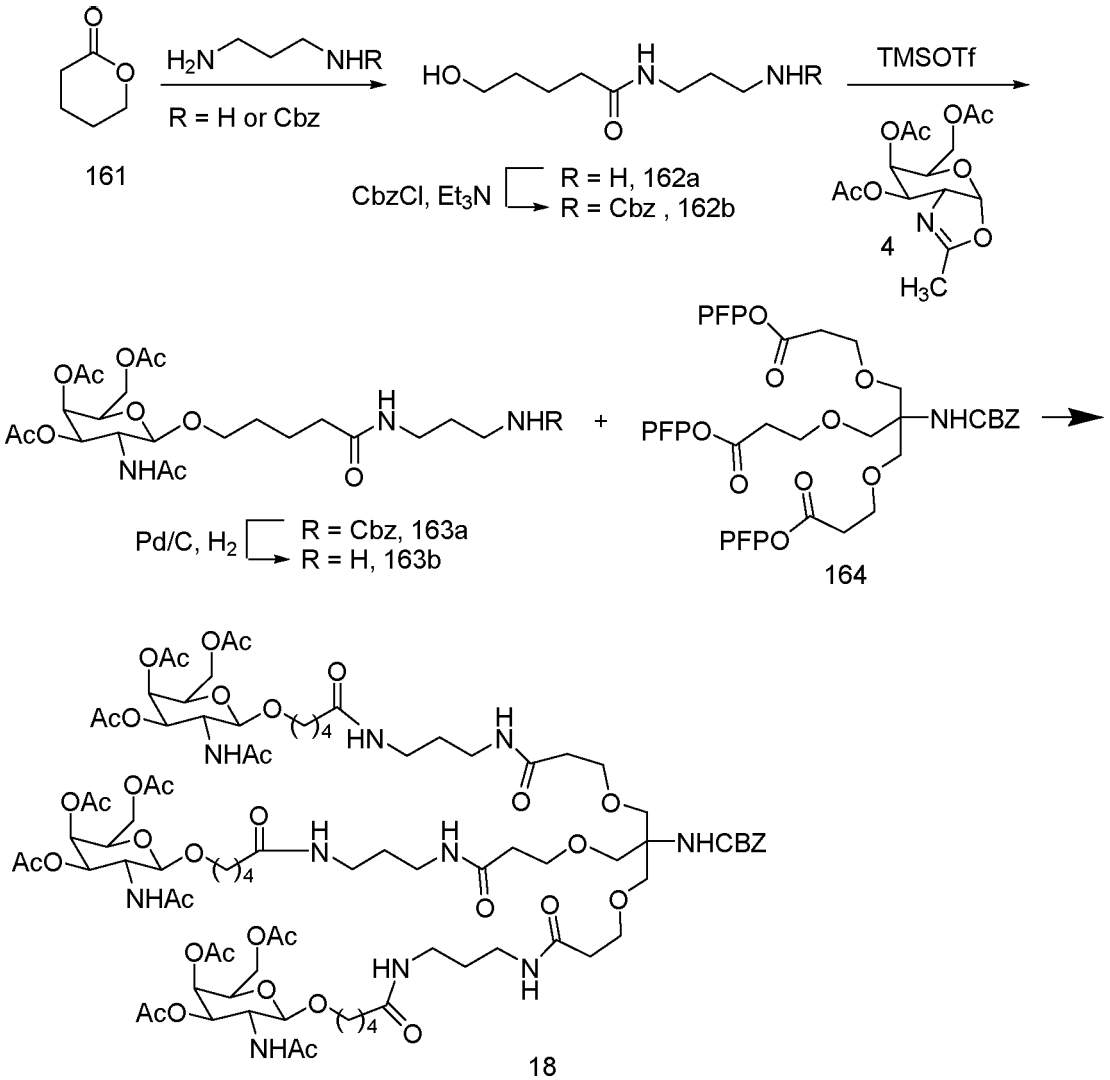
160

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:



Example 53: Alternate procedure for preparation of Compound 18 ($GalNAc_3$-1a and $GalNAc_3$-3a)

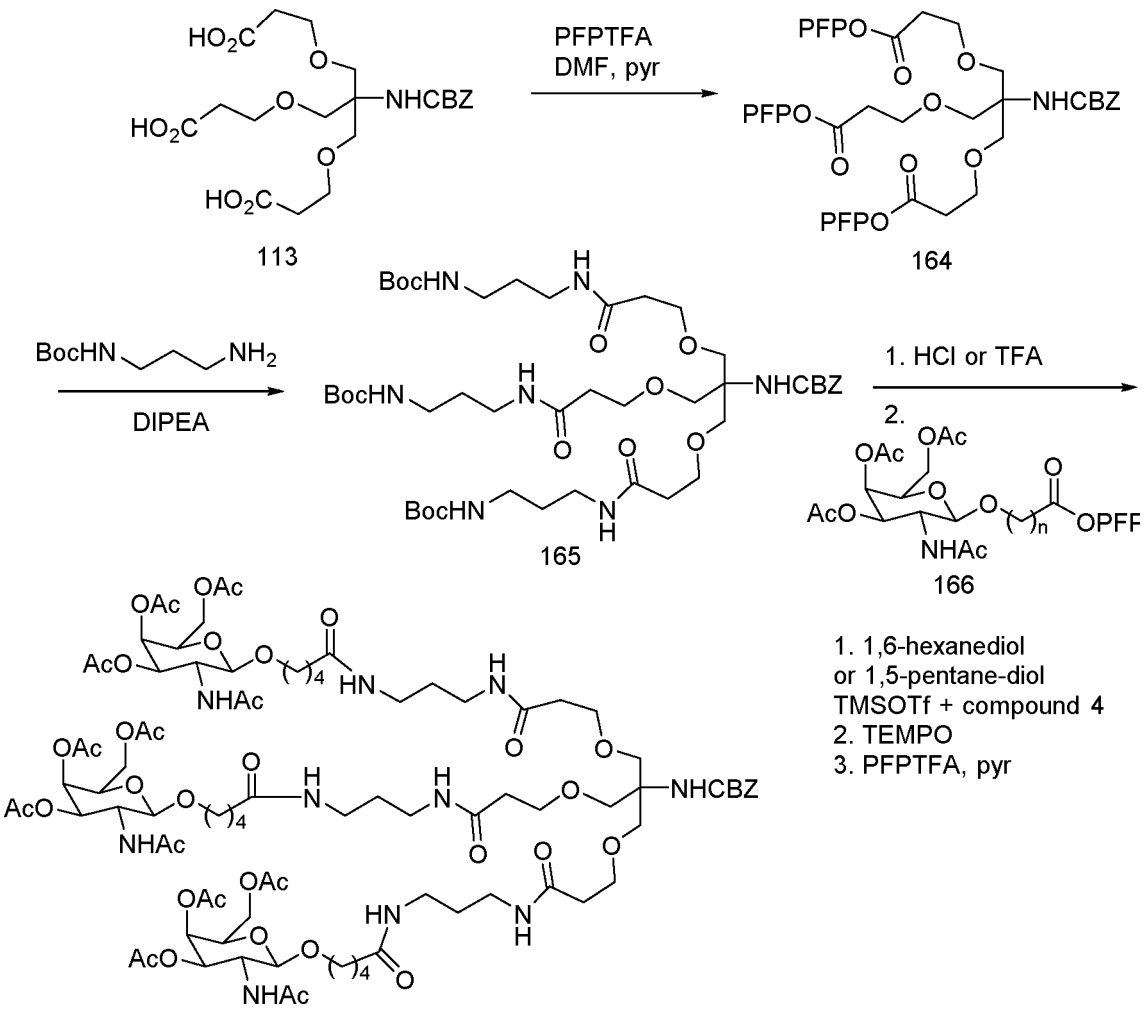
Lactone 161 was reacted with diamino propane (3-5 eq) or Mono-Boc protected diamino propane (1 eq) to provide alcohol 162a or 162b. When unprotected propanediamine was used for the above reaction, the excess diamine was removed by evaporation under high vacuum and the free amino group in 162a was protected 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	2304

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**	2305
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**	2305
ISIS 661161	**GalNAc$_3$-3$_a$-$_{o'}$A$_{do}$** $G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}$ $^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-3**	2304
ISIS 665001	**GalNAc$_3$-8$_a$-$_{o'}$A$_{do}$** $G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}$ $^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-8**	2304

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	2304
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**	2305
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**	2306
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**	2304
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**	2306
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**	2306
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**	2306
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**	2306

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	2296
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	2297
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	2297

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	2298
		2	59.66	
		6	23.50	
ISIS 651900	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do'}}$-**$GalNAc_3$-$1_a$**	0.2	62.75	2299
		0.6	29.14	
		2	8.61	
		6	5.62	

ISIS 663748	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}$ $^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}$**$A_{do'}$-GalNAc$_4-11_a$**	0.2	63.99	2299
		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	2307

ISIS 656172	$T_{es}G_{es}G_{es}T_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{es}G_{es}A_{es}G_{es}G_{eo}$**$A_{do}$'-GalNAc$_3-1_a$**	PS	2308
ISIS 656173	$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{eo}$**$A_{do}$'-GalNAc$_3-1_a$**	PO/PS	2308

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	2304
ISIS 655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	5/10/5	**$GalNAc_3$-1**	2305
ISIS 655862	$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	5/10/5	**$GalNAc_3$-1**	2305
ISIS 661161	$\mathbf{GalNAc_3\text{-}3_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-3**	2306
ISIS 665001	$\mathbf{GalNAc_3\text{-}8_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-8**	2306
ISIS 664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}9_a}$	5/10/5	**$GalNAc_3$-9**	2305
ISIS 666961	$\mathbf{GalNAc_3\text{-}6_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-6**	2306
ISIS 664507	$\mathbf{GalNAc_3\text{-}2_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-2**	2306
ISIS 666881	$\mathbf{GalNAc_3\text{-}10_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-10**	2306
ISIS 666224	$\mathbf{GalNAc_3\text{-}5_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-5**	2306
ISIS 666981	$\mathbf{GalNAc_3\text{-}7_{a\text{-}o}}\mathbf{,A_{do}}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-7**	2306

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®.

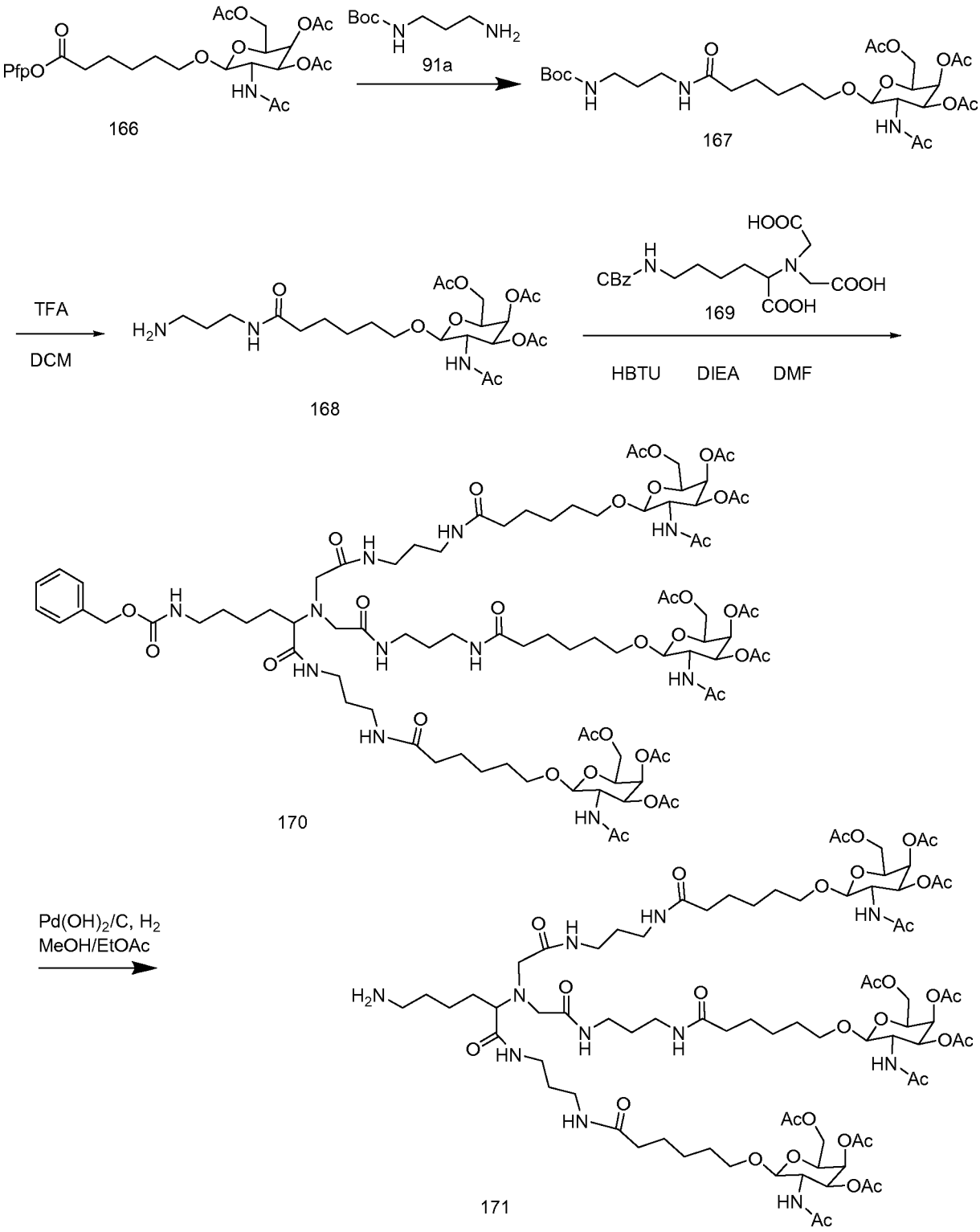
The IC_{50} was calculated using standard methods and the results are presented in Table 53. The results show that, under free uptake conditions in which no reagents or electroporation techniques are used to artificially promote entry of the oligonucleotides into cells, the oligonucleotides comprising a GalNAc conjugate were significantly more potent in hepatocytes than the parent oligonucleotide (ISIS 353382) that does not comprise a GalNAc conjugate.

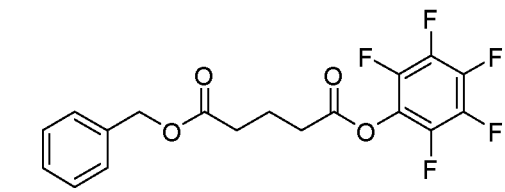
Table 53

ASO	IC_{50} (nM)	Internucleoside linkages	Conjugate	SEQ ID No.
ISIS 353382	190[a]	PS	none	2304
ISIS 655861	11[a]	PS	**$GalNAc_3$-1**	2305
ISIS 655862	3	PO/PS	**$GalNAc_3$-1**	2305
ISIS 661161	15[a]	PS	**$GalNAc_3$-3**	2306
ISIS 665001	20	PS	**$GalNAc_3$-8**	2306
ISIS 664078	55	PS	**$GalNAc_3$-9**	2305
ISIS 666961	22[a]	PS	**$GalNAc_3$-6**	2306
ISIS 664507	30	PS	**$GalNAc_3$-2**	2306
ISIS 666881	30	PS	**$GalNAc_3$-10**	2306
ISIS 666224	30[a]	PS	**$GalNAc_3$-5**	2306
ISIS 666981	40	PS	**$GalNAc_3$-7**	2306

[a]Average of multiple runs.

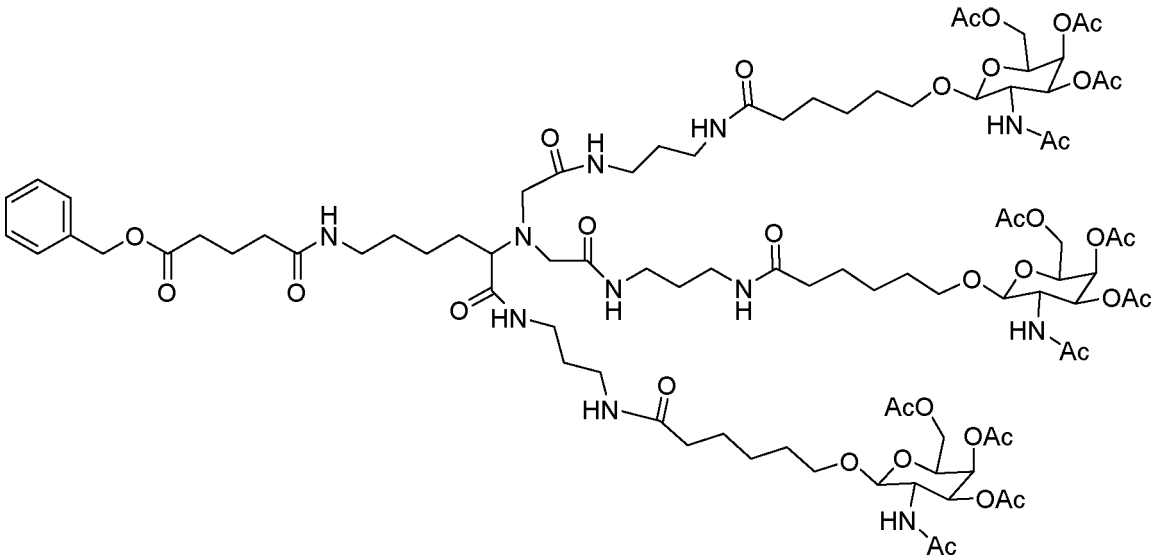
Example 61: Preparation of oligomeric compound 175 comprising $GalNAc_3$-12


166
91a
167
TFA
DCM
168
169
HBTU DIEA DMF
170
Pd(OH)2/C, H2
MeOH/EtOAc
171

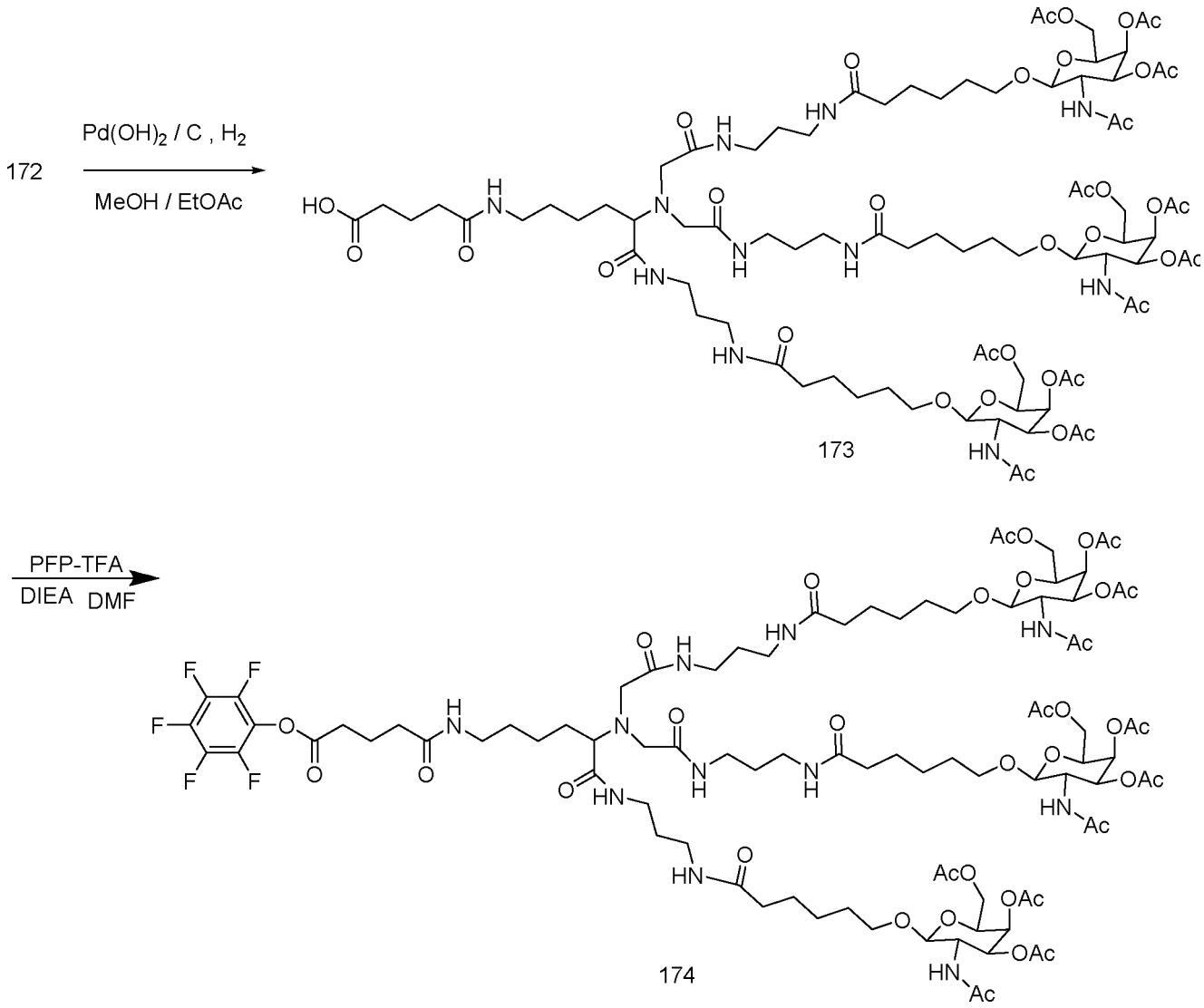


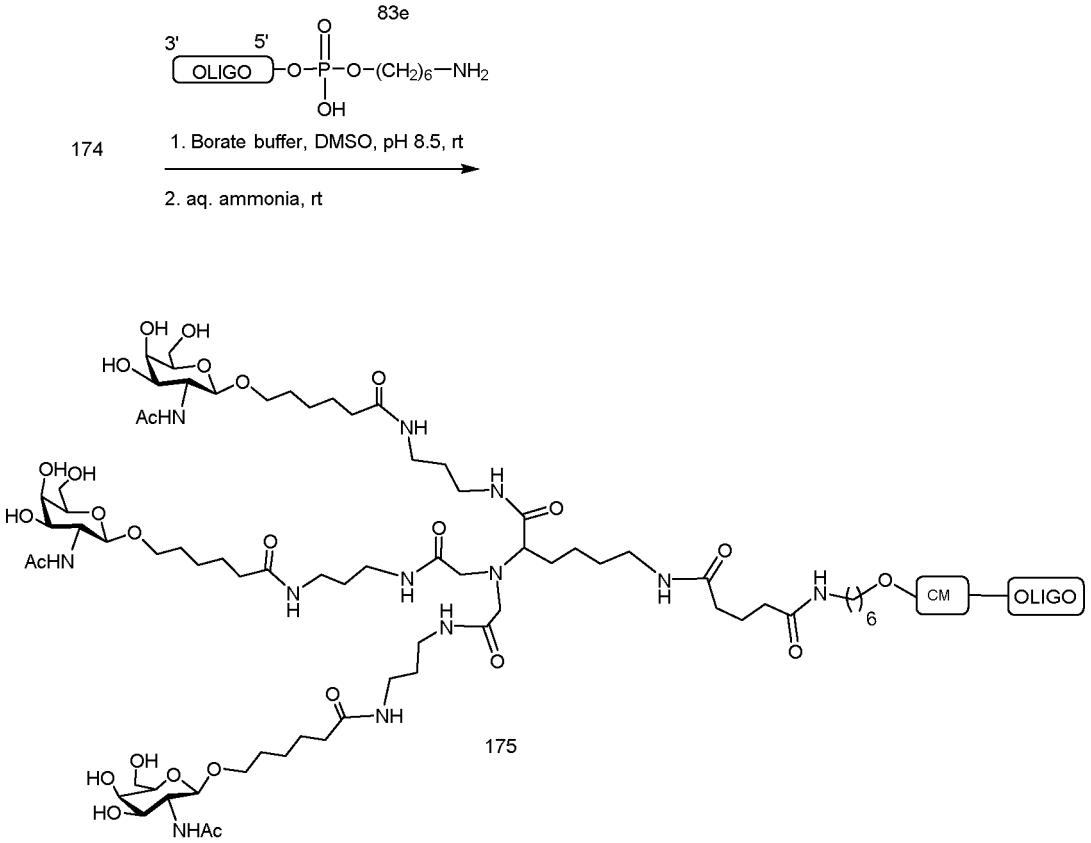
benzyl (perfluorophenyl) glutarate

DMF

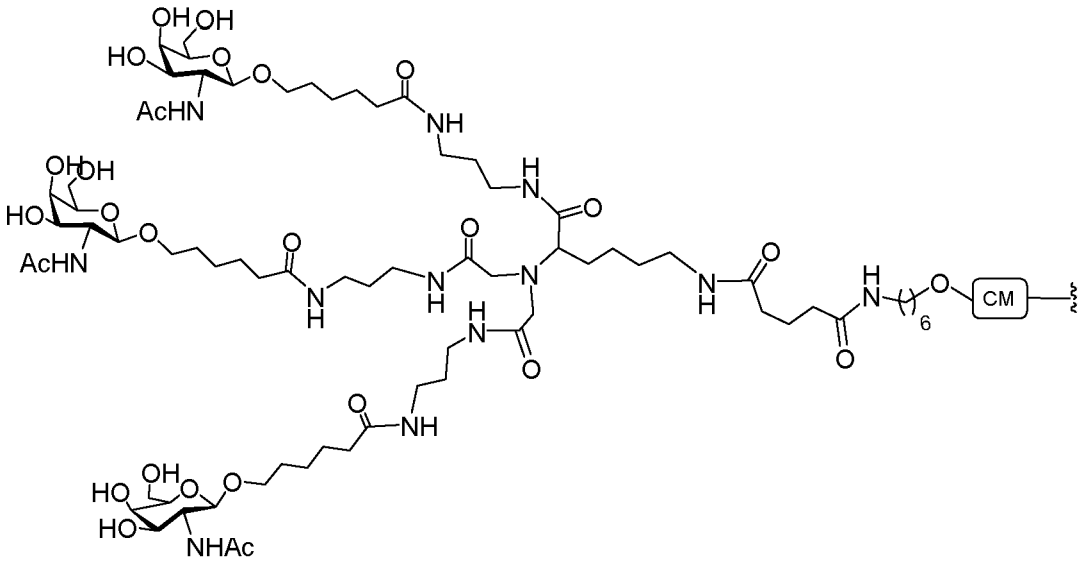


172

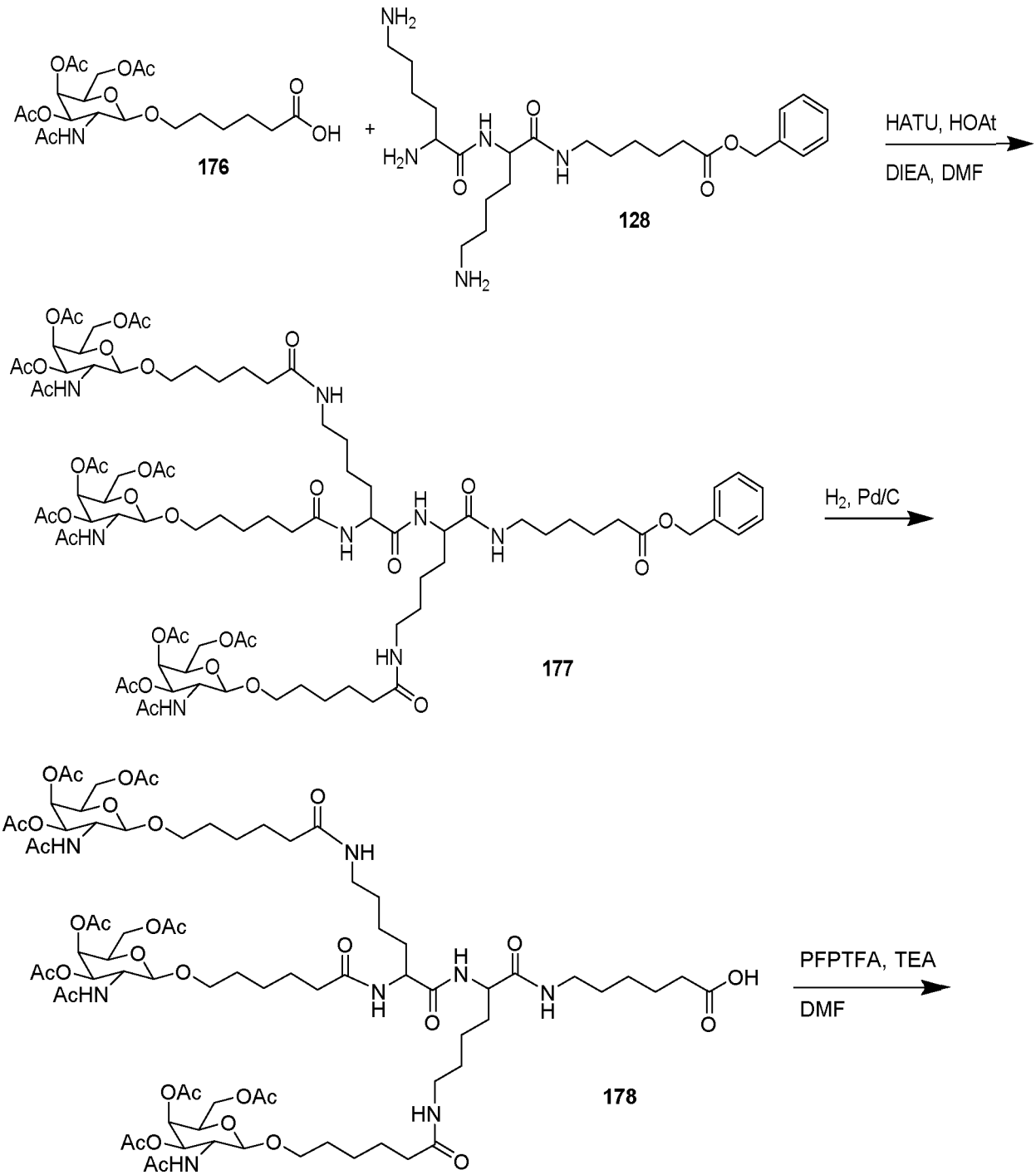

172
Pd(OH)2 / C , H2
MeOH / EtOAc
173
PFP-TFA
DIEA DMF
174

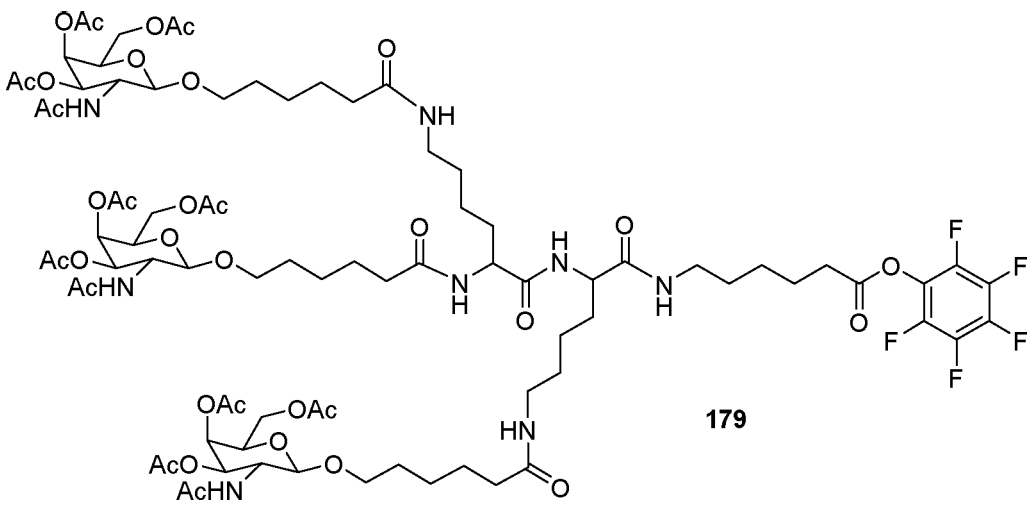


Compound 169 is commercially available. Compound 172 was prepared by addition of benzyl (perfluorophenyl) glutarate to compound 171. The benzyl (perfluorophenyl) glutarate was prepared by adding PFP-TFA and DIEA to 5-(benzyloxy)-5-oxopentanoic acid in DMF. Oligomeric compound 175, comprising a $GalNAc_3$-12 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:

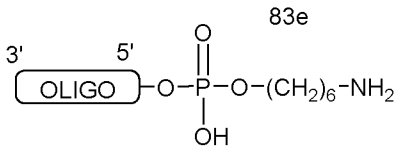


Example 62: Preparation of oligomeric compound 180 comprising GalNAc$_3$-13


176
128
HATU, HOAt
DIEA, DMF
177
H2, Pd/C
178
PFPTFA, TEA
DMF



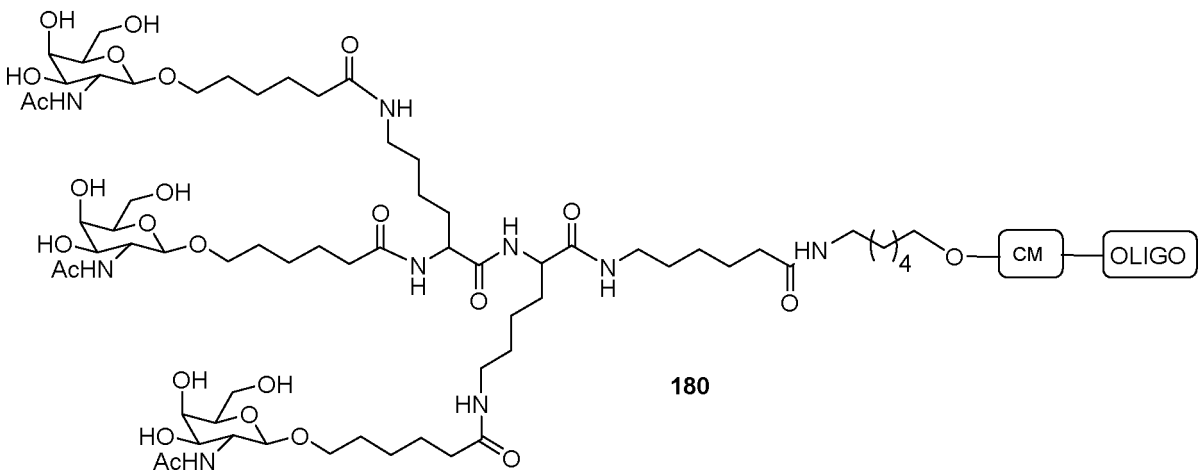
179



83e

1. Borate buffer, DMSO, pH 8.5, rt

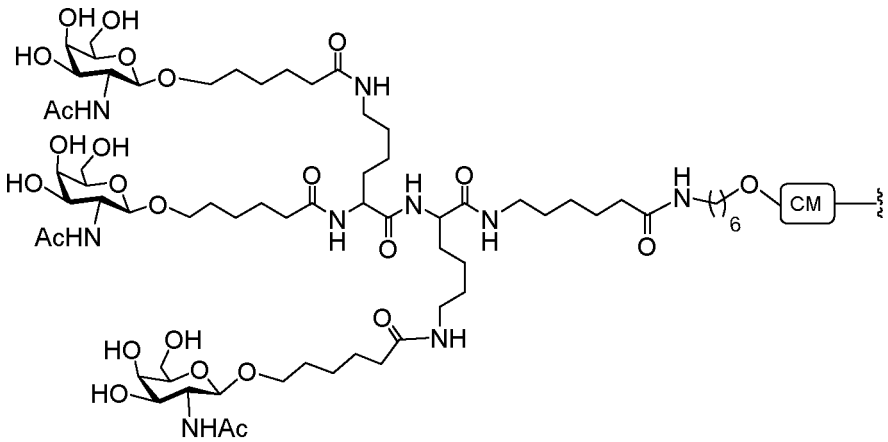
2. aq. ammonia, rt



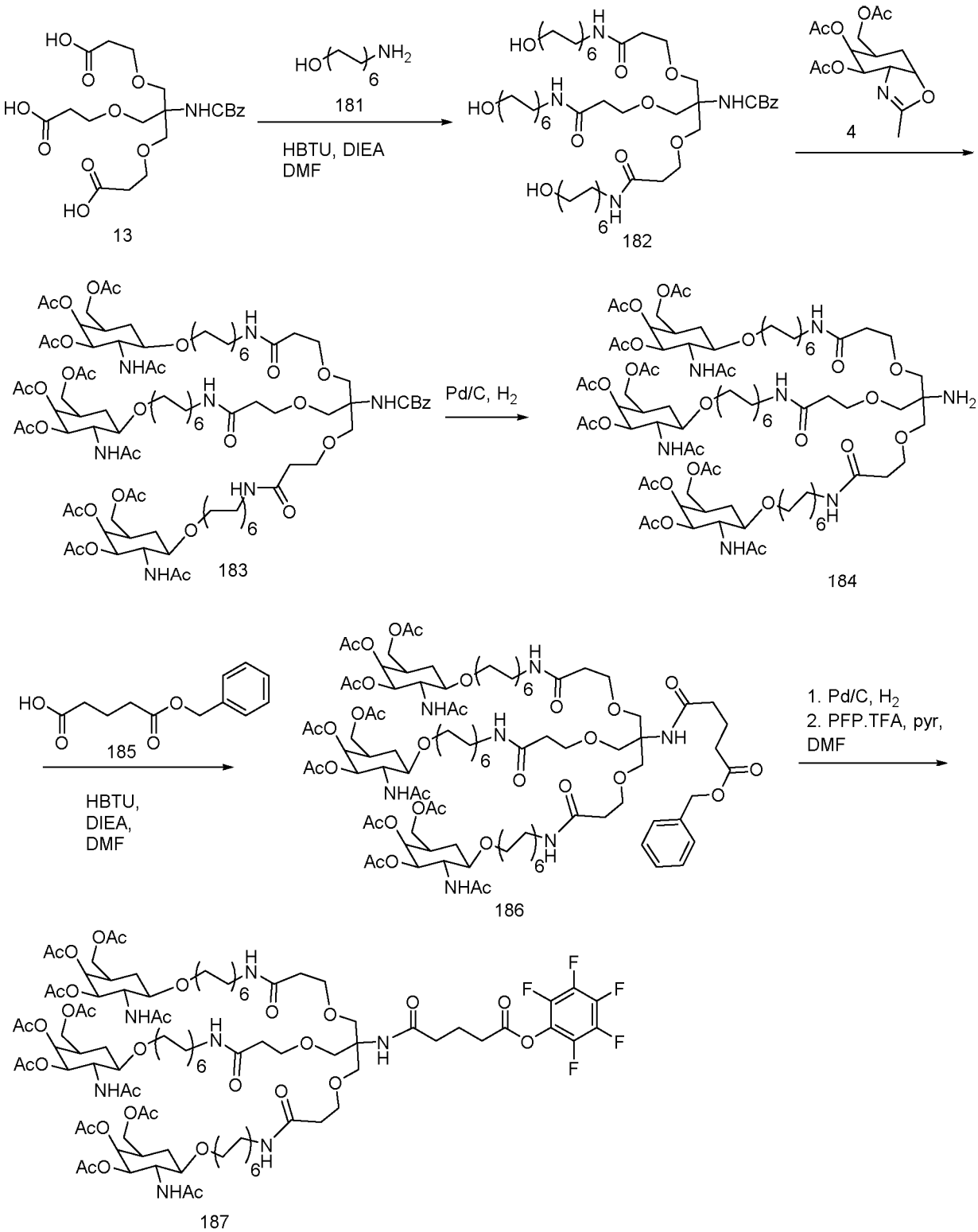
180

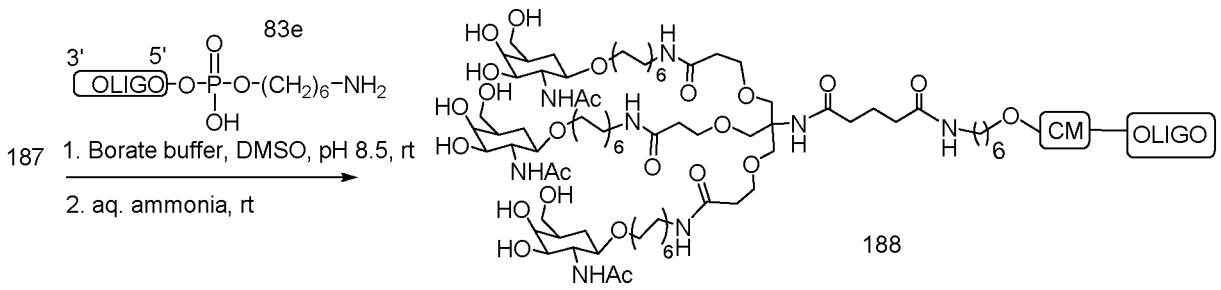
Compound 176 was prepared using the general procedure shown in Example 2. Oligomeric compound 180, comprising a $GalNAc_3$-13 conjugate group, was prepared from compound 177 using the general procedures illustrated in Example 49. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-13 ($GalNAc_3$-13_a) 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:

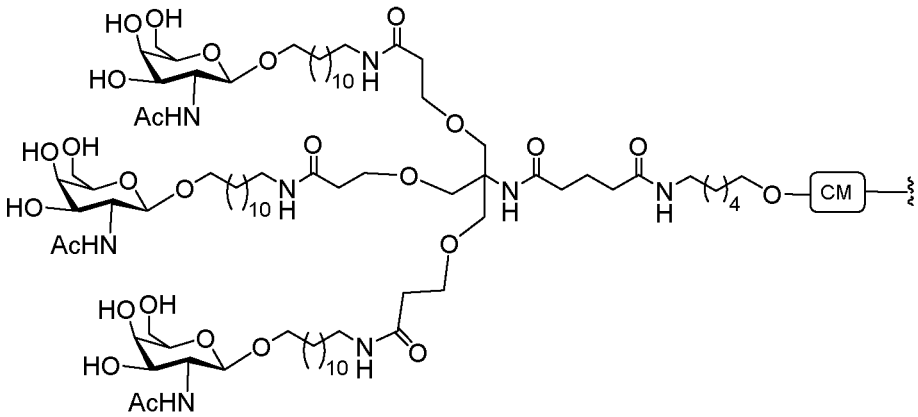


Example 63: Preparation of oligomeric compound 188 comprising $GalNAc_3$-14

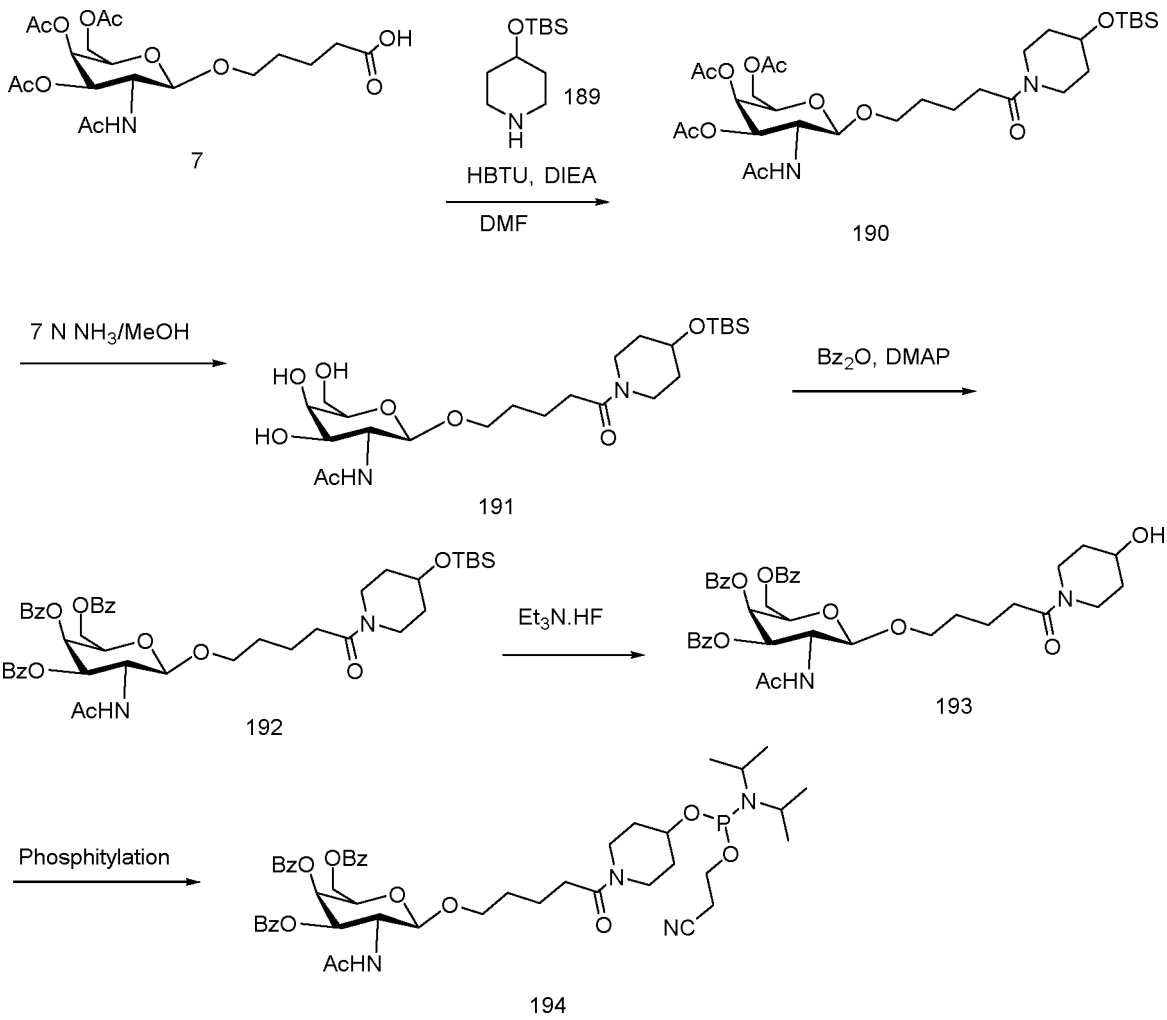

181
HBTU, DIEA
DMF
13
182
4
Pd/C, H2
183
184
185
HBTU,
DIEA,
DMF
186
1. Pd/C, H2
2. PFP.TFA, pyr,
DMF
187

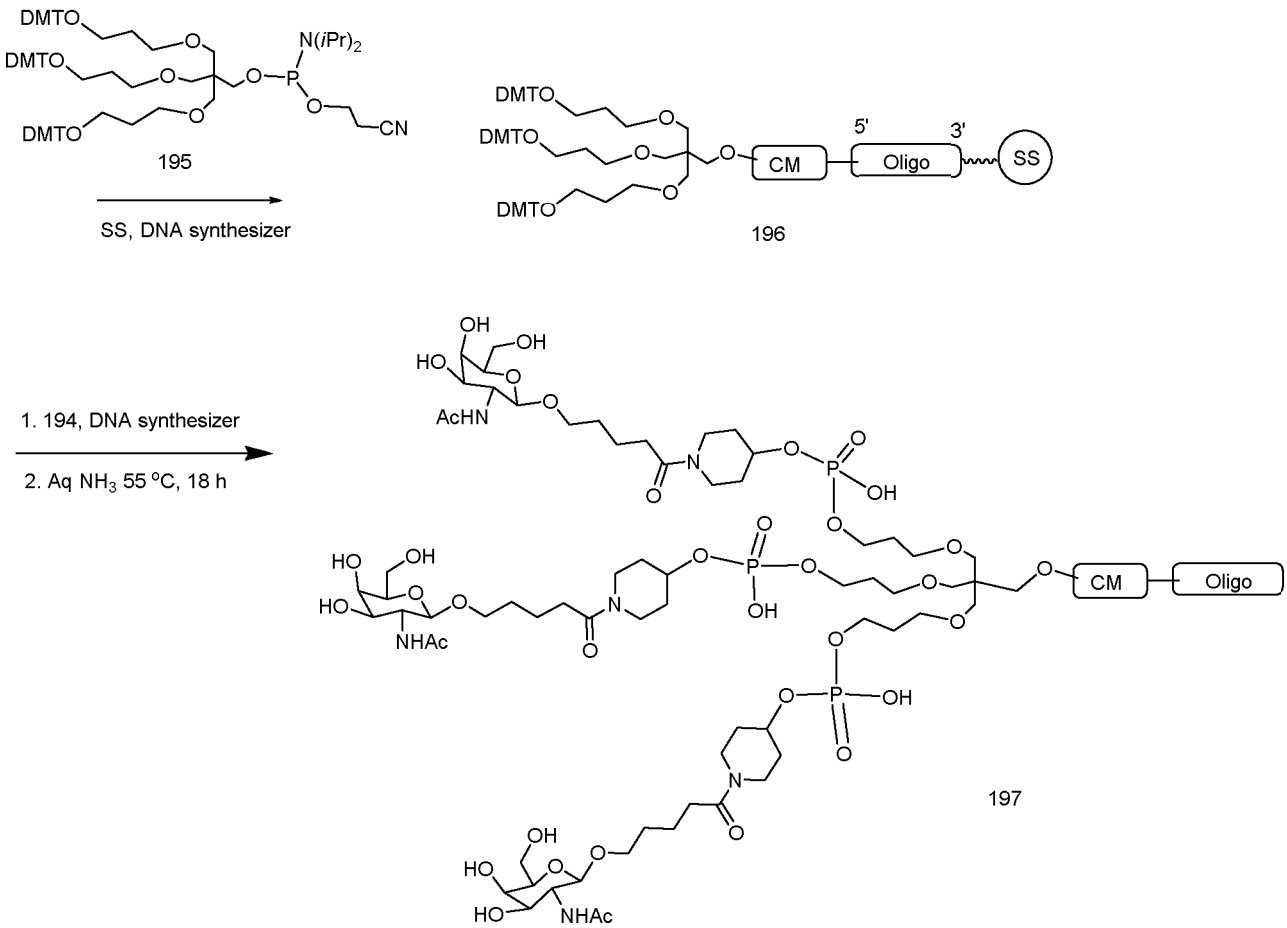


Compounds 181 and 185 are commercially available. Oligomeric compound 188, comprising a $GalNAc_3$-14 conjugate group, was prepared from compound 187 using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-14 ($GalNAc_3$-14_a) can be combined 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:

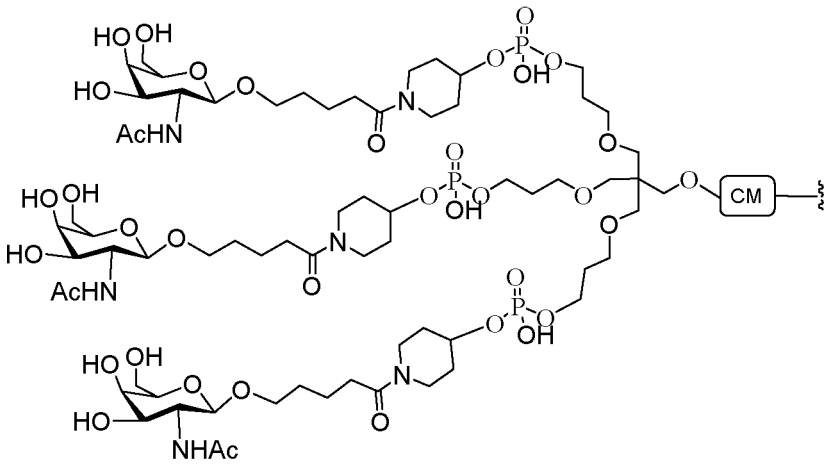


Example 64: Preparation of oligomeric compound 197 comprising $GalNAc_3$-15


AcO
OAc
AcO
AcHN
OH
O
7
OTBS
N
H
189
HBTU, DIEA
DMF
190
7 N NH3/MeOH
HO
OH
HO
AcHN
191
Bz2O, DMAP
BzO
OBz
BzO
AcHN
192
Et3N.HF
193
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	2304
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$_3$-3	2306
671144	**GalNAc$_3$-12$_{a\text{-}o}$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$_3$-12	2306
670061	**GalNAc$_3$-13$_{a\text{-}o}$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$_3$-13	2306
671261	**GalNAc$_3$-14$_{a\text{-}o}$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$_3$-14	2306
671262	**GalNAc$_3$-15$_{a\text{-}o}$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$_3$-15	2306

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$_d$	2306
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$_d$	2309
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$_e$	2306
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$_e$	2309
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$_d$	2306

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 C57BL/6 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 demonstrated 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		

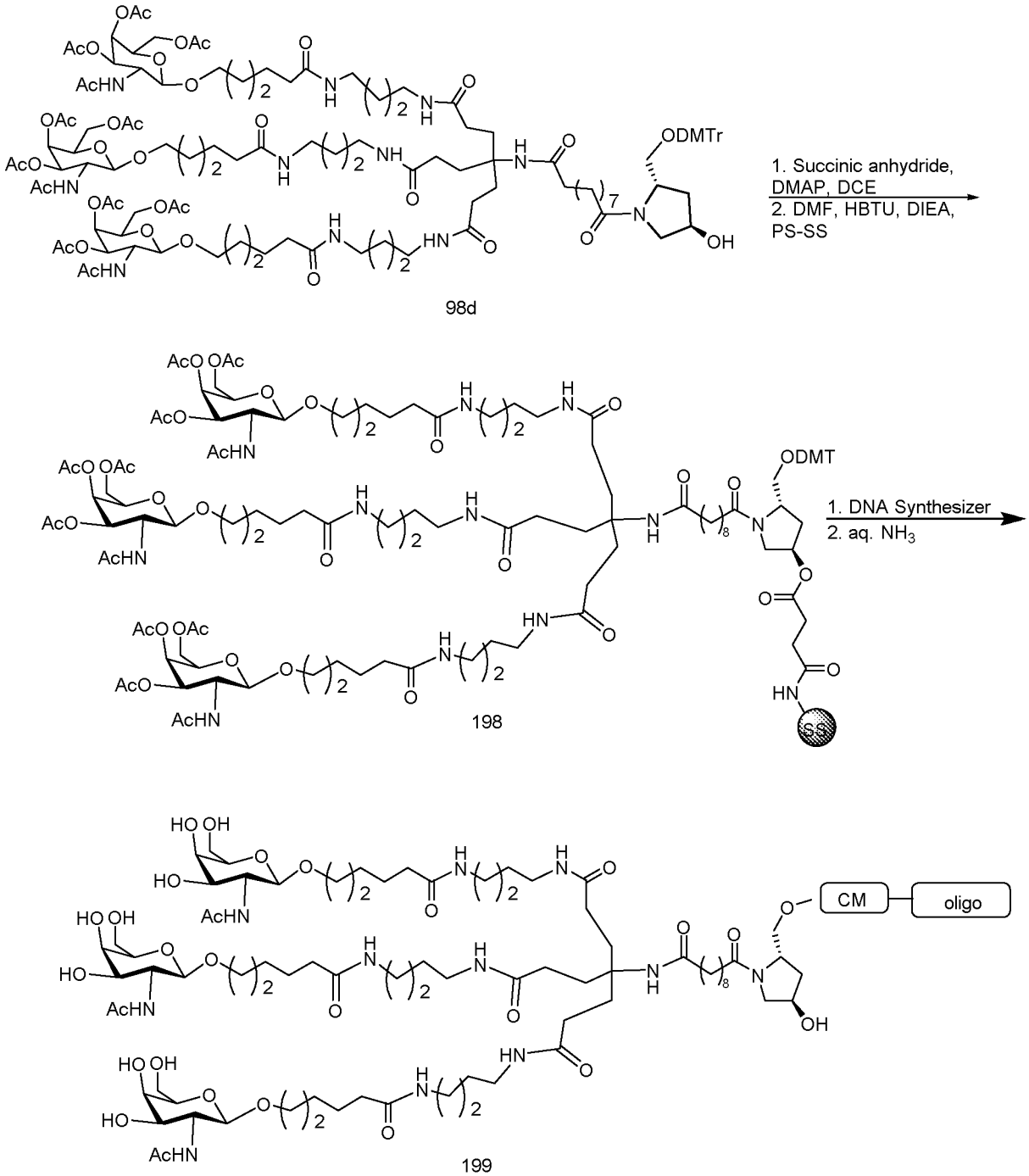
Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Total bilirubin and BUN were also evaluated. The changes in body weights were evaluated with no significant differences from the saline group (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 59 below.

Table 59

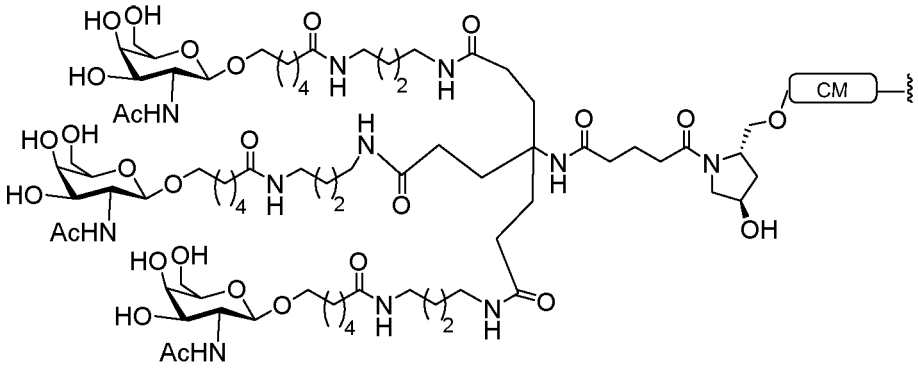
ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	$GalNAc_3$ Cluster	CM
Saline	n/a	24	64	0.2	31	n/a	n/a
661161	0.5	25	64	0.2	31	$GalNAc_3$-3a	A_d
	1.5	24	50	0.2	32		
	5	26	55	0.2	28		
	15	27	52	0.2	31		
670699	0.5	42	83	0.2	31	$GalNAc_3$-3a	T_d
	1.5	33	58	0.2	32		
	5	26	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		

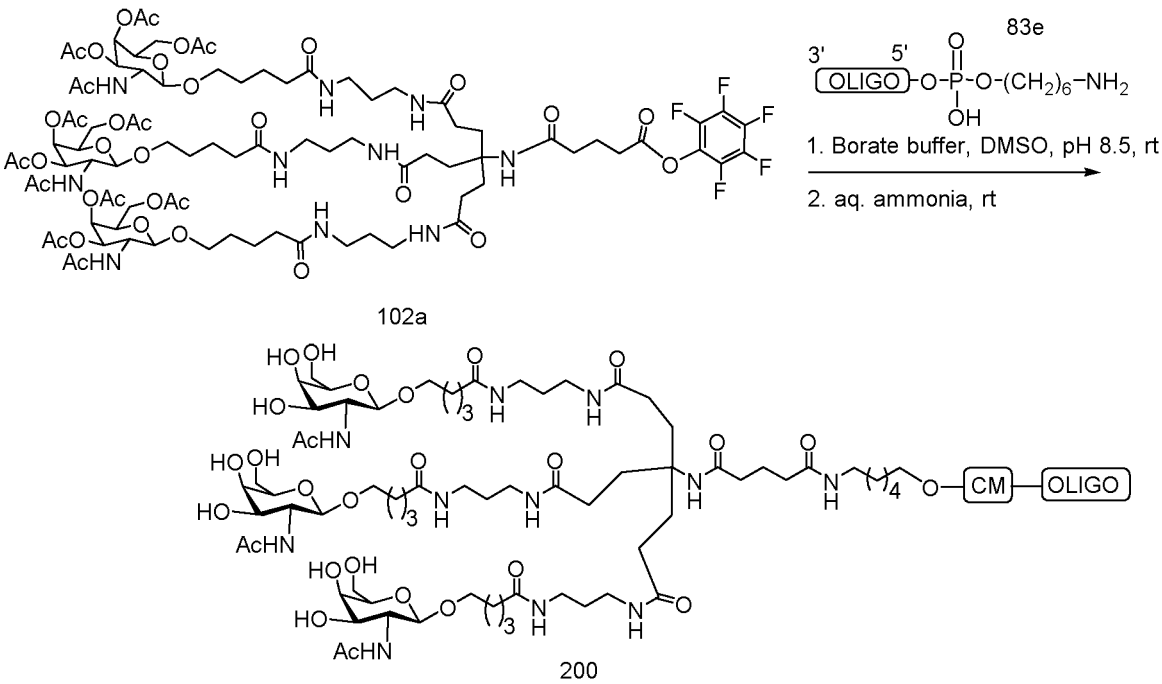
Example 67: Preparation of oligomeric compound 199 comprising GalNAc$_3$-16



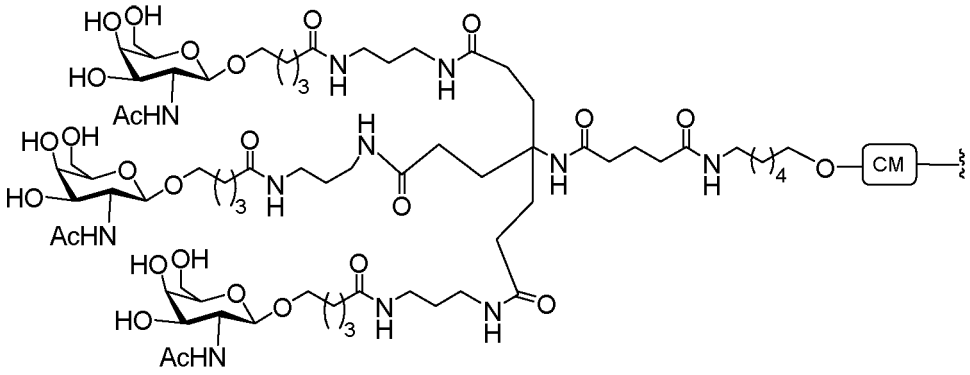
Oligomeric compound 199, comprising a GalNAc$_3$-16 conjugate group, is prepared using the general procedures illustrated in Examples 7 and 9. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-16 (GalNAc$_3$-16$_a$) can be combined with any cleavable moiety to provide a variety of conjugate 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:



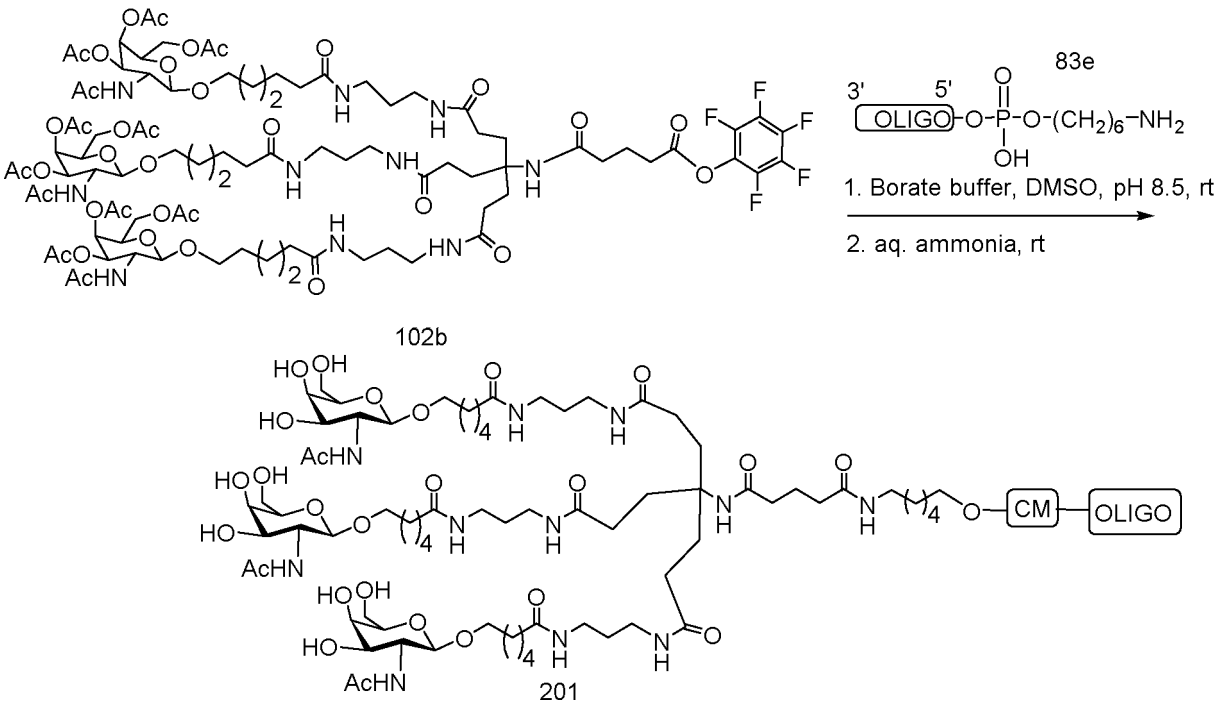
Example 68: Preparation of oligomeric compound 200 comprising GalNAc$_3$-17



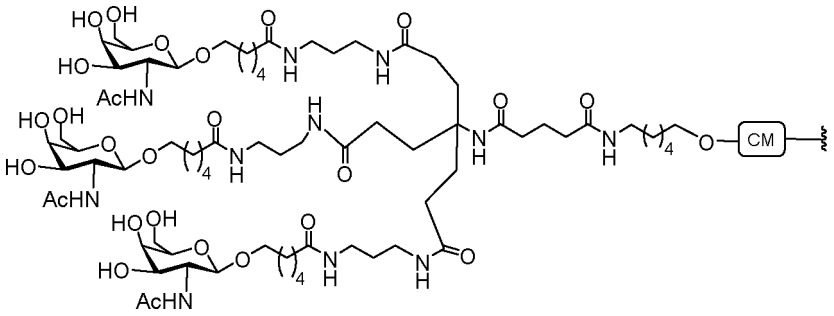
Oligomeric compound 200, comprising a GalNAc$_3$-17 conjugate group, was prepared using the general procedures illustrated in Example 46. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-17 (GalNAc$_3$-17$_a$) can be combined with any cleavable moiety to provide a variety of conjugate 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:



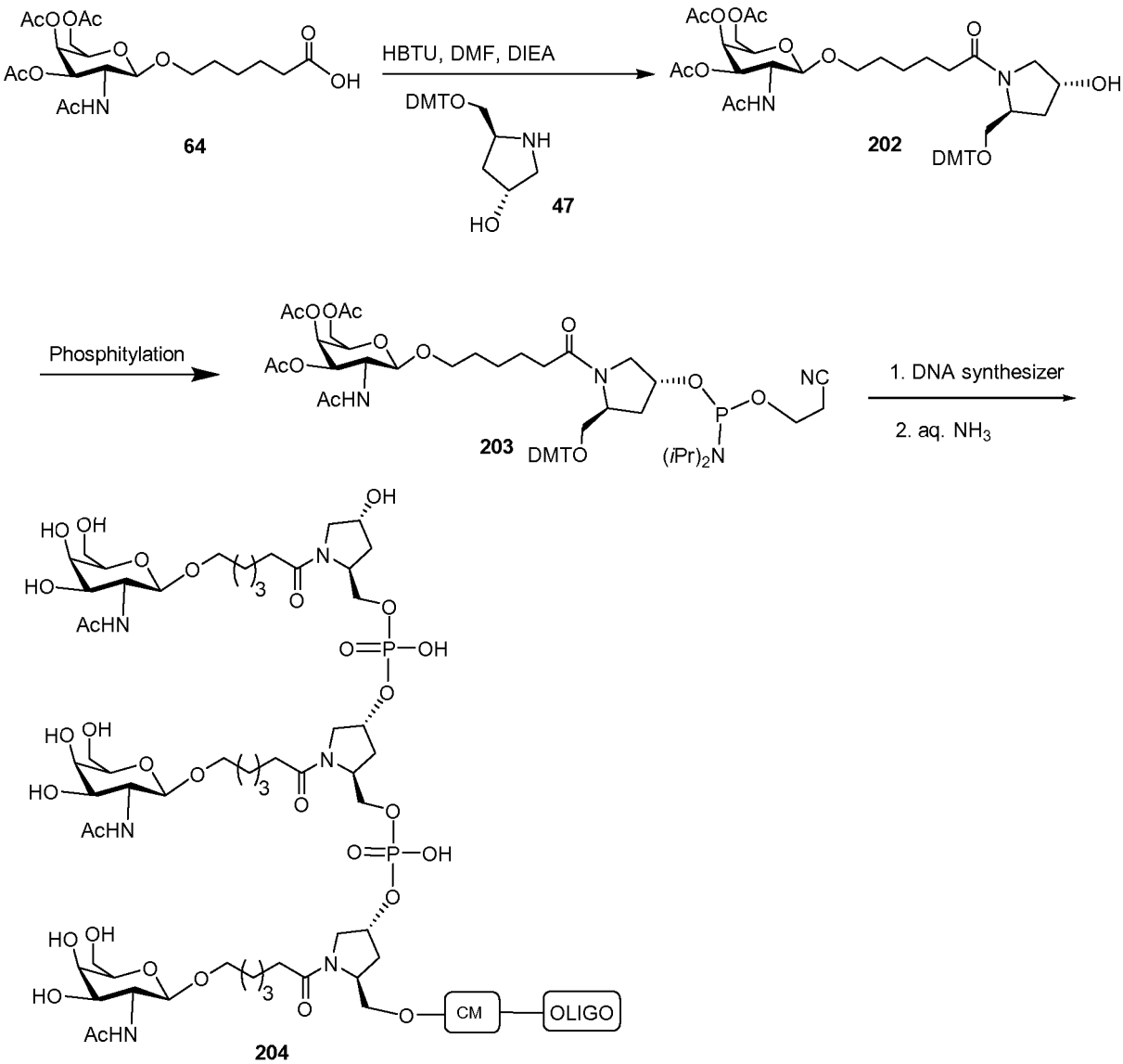
Example 69: Preparation of oligomeric compound 201 comprising GalNAc$_3$-18



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:

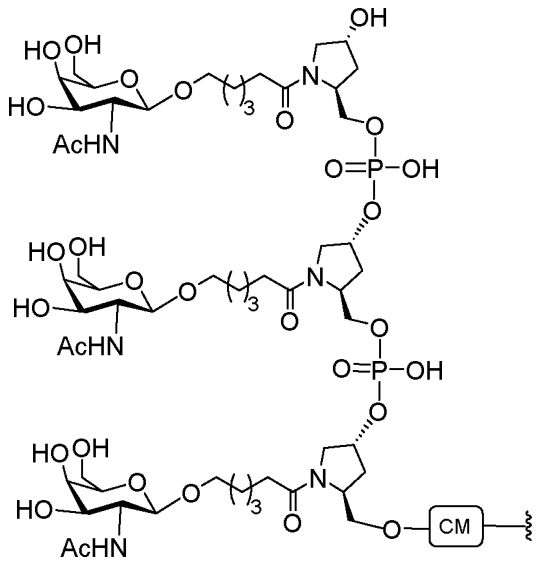


Example 70: Preparation of oligomeric compound 204 comprising GalNAc$_3$-19

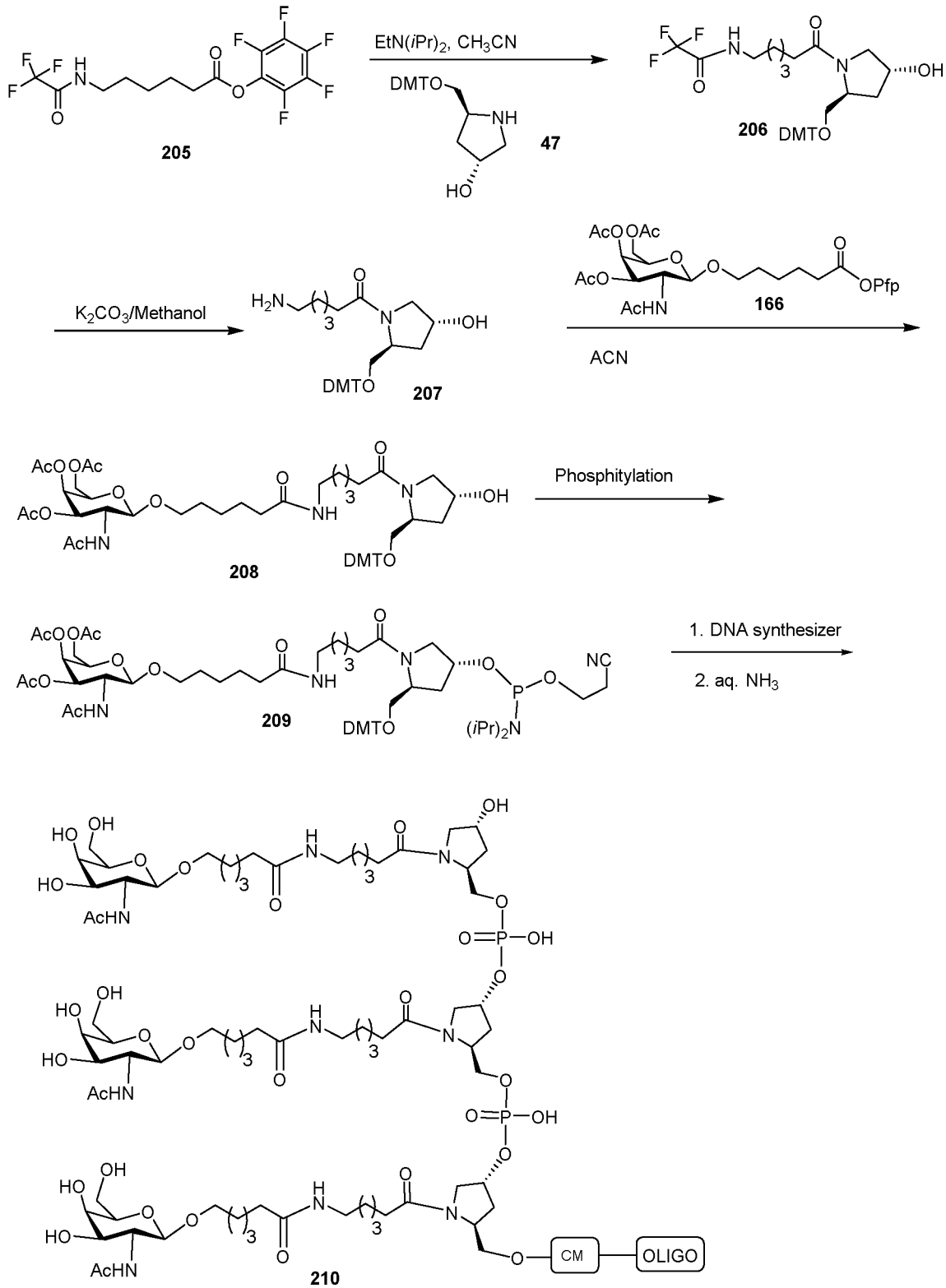


Oligomeric compound 204, comprising a GalNAc$_3$-19 conjugate group, was prepared from compound 64 using the general procedures illustrated in Example 52. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-19 (GalNAc$_3$-19$_a$) can be combined with any cleavable moiety to provide a variety

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:

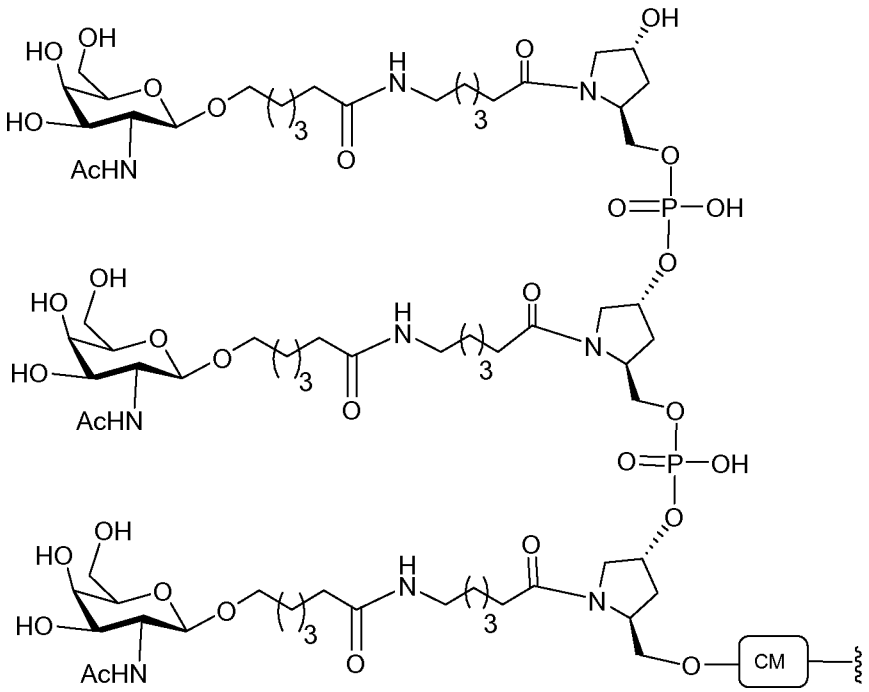


Example 71: Preparation of oligomeric compound 210 comprising GalNAc$_3$-20

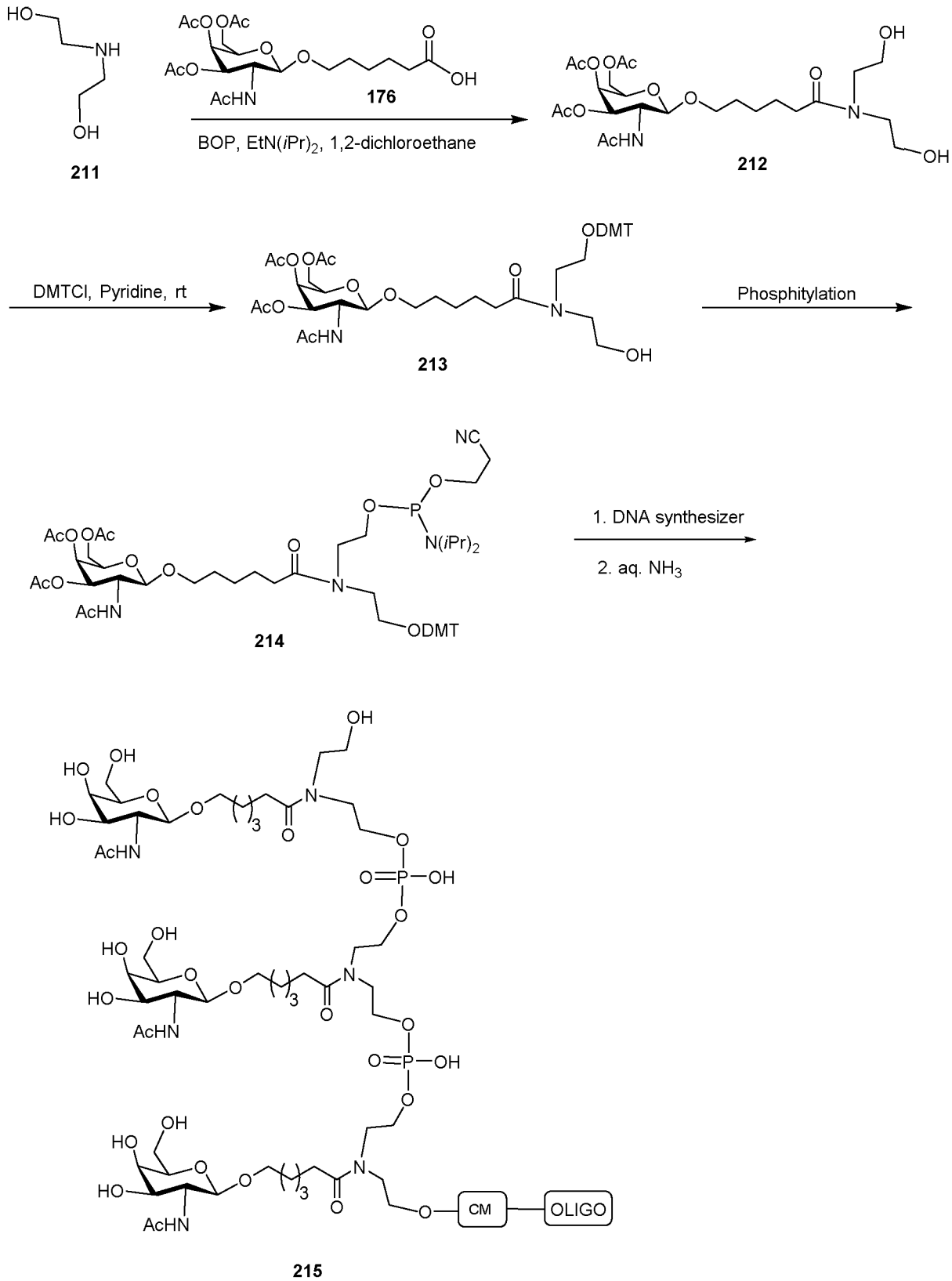


Compound 205 was prepared by adding PFP-TFA and DIEA to 6-(2,2,2-trifluoroacetamido)hexanoic acid in acetonitrile ,which was prepared by adding triflic anhydride to 6-aminohexanoic acid. The reaction mixture was heated to 80 °C, then lowered to rt. Oligomeric compound 210, comprising a $GalNAc_3$-20 conjugate group, was prepared from compound 208 using the general procedures illustrated in Example 52.

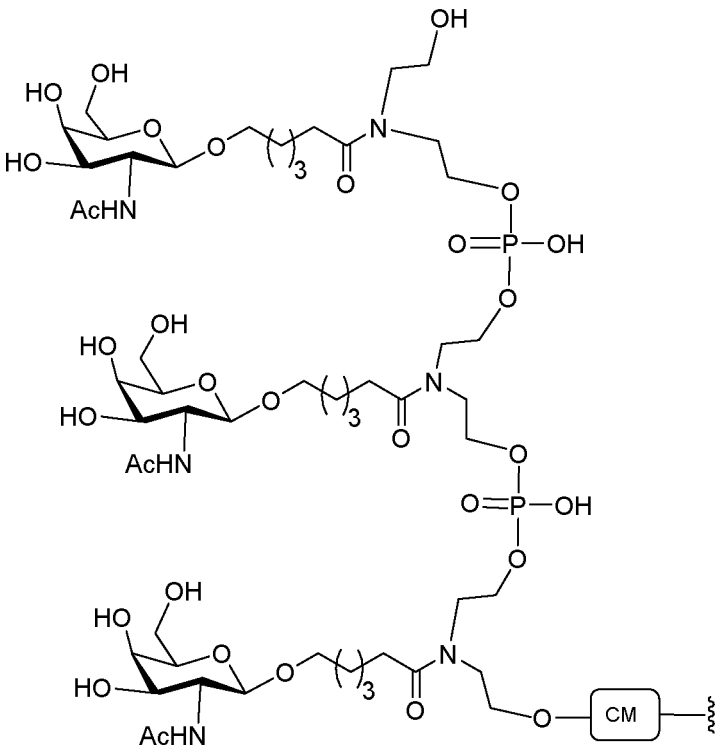
The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-20 ($GalNAc_3$-20_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-20 ($GalNAc_3$-20_a-CM-) is shown below:



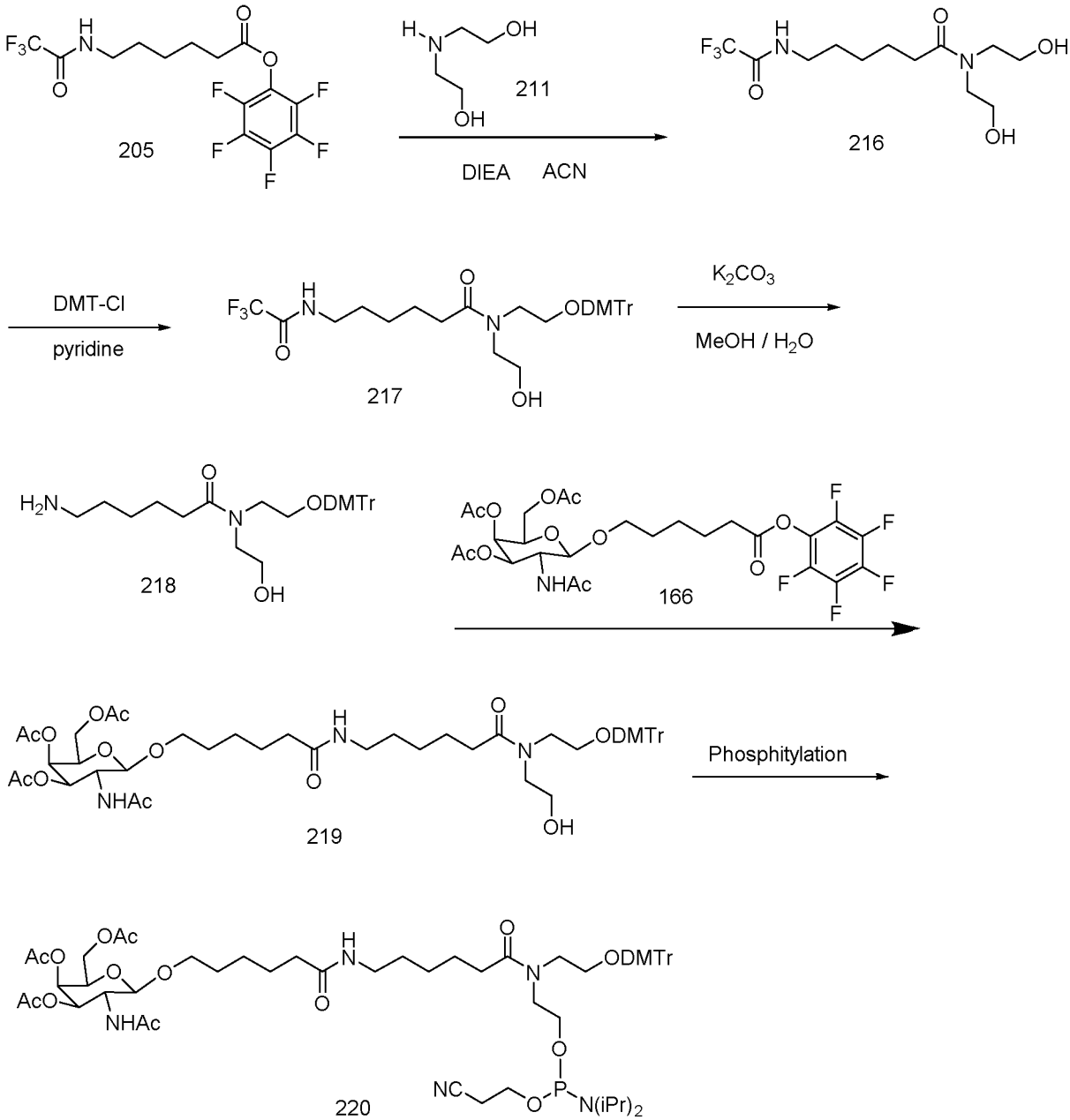
Example 72: Preparation of oligomeric compound 215 comprising GalNAc$_3$-21

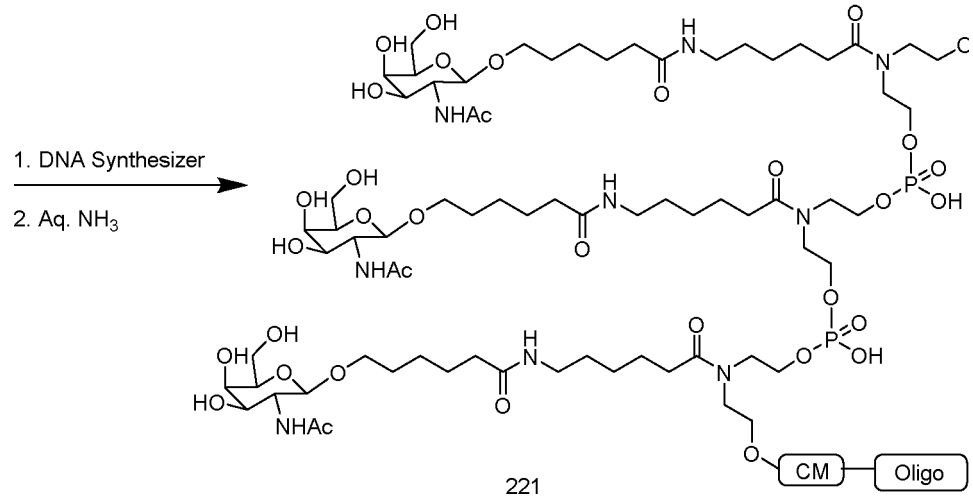


Compound 211 is commercially available. Oligomeric compound 215, comprising a $GalNAc_3$-21 conjugate group, was prepared from compound 213 using the general procedures illustrated in Example 52. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-21 ($GalNAc_3$-21_a) can be combined with 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:



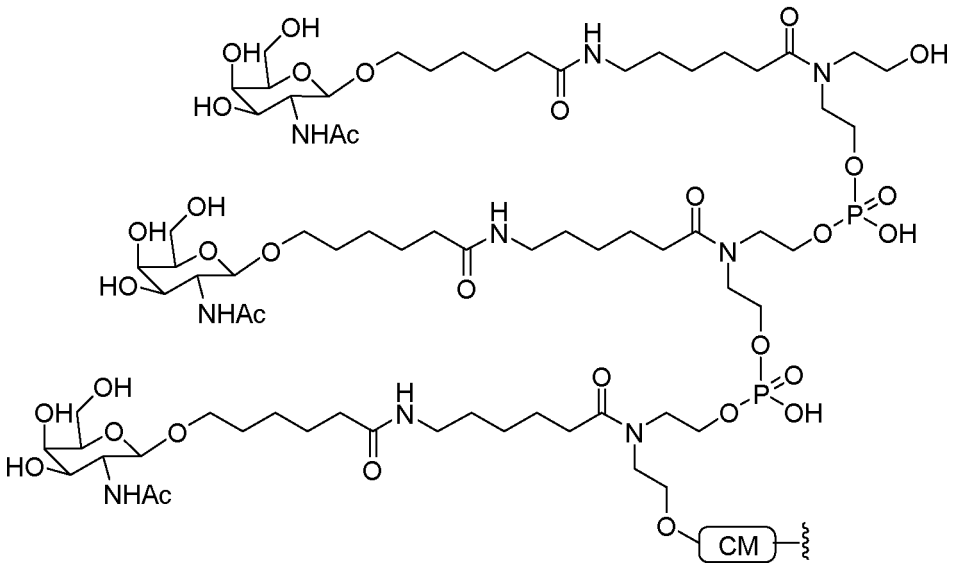
Example 73: Preparation of oligomeric compound 221 comprising GalNAc$_3$-22





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	2304
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	2306
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	2304
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	2306
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	2306

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).

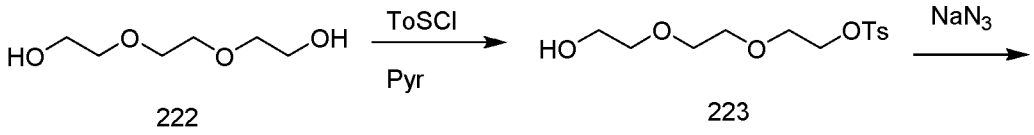
Table 63

PK Analysis in Liver

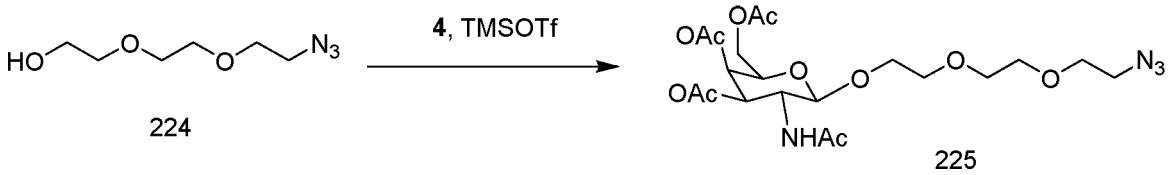
ISIS No.	Dosage (mg/kg)	Total Tissue Level by UV (μg/g)	Parent ASO Tissue Level by EIC (μg/g)	$GalNAc_3$ Cluster	CM
353382	3	8.9	8.6	n/a	n/a
	10	22.4	21.0		
	30	54.2	44.2		
661161	5	32.4	20.7	$GalNAc_3$-3a	A_d
	15	63.2	44.1		
671144	5	20.5	19.2	$GalNAc_3$-12a	A_d
	15	48.6	41.5		
670061	5	31.6	28.0	$GalNAc_3$-13a	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.

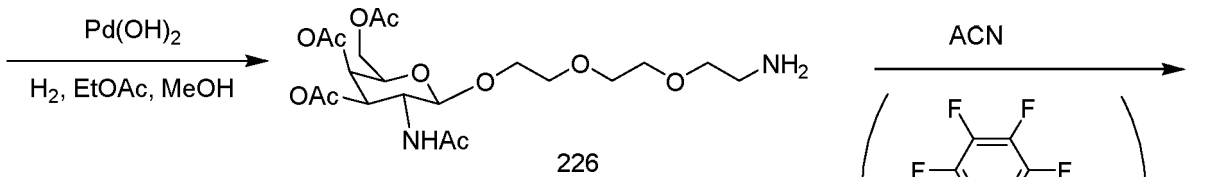
Example 76: Preparation of oligomeric compound 230 comprising $GalNAc_3$-23



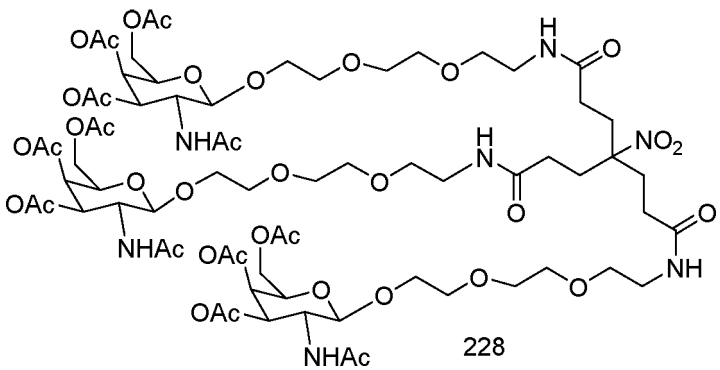
222 223



224 225

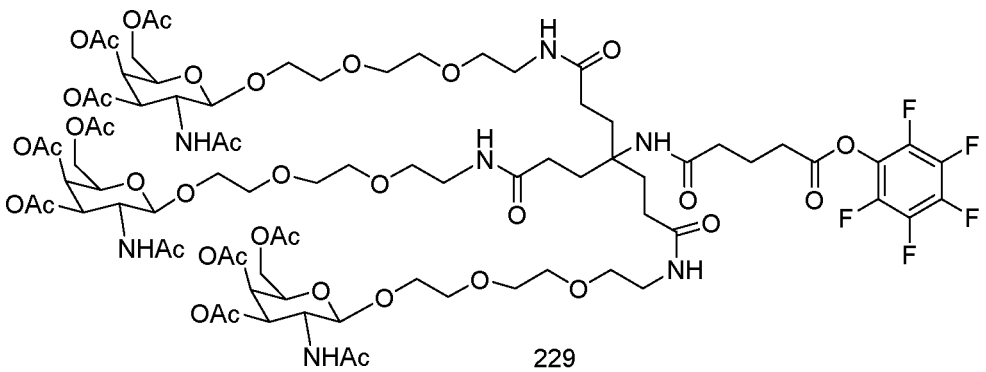


226 227

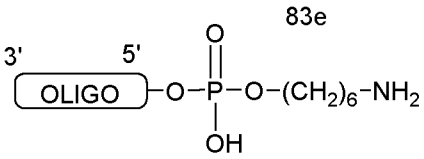


228

1) Reduce
2) Couple Diacid
3) Pd/C
4) PFPTFA

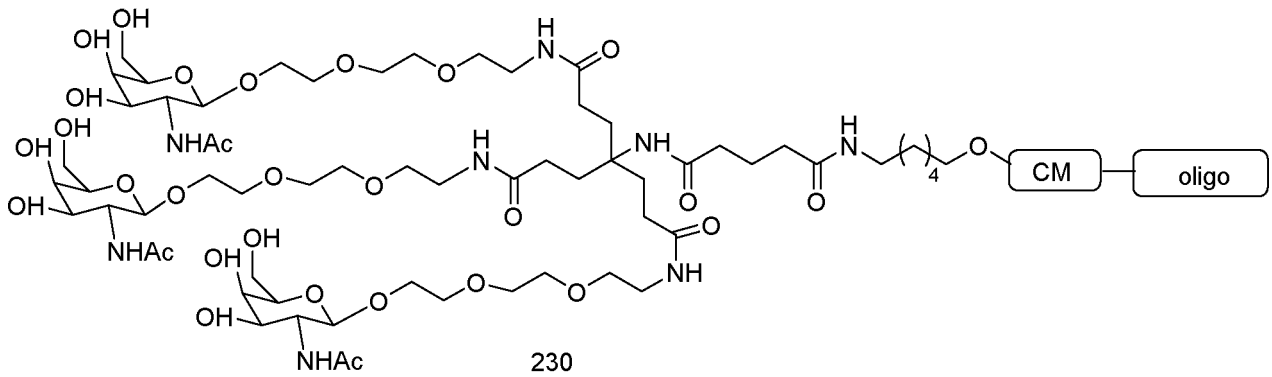


229



1. Borate buffer, DMSO, pH 8.5, rt

2. aq. ammonia, rt



230

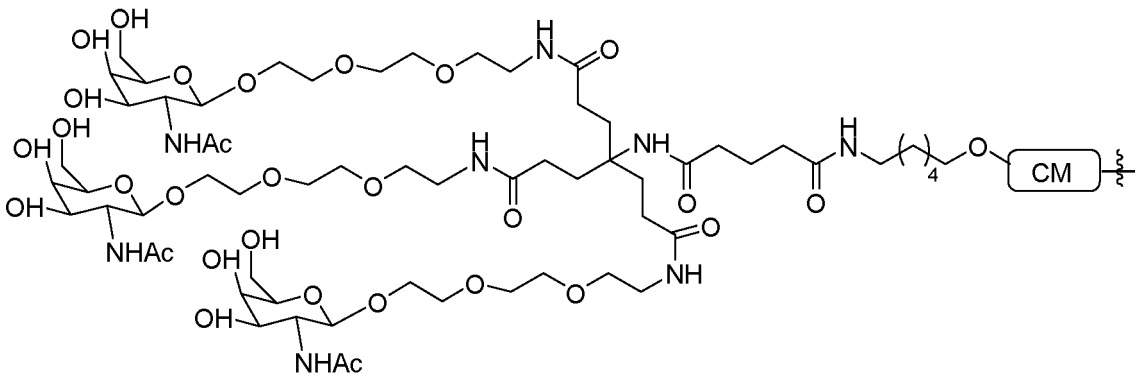
Compound 222 is commercially available. 44.48 ml (0.33 mol) of compound 222 was treated with tosyl chloride (25.39 g, 0.13 mol) in pyridine (500mL) for 16 hours. The reaction was then evaporated to an oil, dissolved in EtOAc and washed with water, sat. $NaHCO_3$, brine, and dried over Na_2SO_4. The ethyl 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-$_o$'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	2306
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	2304
673502	**$GalNAc_3$-10_a-$_o$'A_{do}**$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_e$	$GalNAc_3$-10a	A_d	2306
677844	**$GalNAc_3$-9_a-$_o$'A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_e$	$GalNAc_3$-9a	A_d	2306
677843	**$GalNAc_3$-23_a-$_o$'A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_e$	$GalNAc_3$-23a	A_d	2306
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	2305
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	2305
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	2305

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	$^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}G_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}G_{es}G_{es}A_{es}T_{e}$	n/a	n/a	2310
669509	$^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}G_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}G_{es}G_{es}A_{es}T_{eo}\mathbf{A_{do}}$**-GalNAc$_3-1_a$**	GalNAc$_3$-1$_a$	A$_d$	2311

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	2296
647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}$ $T_{es}A_{es}T_{eo}\mathbf{A_{do}}$-**$GalNAc_3$-$1_a$**	$GalNAc_3$-1a	A_d	2297
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	2312
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	2312
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	2312
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	2312

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	2313
656326	$A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_{eo}$**$A_{do}$-GalNAc$_3-1_a$**	GalNAc$_3$-1a	A_d	2314
678381	**GalNAc$_3$-3$_a$-$_o$,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	2315
678382	**GalNAc$_3$-7$_a$-$_o$,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	2315
678383	**GalNAc$_3$-10$_a$-$_o$,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	2315
678384	**GalNAc$_3$-13$_a$-$_o$,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	2315

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 $GalNAc_3$ conjugate

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	2304
655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do}}$-**GalNAc$_3-1_a$**	PS	GalNAc$_3$-1$_a$	A_d	40	2305
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	2306
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	2306
664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}\mathbf{A_{do}}$-**GalNAc$_3-9_a$**	PS	GalNAc$_3$-9$_a$	A_d	20	2305
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	2306
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	2306
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	2304
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	2306
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	2304
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	2309
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	2306
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	2306
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	2306
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	2309
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	2306
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	2306
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	2306

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	2306
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	2306
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	2306
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	2306
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	2306
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	2306
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	2306
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	2305
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	2305
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	2306

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$_3$ conjugate

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$_{ds}$^{m}C$_{ds}$A$_{es}$G$_{es}$ A$_{es}$G$_{es}$G$_e$	n/a	n/a	2307
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$_{ds}$^{m}C$_{ds}$A$_{eo}$G$_{eo}$ A$_{es}$G$_{es}$G$_{eo}$**A$_{do}$-GalNAc$_3$-1$_a$**	GalNAc$_3$-1$_a$	A$_d$	2308
663086	**GalNAc$_3$-3$_a$-$_o$,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$_{ds}$	GalNAc$_3$-3$_a$	A$_d$	2316

	$T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$			
678347	**GalNAc$_3$-7$_a$-$_o$,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$_3$-7$_a$	A$_d$	2316
678348	**GalNAc$_3$-10$_a$-$_o$,A$_{do}$**$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	GalNAc$_3$-10$_a$	A$_d$	2316
678349	**GalNAc$_3$-13$_a$-$_o$,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$_3$-13$_a$	A$_d$	2316

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 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	2307
	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	2308
	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	2316
	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	2316
	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	2316
	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	2316
	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	2307
		10	47			
		17	52			
656173	6	3	1	$GalNAc_3$-1a	A_d	2308
		10	3			
		17	21			
663086	6	3	1	$GalNAc_3$-3a	A_d	2316
		10	2			
		17	9			
678347	6	3	1	$GalNAc_3$-7a	A_d	2316
		10	1			
		17	8			
678348	6	3	1	$GalNAc_3$-10a	A_d	2316
		10	1			

		17	6			
678349	6	3	1	$GalNAc_3$-13a	A_d	2316
		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$_3$ conjugate

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 84-87. 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	2317
660261	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	PS	GalNAc$_3$-1a	A_d	2318
682883	$\mathbf{GalNAc_3\text{-}3_{a\text{-}o}}$,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-3a	PO	2317
682884	$\mathbf{GalNAc_3\text{-}7_{a\text{-}o}}$,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-7a	PO	2317

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	2317
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	2317
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	2318

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	2317
	20	48	65			
	60	18	28			
660261	0.6	113	87	GalNAc$_3$-1a	A_d	2318
	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	2317
	20	43	102	66	61	58			
	60	24	92	43	29	32			
682883	0.6	60	88	73	63	68	GalNAc$_3$-3a	PO	2317
	2	18	75	38	23	23			
	6	10	80	35	11	9			
682884	0.6	56	88	78	63	67	GalNAc$_3$-7a	PO	2317
	2	19	76	44	25	23			
	6	15	82	35	21	24			
682885	0.6	60	92	77	68	76	GalNAc$_3$-10a	PO	2317
	2	22	93	58	32	32			
	6	17	85	37	25	20			
682886	0.6	57	91	70	64	69	GalNAc$_3$-13a	PO	2317
	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	2318
	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	2317
	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	2318
	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	2317
	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	2317
	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	2317
	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	2317
	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	2317
	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	2318
	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 $GalNAc_3$ conjugate

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	2317
		7	23			
		10	35			
		17	53			
		24	75			
		39	100			
660261	13.5	3	27	$GalNAc_3$-1a	A_d	2318
		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	2317
		7	48			
		10	48			
		17	66			

		31	80			
682883	10.0	3	45	GalNAc$_3$-3a	PO	2317
		7	37			
		10	38			
		17	42			
		31	65			
682885	10.0	3	40	GalNAc$_3$-10a	PO	2317
		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

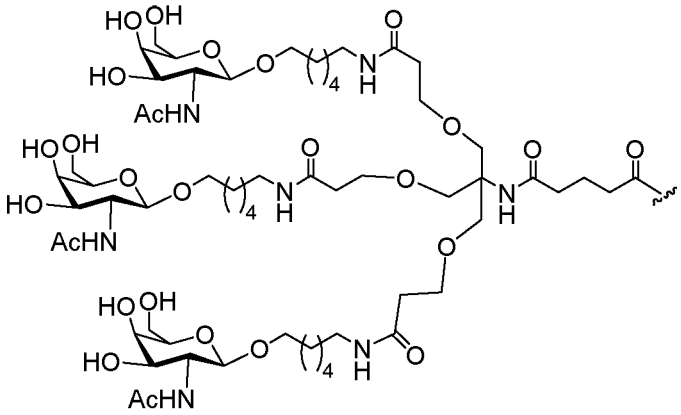
The oligonucleotides listed in Table 90 were tested for splicing modulation of human survival of motor neuron (SMN) in mice.

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	2319
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	2319
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	2319
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$_d$	2320
703421	X-ATT^{m}CA^{m}CTTT^{m}CATAATG^{m}CTGG	n/a	n/a	2319
703422	**GalNAc$_3$-7$_{b}$**-X-ATT^{m}CA^{m}CTTT^{m}CATAATG^{m}CTGG	GalNAc$_3$-7b	n/a	2319

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	2319
387954	288	5.00	n/a	n/a	2319
699819	32	7.84	$GalNAc_3$-7a	PO	2319
699821	32	7.22	$GalNAc_3$-7a	PO	2319
700000	32	6.91	$GalNAc_3$-1a	A_d	2320
703421	32	1.27	n/a	n/a	2319
703422	32	4.12	$GalNAc_3$-7b	n/a	2319

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	2321
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	2321

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 $GalNAc_3$ conjugate

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	2317
682883	**$GalNAc_3$-3_{a-o}**.$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}$	PS/PO	$GalNAc_3$-3a	PO	2317

	$T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$				
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	2322
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	2322
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	2322
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	2322

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	2323
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	2323

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 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	2324
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	2325
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	2324
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	2324
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	2324
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	2324
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	2324
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	2324
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	2325

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	2326
699806	**GalNAc$_3$-3$_{a\text{-}o}$**-$T_{ks}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	GalNAc$_3$-3a	PO	2326
699807	**GalNAc$_3$-7$_{a\text{-}o}$**-$T_{ks}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	GalNAc$_3$-7a	PO	2326

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	2326
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	2326
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	2326
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	2326

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 are 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	2304
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	2327
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	2304
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	2327

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	2298
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	2298
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	2298
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	2298
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$_d$	2299
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	2298
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	2298

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	2321
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	2321
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	2321
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	2321

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$_d$	2322
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$_d$	2318
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	2317
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	2317
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	2317
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	2317
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$_d$	2322
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$_d$	2322
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$_d$	2322
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$_d$	2318

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	2321
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	2321

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	2324
			6	86	
			20	59	
			60	37	
680772	**GalNAc$_3$-7$_{a-o}$**,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}$ $G_{ds}G_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	PO	0.6	79	2324
			2	58	
			6	31	
			20	13	
696847	**GalNAc$_3$-7$_{a-s}$**,$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}$ $G_{ds}G_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	n/a (PS)	0.6	83	2324
			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	2296
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$_d$	2312
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$_d$	2297

The structure of GalNAc$_3$-3$_a$ was shown in Example 39, and GalNAc$_3$-19$_a$ was shown in Example 70.

Treatment

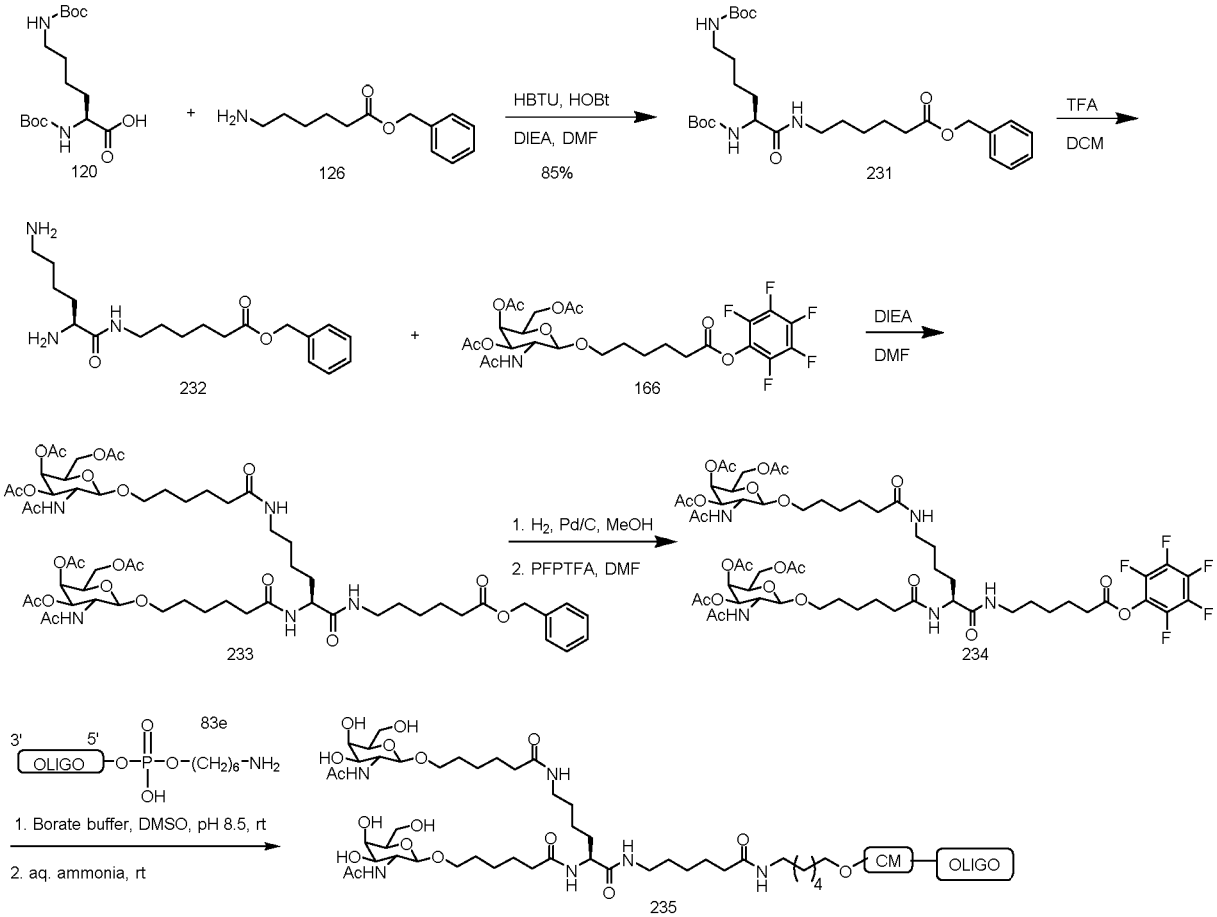
Female transgenic mice that express human APOC-III were each injected subcutaneously once with an oligonucleotide listed in Table 114 or with PBS. Each treatment group consisted of 3 animals. Blood was drawn before dosing to determine baseline and at 3, 7, 14, 21, 28, 35, and 42 days following the dose. 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

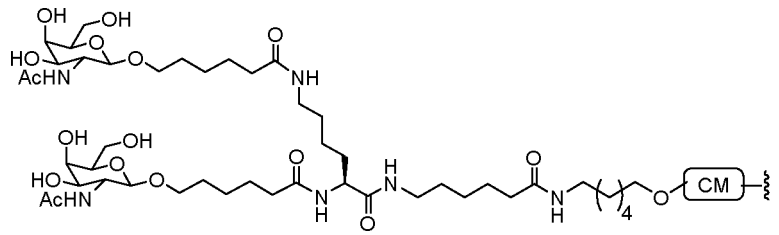
ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	Triglycerides (% baseline)	APOC-III protein (% baseline)	$GalNAc_3$ Cluster	CM
PBS	n/a	3	96	101	n/a	n/a
		7	88	98		
		14	91	103		
		21	69	92		
		28	83	81		
		35	65	86		
		42	72	88		
304801	30	3	42	46	n/a	n/a
		7	42	51		
		14	59	69		
		21	67	81		
		28	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

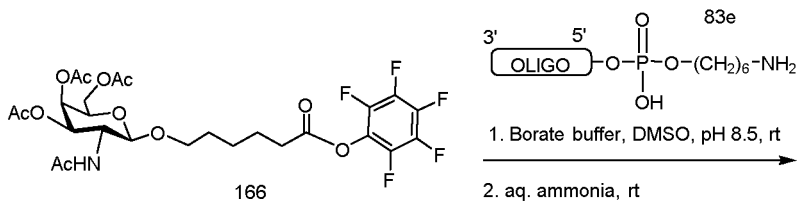


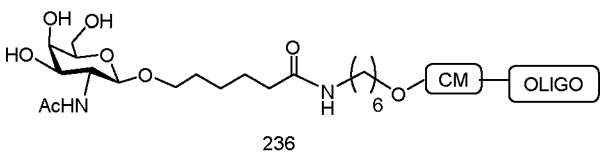
Compound 120 is commercially available, and the synthesis of compound 126 is described in Example 49. Compound 120 (1 g, 2.89 mmol), HBTU (0.39 g, 2.89 mmol), and HOBt (1.64 g, 4.33 mmol) were dissolved in DMF (10 mL. and *N*,*N*-diisopropylethylamine (1.75 mL, 10.1 mmol) were added. After about 5 min, 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:



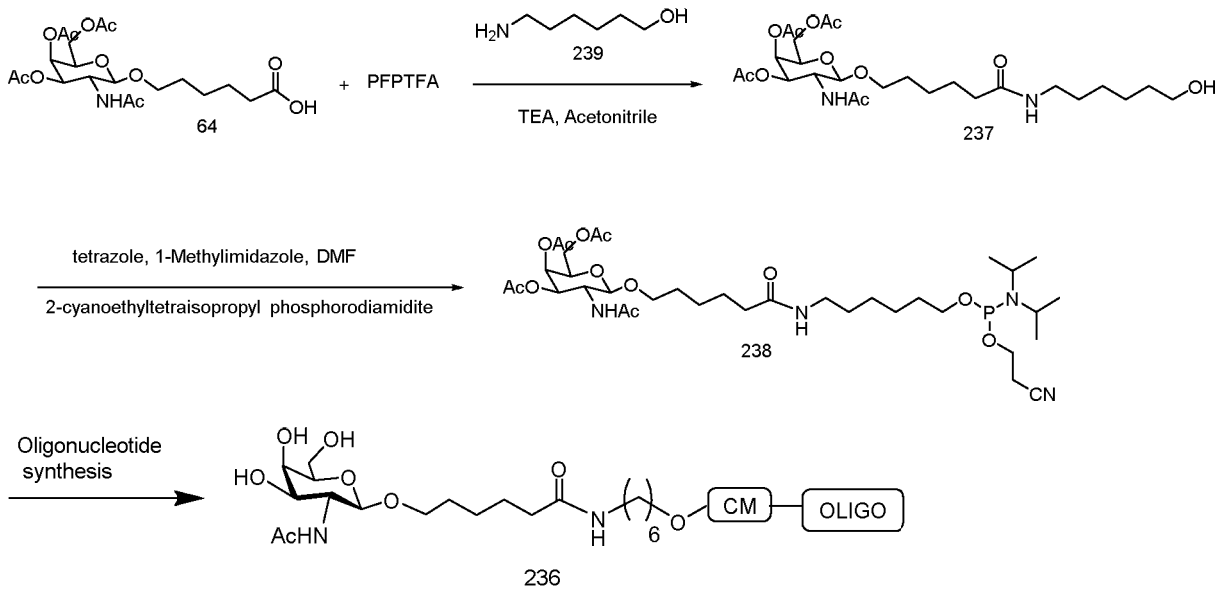
Example 105: Synthesis of oligonucleotides comprising a $GalNAc_1$-25 conjugate



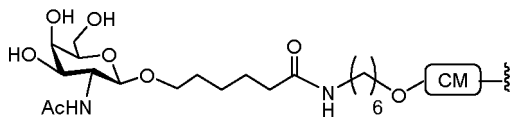


236

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	2298
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	2302
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	2302

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	2298
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	2298

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		

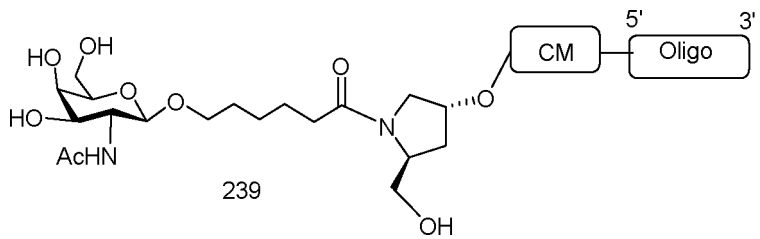
	6	26.5		
686222	0.2	0.5	$GalNAc_3$-13_a	A_d
	0.6	1.6		
	2	11.6		
	6	19.8		

Table 117b

Liver concentrations of oligonucleotides comprising a $GalNAc_1$ conjugate group

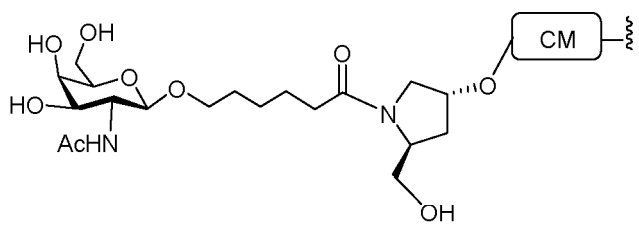
ISIS No.	Dosage (mg/kg)	Antisense oligonucleotide (μg/g)	GalNAc cluster	CM
440762	2	2.3	n/a	n/a
	7	8.9		
	20	23.7		
708561	0.2	0.4	$GalNAc_1$-25_a	PO
	0.6	1.1		
	2	5.9		
	6	23.7		
	20	53.9		

Example 107: Synthesis of oligonucleotides comprising a $GalNAc_1$-26 or $GalNAc_1$-27 conjugate



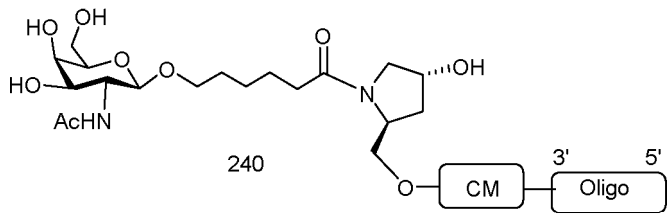
239

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:

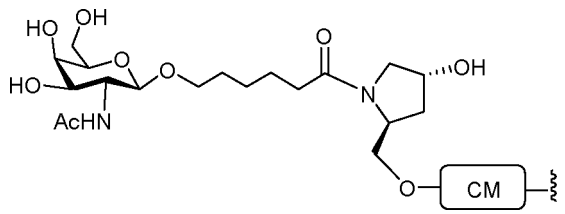


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In order to add the $GalNAc_1$ conjugate group to the 3'-end of an oligonucleotide, the amide formed from the reaction of compounds 47 and 64 is added to a solid support using procedures described in Example 7. The oligonucleotide synthesis is then 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	2321
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	2321
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	2321
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	2321

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	2321
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	2321
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$_d$	2328

The structure of GalNAc$_3$-7$_a$ was shown in Example 48.

Treatment

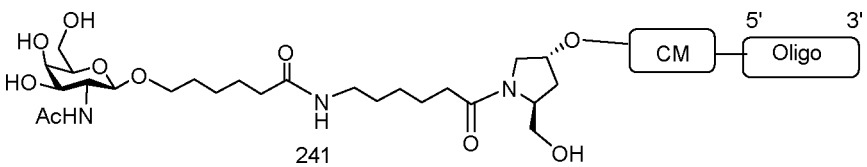
Male transgenic mice that express human Apo(a) were each injected subcutaneously once with an oligonucleotide and dosage listed in Table 119 or with PBS. Each treatment group consisted of 4 animals. Blood was drawn the day before dosing to determine baseline levels of Apo(a) protein in plasma and at 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

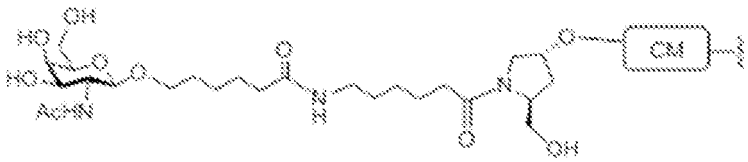
ISIS No.	Dosage (mg/kg)	Apo(a) at 1 week (% BL)
PBS	n/a	143
494372	50	58
681251	10	15
681255	10	14
681256	10	17
681257	10	24
681258	10	22
681260	10	26

Example 109: Synthesis of oligonucleotides comprising a GalNAc$_1$-28 or GalNAc$_1$-29 conjugate

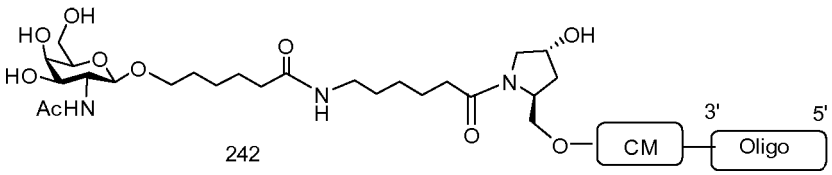


Oligonucleotide 241 is synthesized using procedures similar to those described in Example 71 to form the phosphoramidite intermediate, followed by procedures described in Example 10 to synthesize the oligonucleotide. The GalNAc$_1$ cluster portion (GalNAc$_1$-28$_a$) of the conjugate group GalNAc$_1$-28 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:

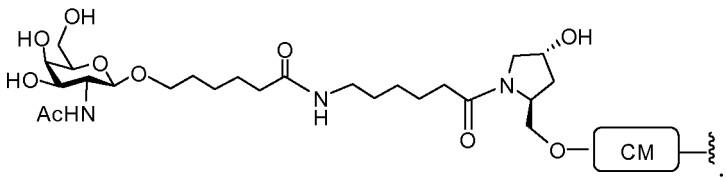


In order to add the GalNAc$_1$ conjugate group to the 3'-end of an oligonucleotide, procedures similar to those described in Example 71 are used to form the hydroxyl intermediate, which is then added to the solid support using procedures described in Example 7. The oligonucleotide synthesis is then completed using procedures described in Example 9 in order to form oligonucleotide 242.

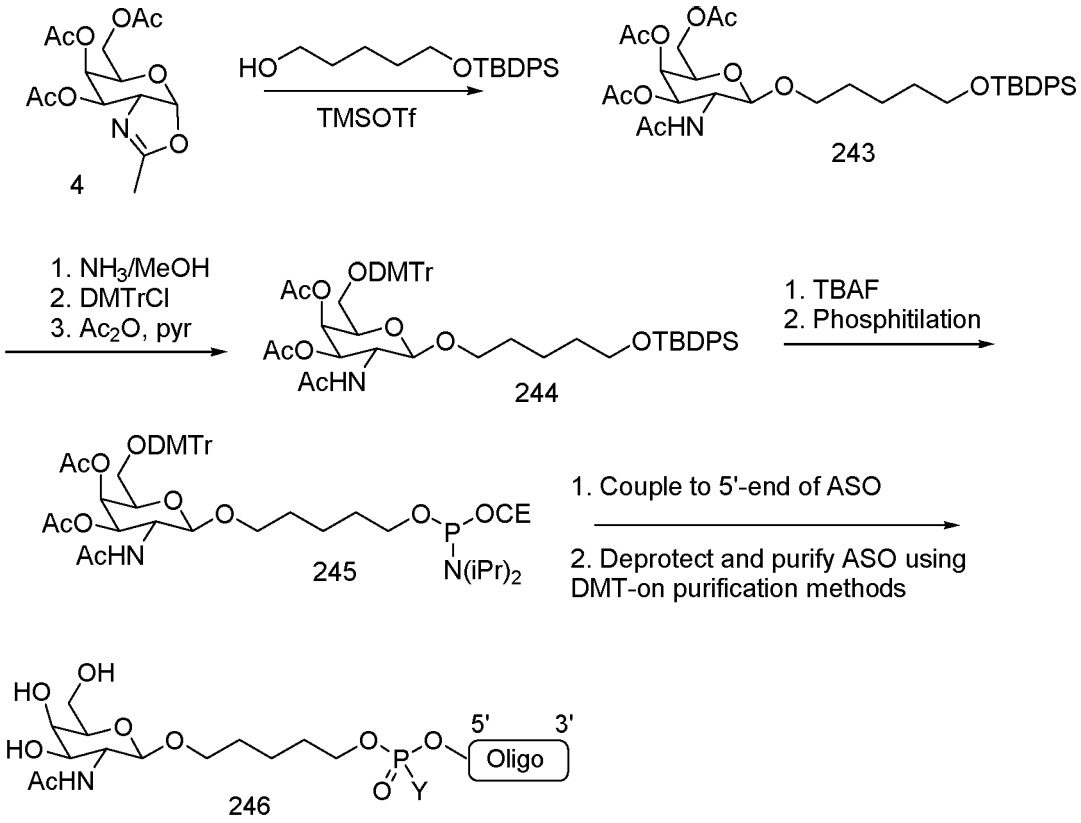


242

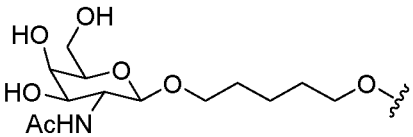
The GalNAc$_1$ cluster portion (GalNAc$_1$-29$_a$) of the conjugate group GalNAc$_1$-29 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of GalNAc$_1$-29 (GalNAc$_1$-29$_a$-CM) is shown below:



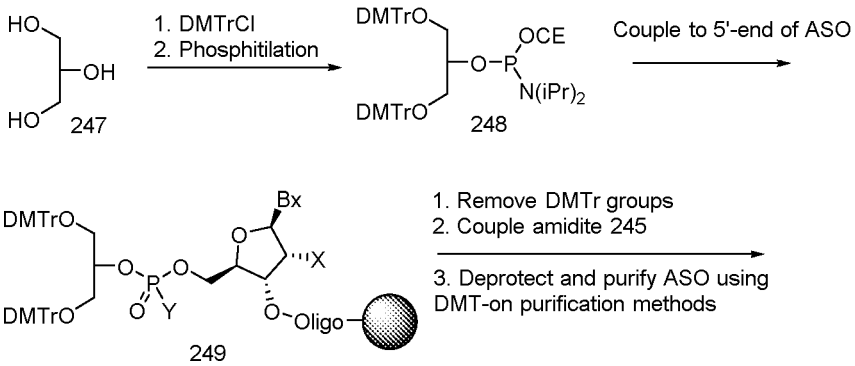
Example 110: Synthesis of oligonucleotides comprising a GalNAc$_1$-30 conjugate

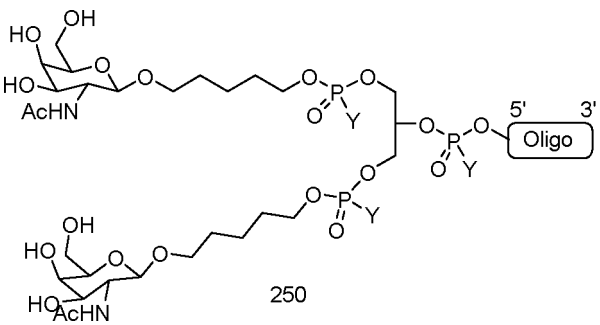


Oligonucleotide 246 comprising a GalNAc$_1$-30 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The GalNAc$_1$ cluster portion (GalNAc$_1$-30$_a$) of the conjugate group 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:

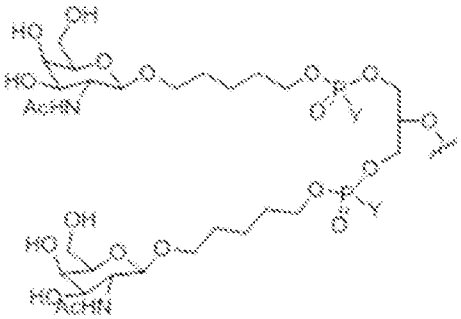


Example 111: Synthesis of oligonucleotides comprising a GalNAc$_2$-31 or GalNAc$_2$-32 conjugate

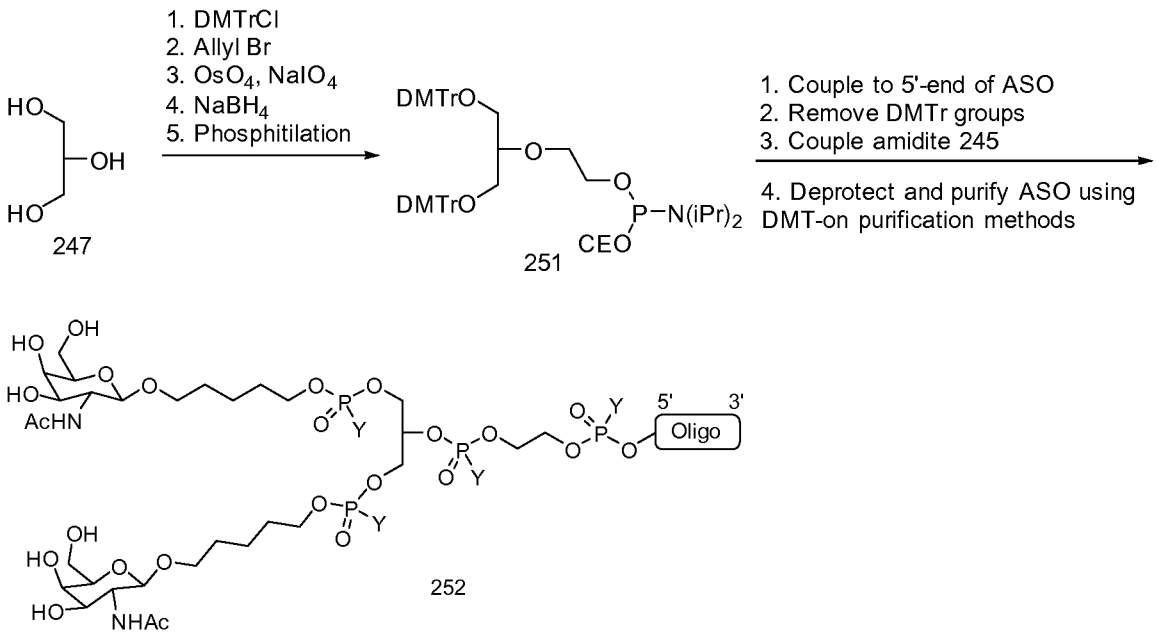




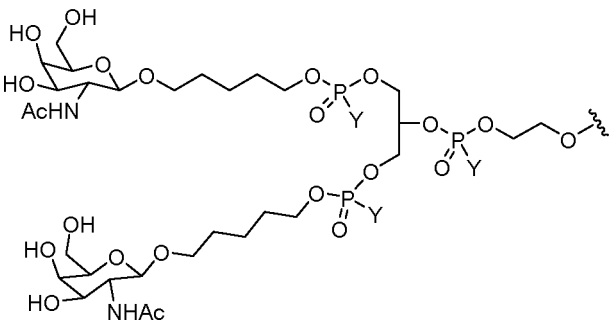
Oligonucleotide 250 comprising a GalNAc$_2$-31 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The GalNAc$_2$ cluster portion (GalNAc$_2$-31$_a$) of the conjugate group 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$_{do}$** $G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-25$_a$	A$_d$	2306
711462	**GalNAc$_1$-25$_{a\text{-}o}$,** $G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-25$_a$	PO	2304
711463	**GalNAc$_1$-25$_{a\text{-}o}$,** $G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-25$_a$	PO	2304
711465	**GalNAc$_1$-26$_{a\text{-}o}$,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$_1$-26$_a$	A$_d$	2306
711466	**GalNAc$_1$-26$_{a\text{-}o}$,** $G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-26$_a$	PO	2304
711467	**GalNAc$_1$-26$_{a\text{-}o}$,** $G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-26$_a$	PO	2304
711468	**GalNAc$_1$-28$_{a\text{-}o}$,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$_1$-28$_a$	A$_d$	2306
711469	**GalNAc$_1$-28$_{a\text{-}o}$,** $G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-28$_a$	PO	2304
711470	**GalNAc$_1$-28$_{a\text{-}o}$,** $G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{e}$	GalNAc$_1$-28$_a$	PO	2304
713844	$G_{es}\ ^{m}C_{es}\ T_{es}\ T_{es}\ ^{m}C_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{es}\ ^{m}C_{es}\ ^{m}C_{es}\ T_{es}\ T_{eo}$-**GalNAc$_1-27_a$**	GalNAc$_1$-27$_a$	PO	2304
713845	$G_{es}\ ^{m}C_{eo}\ T_{eo}\ T_{eo}\ ^{m}C_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^{m}C_{ds}\ T_{ds}\ T_{eo}\ ^{m}C_{eo}\ ^{m}C_{es}\ T_{es}\ T_{eo}$-**GalNAc$_1-27_a$**	GalNAc$_1$-27$_a$	PO	2304
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$_d$	2305
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	2304

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	2304
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$_d$	2305
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$_d$	2305

Example 113: Antisense oligonucleotides targeting growth hormone receptor and comprising a GalNAc cluster

The oligonucleotides in Table 121 were designed to target human growth hormone receptor (GHR).

Table 121

Sequences (5' to 3')	SEQ ID No.
GalNAc$_3$-3-$^{m}C_{es}\ ^{m}C_{es}A_{es}\ ^{m}C_{es}\ ^{m}C_{es}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{es}A_{es}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-3-$^{m}C_{es}\ ^{m}C_{eo}A_{eo}\ ^{m}C_{eo}\ ^{m}C_{eo}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{eo}A_{eo}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-7-$^{m}C_{es}\ ^{m}C_{es}A_{es}\ ^{m}C_{es}\ ^{m}C_{es}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{es}A_{es}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-7-$^{m}C_{es}\ ^{m}C_{eo}A_{eo}\ ^{m}C_{eo}\ ^{m}C_{eo}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{eo}A_{eo}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-10-$^{m}C_{es}\ ^{m}C_{es}A_{es}\ ^{m}C_{es}\ ^{m}C_{es}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{es}A_{es}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-10-$^{m}C_{es}\ ^{m}C_{eo}A_{eo}\ ^{m}C_{eo}\ ^{m}C_{eo}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{eo}A_{eo}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-13-$^{m}C_{es}\ ^{m}C_{es}A_{es}\ ^{m}C_{es}\ ^{m}C_{es}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{es}A_{es}G_{es}\ ^{m}C_{es}A_{e}$	703
GalNAc$_3$-13-$^{m}C_{es}\ ^{m}C_{eo}A_{eo}\ ^{m}C_{eo}\ ^{m}C_{eo}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{eo}A_{eo}G_{es}\ ^{m}C_{es}A_{e}$	703
$^{m}C_{es}\ ^{m}C_{es}A_{es}\ ^{m}C_{es}\ ^{m}C_{es}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{es}A_{es}G_{es}\ ^{m}C_{es}A_{e}$ **-GalNAc$_3$-19**	703
$^{m}C_{es}\ ^{m}C_{eo}A_{eo}\ ^{m}C_{eo}\ ^{m}C_{eo}T_{ds}T_{ds}T_{ds}G_{ds}G_{ds}G_{ds}T_{ds}G_{ds}A_{ds}A_{ds}T_{eo}A_{eo}G_{es}\ ^{m}C_{es}A_{e}$**-GalNAc$_3$-19**	703

Example 114: Antisense inhibition of human growth hormone receptor in Hep3B cells by MOE gapmers

Antisense oligonucleotides were designed targeting a growth hormone receptor (GHR) nucleic acid and were tested for their effects on GHR mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured Hep3B cells at a density of 20,000 cells per well were transfected using electroporation with 4,500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB (forward sequence CGAGTTCAGTGAGGTGCTCTATGT, designated herein as SEQ ID NO: 2329; reverse sequence AAGAGCCATGGAAAGTAGAAATCTTC, designated herein as SEQ ID NO: 2330; probe sequence TTCCTCAGATGAGCCAATT, designated herein as SEQ ID NO: 2331) was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as 5-10-5 MOE or 3-10-4 MOE gapmers. The 5-10-5 MOE gapmers are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. The 3-10-4 MOE gapmers are 17 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising three and four nucleosides respectively. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human GHR mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_000163.4) or the human GHR genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000). 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity. In case the sequence alignment for a target gene in a particular table is not shown, it is understood that none of the oligonucleotides presented in that table align with 100% complementarity with that target gene.

Table 122

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
523266	164	183	Exon 1	ACCTCCGAGCTTCGCCTCTG	64	3040	3059	20
523267	171	190	Exon-exon junction	CTGTAGGACCTCCGAGCTTC	31	n/a	n/a	21
523268	178	197	Exon-exon junction	TCCATACCTGTAGGACCTCC	37	n/a	n/a	22
523271	206	225	Exon 2	TGCCAAGGTCAACAGCAGCT	80	144990	145009	23
523272	213	232	Exon 2	CTGCCAGTGCCAAGGTCAAC	53	144997	145016	24
523273	220	239	Exon 2	CTTGATCCTGCCAGTGCCAA	49	145004	145023	25
523274	227	246	Exon 2	AGCATCACTTGATCCTGCCA	67	145011	145030	26
523275	234	253	Exon 2	CAGAAAAAGCATCACTTGAT	0	145018	145037	27
523276	241	260	Exon 2	TCACTTCCAGAAAAAGCATC	1	145025	145044	28
523284	361	380	Exon 4	GTCTCTCGCTCAGGTGAACG	48	268024	268043	29
523285	368	387	Exon 4	TGAAAAAGTCTCTCGCTCAG	15	268031	268050	30
523286	375	394	Exon 4	AGTGGCATGAAAAAGTCTCT	14	268038	268057	31

523287	382	401	Exon 4	TCTGTCCAGTGGCATGAAAA	4	268045	268064	32
523301	625	644	Exon 6	GGATCTGGTTGCACTATTTC	36	n/a	n/a	33
523302	632	651	Exon 6	AATGGGTGGATCTGGTTGCA	28	278926	278945	34
523303	647	666	Exon 6	AGTCCAGTTGAGGGCAATGG	26	278941	278960	35
523304	654	673	Exon 6	TCAGTAAAGTCCAGTTGAGG	0	278948	278967	36
523305	675	694	Exon 6	GAATCCCAGTTAAACTGACG	19	278969	278988	37
523306	682	701	Exon 6	TCTGCATGAATCCCAGTTAA	39	278976	278995	38
523309	736	755	Exon 6	ATCCATCCTTTCTGAATATC	34	279030	279049	39
523310	743	762	Exon 6	CAGAACCATCCATCCTTTCT	31	279037	279056	40
523311	750	769	Exon 6	CATACTCCAGAACCATCCAT	44	279044	279063	41
523312	757	776	Exon 6	TGAAGTTCATACTCCAGAAC	23	279051	279070	42
523313	764	783	Exon 6	TTTGTATTGAAGTTCATACT	6	279058	279077	43
523314	771	790	Exon 6	TTACTTCTTTGTATTGAAGT	0	279065	279084	44
523315	778	797	Exon 6	GTTTCATTTACTTCTTTGTA	3	279072	279091	45
523316	785	804	Exon 6	CCATTTAGTTTCATTTACTT	0	279079	279098	46
523317	792	811	Exon 4-exon 5 junction	TCATTTTCCATTTAGTTTCA	19	n/a	n/a	47
523323	862	881	Exon 7	ACACGCACTTCATATTCCTT	63	290360	290379	48
523324	869	888	Exon 7	GGATCTCACACGCACTTCAT	80	290367	290386	49
523328	926	945	Exon 7	AAGTGTTACATAGAGCACCT	56	290424	290443	50
523329	933	952	Exon 7	TCTGAGGAAGTGTTACATAG	53	290431	290450	51
523330	957	976	Exon 7	CTTCTTCACATGTAAATTGG	32	290455	290474	52
523331	964	983	Exon 5-exon 6 junction	TAGAAATCTTCTTCACATGT	4	n/a	n/a	53
523332	971	990	Exon 5-exon 6 junction	TGGAAAGTAGAAATCTTCTT	9	n/a	n/a	54
523333	978	997	Exon 8	AGAGCCATGGAAAGTAGAAA	46	292532	292551	55
523334	985	1004	Exon 8	ATAATTAAGAGCCATGGAAA	0	292539	292558	56

Table 123

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
523421	2072	2091	exon 10	CAGTTGGTCTGTGCTCACAT	76	298489	298508	57
533002	207	226	exon 2	GTGCCAAGGTCAACAGCAGC	63	144991	145010	58
533003	208	227	exon 2	AGTGCCAAGGTCAACAGCAG	62	144992	145011	59
533004	225	244	exon 2	CATCACTTGATCCTGCCAGT	53	145009	145028	60
533005	226	245	exon 2	GCATCACTTGATCCTGCCAG	80	145010	145029	61
533006	228	247	exon 2	AAGCATCACTTGATCCTGCC	75	145012	145031	62

533007	229	248	exon 2	AAAGCATCACTTGATCCTGC	61	145013	145032	63
533019	867	886	exon 7	ATCTCACACGCACTTCATAT	35	290365	290384	64
533020	868	887	exon 7	GATCTCACACGCACTTCATA	47	290366	290385	65
533021	870	889	exon 7	TGGATCTCACACGCACTTCA	86	290368	290387	66
533022	871	890	exon 7	TTGGATCTCACACGCACTTC	70	290369	290388	67
533037	1360	1379	exon 10	TCCAGAATGTCAGGTTCACA	59	297777	297796	68
533038	1361	1380	exon 10	CTCCAGAATGTCAGGTTCAC	74	297778	297797	69
533039	1363	1382	exon 10	GTCTCCAGAATGTCAGGTTC	45	297780	297799	70
533040	1364	1383	exon 10	AGTCTCCAGAATGTCAGGTT	51	297781	297800	71
533042	1525	1544	exon 10	GCTTGGATAACACTGGGCTG	41	297942	297961	72
533043	1526	1545	exon 10	TGCTTGGATAACACTGGGCT	46	297943	297962	73
533044	1528	1547	exon 10	TCTGCTTGGATAACACTGGG	55	297945	297964	74
533045	1529	1548	exon 10	CTCTGCTTGGATAACACTGG	47	297946	297965	75
533046	1530	1549	exon 10	TCTCTGCTTGGATAACACTG	54	297947	297966	76
533047	1744	1763	exon 10	CAGAGTGAGACCATTTCCGG	47	298161	298180	77
533048	1745	1764	exon 10	GCAGAGTGAGACCATTTCCG	60	298162	298181	78
533049	1747	1766	exon 10	TGGCAGAGTGAGACCATTTC	65	298164	298183	79
533050	1748	1767	exon 10	TTGGCAGAGTGAGACCATTT	47	298165	298184	80
533051	1749	1768	exon 10	CTTGGCAGAGTGAGACCATT	30	298166	298185	81
533066	2685	2704	exon 10	CAGTGTGTAGTGTAATATAA	53	299102	299121	82
533067	2686	2705	exon 10	ACAGTGTGTAGTGTAATATA	68	299103	299122	83
533068	2688	2707	exon 10	ACACAGTGTGTAGTGTAATA	62	299105	299124	84
533069	2689	2708	exon 10	TACACAGTGTGTAGTGTAAT	55	299106	299125	85
533070	2690	2709	exon 10	GTACACAGTGTGTAGTGTAA	50	299107	299126	86
533071	3205	3224	exon 10	TGTACCTTATTCCCTTCCTG	68	299622	299641	87
533072	3206	3225	exon 10	TTGTACCTTATTCCCTTCCT	61	299623	299642	88
533073	3208	3227	exon 10	TCTTGTACCTTATTCCCTTC	60	299625	299644	89
533074	3209	3228	exon 10	TTCTTGTACCTTATTCCCTT	46	299626	299645	90

Table 124

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intronic and exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532174	n/a	n/a	Intron 1	ACATGTACCCAAACCAACAC	37	18731	18750	91
533086	3210	3229	Exon 10	CTTCTTGTACCTTATTCCCT	72	299627	299646	92
533087	3212	3231	Exon 10	TGCTTCTTGTACCTTATTCC	77	299629	299648	93
533088	3213	3232	Exon 10	ATGCTTCTTGTACCTTATTC	63	299630	299649	94
533089	3215	3234	Exon 10	AAATGCTTCTTGTACCTTAT	67	299632	299651	95
533090	3216	3235	Exon 10	AAAATGCTTCTTGTACCTTA	50	299633	299652	96
533091	3217	3236	Exon 10	CAAAATGCTTCTTGTACCTT	44	299634	299653	97

533092	3518	3537	Exon 10	CTTCTGAATGCTTGCTTTGA	29	299935	299954	98
533093	3519	3538	Exon 10	TCTTCTGAATGCTTGCTTTG	47	299936	299955	99
533094	3521	3540	Exon 10	TTTCTTCTGAATGCTTGCTT	63	299938	299957	100
533095	3522	3541	Exon 10	TTTTCTTCTGAATGCTTGCT	51	299939	299958	101
533096	3523	3542	Exon 10	TTTTTCTTCTGAATGCTTGC	34	299940	299959	102
533097	4041	4060	Exon 10	TGCGATAAATGGGAAATACT	36	300458	300477	103
533098	4042	4061	Exon 10	CTGCGATAAATGGGAAATAC	52	300459	300478	104
533099	4043	4062	Exon 10	TCTGCGATAAATGGGAAATA	41	300460	300479	105
533100	4045	4064	Exon 10	GGTCTGCGATAAATGGGAAA	40	300462	300481	106
533101	4046	4065	Exon 10	AGGTCTGCGATAAATGGGAA	39	300463	300482	107
533102	4048	4067	Exon 10	AAAGGTCTGCGATAAATGGG	34	300465	300484	108
533103	4049	4068	Exon 10	AAAAGGTCTGCGATAAATGG	35	300466	300485	109
533104	4050	4069	Exon 10	AAAAAGGTCTGCGATAAATG	15	300467	300486	110
533115	n/a	n/a	Intron 1	CATGAAGGCCACTCTTCCAA	63	12777	12796	111
533116	n/a	n/a	Intron 1	CCATGAAGGCCACTCTTCCA	78	12778	12797	112
533117	n/a	n/a	Intron 1	CCCATGAAGGCCACTCTTCC	71	12779	12798	113
533118	n/a	n/a	Intron 1	TGCCCATGAAGGCCACTCTT	66	12781	12800	114
533119	n/a	n/a	Intron 1	TTGCCCATGAAGGCCACTCT	60	12782	12801	115
533120	n/a	n/a	Intron 1	GTTGCCCATGAAGGCCACTC	74	12783	12802	116
533121	n/a	n/a	Intron 1	GGTCTTTCATGAATCAAGCT	79	17927	17946	117
533122	n/a	n/a	Intron 1	TGGTCTTTCATGAATCAAGC	83	17928	17947	118
533123	n/a	n/a	Intron 1	ATGGTCTTTCATGAATCAAG	83	17929	17948	119
533124	n/a	n/a	Intron 1	TGATGGTCTTTCATGAATCA	78	17931	17950	120
533125	n/a	n/a	Intron 1	CTGATGGTCTTTCATGAATC	82	17932	17951	121
533126	n/a	n/a	Intron 1	GCTGATGGTCTTTCATGAAT	74	17933	17952	122
533127	n/a	n/a	Intron 1	GTACCCAAACCAACACTAAT	57	18727	18746	123
533128	n/a	n/a	Intron 1	TGTACCCAAACCAACACTAA	65	18728	18747	124
533129	n/a	n/a	Intron 1	ATGTACCCAAACCAACACTA	64	18729	18748	125
533130	n/a	n/a	Intron 1	GACATGTACCCAAACCAACA	63	18732	18751	126
533131	n/a	n/a	Intron 1	AGACATGTACCCAAACCAAC	81	18733	18752	127
533132	n/a	n/a	Intron 1	AGGAATGGAAAACCAAATAT	49	26494	26513	128
533133	n/a	n/a	Intron 1	CAGGAATGGAAAACCAAATA	74	26495	26514	129
						121986	122005	
533134	n/a	n/a	Intron 1	TCAGGAATGGAAAACCAAAT	73	26496	26515	130
						121987	122006	
533135	n/a	n/a	Intron 1	ACTCAGGAATGGAAAACCAA	77	26498	26517	131
						113032	113051	
						121989	122008	
533136	n/a	n/a	Intron 1	AACTCAGGAATGGAAAACCA	79	26499	26518	132
						113033	113052	
						121990	122009	
533137	n/a	n/a	Intron 1	TAACTCAGGAATGGAAAACC	67	26500	26519	133
						113034	113053	

						121991	122010	
533138	n/a	n/a	Intron 1	CAAAATTACTGCAGTCACAG	67	39716	39735	134
533139	n/a	n/a	Intron 1	ACAAAATTACTGCAGTCACA	81	39717	39736	135
533140	n/a	n/a	Intron 1	TACAAAATTACTGCAGTCAC	81	39718	39737	136
533141	n/a	n/a	Intron 1	CATACAAAATTACTGCAGTC	67	39720	39739	137
533142	n/a	n/a	Intron 1	ACATACAAAATTACTGCAGT	48	39721	39740	138
533143	n/a	n/a	Intron 1	AACATACAAAATTACTGCAG	53	39722	39741	139
533144	n/a	n/a	Intron 1	TTTTAGTATGAACCTTAAAA	0	42139	42158	140
533145	n/a	n/a	Intron 1	CTTTTAGTATGAACCTTAAA	38	42140	42159	141
533146	n/a	n/a	Intron 1	TCTTTTAGTATGAACCTTAA	57	42141	42160	142
533147	n/a	n/a	Intron 1	AATCTTTTAGTATGAACCTT	60	42143	42162	143
533148	n/a	n/a	Intron 1	CAATCTTTTAGTATGAACCT	70	42144	42163	144
533149	n/a	n/a	Intron 1	ACAATCTTTTAGTATGAACC	60	42145	42164	145
533150	n/a	n/a	Intron 1	AAGTTATGTGACTCTGAGCA	67	43174	43193	146
533151	n/a	n/a	Intron 1	CAAGTTATGTGACTCTGAGC	67	43175	43194	147
533152	n/a	n/a	Intron 1	TCAAGTTATGTGACTCTGAG	63	43176	43195	148
533153	n/a	n/a	Intron 1	AGTTCTCCATTAGGGTTCTG	83	50948	50967	149
533154	n/a	n/a	Intron 1	TAGTTCTCCATTAGGGTTCT	76	50949	50968	150
533155	n/a	n/a	Intron 1	ATAGTTCTCCATTAGGGTTC	51	50950	50969	151
533156	n/a	n/a	Intron 1	AAGCAGGTTGGCAGACAGAC	79	53467	53486	152
533157	n/a	n/a	Intron 1	GAAGCAGGTTGGCAGACAGA	60	53468	53487	153
533158	n/a	n/a	Intron 1	GGAAGCAGGTTGGCAGACAG	67	53469	53488	154
533159	n/a	n/a	Intron 1	TCTTCTTGTGAGCTGGCTTC	61	64882	64901	155
533160	n/a	n/a	Intron 1	GTCTTCTTGTGAGCTGGCTT	83	64883	64902	156
533161	n/a	n/a	Intron 1	AGTCTTCTTGTGAGCTGGCT	81	64884	64903	157

Table 125

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intronic and exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
533133	n/a	n/a	Intron 1	CAGGAATGGAAAACCAAATA	76	26495	26514	129
						121986	122005	
533134	n/a	n/a	Intron 1	TCAGGAATGGAAAACCAAAT	83	26496	26515	130
						121987	122006	
533174	n/a	n/a	Intron 1	TAAGTCTTCTTGTGAGCTGG	73	64886	64905	158
533175	n/a	n/a	Intron 1	TTAAGTCTTCTTGTGAGCTG	58	64887	64906	159
533176	n/a	n/a	Intron 1	ATTAAGTCTTCTTGTGAGCT	51	64888	64907	160
533177	n/a	n/a	Intron 1	TCTCTTCCACTCACATCCAT	72	65989	66008	161
533178	n/a	n/a	Intron 1	GTCTCTTCCACTCACATCCA	86	65990	66009	162
533179	n/a	n/a	Intron 1	AGTCTCTTCCACTCACATCC	80	65991	66010	163

533180	n/a	n/a	Intron 1	TAAGTATTTGTAGCAGTTGC	31	78195	78214	164
533181	n/a	n/a	Intron 1	CTAAGTATTTGTAGCAGTTG	14	78196	78215	165
533182	n/a	n/a	Intron 1	GCTAAGTATTTGTAGCAGTT	59	78197	78216	166
533183	n/a	n/a	Intron 1	TGGCTAAGTATTTGTAGCAG	34	78199	78218	167
533184	n/a	n/a	Intron 1	TTGGCTAAGTATTTGTAGCA	18	78200	78219	168
533185	n/a	n/a	Intron 1	TTTGGCTAAGTATTTGTAGC	21	78201	78220	169
533186	n/a	n/a	Intron 1	AAAATGTCAACAGTGCATAG	61	80636	80655	170
533187	n/a	n/a	Intron 1	CAAAATGTCAACAGTGCATA	78	80637	80656	171
533188	n/a	n/a	Intron 1	CCAAAATGTCAACAGTGCAT	85	80638	80657	172
533189	n/a	n/a	Intron 1	GCCCAAAATGTCAACAGTGC	82	80640	80659	173
533190	n/a	n/a	Intron 1	GGCCCAAAATGTCAACAGTG	60	80641	80660	174
533191	n/a	n/a	Intron 1	TGGCCCAAAATGTCAACAGT	31	80642	80661	175
533192	n/a	n/a	Intron 1	CAGAATCTTCTCTTTGGCCA	66	98624	98643	176
533193	n/a	n/a	Intron 1	GCAGAATCTTCTCTTTGGCC	81	98625	98644	177
533194	n/a	n/a	Intron 1	TGCAGAATCTTCTCTTTGGC	72	98626	98645	178
533195	n/a	n/a	Intron 1	TTTGCAGAATCTTCTCTTTG	33	98628	98647	179
533196	n/a	n/a	Intron 1	ATTTGCAGAATCTTCTCTTT	27	98629	98648	180
533197	n/a	n/a	Intron 1	AATTTGCAGAATCTTCTCTT	38	98630	98649	181
533198	n/a	n/a	Intron 1	ATAAAGCTATGCCATAAAGC	37	99478	99497	182
533199	n/a	n/a	Intron 1	CATAAAGCTATGCCATAAAG	14	99479	99498	183
533200	n/a	n/a	Intron 1	CCATAAAGCTATGCCATAAA	30	99480	99499	184
533201	n/a	n/a	Intron 1	GACCATAAAGCTATGCCATA	54	99482	99501	185
533202	n/a	n/a	Intron 1	TGACCATAAAGCTATGCCAT	64	99483	99502	186
533203	n/a	n/a	Intron 1	CTGACCATAAAGCTATGCCA	61	99484	99503	187
533204	n/a	n/a	Intron 1	CAAAAAGTTGAGCTGAGAAA	0	101078	101097	188
533205	n/a	n/a	Intron 1	CCAAAAAGTTGAGCTGAGAA	28	101079	101098	189
533206	n/a	n/a	Intron 1	CCCAAAAAGTTGAGCTGAGA	52	101080	101099	190
533207	n/a	n/a	Intron 1	CACCCAAAAAGTTGAGCTGA	60	101082	101101	191
533208	n/a	n/a	Intron 1	ACACCCAAAAAGTTGAGCTG	34	101083	101102	192
533209	n/a	n/a	Intron 1	TACACCCAAAAAGTTGAGCT	36	101084	101103	193
533210	n/a	n/a	Intron 1	CTTTTAATGGCACCCAAGCA	41	103566	103585	194
533211	n/a	n/a	Intron 1	GCTTTTAATGGCACCCAAGC	54	103567	103586	195
533212	n/a	n/a	Intron 1	TGCTTTTAATGGCACCCAAG	67	103568	103587	196
533213	n/a	n/a	Intron 1	AATGCTTTTAATGGCACCCA	73	103570	103589	197
533214	n/a	n/a	Intron 1	AAATGCTTTTAATGGCACCC	73	103571	103590	198
533215	n/a	n/a	Intron 1	GAAATGCTTTTAATGGCACC	41	103572	103591	199
533216	n/a	n/a	Intron 1	TAATTCTTAAGGGCCCTCTG	36	106963	106982	200
533217	n/a	n/a	Intron 1	ATAATTCTTAAGGGCCCTCT	45	106964	106983	201
533218	n/a	n/a	Intron 1	CATAATTCTTAAGGGCCCTC	50	106965	106984	202
533219	n/a	n/a	Intron 1	AGCATAATTCTTAAGGGCCC	48	106967	106986	203
533220	n/a	n/a	Intron 1	TAGCATAATTCTTAAGGGCC	52	106968	106987	204
533221	n/a	n/a	Intron 1	TTAGCATAATTCTTAAGGGC	28	106969	106988	205
533222	n/a	n/a	Intron 1	AGGAATGGAAAACCAAACAT	13	113028	113047	206

533223	n/a	n/a	Intron 1	CAGGAATGGAAAACCAAACA	64	113029	113048	207
533224	n/a	n/a	Intron 1	TCAGGAATGGAAAACCAAAC	61	113030	113049	208
533225	n/a	n/a	Intron 1	AGGAATGGAAAACCAAATAC	18	121985	122004	209
533226	n/a	n/a	Intron 1	CATGACTATGTTCTGGCAAG	37	125591	125610	210
533227	n/a	n/a	Intron 1	ACATGACTATGTTCTGGCAA	44	125592	125611	211
533228	n/a	n/a	Intron 1	CACATGACTATGTTCTGGCA	63	125593	125612	212
533229	n/a	n/a	Intron 1	GTCACATGACTATGTTCTGG	47	125595	125614	213
533230	n/a	n/a	Intron 1	GGTCACATGACTATGTTCTG	49	125596	125615	214
533231	n/a	n/a	Intron 1	TGGTCACATGACTATGTTCT	30	125597	125616	215
533232	n/a	n/a	Intron 2	CTGAATTCTGAGCTCTGGAA	73	145428	145447	216
533233	n/a	n/a	Intron 2	CCTGAATTCTGAGCTCTGGA	88	145429	145448	217
533234	n/a	n/a	Intron 2	GCCTGAATTCTGAGCTCTGG	92	145430	145449	218
533235	n/a	n/a	Intron 2	AAGCCTGAATTCTGAGCTCT	83	145432	145451	219
533236	n/a	n/a	Intron 2	CAAGCCTGAATTCTGAGCTC	68	145433	145452	220
533237	n/a	n/a	Intron 2	ACAAGCCTGAATTCTGAGCT	81	145434	145453	221
533238	n/a	n/a	Intron 2	GGATCTCAGCTGCAATTCTT	72	146235	146254	222
533239	n/a	n/a	Intron 2	AGGATCTCAGCTGCAATTCT	53	146236	146255	223
533240	n/a	n/a	Intron 2	GAGGATCTCAGCTGCAATTC	69	146237	146256	224
533241	n/a	n/a	Intron 2	CAGAGGATCTCAGCTGCAAT	69	146239	146258	225
533242	n/a	n/a	Intron 2	GCAGAGGATCTCAGCTGCAA	76	146240	146259	226
533243	230	249	Exon 2	AAAAGCATCACTTGATCCTG	23	145014	145033	227

Table 126

Inhibition of GHR mRNA by 3-10-4 MOE gapmers targeting intronic and exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Target Region	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
539284	206	222	Exon 2	CAAGGTCAACAGCAGCT	62	144990	145006	228
539285	207	223	Exon 2	CCAAGGTCAACAGCAGC	74	144991	145007	229
539286	208	224	Exon 2	GCCAAGGTCAACAGCAG	73	144992	145008	230
539290	869	885	Exon 7	TCTCACACGCACTTCAT	29	290367	290383	231
539291	870	886	Exon 7	ATCTCACACGCACTTCA	51	290368	290384	232
539292	871	887	Exon 7	GATCTCACACGCACTTC	56	290369	290385	233
539299	n/a	n/a	Intron 1	CTTTCATGAATCAAGCT	63	17927	17943	234
539300	n/a	n/a	Intron 1	TCTTTCATGAATCAAGC	49	17928	17944	235
539301	n/a	n/a	Intron 1	GTCTTTCATGAATCAAG	61	17929	17945	236
539302	n/a	n/a	Intron 1	GGTCTTTCATGAATCAA	93	17930	17946	237
539303	n/a	n/a	Intron 1	ATGGTCTTTCATGAATC	74	17932	17948	238
539304	n/a	n/a	Intron 1	GATGGTCTTTCATGAAT	56	17933	17949	239
539305	n/a	n/a	Intron 1	TATATCAATATTCTCCC	42	21820	21836	240
539306	n/a	n/a	Intron 1	TTATATCAATATTCTCC	33	21821	21837	241

539307	n/a	n/a	Intron 1	GTTATATCAATATTCTC	12	21822	21838	242
539308	n/a	n/a	Intron 1	TTTCTTTAGCAATAGTT	21	22518	22534	243
539309	n/a	n/a	Intron 1	CTTTCTTTAGCAATAGT	38	22519	22535	244
539310	n/a	n/a	Intron 1	GCTTTCTTTAGCAATAG	39	22520	22536	245
539311	n/a	n/a	Intron 1	AGGAATGGAAAACCAAA	18	26497	26513	246
						113031	113047	
						121988	122004	
539312	n/a	n/a	Intron 1	CAGGAATGGAAAACCAA	40	26498	26514	247
						113032	113048	
						121989	122005	
539313	n/a	n/a	Intron 1	TCAGGAATGGAAAACCA	49	26499	26515	248
						113033	113049	
						121990	122006	
539314	n/a	n/a	Intron 1	TCTCCATTAGGGTTCTG	87	50948	50964	249
539315	n/a	n/a	Intron 1	TTCTCCATTAGGGTTCT	57	50949	50965	250
539316	n/a	n/a	Intron 1	GTTCTCCATTAGGGTTC	73	50950	50966	251
539317	n/a	n/a	Intron 1	AGGTTGGCAGACAGACA	73	53466	53482	252
539318	n/a	n/a	Intron 1	CAGGTTGGCAGACAGAC	84	53467	53483	253
539319	n/a	n/a	Intron 1	GCAGGTTGGCAGACAGA	85	53468	53484	254
539320	n/a	n/a	Intron 1	CTTCTTGTGAGCTGGCT	87	64884	64900	255
539321	n/a	n/a	Intron 1	TCTTCTTGTGAGCTGGC	89	64885	64901	256
539322	n/a	n/a	Intron 1	GTCTTCTTGTGAGCTGG	87	64886	64902	257
539323	n/a	n/a	Intron 1	AGTCTTCTTGTGAGCTG	70	64887	64903	258
539324	n/a	n/a	Intron 1	TCTTCCACTCACATCCA	65	65990	66006	259
539325	n/a	n/a	Intron 1	CTCTTCCACTCACATCC	78	65991	66007	260
539326	n/a	n/a	Intron 1	TCTCTTCCACTCACATC	68	65992	66008	261
539327	n/a	n/a	Intron 1	GTCTCTTCCACTCACAT	74	65993	66009	262
539328	n/a	n/a	Intron 1	ATAGATTTTGACTTCCC	57	72107	72123	263
539329	n/a	n/a	Intron 1	CATAGATTTTGACTTCC	35	72108	72124	264
539330	n/a	n/a	Intron 1	GCATAGATTTTGACTTC	53	72109	72125	265
539331	n/a	n/a	Intron 1	AAAATGTCAACAGTGCA	86	80639	80655	266
539332	n/a	n/a	Intron 1	CAAAATGTCAACAGTGC	73	80640	80656	267
539333	n/a	n/a	Intron 1	CCAAAATGTCAACAGTG	34	80641	80657	268
539334	n/a	n/a	Intron 1	CCCAAAATGTCAACAGT	66	80642	80658	269
539335	n/a	n/a	Intron 1	CATGACTATGTTCTGGC	67	125594	125610	270
539336	n/a	n/a	Intron 1	ACATGACTATGTTCTGG	42	125595	125611	271
539337	n/a	n/a	Intron 1	CACATGACTATGTTCTG	29	125596	125612	272
539338	n/a	n/a	Intron 2	GAATTCTGAGCTCTGGA	77	145429	145445	273
539339	n/a	n/a	Intron 2	TGAATTCTGAGCTCTGG	84	145430	145446	274
539340	n/a	n/a	Intron 2	CTGAATTCTGAGCTCTG	80	145431	145447	275
539341	n/a	n/a	Intron 2	CCTGAATTCTGAGCTCT	84	145432	145448	276
539342	n/a	n/a	Intron 2	GCCTGAATTCTGAGCTC	84	145433	145449	277
539343	n/a	n/a	Intron 2	AGCCTGAATTCTGAGCT	80	145434	145450	278

539344	n/a	n/a	Intron 2	ATATTGTAATTCTTGGT	0	148059	148075	279
539345	n/a	n/a	Intron 2	GATATTGTAATTCTTGG	20	148060	148076	280
539346	n/a	n/a	Intron 2	TGATATTGTAATTCTTG	13	148061	148077	281
539347	n/a	n/a	Intron 2	CTGATATTGTAATTCTT	8	148062	148078	282
539348	n/a	n/a	Intron 2	CCTGATATTGTAATTCT	67	148063	148079	283
539349	n/a	n/a	Intron 2	GCCTGATATTGTAATTC	73	148064	148080	284
539350	n/a	n/a	Intron 2	TGCCTGATATTGTAATT	32	148065	148081	285
539351	n/a	n/a	Intron 2	AATTATGTGCTTTGCCT	58	148907	148923	286
539352	n/a	n/a	Intron 2	CAATTATGTGCTTTGCC	82	148908	148924	287
539353	n/a	n/a	Intron 2	TCAATTATGTGCTTTGC	68	148909	148925	288
539354	n/a	n/a	Intron 2	GTCAATTATGTGCTTTG	80	148910	148926	289
539355	n/a	n/a	Intron 2	GCCATCACCAAACACCA	94	150972	150988	290
539356	n/a	n/a	Intron 2	TGCCATCACCAAACACC	84	150973	150989	291
539357	n/a	n/a	Intron 2	TTGCCATCACCAAACAC	74	150974	150990	292
539358	n/a	n/a	Intron 2	TGGTGACTCTGCCTGAT	85	151387	151403	293
539359	n/a	n/a	Intron 2	CTGGTGACTCTGCCTGA	86	151388	151404	294

Table 127

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intron 1 of SEQ ID NO: 2

ISIS NO	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
523561	TATTTCAGAAAGACTTTCTG	11	10373	10392	295
523562	AGGAAAAAATCAAGGAGTTA	8	11173	11192	296
523563	TATTTACTGAACACCTATTC	12	11973	11992	297
523564	GCCCATGAAGGCCACTCTTC	70	12780	12799	298
523565	ACCTATAAATAAAGTGAGGA	0	13581	13600	299
523566	GTTTCATAACCTGCTAATAA	40	14451	14470	300
523567	ATGTGCCTTACAGTTATCAG	36	15251	15270	301
523568	TTCTGAATTTAGAATTATAG	0	16051	16070	302
523569	GTTTATAATCTAGCAGTTAC	26	17130	17149	303
523570	GATGGTCTTTCATGAATCAA	62	17930	17949	304
523571	CATGTACCCAAACCAACACT	65	18730	18749	305
523572	TAAAATACAGCCTACATCAT	0	19637	19656	306
523573	CCATCACTACAACAAACTCA	39	20451	20470	307
523574	ATCTGAAATGATCCCCTTTC	33	21283	21302	308
523575	TGTTGCCCCTCCAAAAAGAC	12	22144	22163	309
523576	ATTAAAATTTTAAATGATGT	0	22944	22963	310
523577	CTCAGGAATGGAAAACCAAA	71	26497	26516	311
			113031	113050	
			121988	122007	
523578	AAAATTCTAGAAGATAACAT	0	27838	27857	312

523579	CTAGAAGTCCTAGCCAGAGT	2	28748	28767	313
523580	AACCGATATCACAGAAATAC	0	29548	29567	314
523581	AAGATAGACAGTAACATAAT	0	30348	30367	315
523582	GCACTACAAGAACTGCTTAA	40	31172	31191	316
523583	TTTCCAGACAAAGAATTCAG	6	31978	31997	317
523584	GTAGACAGCCTTTCTGGAAC	20	32827	32846	318
523585	CATCCTACATAGTGGCTGTG	47	33635	33654	319
523586	CAGAACAGTGTGTGGAGACT	8	34452	34471	320
523587	AGCTTTAAAAATACCTCTGC	52	35466	35485	321
523588	CCCAGGTACTTGCTCTCAGA	22	36266	36285	322
523589	TTACACCTGATTCTAGAAAT	30	37066	37085	323
523590	CTTTTCTCTACAACCTCACA	34	38094	38113	324
523591	TAGTAGTTTGAATTTCAAAG	1	38909	38928	325
523592	ATACAAAATTACTGCAGTCA	60	39719	39738	326
523593	GCCACTGCCAAAAAGGAGGA	30	40519	40538	327
523594	TGACAGAAACAGAGCTATGA	33	41342	41361	328
523595	ATCTTTTAGTATGAACCTTA	65	42142	42161	329
523596	AGTTATGTGACTCTGAGCAC	63	43173	43192	330
523597	ACTATGCCCTAGTTACTTCT	29	43973	43992	331
523598	TATAGTGGAAGTGATAGATC	0	44812	44831	332
523599	TGTTTTCTGAAATGGAATGT	0	45733	45752	333
523600	GCTGTAAATGTAATGAGTGT	34	46553	46572	334
523601	GAGAGAAGCCATGGCCCTAG	20	47392	47411	335
523602	CTCTCTTTCCCAGAACAAGA	32	48210	48229	336
523603	TCCAAAATGTCCAGTATAAT	33	50072	50091	337
523604	GTTCTCCATTAGGGTTCTGG	74	50947	50966	338
523605	TTAGTCACCCATCCACCACT	41	51747	51766	339
523606	CATGAATTCACCGAGTTAGG	51	52573	52592	340
523607	AGCAGGTTGGCAGACAGACA	62	53466	53485	341
523608	GAAAGACTTAAATTTTCACA	0	54306	54325	342
523609	TAGTAGAGGAAAAGGAGAAT	0	55730	55749	343
523610	AAACAGGGTCTGGAGTGGAC	3	61243	61262	344
523611	CAAGCTGATAATTAAAAAGA	0	62462	62481	345
523612	ATAAAGATACATTTTCTGGG	8	63277	63296	346
523613	CAGGATTCTTCCTGCCTGGC	47	64085	64104	347
523614	AAGTCTTCTTGTGAGCTGGC	71	64885	64904	348
523615	CTCTTCCACTCACATCCATT	63	65988	66007	349
523616	CCTATATCAGAAGACAAATG	5	66806	66825	350
523617	TCAAAACCCTGCCAAGGTAC	44	67662	67681	351
523618	TCATATTCTACTTCTGTTTA	11	68462	68481	352
523619	CATTCCAGTGTTTCAGTAAG	13	69262	69281	353
523620	GGCCTGGAATTAATCCTCAG	49	70114	70133	354
523621	AATGCCCTCTCCCTGTGCCT	48	70925	70944	355

523622	TTTATAATCAACCTTTGCTA	9	71741	71760	356
523623	ATATAACTACTTAAAATAAT	0	72541	72560	357
523624	TTAGCCAGGATATGGTTGCC	50	73350	73369	358
523625	CTACCTCCATCAAAGAAAAT	0	74190	74209	359
523626	GCATGCATAGATAAGTTTGA	20	74990	75009	360
523627	ATGAGAGTAAATGGATTTTC	10	75790	75809	361
523628	TTGGCAATCCTTGCTTAAAA	34	76598	76617	362
523629	GAATTAAGCCAGACTTATTT	3	77398	77417	363
523630	GGCTAAGTATTTGTAGCAGT	55	78198	78217	364
523631	TTGCCTGTGTGCAACTGGCG	0	79005	79024	365
523632	GTGGCCTTAGTAGGCCAGCT	0	79827	79846	366
523633	CCCAAAATGTCAACAGTGCA	70	80639	80658	367
523634	TTAAGCCTTCAATTTGAAAA	0	81455	81474	368
523635	TGCTCAGAAGGTTGAGCATA	0	82261	82280	369
523636	TTAATGCTTTCCCAAAGCTC	35	83061	83080	370
523637	AAAAGACTTCATACCTTTAC	52	83884	83903	371

Table 128

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intron 1 of SEQ ID NO: 2

ISIS NO	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532146	GGCCCCCTGGCACAACAGGA	60	3097	3116	372
532147	TCTAGGGTGATTCAGGTGGA	62	4537	4556	373
532148	CTTAGATTAATGCAAAACAA	25	4875	4894	374
532149	AGGCAGAGGAGGGTGGAACC	34	6246	6265	375
532150	AGTCTAATGAGATCTGATGG	76	6499	6518	376
532151	GCTGAAATGAGTTAAGACTT	89	6737	6756	377
532152	ACTTTGGACTGTGGATTTTT	78	6765	6784	378
532153	GCATATTTACACAATGCCTG	84	6871	6890	379
532154	GGAAATGCCTGGATGTCCAG	27	7241	7260	380
532155	CTGCTGATTTTGGAATGGAG	68	10660	10679	381
532156	ACTGAACACCTATTCTATGG	51	11968	11987	382
532157	TTTACTGAACACCTATTCTA	23	11971	11990	383
532158	CCCTCAAATTATCCACAAAC	89	12053	12072	384
532159	CTTCTAAATGTTTCCAAGGC	63	12186	12205	385
532160	TTACATCCTGTAGGCTAATT	82	12469	12488	386
532161	CCACTAGCCTGGCCAGACTT	73	12487	12506	387
532162	CTGGTAGATGATCTCAAGTT	84	13351	13370	388
532163	AAAGAATTGAGTTATAAATC	23	13670	13689	389
532164	AACTCATCTCTGGCCAGCAG	89	14361	14380	390
532165	CAACATCATTGTATTTTCTG	33	14965	14984	391

532166	TCTTAGCTTACCAATGAGGA	81	15085	15104	392
532167	TTCCCAGAGCCAAAGCTCAA	77	15982	16001	393
532168	TTTGGCCAATCCCAGCTTAT	59	16253	16272	394
532169	GTTTGCAAATCTTCATTCAC	71	16447	16466	395
532170	CAATAGTCCCTGAGGCTTGG	74	16476	16495	396
532171	TTTCCCCAGATTAAATGCCC	85	17650	17669	397
532172	TTCAATAATGCAGTTATTAT	0	18308	18327	398
532173	AAATTCTTGGGCTTAAGCAC	69	18638	18657	399
532174	ACATGTACCCAAACCAACAC	71	18731	18750	91
532175	TGATCCAAATTCAGTACCTA	82	18752	18771	400
532176	GATGATCCAAATTCAGTACC	54	18754	18773	401
532177	CAATATTCATCTTTATATTC	25	19106	19125	402
532178	ATTGCTCTTAAGATAAGTAA	41	19661	19680	403
532179	CAGCTCCCTGAATATCTCTT	74	19783	19802	404
532180	ACTTCACAAATATATTATAA	0	19885	19904	405
532181	GTACAGTCAACTTTACTTCA	89	19899	19918	406
532182	CAATTCCCACTCTTGTCAAC	55	20288	20307	407
532183	TCAACTGCTTTCTGGAGCAG	66	21215	21234	408
532184	ACTGCTGAGCACCTCCAAAA	73	21454	21473	409
532185	CTTAGATTCCTGGTTTATCA	78	21587	21606	410
532186	AGTTATATCAATATTCTCCC	88	21820	21839	411
532187	TATACCATCTTCCCCATAAA	32	22038	22057	412
532188	GGCTTTCTTTAGCAATAGTT	86	22518	22537	413
532189	TACCAGGGATGTAGGTTTAC	82	29050	29069	414
532190	TCACAGCTGAATTCTATCTG	80	29323	29342	415
532191	GGAGATGGACAAATTCCTGC	77	29470	29489	416
532192	CTAGACATGTCATCAAGACA	19	30294	30313	417
532193	CAAATTAATAAAACAATTAC	10	30385	30404	418
532194	TATTCTTATATCAGACAAAA	30	30532	30551	419
532195	TCAAGGGATCCCTGCCATTC	32	32361	32380	420
532196	CGTCAAGGGATCCCTGCCAT	47	32363	32382	421
532197	GGCACTCCCAGTCTCCAGCT	83	34138	34157	422
532198	TTTCTCCAGCAGAAGTGTCA	60	34845	34864	423
532199	AAGTCCTCTTCCGCCTCCCT	82	36023	36042	424
532200	GGAATTTACCAAAAACAGTT	63	36721	36740	425
532201	AGTTAGGTATTGTCCATTTT	74	37032	37051	426
532202	ACATGGGTATCTTCTAGGAA	77	37111	37130	427
532203	TCAGTTTCAGAGAGACAAAA	41	37276	37295	428
532204	TTTGCCAGGTCCTATGTCGA	69	37656	37675	429
532205	ATTCCCTTTTCTCTACAACC	70	38099	38118	430
532206	ATGATAAGAGCCAAGATTTG	13	38994	39013	431
532207	GAAAAAAGGTCCACTGTGGT	49	40356	40375	432
532208	CCTGTCCTGGAATAGTTTCA	49	41164	41183	433

532209	TAGAAAAGTAAATAAGGAAT	15	41501	41520	434
532210	TTATAAAACTATGCAATAGG	0	41889	41908	435
532211	TTATTTCATATTTCCAGAAA	0	42675	42694	436
532212	CATGAATTACAGCTAAAGAT	20	42741	42760	437
532213	TTGCATGTATGTGTTTCTGA	62	43518	43537	438
532214	TCAATCTCTTTATACCCTTA	75	43765	43784	439
532215	TCTTCAATCTCTTTATACCC	58	43768	43787	440
532216	CTATGCCCTAGTTACTTCTA	47	43972	43991	441
532217	AAAGAGAATCTCTTCCTTTT	27	44070	44089	442
532218	TCATTAAAGATTATTATAAC	0	44222	44241	443
532219	TTTGGATGAGTGGAAGGCTA	0	44528	44547	444
532220	GGAAATGGCCTTTTTCCTTA	72	45400	45419	445
532221	GGAGAAGCCCTCTGCCTGTA	60	46477	46496	446
532222	AAACCATATTGTCCACCAGA	84	46510	46529	447

Table 129

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intron 1 of SEQ ID NO: 2

ISIS NO	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532223	CTCAAACCATATTGTCCACC	90	46513	46532	448
532224	GTGTAAATAGTGACTTGTAC	76	50123	50142	449
532225	TGAGGCACAGGAAAGTTAAC	52	50719	50738	450
532226	AGCTATAGTTCTCCATTAGG	74	50954	50973	451
532227	TTACTTGCTGACTAAGCCAT	69	51071	51090	452
532228	GTTTGTCAACTCAACATCAA	73	51215	51234	453
532229	GACTATTTGTATATATATAC	33	51491	51510	454
532230	ATGACTATTTGTATATATAT	11	51493	51512	455
532231	ACTCTTCCTTATATTTGCTC	76	51778	51797	456
532232	ATACACTGACTTTTAACATT	67	52039	52058	457
532233	CTTAGAAACAGTAGTTTCAT	42	52124	52143	458
532234	CTGAGCTTTGCCTTAAGAAT	79	52633	52652	459
532235	CACCAGACAGCAGGTAGAGC	81	53540	53559	460
532236	GAGATGGAGTAGAAGGCAAA	43	55926	55945	461
532237	TAGGAAAGGAAGAATACACT	33	63881	63900	462
532238	TAGACCAGGAAGGGTGAGAG	27	64376	64395	463
532239	AAGTTGGATCTGGCATGCAT	64	64574	64593	464
532240	AAAGTTGGATCTGGCATGCA	70	64575	64594	465
532241	CCATAACTCTTCTAACTGGG	84	64643	64662	466
532242	ATATTAAAGTTTGAGAACTA	37	65080	65099	467
532243	CTTAACTACAAAATGCTGGA	71	66164	66183	468
532244	TGAGCAGCTGTCCTCAGTTC	43	67061	67080	469

532245	GAGTTCATAAAAGTTTTACT	26	67251	67270	470
532246	CTATCCACACCATTCCATAA	73	69203	69222	471
532247	AACATCTAAGTAATGCAAAC	58	69223	69242	472
532248	TTTGCATTCAAAGCCCTGGG	91	69565	69584	473
532249	TCCATATTATAGGCTATGAT	73	69889	69908	474
532250	ATTTTATGATAATGTAAAAC	27	69942	69961	475
532251	GAGATCACATTTTCTGAGTA	50	70352	70371	476
532252	ACCTCCCTAGGATTACCTCA	56	71617	71636	477
532253	AAAATCTGATTTATAATCAA	40	71750	71769	478
532254	AGCATAGATTTTGACTTCCC	92	72107	72126	479
532255	AAAGTCATATACACAGGTCT	53	72584	72603	480
532256	CTCATAGCAAATTCCCAGAA	66	73689	73708	481
532257	CAACATGGAGGCTAGCATGT	55	74112	74131	482
532258	AGACTAAGTGGCCTGAATGT	52	74317	74336	483
532259	ACCTACCATGTCACTCTCAA	61	74418	74437	484
532260	AACTTTCTTGTGTTTTATCA	9	75511	75530	485
532261	TTTGCAAGACAAAGAAATGA	31	75915	75934	486
532262	CATGCAAAGTGTTCCTCTTC	63	76024	76043	487
532263	AGTGCTTTGCTTTCTCTTAT	79	76047	76066	488
532264	GAACAAGAAACACTTGGTAA	44	76555	76574	489
532265	AGTGTTCCAATTAAATGGCA	34	76643	76662	490
532266	AAACAATGCCCTTGTAGTGA	57	76703	76722	491
532267	TATTCTAGGTTTTGAGGTGA	60	76752	76771	492
532268	ATATTCTAGGTTTTGAGGTG	24	76753	76772	493
532269	GTTTTCCATTCTTTAAGAAA	41	76896	76915	494
532270	AGCAATCCATTGATTGTATG	59	77044	77063	495
532271	AATTATGGCAAAATGGAAAA	37	77076	77095	496
532272	ACATTTGCTTATGAGACTAT	62	77638	77657	497
532273	GCAGAGATAATCCTATGATG	42	77841	77860	498
532274	TCCATCTGTTACCTCTCTGT	77	78122	78141	499
532275	TTTGCCTGAAGGGCAGAACC	40	79478	79497	500
532276	GAAAAAATCAGATTTTCACA	0	79664	79683	501
532277	AACTTAATTTAATCATTTCT	0	79959	79978	502
532278	TTTGGTTGTCATGAGTTGAG	67	80756	80775	503
532279	TTCCATCTCTAGGGCACTTT	74	80900	80919	504
532280	AGAGCTTATTTTCAAAATTC	36	80920	80939	505
532281	ATAAAGAGCAAACAAACATA	42	81524	81543	506
532282	TATAAATTCCTTGGTCTGAT	33	82835	82854	507
532283	AAAATATAAATTCCTTGGTC	13	82839	82858	508
532284	TTTTATAACAGCCTCTGACA	38	82959	82978	509
532285	AAAAGACCATGTTGCTTATT	72	83179	83198	510
532286	ATAGTCAGTCAGAATGTGGT	72	83330	83349	511
532287	TGCCTTAGCTTGGAAAAGAC	78	83897	83916	512

532288	AGGGCTAGCTGATGCCTCTC	69	84026	84045	513
532289	TTGGACTGGGCTCAAACAGA	72	84381	84400	514
532290	AAAGTCAGGCTAGAGGGACT	49	85713	85732	515
532291	TCCTTGTTTTCTTGTAATGA	50	85945	85964	516
532292	ACACCAGAGGAAGGAAATCA	44	86554	86573	517
532293	GATGTACACCATTTTGAATT	15	86629	86648	518
532294	TGCTCTGGCCTAGCCTATGT	62	86901	86920	519
532295	CAGAGGTGTCTCCCAAGAAA	60	89940	89959	520
532296	AAAGAGAATGGATCAAAGCT	36	91930	91949	521
532297	GATTTGCAGAACAAATCTTG	37	93332	93351	522
532298	TGGTTATGAAGGTTGGACCA	52	94839	94858	523
532299	TGGCTAATTAATGGGCAATT	63	95292	95311	524

Table 130

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intron 1 of SEQ ID NO: 2

ISIS NO	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532300	CTGTGCCATATTGCCTCTAA	87	95471	95490	525
532301	GATTTCAACCAGCTCACCTG	48	95510	95529	526
532302	GCAAAAGGGAACCCTGAAGC	71	95564	95583	527
532303	CTAAGTGTTATAACAAACAC	43	96137	96156	528
532304	GTCCATTGGTATAAAACTCA	84	96282	96301	529
532305	TTTCAATACAATAAGATTTA	34	96793	96812	530
532306	GTCCTTAGACCCCTCAATGG	62	96987	97006	531
532307	GAGGATTTATTCATCTAGGC	68	97806	97825	532
532308	CAGTGGGAGGATCAGATATC	46	97870	97889	533
532309	ATCCCATCCAGCAGCTGGAC	67	98132	98151	534
532310	AACTTGGGATGAGTTACTGA	56	98653	98672	535
532311	GAAGGCTACCTAAAAGAAAT	43	98810	98829	536
532312	AAAGAAATATTCACAACATT	39	99096	99115	537
532313	ATGCTTATACTGCTGCTGTA	69	99791	99810	538
532314	TCCTCACTTCAATCACCTTT	70	99819	99838	539
532315	CTCTTTCTTCATAAATAAGT	33	100809	100828	540
532316	TGGTAATCTGTGTCCCTTTA	96	101242	101261	541
532317	TAATAAAAAAGTTTGAAACA	41	102549	102568	542
532318	GGTGGTGGCAAGAGAAAAAT	56	103015	103034	543
532319	CAAAAGGCCCTTTTTACATG	28	103034	103053	544
532320	ACTCTACTGGTACCAATTTA	31	103173	103192	545
532321	TCTGAACTTTTATGCTCTGT	76	103606	103625	546
532322	AACTTTTGCCTGGGCATCCA	16	104067	104086	547
532323	TGACTCCATGTCTCACATCC	66	104392	104411	548

532324	TTACTTCCTAGATACAACAG	53	104541	104560	549
532325	CTGGCCCCCATGATTCAATT	44	104835	104854	550
532326	AAGACTGGCCCCCATGATTC	49	104839	104858	551
532327	TGTCACTGGTCTGTGTATTT	60	106233	106252	552
532328	ACAGAGTAGATTTAGCATAA	23	106980	106999	553
532329	TAAACAGGTGTACTATTACA	27	107030	107049	554
532330	GCTTTATCAACTAAGTTTAT	22	107716	107735	555
532331	CAGAACTTCTTTTAAAATTG	8	107763	107782	556
532332	GAATACAGACATACCTTGAA	25	108514	108533	557
532333	CCATGACAACAATTTCAGAG	58	109486	109505	558
532334	ACAAATAGCAATGAATGGGT	45	110878	110897	559
532335	CAACAAATAGCAATGAATGG	47	110880	110899	560
532336	GTACACAAATCAGTAGCTCT	72	115087	115106	561
532337	CTATGTCAAAAAGACTGAAA	4	116370	116389	562
532338	ATATACAGAACATTTCATCC	13	116743	116762	563
532339	AGAATAGATAAGAACTCACC	32	117195	117214	564
532340	AGGAAAGATACAGTCATTTT	5	117507	117526	565
532341	GCACAAAGAACACCTGGGAA	43	117781	117800	566
532342	CAAGAAGTCTGGGATTATGT	0	117938	117957	567
532343	GTTAGTTATTAAGCTAATCA	48	118245	118264	568
532344	AACCATTATTTATAGGCTAA	14	119127	119146	569
532345	CCAGAATGCGATCACTTCTT	76	120826	120845	570
532346	CCAGAAATTATCCTCCTCTC	70	121209	121228	571
532347	AGGGAAATGCAAATTAAAAC	20	122479	122498	572
532348	GCATCAAGATACAGAAAAAT	24	122751	122770	573
532349	GAATGTTTATGAGATTTTTC	0	123571	123590	574
532350	GCCAATTATATTGCCACATT	23	124413	124432	575
532351	ATACTTGCTTATGTAGAAAT	45	124589	124608	576
532352	TAATACTTGCTTATGTAGAA	3	124591	124610	577
532353	GAACACATGGCATTCTGATA	36	125178	125197	578
532354	CAGAATTTGCAGTATAAATC	0	126051	126070	579
532355	TATGTTTTGAAATCTTATTT	0	126157	126176	580
532356	ACTCACTGCTACCTCATTAA	11	126998	127017	581
532357	AAGCAGTGATAGGGTATCTG	59	127080	127099	582
532358	ATGAGGCCTATTACAATGGA	14	127170	127189	583
532359	CTGGAGTCTCATGAGGCCTA	53	127180	127199	584
532360	TGACTATCAGCCTTTTAATC	45	127663	127682	585
532361	TTCAGAGAACAACCTTTGAA	0	127959	127978	586
532362	AGCCATGTGTGATCTGATGT	53	128813	128832	587
532363	GAAATTTACTCCAAACTAGC	17	128992	129011	588
532364	AACATCCAGACCACCATCTA	35	130094	130113	589
532365	GTACCAAACCATTCATGCTC	56	131036	131055	590
532366	AGTACCAAACCATTCATGCT	24	131037	131056	591

532367	TTATAGAGCTTGAGATTGAC	7	132165	132184	592
532368	AGTCCATTATAGAGCTTGAG	58	132171	132190	593
532369	AACCATGAGATGCAATGCAG	40	132498	132517	594
532370	AGGATTGAGAATCGCTGATT	42	133168	133187	595
532371	TCTAAAGCATGGCCAGGATT	48	133182	133201	596
532372	GGGACTGAGTATTGATACTT	44	133222	133241	597
532373	AGAAGTAGGGTGTTCCAGAT	29	133523	133542	598
532374	AGAAATAGTCTTCCTACTAA	0	133547	133566	599
532375	GCCTCCTTTAAGCTTCTATG	22	134240	134259	600
532376	GGCCTGCCTTTACTTTCCCA	36	134598	134617	601

Table 131

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 1 and 2 of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Target region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
523638	n/a	n/a	ACCTCAGTGGACTCTTTCCA	Intron 1	4	84684	84703	602
523639	n/a	n/a	CAAACCTAAGTTCAAGTCCT	Intron 1	62	85523	85542	603
523640	n/a	n/a	AGTTTCACTTCTTGAATCAA	Intron 1	38	86373	86392	604
523641	n/a	n/a	AAGATCAAATGAGGTCAAGG	Intron 1	30	87181	87200	605
523642	n/a	n/a	TAGATACAAATTTCATCACA	Intron 1	23	88063	88082	606
523643	n/a	n/a	ATTCCTAAAATAGGAGCAGG	Intron 1	45	88870	88889	607
523644	n/a	n/a	TTTTTATGTTGTATAAGATA	Intron 1	0	89670	89689	608
523645	n/a	n/a	GTTCAGCCAATACATGAGTA	Intron 1	48	90473	90492	609
523646	n/a	n/a	CCAGAGGGAGTTCATTACCA	Intron 1	62	91273	91292	610
523647	n/a	n/a	TCTCTCTAATTCAACCTTAT	Intron 1	44	92107	92126	611
523648	n/a	n/a	ATAATCCTCAGACCTCTTTA	Intron 1	29	92925	92944	612
523649	n/a	n/a	CACTGTGGCAGAATTCCAAG	Intron 1	28	93762	93781	613
523650	n/a	n/a	ACACCTTGGTGCCTAGAAGC	Intron 1	54	94581	94600	614
523651	n/a	n/a	GTAGCAATGACACCTAAGAA	Intron 1	58	95394	95413	615
523652	n/a	n/a	TTTAAAATAATAAATGCTTA	Intron 1	0	96194	96213	616
523653	n/a	n/a	TCATTTGGTCCTTAGACCCC	Intron 1	27	96994	97013	617
523654	n/a	n/a	TTATTCATCTAGGCCGAGTG	Intron 1	57	97800	97819	618
523655	n/a	n/a	TTGCAGAATCTTCTCTTTGG	Intron 1	65	98627	98646	619
523656	n/a	n/a	ACCATAAAGCTATGCCATAA	Intron 1	63	99481	99500	620
523657	n/a	n/a	GGCAAGGAGCACAATAGGAC	Intron 1	20	100281	100300	621
523658	n/a	n/a	ACCCAAAAAGTTGAGCTGAG	Intron 1	66	101081	101100	622
523659	n/a	n/a	TAGATTTTCAGACTCTTTCT	Intron 1	46	101887	101906	623
523660	n/a	n/a	AATTTCAATATTGTTGTGTT	Intron 1	0	102760	102779	624
523661	n/a	n/a	ATGCTTTTAATGGCACCCAA	Intron 1	69	103569	103588	625
523662	n/a	n/a	CATGTCTCACATCCAGGTCA	Intron 1	37	104386	104405	626

523663	n/a	n/a	TTCACTGGAGTAGACTTTTA	Intron 1	45	105255	105274	627
523664	n/a	n/a	CTTATAAGGGAGGTCTGGTA	Intron 1	41	106147	106166	628
523665	n/a	n/a	GCATAATTCTTAAGGGCCCT	Intron 1	71	106966	106985	629
523666	n/a	n/a	CCACAGAACTTCTTTTAAAA	Intron 1	27	107766	107785	630
523667	n/a	n/a	GGTGACCATGATTTTAACAA	Intron 1	25	108566	108585	631
523668	n/a	n/a	AACAGCTGCATGACAATTTT	Intron 1	50	109382	109401	632
523669	n/a	n/a	AGAAACAGAATCAGTGACTT	Intron 1	44	110403	110422	633
523670	n/a	n/a	CAGATTCCAGAGAAAAGCCA	Intron 1	14	111203	111222	634
523671	n/a	n/a	TGTGAGAAGAACTCTATCAC	Intron 1	12	112030	112049	635
523672	n/a	n/a	CTCACAAATCACCACTAAAG	Intron 1	31	112842	112861	636
523673	n/a	n/a	CAACGAGTGGATAAAGAAAC	Intron 1	28	113646	113665	637
523674	n/a	n/a	ATAAAACTGGATCCTCATCT	Intron 1	13	114446	114465	638
523675	n/a	n/a	ATTAAAACTCTCAGCAAAAT	Intron 1	0	115450	115469	639
523676	n/a	n/a	AAAGACTGAAAGAACACAAA	Intron 1	0	116361	116380	640
523677	n/a	n/a	TATCTGCTGCCTTCAGGAGA	Intron 1	0	117168	117187	641
523678	n/a	n/a	TTTGAATTAACCCAATTCAA	Intron 1	0	117999	118018	642
523679	n/a	n/a	TCTTAATTTACAACAGAGGA	Intron 1	25	118821	118840	643
523680	n/a	n/a	AGAAAAGTGACAGGCTTCCC	Intron 1	31	119659	119678	644
523681	n/a	n/a	ATGTTCCTTGAAGATCCCAA	Intron 1	37	120478	120497	645
523682	n/a	n/a	ATGAATAACACTTGCCACAA	Intron 1	0	121379	121398	646
523683	n/a	n/a	GTATGTTTATCACAGCACAG	Intron 1	56	122180	122199	647
523684	n/a	n/a	AAACACTGCAATATTAGGTT	Intron 1	34	123031	123050	648
523685	n/a	n/a	GATTGGTGCTTTTCAAACTG	Intron 1	39	123936	123955	649
523686	n/a	n/a	ATTTGTAAGACAAACATGAA	Intron 1	9	124764	124783	650
523687	n/a	n/a	TCACATGACTATGTTCTGGC	Intron 1	72	125594	125613	651
523688	n/a	n/a	AGTCCTGTCCACACTATTAA	Intron 1	6	126415	126434	652
523689	n/a	n/a	CTGGGCTCTGCCTGCTGAAC	Intron 1	17	127217	127236	653
523690	n/a	n/a	AAAACCCTTAAGTATTTCCT	Intron 1	12	128054	128073	654
523691	n/a	n/a	CTCTGTTTCAAACCCCCCAG	Intron 1	21	128854	128873	655
523692	n/a	n/a	GGACAGAACACCAATCACAA	Intron 1	18	129654	129673	656
523693	n/a	n/a	ACCTACCCTTCAAAGTCACG	Intron 1	0	130486	130505	657
523694	n/a	n/a	TTCAGTTCCCAGGAGGCTTA	Intron 1	5	131286	131305	658
523695	n/a	n/a	TTTTGCAATGTCTAGCAATT	Intron 1	0	132086	132105	659
523696	n/a	n/a	ATTAAGATCAGAAAATATTA	Intron 1	0	132953	132972	660
523697	n/a	n/a	TTAATGAGATATTTTGCACC	Intron 1	34	133858	133877	661
523698	n/a	n/a	GAGAGGTTAAGTAAATCTCC	Intron 1	0	134678	134697	662
523699	n/a	n/a	CAGACTCAAATTTGAAAATT	Intron 1	14	135500	135519	663
523700	n/a	n/a	GATAAGGCAATAATACAGCC	Intron 1	1	136306	136325	664
523701	n/a	n/a	ATCATTTGCCAATTTCTGTG	Intron 1	28	137133	137152	665
523702	n/a	n/a	CAAGAAGAAAAGATGCAAAA	Intron 1	0	138035	138054	666
523703	n/a	n/a	AATTTATTTCCTTCCTATGA	Intron 1	0	138857	138876	667
523704	n/a	n/a	TTTTGGAAATGTGAGAAACG	Intron 1	0	139771	139790	668
523705	n/a	n/a	AAACACATGAGAAAAGATGA	Intron 1	0	140593	140612	669

523706	n/a	n/a	TGTTGGCTCAGTGGGAATGA	Intron 1	0	141412	141431	670
523707	n/a	n/a	TGAACAGGTTTGCATTTCTC	Intron 1	42	142229	142248	671
523708	n/a	n/a	TCCTAGGTGAACAGGCTATG	Intron 1	38	143029	143048	672
523709	n/a	n/a	CCCTAATCAGGCTGAAATAA	Intron 1	0	143829	143848	673
523710	n/a	n/a	AGGGCCAGTAAGGTTTGCTT	Intron 1	12	144631	144650	674
523711	n/a	n/a	AGCCTGAATTCTGAGCTCTG	Intron 2	88	145431	145450	675
523712	n/a	n/a	AGAGGATCTCAGCTGCAATT	Intron 2	71	146238	146257	676
523713	n/a	n/a	GAAAATCCCTGCTCAAGTGC	Intron 2	67	147262	147281	677
523714	n/a	n/a	TGCCTGATATTGTAATTCTT	Intron 2	90	148062	148081	678

Table 132

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 1 and 2 of SEQ ID NO: 2

ISIS NO	Sequence	Target Region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532377	CTCATACAGTGAAGTCTTCA	Intron 1	73	135431	135450	679
532378	CTCACTAAGCTTGATTCACT	Intron 1	67	135818	135837	680
532379	GATACAGAAATCCCAGTGAC	Intron 1	46	136111	136130	681
532380	TGTGCTTGGGTGTACAGGCA	Intron 1	71	136282	136301	682
532381	TCAAGCACTTACATCATATG	Intron 1	42	136377	136396	683
532382	AGGGTTAGTTATTACACTTA	Intron 1	60	136576	136595	684
532383	AGGCTTCATGTGAGGTAACA	Intron 1	58	136996	137015	685
532384	TGAAAGCTTAGTACAAGAAG	Intron 1	51	138048	138067	686
532385	CTCTCCTCTTGGAGATCCAG	Intron 1	58	138782	138801	687
532386	GCTGAGATTTCTCTCCTCTT	Intron 1	78	138792	138811	688
532387	CTTTTGCTGAGATTTCTCTC	Intron 1	58	138797	138816	689
532388	GAACATATGTCCATAGAATG	Intron 1	57	141700	141719	690
532389	GAACAGGCTATGTAATCAAA	Intron 1	68	143021	143040	691
532390	TTTTTATTACTGTGCAAACC	Intron 1	41	143878	143897	692
532391	ACTGAGGGTGGAAATGGAAA	Intron 2	23	145059	145078	693
532392	ATGCCATACTTTTCATTTCA	Intron 2	87	146351	146370	694
532393	TCTTTAAAGATTTCCTATGC	Intron 2	66	146367	146386	695
532394	TCACAATTAAATTATGTTTA	Intron 2	47	149858	149877	696
532395	TTTGCCATCACCAAACACCA	Intron 2	94	150972	150991	697
532396	TCAGAATGCTGAAGGATGGG	Intron 2	70	152208	152227	698
532397	ACAATTGCAGGAGAGAACTG	Intron 2	57	152296	152315	699
532398	GTTCAGTCACCTGGAAAGAG	Intron 2	62	152549	152568	700
532399	CGGAGTTCAGTCACCTGGAA	Intron 2	77	152553	152572	701
532400	AATCTAAAGTTCAATGTCCA	Intron 2	77	152752	152771	702
532401	CCACCTTTGGGTGAATAGCA	Intron 2	95	153921	153940	703
532402	CAACATCAAAAGTTTCCACC	Intron 2	81	153936	153955	704
532403	AAGCTTCTATCAACCAACTG	Intron 2	87	154093	154112	705

532404	ACCATTTTCTAATAATTCAC	Intron 2	46	154502	154521	706
532405	ACCTGCACTTGGACAACTGA	Intron 2	60	154727	154746	707
532406	GTCAGTGCTTTGGTGATGTA	Intron 2	11	155283	155302	708
532407	TAGAAGCACAGGAACTAGAG	Intron 2	68	155889	155908	709
532408	TTTAATTTTATTAGAAGCAC	Intron 2	14	155900	155919	710
532409	GAGCAAGAATTAAGAAAATC	Intron 2	29	155973	155992	711
532410	CTCTGCAGTCATGTACACAA	Intron 2	93	156594	156613	712
532411	GCTTGGTTTGTCAATCCTTT	Intron 2	95	156889	156908	713
532412	GTTCTCAAGCAGGAGCCATT	Intron 2	70	157330	157349	714
532413	AGGGTGATCTTCCAAAACAA	Intron 2	87	158612	158631	715
532414	TCTCCTATGCTTCCTTTAAT	Intron 2	25	158813	158832	716
532415	GACATAAATATGTTCACTGA	Intron 2	81	159216	159235	717
532416	TTACTGAGTGACAGTACAGT	Intron 2	65	161588	161607	718
532417	CCAGGCACCAGCACAGGCAC	Intron 2	47	161950	161969	719
532418	TTAATGTCAGTAGAAAGCTG	Intron 2	0	162349	162368	720
532419	GCAGGTGGAAAGAAGATGTC	Intron 2	50	162531	162550	721
532420	GCCAGGGTCTTTACAAAGTT	Intron 2	93	162751	162770	722
532421	CATTACCTTTGTACATGTAC	Intron 2	83	164839	164858	723
532422	GAAGCAACTTCTCTGAGGTC	Intron 2	68	165040	165059	724
532423	GCCTGGCAAGAAGGGCCCTT	Intron 2	56	165856	165875	725
532424	ACACATGTTTTTAAATTTAT	Intron 2	21	166241	166260	726
532425	TCACAATGCACTAAAAGAAA	Intron 2	53	168760	168779	727
532426	TCCCAATGACTTACTGTAGA	Intron 2	78	169073	169092	728
532427	TAAGCATTTATGGAGGAATG	Intron 2	46	169134	169153	729
532428	TGAGGTGGGTGGCCAACAGG	Intron 2	66	170081	170100	730
532429	GTTTTTCATTTTGATTGCAG	Intron 2	88	170158	170177	731
532430	AGCTCAAGTGTTTTTCATTT	Intron 2	64	170167	170186	732
532431	CAATGTCACAGCTGTTTCCT	Intron 2	62	170272	170291	733
532432	GAACTTTGGAGGCTTTTAGA	Intron 2	55	170703	170722	734
532433	TGTATGCCCCAAACTCCCAT	Intron 2	83	171431	171450	735
532434	ACACAAATAAGGGAATAATA	Intron 2	24	171549	171568	736
532435	TAGTTCAGCCACTATGGAAA	Intron 2	47	171926	171945	737
532436	CTCCAAATTCCAGTCCTAGG	Intron 2	93	172746	172765	738
532437	AGTTGGCACTGCTATATCAG	Intron 2	66	173668	173687	739
532438	GGCCTTAGATTGTAAGTTTT	Intron 2	69	174122	174141	740
532439	TTTTAGTATTATTGTAGGAA	Intron 2	16	174188	174207	741
532440	TTTCATTAATGAAACCTGAT	Intron 2	39	174812	174831	742
532441	CCCTCAGCTGCCTCTTCAAT	Intron 2	51	175014	175033	743
532442	TATTGTATCCTGGCCCCTAA	Intron 2	68	175689	175708	744
532443	AGAACAAGAGCCTAGAAGTA	Intron 2	35	176592	176611	745
532444	GTGACTATGTCACTGAATTT	Intron 2	14	176918	176937	746
532445	GCCCTACCCAGCAGCCTGTG	Intron 2	79	177540	177559	747
532446	CAAACATAAAGAGAGTTCCA	Intron 2	79	177811	177830	748

532447	CTTTAAATGAAGTAGAGCTC	Intron 2	0	178090	178109	749
532448	CTGTTCAAAGAATGCAGGCC	Intron 2	70	178905	178924	750
532449	GTCTAGCCTAACAGAGATAT	Intron 2	47	179137	179156	751
532450	AAAGAGTGATGTCTAGCCTA	Intron 2	55	179147	179166	752
532451	CACTTCTTACTCCTTTGAGG	Intron 2	50	179631	179650	753
532452	TTCCACAAGAAACTCAGTTT	Intron 2	56	181514	181533	754
532453	AGAAATGCCAAAGATAGCTC	Intron 2	56	182105	182124	755

Table 133

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intron 2 of SEQ ID NO: 2

ISIS NO	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
533249	AGCAGAGGATCTCAGCTGCA	84	146241	146260	756
533250	AATCCCTGCTCAAGTGCTAC	75	147259	147278	757
533251	AAATCCCTGCTCAAGTGCTA	71	147260	147279	758
533252	AAAATCCCTGCTCAAGTGCT	73	147261	147280	759
533253	AGAAAATCCCTGCTCAAGTG	56	147263	147282	760
533254	AAGAAAATCCCTGCTCAAGT	58	147264	147283	761
533255	CAAGAAAATCCCTGCTCAAG	46	147265	147284	762
533256	CTGATATTGTAATTCTTGGT	91	148059	148078	763
533257	CCTGATATTGTAATTCTTGG	90	148060	148079	764
533258	GCCTGATATTGTAATTCTTG	94	148061	148080	765
533259	ATGCCTGATATTGTAATTCT	91	148063	148082	766
533260	AATGCCTGATATTGTAATTC	74	148064	148083	767
533261	CAATGCCTGATATTGTAATT	76	148065	148084	768
533262	AATTATGTGCTTTGCCTGCA	92	148904	148923	769
533263	CAATTATGTGCTTTGCCTGC	83	148905	148924	770
533264	TCAATTATGTGCTTTGCCTG	83	148906	148925	771
533265	TGTCAATTATGTGCTTTGCC	91	148908	148927	772
533266	ATGTCAATTATGTGCTTTGC	83	148909	148928	773
533267	GATGTCAATTATGTGCTTTG	74	148910	148929	774
533268	CTGGTGACTCTGCCTGATGA	77	151385	151404	775
533269	GCTGGTGACTCTGCCTGATG	87	151386	151405	776
533270	TGCTGGTGACTCTGCCTGAT	89	151387	151406	777
533271	GCTGCTGGTGACTCTGCCTG	94	151389	151408	778
533272	GGCTGCTGGTGACTCTGCCT	77	151390	151409	779
533273	TGGCTGCTGGTGACTCTGCC	82	151391	151410	780
533274	GCTGAAGGATGGGCATCCAG	85	152201	152220	781
533275	TGCTGAAGGATGGGCATCCA	85	152202	152221	782
533276	ATGCTGAAGGATGGGCATCC	78	152203	152222	783
533277	GAATGCTGAAGGATGGGCAT	66	152205	152224	784

533278	AGAATGCTGAAGGATGGGCA	81	152206	152225	785
533279	CAGAATGCTGAAGGATGGGC	85	152207	152226	786
533280	TCCAGTAGTCAATATTATTT	87	153001	153020	787
533281	ATCCAGTAGTCAATATTATT	85	153002	153021	788
533282	TATCCAGTAGTCAATATTAT	69	153003	153022	789
533283	GTTATCCAGTAGTCAATATT	77	153005	153024	790
533284	GGTTATCCAGTAGTCAATAT	85	153006	153025	791
533285	TGGTTATCCAGTAGTCAATA	86	153007	153026	792
533286	CAACTTGAGGACAATAAGAG	35	155591	155610	793
533287	TCAACTTGAGGACAATAAGA	62	155592	155611	794
533288	CTCAACTTGAGGACAATAAG	86	155593	155612	795
533289	AACTCAACTTGAGGACAATA	82	155595	155614	796
533290	TAACTCAACTTGAGGACAAT	66	155596	155615	797
533291	ATAACTCAACTTGAGGACAA	87	155597	155616	798
533292	CAGGAAGAAAGGAACCTTAG	77	156391	156410	799
533293	CCAGGAAGAAAGGAACCTTA	84	156392	156411	800
533294	ACCAGGAAGAAAGGAACCTT	86	156393	156412	801
533295	AGACCAGGAAGAAAGGAACC	74	156395	156414	802
533296	TAGACCAGGAAGAAAGGAAC	59	156396	156415	803
533297	ATAGACCAGGAAGAAAGGAA	65	156397	156416	804
533298	TACAATGCACAGGACACGCC	73	157198	157217	805
533299	CTACAATGCACAGGACACGC	85	157199	157218	806
533300	GCTACAATGCACAGGACACG	83	157200	157219	807
533301	ATGCTACAATGCACAGGACA	89	157202	157221	808
533302	TATGCTACAATGCACAGGAC	82	157203	157222	809
533303	ATATGCTACAATGCACAGGA	84	157204	157223	810
533304	CTGATATTTATTGCTGTACG	76	158006	158025	811
533305	CTCTGATATTTATTGCTGTA	80	158008	158027	812
533306	TCTCTGATATTTATTGCTGT	86	158009	158028	813
533307	GTCTCTGATATTTATTGCTG	80	158010	158029	814
533308	CCAGAAGAATTACCCATGCA	85	165550	165569	815
533309	TCCAGAAGAATTACCCATGC	84	165551	165570	816
533310	TTCCAGAAGAATTACCCATG	81	165552	165571	817
533311	TCTTCCAGAAGAATTACCCA	58	165554	165573	818
533312	ATCTTCCAGAAGAATTACCC	64	165555	165574	819
533313	CATCTTCCAGAAGAATTACC	58	165556	165575	820
533314	TTTCTGCAGTATCCTAGCCT	78	166350	166369	821
533315	GTTTCTGCAGTATCCTAGCC	88	166351	166370	822
533316	AGTTTCTGCAGTATCCTAGC	86	166352	166371	823
533317	TCAGTTTCTGCAGTATCCTA	88	166354	166373	824
533318	TTCAGTTTCTGCAGTATCCT	87	166355	166374	825
533319	TTTCAGTTTCTGCAGTATCC	80	166356	166375	826
533320	GTTTCCATTTTCTTGATTCC	70	169601	169620	827

533321	TGTTTCCATTTTCTTGATTC	54	169602	169621	828
533322	GTGTTTCCATTTTCTTGATT	55	169603	169622	829
533323	TGGTGTTTCCATTTTCTTGA	73	169605	169624	830
533324	ATGGTGTTTCCATTTTCTTG	76	169606	169625	831
533325	AATGGTGTTTCCATTTTCTT	78	169607	169626	832

Table 134

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 2 and 3 of SEQ ID NO: 2

ISIS NO	Sequence	Target region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
533326	AACCCATTTCATCCATTTAA	Intron 2	93	175369	175388	833
533327	GAACCCATTTCATCCATTTA	Intron 2	83	175370	175389	834
533328	GGAACCCATTTCATCCATTT	Intron 2	92	175371	175390	835
533329	TAGGAACCCATTTCATCCAT	Intron 2	91	175373	175392	836
533330	GTAGGAACCCATTTCATCCA	Intron 2	95	175374	175393	837
533331	GGTAGGAACCCATTTCATCC	Intron 2	92	175375	175394	838
533332	TGAGGGATTGCCTCAGTAGC	Intron 2	66	179616	179635	839
533333	TTGAGGGATTGCCTCAGTAG	Intron 2	72	179617	179636	840
533334	TTTGAGGGATTGCCTCAGTA	Intron 2	67	179618	179637	841
533335	CCTTTGAGGGATTGCCTCAG	Intron 2	74	179620	179639	842
533336	TCCTTTGAGGGATTGCCTCA	Intron 2	66	179621	179640	843
533337	CTCCTTTGAGGGATTGCCTC	Intron 2	76	179622	179641	844
533338	AACTTAGGACTTGGGACATT	Intron 2	64	184575	184594	845
533339	TAACTTAGGACTTGGGACAT	Intron 2	54	184576	184595	846
533340	CTAACTTAGGACTTGGGACA	Intron 2	63	184577	184596	847
533341	CACTAACTTAGGACTTGGGA	Intron 2	82	184579	184598	848
533342	TCACTAACTTAGGACTTGGG	Intron 2	77	184580	184599	849
533343	GTCACTAACTTAGGACTTGG	Intron 2	83	184581	184600	850
533344	TGGGCTAGATCAGGATTGGT	Intron 2	81	188617	188636	851
533345	ATGGGCTAGATCAGGATTGG	Intron 2	70	188618	188637	852
533346	CATGGGCTAGATCAGGATTG	Intron 2	64	188619	188638	853
533347	ACCATGGGCTAGATCAGGAT	Intron 2	82	188621	188640	854
533348	TACCATGGGCTAGATCAGGA	Intron 2	88	188622	188641	855
533349	CTACCATGGGCTAGATCAGG	Intron 2	87	188623	188642	856
533350	ATGAGCTTAGCAGTCACTTA	Intron 2	83	189482	189501	857
533351	CATGAGCTTAGCAGTCACTT	Intron 2	87	189483	189502	858
533352	CCATGAGCTTAGCAGTCACT	Intron 2	92	189484	189503	859
533353	GTCTCAGCAAACCTGGGATA	Intron 2	84	190283	190302	860
533354	TGTCTCAGCAAACCTGGGAT	Intron 2	82	190284	190303	861
533355	ATGTCTCAGCAAACCTGGGA	Intron 2	81	190285	190304	862
533356	GAATGTCTCAGCAAACCTGG	Intron 2	76	190287	190306	863

533357	GGAATGTCTCAGCAAACCTG	Intron 2	82	190288	190307	864
533358	AGGAATGTCTCAGCAAACCT	Intron 2	85	190289	190308	865
533359	TACAGACATAGCTCTAACCT	Intron 2	79	191139	191158	866
533360	ATACAGACATAGCTCTAACC	Intron 2	79	191140	191159	867
533361	GATACAGACATAGCTCTAAC	Intron 2	71	191141	191160	868
533362	TGGATACAGACATAGCTCTA	Intron 2	79	191143	191162	869
533363	CTGGATACAGACATAGCTCT	Intron 2	82	191144	191163	870
533364	GCTGGATACAGACATAGCTC	Intron 2	95	191145	191164	871
533365	ACACTGTTTGTGAGGGTCAA	Intron 2	87	191939	191958	872
533366	AACACTGTTTGTGAGGGTCA	Intron 2	81	191940	191959	873
533367	CAACACTGTTTGTGAGGGTC	Intron 2	85	191941	191960	874
533368	AACAACACTGTTTGTGAGGG	Intron 2	65	191943	191962	875
533369	AAACAACACTGTTTGTGAGG	Intron 2	76	191944	191963	876
533370	CAAACAACACTGTTTGTGAG	Intron 2	67	191945	191964	877
533371	TTCAAGTTTAGGATCTGCAG	Intron 2	73	196536	196555	878
533372	CTTCAAGTTTAGGATCTGCA	Intron 2	88	196537	196556	879
533373	GCTTCAAGTTTAGGATCTGC	Intron 2	86	196538	196557	880
533374	GGGCTTCAAGTTTAGGATCT	Intron 2	67	196540	196559	881
533375	AGGGCTTCAAGTTTAGGATC	Intron 2	66	196541	196560	882
533376	CAGGGCTTCAAGTTTAGGAT	Intron 2	74	196542	196561	883
533377	TGTGGCTTTAATTCACTAAT	Intron 2	84	198145	198164	884
533378	ATGTGGCTTTAATTCACTAA	Intron 2	86	198146	198165	885
533379	TATGTGGCTTTAATTCACTA	Intron 2	79	198147	198166	886
533380	GGTATGTGGCTTTAATTCAC	Intron 2	83	198149	198168	887
533381	TGGTATGTGGCTTTAATTCA	Intron 2	81	198150	198169	888
533382	GTGGTATGTGGCTTTAATTC	Intron 2	86	198151	198170	889
533383	TCTGTGTTCAGTTGCATCAC	Intron 2	75	199817	199836	890
533384	TTCTGTGTTCAGTTGCATCA	Intron 2	82	199818	199837	891
533385	GTTCTGTGTTCAGTTGCATC	Intron 2	86	199819	199838	892
533386	GTACTCATGAGGAGGCACTT	Intron 2	81	201413	201432	893
533387	GGTACTCATGAGGAGGCACT	Intron 2	82	201414	201433	894
533388	TGGTACTCATGAGGAGGCAC	Intron 2	78	201415	201434	895
533389	ATTGGTACTCATGAGGAGGC	Intron 2	64	201417	201436	896
533390	AATTGGTACTCATGAGGAGG	Intron 2	47	201418	201437	897
533391	CAATTGGTACTCATGAGGAG	Intron 2	54	201419	201438	898
533392	AAACTCTGCAACTCCAACCC	Intron 2	69	205549	205568	899
533393	GAAACTCTGCAACTCCAACC	Intron 2	64	205550	205569	900
533394	GGAAACTCTGCAACTCCAAC	Intron 2	83	205551	205570	901
533395	ATGGAAACTCTGCAACTCCA	Intron 2	88	205553	205572	902
533396	CATGGAAACTCTGCAACTCC	Intron 2	70	205554	205573	903
533397	TCATGGAAACTCTGCAACTC	Intron 2	69	205555	205574	904
533398	ACATCTGGATGTGAGGCTCG	Intron 3	64	210559	210578	905
533399	CACATCTGGATGTGAGGCTC	Intron 3	84	210560	210579	906

533400	GTCACATCTGGATGTGAGGC	Intron 3	75	210562	210581	907
533401	TGTCACATCTGGATGTGAGG	Intron 3	51	210563	210582	908
533402	CTGTCACATCTGGATGTGAG	Intron 3	30	210564	210583	909

Table 135

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 2 and 3 of SEQ ID NO: 2

ISIS NO	Sequence	Target region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
523715	GTCAATTATGTGCTTTGCCT	Intron 2	91	148907	148926	910
523716	ACATTCAAAATTCTTCCTTG	Intron 2	50	149787	149806	911
523717	ATCCTGCATATATTTTATTG	Intron 2	20	150588	150607	912
523718	CTGCTGGTGACTCTGCCTGA	Intron 2	77	151388	151407	913
523719	AATGCTGAAGGATGGGCATC	Intron 2	66	152204	152223	914
523720	TTATCCAGTAGTCAATATTA	Intron 2	71	153004	153023	915
523721	TCTCATGTTAAAGTTCTTAA	Intron 2	48	153831	153850	916
523722	TGCACTTGGACAACTGATAG	Intron 2	29	154724	154743	917
523723	ACTCAACTTGAGGACAATAA	Intron 2	88	155594	155613	918
523724	GACCAGGAAGAAAGGAACCT	Intron 2	72	156394	156413	919
523725	TGCTACAATGCACAGGACAC	Intron 2	80	157201	157220	920
523726	TCTGATATTTATTGCTGTAC	Intron 2	73	158007	158026	921
523727	ATGCTTCCTTTAATAAATGT	Intron 2	0	158807	158826	922
523728	AACATTTAGAACCTAGGAGA	Intron 2	20	159610	159629	923
523729	CAAGCTTGCAAGTAGGAAAA	Intron 2	51	160410	160429	924
523730	CCAGGCTGTTCATGCCAAGG	Intron 2	26	161248	161267	925
523731	CCTGCCAAGGGCAAGCCAGG	Intron 2	17	162064	162083	926
523732	TTTCACCTGGTGACTGGAAG	Intron 2	51	163019	163038	927
523733	ATTTTCTACCATCAAAGAGA	Intron 2	4	163943	163962	928
523734	GATTAAGTTTTCTTTAAAAA	Intron 2	0	164746	164765	929
523735	CTTCCAGAAGAATTACCCAT	Intron 2	56	165553	165572	930
523736	CAGTTTCTGCAGTATCCTAG	Intron 2	77	166353	166372	931
523737	TATTTTGAAAATGAGATTCA	Intron 2	0	167195	167214	932
523738	GTGGCCCGAGTAAAGATAAA	Intron 2	21	167995	168014	933
523739	CCTGTCAATCCTCTTATATG	Intron 2	37	168804	168823	934
523740	GGTGTTTCCATTTTCTTGAT	Intron 2	65	169604	169623	935
523741	ACAGGGTCAAAAGTTCACTT	Intron 2	44	170407	170426	936
523742	TAGGAAAGCTGAGAGAATCC	Intron 2	35	171207	171226	937
523743	AGCATATGAAAAAATACTCA	Intron 2	0	172101	172120	938
523744	CTTCAGAAATCAGCATCTGA	Intron 2	45	172937	172956	939
523745	TTACAAGTGACAGTGTTTGT	Intron 2	28	173737	173756	940
523746	ATCAGACCCTGAAGAATTTA	Intron 2	29	174560	174579	941
523747	AGGAACCCATTTCATCCATT	Intron 2	83	175372	175391	942

523748	CACATTGGTAACTTAAAGTT	Intron 2	18	176263	176282	943
523749	TATTATCTGACTCATTTCTG	Intron 2	16	177072	177091	944
523750	AAATAAGACAAAGAAAATTC	Intron 2	0	177872	177891	945
523751	TTTTAAAAATAACCAATTCA	Intron 2	0	178788	178807	946
523752	CTTTGAGGGATTGCCTCAGT	Intron 2	66	179619	179638	947
523753	ACAGTCCTCATGAACAGATT	Intron 2	37	180513	180532	948
523754	ACTATCATTAATAATATTGT	Intron 2	0	181323	181342	949
523755	ATCTAGATTTGCCTTATAAG	Intron 2	27	182123	182142	950
523756	TGGTTGAGGAAGACAGTCTC	Intron 2	16	182962	182981	951
523757	TGGCTCATAACTTCCTTAGC	Intron 2	43	183762	183781	952
523758	ACTAACTTAGGACTTGGGAC	Intron 2	72	184578	184597	953
523759	CTTATAGCATTACTAAGTGG	Intron 2	49	185403	185422	954
523760	TGGTGGCAGGAGAGAGGGAA	Intron 2	48	186203	186222	955
523761	TTTGCCAGGAAATCTTGAAA	Intron 2	35	187003	187022	956
523762	ATAACTTTTCTCTGAAATTT	Intron 2	8	187803	187822	957
523763	CCATGGGCTAGATCAGGATT	Intron 2	59	188620	188639	958
523764	TGAGCTTAGCAGTCACTTAG	Intron 2	62	189481	189500	959
523765	AATGTCTCAGCAAACCTGGG	Intron 2	62	190286	190305	960
523766	GGATACAGACATAGCTCTAA	Intron 2	75	191142	191161	961
523767	ACAACACTGTTTGTGAGGGT	Intron 2	66	191942	191961	962
523768	TCTATTTTCTAATAGCTGTT	Intron 2	49	192742	192761	963
523769	GGCCCCACCTCTGACCTTCA	Intron 2	7	193542	193561	964
523770	TGGTAAAGCTAGAAAAAAAA	Intron 2	0	194346	194365	965
523771	AAGTGGTAAATATGATCACA	Intron 2	23	195159	195178	966
523772	GGCTTCAAGTTTAGGATCTG	Intron 2	52	196539	196558	967
523773	TTGTTGACACTCTCTTTTGG	Intron 2	18	197348	197367	968
523774	GTATGTGGCTTTAATTCACT	Intron 2	71	198148	198167	969
523775	AATTAGTTGTTTTGGCAAAT	Intron 2	14	198988	199007	970
523776	CTGTGTTCAGTTGCATCACG	Intron 2	75	199816	199835	971
523777	AATGTGGAAGTTTCCTAACA	Intron 2	15	200616	200635	972
523778	TTGGTACTCATGAGGAGGCA	Intron 2	58	201416	201435	973
523779	TTTCTCTGTGTTTAAAATTG	Intron 2	13	202308	202327	974
523780	GTAAAGCACAATGAACAAAA	Intron 2	21	203115	203134	975
523781	ATCACAGATCTTTGCTACAA	Intron 2	51	203915	203934	976
523782	TCCTGCCTTTCTGAACCAAA	Intron 2	50	204721	204740	977
523783	TGGAAACTCTGCAACTCCAA	Intron 2	58	205552	205571	978
523784	ACACAGTAGGGAACAATTTT	Intron 2	8	206412	206431	979
523785	AGACAGATGGTGAAATGATG	Intron 2	0	207219	207238	980
523786	AAACAGAAAGAGAAGAAAAC	Intron 2	0	208117	208136	981
523787	CTTAGATAAATACTTCAAGA	Intron 3	0	208938	208957	982
523788	AGCCACTTCTTTTACAACCT	Intron 3	0	209742	209761	983
523789	TCACATCTGGATGTGAGGCT	Intron 3	80	210561	210580	984
523790	GACTGAAACTTAAAGGTGGG	Intron 3	7	211399	211418	985

523791	AAAGATGTGCAATCATCTAA	Intron 3	44	212204	212223	986

Table 136

Inhibition of GHR mRNA by 3-10-4 MOE gapmers targeting introns 2 and 3 of SEQ ID NO: 2

ISIS NO	Sequence	Target region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
539360	GCTGGTGACTCTGCCTG	Intron 2	95	151389	151405	987
539361	TGCTGGTGACTCTGCCT	Intron 2	95	151390	151406	988
539362	CTGCTGGTGACTCTGCC	Intron 2	93	151391	151407	989
539363	AGTAGTCAATATTATTT	Intron 2	31	153001	153017	990
539364	CAGTAGTCAATATTATT	Intron 2	13	153002	153018	991
539365	CCAGTAGTCAATATTAT	Intron 2	34	153003	153019	992
539366	CCTTTGGGTGAATAGCA	Intron 2	64	153921	153937	993
539367	ACCTTTGGGTGAATAGC	Intron 2	78	153922	153938	994
539368	CACCTTTGGGTGAATAG	Intron 2	40	153923	153939	995
539369	CAACTTGAGGACAATAA	Intron 2	38	155594	155610	996
539370	TCAACTTGAGGACAATA	Intron 2	63	155595	155611	997
539371	CTCAACTTGAGGACAAT	Intron 2	81	155596	155612	998
539372	CAGGAAGAAAGGAACCT	Intron 2	70	156394	156410	999
539373	CCAGGAAGAAAGGAACC	Intron 2	59	156395	156411	1000
539374	ACCAGGAAGAAAGGAAC	Intron 2	43	156396	156412	1001
539375	TGCAGTCATGTACACAA	Intron 2	93	156594	156610	1002
539376	CTGCAGTCATGTACACA	Intron 2	91	156595	156611	1003
539377	TCTGCAGTCATGTACAC	Intron 2	87	156596	156612	1004
539378	TGGTTTGTCAATCCTTT	Intron 2	95	156889	156905	1005
539379	TTGGTTTGTCAATCCTT	Intron 2	97	156890	156906	1006
539380	CTTGGTTTGTCAATCCT	Intron 2	97	156891	156907	1007
539381	TACAATGCACAGGACAC	Intron 2	65	157201	157217	1008
539382	CTACAATGCACAGGACA	Intron 2	85	157202	157218	1009
539383	GCTACAATGCACAGGAC	Intron 2	96	157203	157219	1010
539384	GATATTTATTGCTGTAC	Intron 2	43	158007	158023	1011
539385	TGATATTTATTGCTGTA	Intron 2	35	158008	158024	1012
539386	CTGATATTTATTGCTGT	Intron 2	38	158009	158025	1013
539387	AGGGTCTTTACAAAGTT	Intron 2	61	162751	162767	1014
539388	CAGGGTCTTTACAAAGT	Intron 2	65	162752	162768	1015
539389	CCAGGGTCTTTACAAAG	Intron 2	88	162753	162769	1016
539390	TTCTGCAGTATCCTAGC	Intron 2	72	166352	166368	1017
539391	TTTCTGCAGTATCCTAG	Intron 2	53	166353	166369	1018
539392	GTTTCTGCAGTATCCTA	Intron 2	84	166354	166370	1019
539393	AGTTTCTGCAGTATCCT	Intron 2	78	166355	166371	1020
539394	CAGTTTCTGCAGTATCC	Intron 2	77	166356	166372	1021
539395	CAAATTCCAGTCCTAGG	Intron 2	60	172746	172762	1022

539396	CCAAATTCCAGTCCTAG	Intron 2	75	172747	172763	1023
539397	TCCAAATTCCAGTCCTA	Intron 2	62	172748	172764	1024
539398	AACCCATTTCATCCATT	Intron 2	82	175372	175388	1025
539399	GAACCCATTTCATCCAT	Intron 2	86	175373	175389	1026
539400	GGAACCCATTTCATCCA	Intron 2	84	175374	175390	1027
539401	GCTTCATGTCTTTCTAG	Intron 2	88	189119	189135	1028
539402	TGCTTCATGTCTTTCTA	Intron 2	77	189120	189136	1029
539403	GTGCTTCATGTCTTTCT	Intron 2	95	189121	189137	1030
539404	TGAGCTTAGCAGTCACT	Intron 2	92	189484	189500	1031
539405	CATGAGCTTAGCAGTCA	Intron 2	82	189486	189502	1032
539406	TACAGACATAGCTCTAA	Intron 2	45	191142	191158	1033
539407	ATACAGACATAGCTCTA	Intron 2	53	191143	191159	1034
539408	GATACAGACATAGCTCT	Intron 2	67	191144	191160	1035
539409	TGTGGCTTTAATTCACT	Intron 2	70	198148	198164	1036
539410	ATGTGGCTTTAATTCAC	Intron 2	40	198149	198165	1037
539411	TATGTGGCTTTAATTCA	Intron 2	35	198150	198166	1038
539412	TGTTCAGTTGCATCACG	Intron 2	84	199816	199832	1039
539413	GTGTTCAGTTGCATCAC	Intron 2	80	199817	199833	1040
539414	TGTGTTCAGTTGCATCA	Intron 2	74	199818	199834	1041
539415	CATCTGGATGTGAGGCT	Intron 3	82	210561	210577	1042
539416	ACATCTGGATGTGAGGC	Intron 3	86	210562	210578	1043
539417	CACATCTGGATGTGAGG	Intron 3	55	210563	210579	1044
539418	TCAGGTAATTTCTGGAA	Intron 3	35	219019	219035	1045
539419	CTCAGGTAATTTCTGGA	Intron 3	44	219020	219036	1046
539420	TCTCAGGTAATTTCTGG	Intron 3	31	219021	219037	1047
539421	TTGCTTATTTACCTGGG	Intron 3	0	225568	225584	1048
539422	TTTGCTTATTTACCTGG	Intron 3	38	225569	225585	1049
539423	TTTTGCTTATTTACCTG	Intron 3	33	225570	225586	1050
539424	ATGATGTTACTACTACT	Intron 3	29	229618	229634	1051
539425	AATGATGTTACTACTAC	Intron 3	10	229619	229635	1052
539426	CAATGATGTTACTACTA	Intron 3	0	229620	229636	1053
539427	CCCCTAGAGCAATGGTC	Intron 3	67	232826	232842	1054
539428	CCCCCTAGAGCAATGGT	Intron 3	65	232827	232843	1055
539429	TCCCCCTAGAGCAATGG	Intron 3	45	232828	232844	1056
539430	TCAATTGCAGATGCTCT	Intron 3	78	237675	237691	1057
539431	CTCAATTGCAGATGCTC	Intron 3	82	237676	237692	1058
539432	GCTCAATTGCAGATGCT	Intron 3	92	237677	237693	1059
539433	AGCTCAATTGCAGATGC	Intron 3	85	237678	237694	1060
539434	GTATATTCAGTCCAAGG	Intron 3	73	248231	248247	1061
539435	AGTATATTCAGTCCAAG	Intron 3	70	248232	248248	1062
539436	CAGTATATTCAGTCCAA	Intron 3	40	248233	248249	1063

Table 137

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 1 and 3 of SEQ ID NO: 2

ISIS NO	Sequence	Target region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532502	GAGTATTTCAGGCTGGAAAA	Intron 3	43	214623	214642	1064
533404	GTAACTCAGGAATGGAAAAC	Intron 1	56	26501	26520	1065
				113035	113054	
				121992	122011	
533405	AGTAACTCAGGAATGGAAAA	Intron 1	41	26502	26521	1066
				113036	113055	
				121993	122012	
533406	AAGTAACTCAGGAATGGAAA	Intron 1	43	26503	26522	1067
				113037	113056	
				121994	122013	
533407	GAGATTTCAAATAAATCTCA	Intron 1	0	143207	143226	1068
				143235	143254	
				143263	143282	
				143291	143310	
				143319	143338	
				143347	143366	
				143375	143394	
				143403	143422	
				143431	143450	
				143459	143478	
533408	TGAGATTTCAAATAAATCTC	Intron 1	11	143208	143227	1069
				143236	143255	
				143264	143283	
				143292	143311	
				143320	143339	
				143348	143367	
				143376	143395	
				143404	143423	
				143432	143451	
				143460	143479	
533409	GTGAGATTTCAAATAAATCT	Intron 1	0	143209	143228	1070
				143237	143256	
				143265	143284	
				143293	143312	
				143321	143340	
				143349	143368	
				143377	143396	

				143405	143424	
				143433	143452	
				143461	143480	
533410	TGTGAGATTTCAAATAAATC	Intron 1	0	143210	143229	1071
				143238	143257	
				143266	143285	
				143294	143313	
				143322	143341	
				143350	143369	
				143378	143397	
				143406	143425	
				143434	143453	
				143462	143481	
533411	TTGTGAGATTTCAAATAAAT	Intron 1	10	143183	143202	1072
				143211	143230	
				143239	143258	
				143267	143286	
				143295	143314	
				143323	143342	
				143351	143370	
				143379	143398	
				143407	143426	
				143435	143454	
				143463	143482	
533412	TTTGTGAGATTTCAAATAAA	Intron 1	0	143184	143203	1073
				143212	143231	
				143240	143259	
				143296	143315	
				143324	143343	
				143352	143371	
				143380	143399	
				143464	143483	
533413	CTTTGTGAGATTTCAAATAA	Intron 1	20	143185	143204	1074
				143213	143232	
				143241	143260	
				143297	143316	
				143325	143344	
				143353	143372	
				143381	143400	
				143465	143484	
533414	ACTTTGTGAGATTTCAAATA	Intron 1	57	143186	143205	1075
				143214	143233	
				143242	143261	

				143298	143317	
				143326	143345	
				143354	143373	
				143382	143401	
				143466	143485	
533415	CACTTTGTGAGATTTCAAAT	Intron 1	69	143187	143206	1076
				143215	143234	
				143243	143262	
				143299	143318	
				143327	143346	
				143355	143374	
				143383	143402	
				143467	143486	
533895	AGTATTTCAGGCTGGAAAAA	Intron 3	35	214622	214641	1077
533896	TGAGTATTTCAGGCTGGAAA	Intron 3	55	214624	214643	1078
533897	TCTGAGTATTTCAGGCTGGA	Intron 3	71	214626	214645	1079
533898	ATCTGAGTATTTCAGGCTGG	Intron 3	77	214627	214646	1080
533899	TATCTGAGTATTTCAGGCTG	Intron 3	58	214628	214647	1081
533900	TTTTGTGTTATGCCTTGAGG	Intron 3	51	221483	221502	1082
533901	TTTTTGTGTTATGCCTTGAG	Intron 3	55	221484	221503	1083
533902	ATTTTTGTGTTATGCCTTGA	Intron 3	57	221485	221504	1084
533903	ATATTTTTGTGTTATGCCTT	Intron 3	56	221487	221506	1085
533904	AATATTTTTGTGTTATGCCT	Intron 3	61	221488	221507	1086
533905	AAATATTTTTGTGTTATGCC	Intron 3	18	221489	221508	1087
533906	TTGCTTATTTACCTGGGTAA	Intron 3	58	225565	225584	1088
533907	TTTGCTTATTTACCTGGGTA	Intron 3	64	225566	225585	1089
533908	TTTTGCTTATTTACCTGGGT	Intron 3	77	225567	225586	1090
533909	CCTTTTGCTTATTTACCTGG	Intron 3	69	225569	225588	1091
533910	GCCTTTTGCTTATTTACCTG	Intron 3	69	225570	225589	1092
533911	TGCCTTTTGCTTATTTACCT	Intron 3	55	225571	225590	1093
533912	ATGATGTTACTACTACTCAA	Intron 3	60	229615	229634	1094
533913	AATGATGTTACTACTACTCA	Intron 3	48	229616	229635	1095
533914	CAATGATGTTACTACTACTC	Intron 3	57	229617	229636	1096
533915	TCCAATGATGTTACTACTAC	Intron 3	69	229619	229638	1097
533916	TTCCAATGATGTTACTACTA	Intron 3	74	229620	229639	1098
533917	ATTCCAATGATGTTACTACT	Intron 3	74	229621	229640	1099
533918	CCCCTAGAGCAATGGTCTAG	Intron 3	71	232823	232842	1100
533919	CCCCCTAGAGCAATGGTCTA	Intron 3	44	232824	232843	1101
533920	TCCCCCTAGAGCAATGGTCT	Intron 3	54	232825	232844	1102
533921	TATCCCCCTAGAGCAATGGT	Intron 3	62	232827	232846	1103
533922	ATATCCCCCTAGAGCAATGG	Intron 3	50	232828	232847	1104
533923	AATATCCCCCTAGAGCAATG	Intron 3	61	232829	232848	1105
533924	GCTCACATTTGGAAGACAGT	Intron 3	68	233623	233642	1106

533925	GGCTCACATTTGGAAGACAG	Intron 3	74	233624	233643	1107
533926	AGGCTCACATTTGGAAGACA	Intron 3	56	233625	233644	1108
533927	AGAGGCTCACATTTGGAAGA	Intron 3	34	233627	233646	1109
533928	TAGAGGCTCACATTTGGAAG	Intron 3	18	233628	233647	1110
533929	TTAGAGGCTCACATTTGGAA	Intron 3	19	233629	233648	1111
533930	CTCAATTGCAGATGCTCTGA	Intron 3	66	237673	237692	1112
533931	GCTCAATTGCAGATGCTCTG	Intron 3	72	237674	237693	1113
533932	AGCTCAATTGCAGATGCTCT	Intron 3	74	237675	237694	1114
533933	AAAGCTCAATTGCAGATGCT	Intron 3	66	237677	237696	1115
533934	TAAAGCTCAATTGCAGATGC	Intron 3	59	237678	237697	1116
533935	ATAAAGCTCAATTGCAGATG	Intron 3	23	237679	237698	1117
533936	GTGAGTCCATTAAACCTCTT	Intron 3	73	244873	244892	1118
533937	TGTGAGTCCATTAAACCTCT	Intron 3	73	244874	244893	1119
533938	ACTGTGAGTCCATTAAACCT	Intron 3	17	244876	244895	1120
533939	AACTGTGAGTCCATTAAACC	Intron 3	19	244877	244896	1121
533940	GAACTGTGAGTCCATTAAAC	Intron 3	28	244878	244897	1122
533941	ATATTGAAAGGCCCATCAAA	Intron 3	13	246498	246517	1123
533942	AATATTGAAAGGCCCATCAA	Intron 3	31	246499	246518	1124
533943	AAATATTGAAAGGCCCATCA	Intron 3	51	246500	246519	1125
533944	GAAAATATTGAAAGGCCCAT	Intron 3	22	246502	246521	1126
533945	GGAAAATATTGAAAGGCCCA	Intron 3	42	246503	246522	1127
533946	AGGAAAATATTGAAAGGCCC	Intron 3	28	246504	246523	1128
533947	GTATATTCAGTCCAAGGATC	Intron 3	65	248228	248247	1129
533948	AGTATATTCAGTCCAAGGAT	Intron 3	63	248229	248248	1130
533949	CAGTATATTCAGTCCAAGGA	Intron 3	67	248230	248249	1131
533950	AACAGTATATTCAGTCCAAG	Intron 3	56	248232	248251	1132
533951	AAACAGTATATTCAGTCCAA	Intron 3	60	248233	248252	1133
533952	AAAACAGTATATTCAGTCCA	Intron 3	59	248234	248253	1134
533953	TCTATTGTTGCCACCTTTAT	Intron 3	45	252838	252857	1135
533954	TTCTATTGTTGCCACCTTTA	Intron 3	52	252839	252858	1136
533955	TTTCTATTGTTGCCACCTTT	Intron 3	46	252840	252859	1137
533956	AGTTTCTATTGTTGCCACCT	Intron 3	59	252842	252861	1138
533957	CAGTTTCTATTGTTGCCACC	Intron 3	41	252843	252862	1139
533958	CCAGTTTCTATTGTTGCCAC	Intron 3	48	252844	252863	1140

Table 138

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting intron 3 of SEQ ID NO: 2

ISIS NO	Sequence	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
532454	GCAGAACTGATTGCTTACTT	78	182862	182881	1141
532455	AGGTCATAAGATTTTCATTT	48	183533	183552	1142

532456	GCCTCTGGCCATAAAGAAAT	54	183578	183597	1143
532457	AAAGTTTAAGAGGCACCCCA	31	184508	184527	1144
532458	GAATAAGCACAAAAGTTTAA	28	184519	184538	1145
532459	GAACCAAATAAACCTCTCTT	52	185452	185471	1146
532460	ATGTTGAAATTTGATCCCCA	79	185763	185782	1147
532461	TGTGAGAGCTCACTCACTAT	42	186134	186153	1148
532462	CTTGTGAGAGCTCACTCACT	72	186136	186155	1149
532463	ACATGGTGGCAGGAGAGAGG	42	186206	186225	1150
532464	CTAGAAAGAAACTACCTGAG	12	186341	186360	1151
532465	AACTTCAGTTGTAAAATAAT	27	187044	187063	1152
532466	GAAAAGGATTTTGAGATTTC	43	188897	188916	1153
532467	CTTAGCTGTCAAGGCCCTTT	80	189084	189103	1154
532468	TGTGCTTCATGTCTTTCTAG	88	189119	189138	1155
532469	CCCTTGAACATGCTATCCTT	85	189256	189275	1156
532470	CTTGCAGGGATGCATCTCAG	87	189625	189644	1157
532471	TCTCTTGCACATCTAATTTC	82	189656	189675	1158
532472	CTTCCAGCACAACCCATCAC	77	190109	190128	1159
532473	GTAACTACATTCCCTTTATC	52	190860	190879	1160
532474	AGTAACTACATTCCCTTTAT	58	190861	190880	1161
532475	CAGATAGCACAGGGCTAAAA	84	190979	190998	1162
532476	AGAATCAGGAATGTTTGCCT	86	192904	192923	1163
532477	TGACTCAATCATTTAGACTT	45	192990	193009	1164
532478	TCAACAGTCAATGGACTTGT	71	193042	193061	1165
532479	AATTTCTACTGCTATGATGC	75	194806	194825	1166
532480	ATGGTTCCAAATTTCTATCT	86	195704	195723	1167
532481	CTGTATGGCTTTAAGTATTC	63	196756	196775	1168
532482	AACTTATGAACTGTTCACCA	86	198307	198326	1169
532483	AATAAGCTTGAAGTCTGAAG	63	199520	199539	1170
532484	TAGTTATCTAACTGCCCAAT	77	199544	199563	1171
532485	TTCTGCAAAGCTTCCCAGTA	72	200314	200333	1172
532486	ACAACTTCAAGCTTCACATA	65	200599	200618	1173
532487	GAATCAATGTTCTGGCAAGA	52	201842	201861	1174
532488	CAGCCTTTCAGCTGTGAAAG	52	204181	204200	1175
532489	AACAATGCCAAGAAATCTAT	74	204369	204388	1176
532490	CCCACAGTAACAATGCCAAG	90	204377	204396	1177
532491	TTTTACCTCCCAGTGAAACT	34	205896	205915	1178
532492	TAATTGTTGATCCATGATGT	5	208856	208875	1179
532493	GTTGGAGAGACAAGTTTAAC	29	208975	208994	1180
532494	AGTCATAAAATTCAAATTAT	39	209537	209556	1181
532495	GGCCTTGGGCACACTTTCTC	82	207510	207529	1182
			210189	210208	
532496	AAGTTTTTATTGAAGTTAAT	0	212551	212570	1183
532497	AAGAAAAATTAGGAAGCTAG	31	212649	212668	1184

532498	CAGGGAGATAAGTTTATTCA	61	212797	212816	1185
532499	ATTTAATACACATTGGAATA	15	213390	213409	1186
532500	GTAGGACTATTTATGATTCC	86	213914	213933	1187
532501	CACTCTCTTGGGCTGTTAAG	82	214479	214498	1188
532502	GAGTATTTCAGGCTGGAAAA	66	214623	214642	1064
532503	TTGTTTGAGTTCCAAAAGAA	39	214932	214951	1189
532504	TTTGCCATGAGACACACAAT	77	215932	215951	1190
532505	CACCAAACCTCAGAGACATG	80	216468	216487	1191
532506	CCACTGTTAAGTGATGCATG	83	217480	217499	1192
532507	CTCTCAGGTAATTTCTGGAA	86	219019	219038	1193
532508	GCTCCTCACAATGACCCTTT	84	219452	219471	1194
532509	GGGACTGGCACTGGTAATTT	56	220062	220081	1195
532510	CTAACCATTAGTTACTGTAT	69	220558	220577	1196
532511	GGATTTTAGGTTCTTGCTGT	51	221588	221607	1197
532512	TGAATCATATACTGATATCA	63	222914	222933	1198
532513	TTGAGGTATTAAATTTTAAA	0	223001	223020	1199
532514	AGTTTGTAATGTAGTGATTT	19	223156	223175	1200
532515	AAATATTTGATAGCTCACAT	18	224409	224428	1201
532516	AGAAATATTTGATAGCTCAC	57	224411	224430	1202
532517	CCACATTTCAAATGTTCTCT	80	224717	224736	1203
532518	GCAGGAAGAGTGGCATGGAC	59	224750	224769	1204
532519	CACTTATCCAAATGCAGAGA	82	225742	225761	1205
532520	CAAGGTAATGGGAGGCTAGC	47	225903	225922	1206
532521	ATAGTCAAAGCTAAGGATAT	4	226177	226196	1207
532522	GTAATTTCATTCATGCTTCC	67	226804	226823	1208
532523	GTCCACATTCAGCTGTGTGT	72	231912	231931	1209
532524	TCATTCAGGAAATTCTGCTA	62	232286	232305	1210
532525	AACATGTCTCATTCAGGAAA	71	232294	232313	1211
532526	TAACATGTCTCATTCAGGAA	85	232295	232314	1212
532527	AGATTCCTCAAATTCAGTGA	66	232389	232408	1213
532528	TAAGCGGAAAAGGAGAAAAG	0	233684	233703	1214
532529	AAAGCAAGAGAATTCCTAAA	32	234203	234222	1215
532530	AATGAACCTTTAACTTAGTA	40	234876	234895	1216

Table 139

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 3-8 and intron-exonic regions of SEQ ID NO: 2

ISIS NO	Sequence	Target region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO
523792	AAAGCTTTGTGGATAAAGTT	Intron 3	44	213025	213044	1217
523793	GAAGGAAAGGTTCTGTGGAA	Intron 3	38	213825	213844	1218
523794	CTGAGTATTTCAGGCTGGAA	Intron 3	84	214625	214644	1219

523795	TTGAATTATCCCTTTAAAAA	Intron 3	38	215446	215465	1220
523796	TTTAGAATGGTTTGGCATAC	Intron 3	66	216365	216384	1221
523797	GATATGTCCACATTGATTAG	Intron 3	65	218132	218151	1222
523798	ATTATTTAAGCTTCTACTTT	Intron 3	44	218973	218992	1223
523799	ATACATGGCAATTAAAAGAT	Intron 3	26	219886	219905	1224
523800	TGAGATAGTGTGGGAAATAT	Intron 3	18	220686	220705	1225
523801	TATTTTTGTGTTATGCCTTG	Intron 3	73	221486	221505	1226
523802	TTATTAACTAGAATATGCCT	Intron 3	16	223110	223129	1227
523803	GATTATTCTATTTTTATTTT	Intron 3	33	223948	223967	1228
523804	AGGAAGAGTGGCATGGACAT	Intron 3	43	224748	224767	1229
523805	CTTTTGCTTATTTACCTGGG	Intron 3	84	225568	225587	1230
523806	TTTATATTATTAATATCATT	Intron 3	31	226371	226390	1231
523807	GGTACATGGCTTTTAAGTGG	Intron 3	53	227218	227237	1232
523808	AATATTGGTCAGGTTTAAGA	Intron 3	28	228018	228037	1233
523809	ATTTCATCTCTTTCTTAGTT	Intron 3	45	228818	228837	1234
523810	CCAATGATGTTACTACTACT	Intron 3	89	229618	229637	1235
523811	GTTCCCCCAACCCCTTGGAA	Intron 3	28	230418	230437	1236
523812	TATAGGAAGTGAGATGTATG	Intron 3	46	231218	231237	1237
523813	ATTATTCTAGAAGAAGATTT	Intron 3	12	232018	232037	1238
523814	ATCCCCCTAGAGCAATGGTC	Intron 3	79	232826	232845	1239
523815	GAGGCTCACATTTGGAAGAC	Intron 3	69	233626	233645	1240
523816	TACACAAATCCAAGGCAGAG	Intron 3	57	234447	234466	1241
523817	AGGAAGAGTGGGAGTGTTAC	Intron 3	35	235258	235277	1242
523818	GTCCCTGACTAGGCATTTTG	Intron 3	43	236071	236090	1243
523819	AAGCTCAATTGCAGATGCTC	Intron 3	80	237676	237695	1244
523820	CTGTGAGTCCATTAAACCTC	Intron 3	81	244875	244894	1245
523821	TGAAATGTGGCTAGTGTGAC	Intron 3	51	245701	245720	1246
523822	AAAATATTGAAAGGCCCATC	Intron 3	68	246501	246520	1247
523823	AATGTCAATAGTGCCCTATT	Intron 3	48	247431	247450	1248
523824	ACAGTATATTCAGTCCAAGG	Intron 3	82	248231	248250	1249
523825	TGTCTATTTAAGTTTGTTGC	Intron 3	45	250001	250020	1250
523826	TTCAAGTACTGTCATGAATA	Intron 3	47	251214	251233	1251
523827	TTTCTTTTTCTTAAACTAAG	Intron 3	11	252041	252060	1252
523828	GTTTCTATTGTTGCCACCTT	Intron 3	70	252841	252860	1253
523829	AAGGCCACATATTATAGTAT	Intron 3	29	253698	253717	1254
523830	ACCTGAACTATTAATTTCTT	Intron 3	19	255397	255416	1255
523831	GAATGGGCTGAGTAGTTGAA	Intron 3	47	256197	256216	1256
523832	TGATGAACATTGCTAATTTG	Intron 3	26	257018	257037	1257
523833	ATCTTGCCTCGATGAAAGTT	Intron 3	17	257818	257837	1258
523834	TTAAGTGGCACAGCCATGAT	Intron 3	9	258774	258793	1259
523835	AATGAGTTAAGTTGGAACAC	Intron 3	25	261294	261313	1260
523836	TCCTTAGTAGAATGCCTGGA	Intron 3	57	263338	263357	1261
523837	TATGTAGAAAAATAAGCTGG	Intron 3	0	266514	266533	1262

523838	GCCGAGGCAGGCACCTGAGT	Intron 3	43	267375	267394	1263
523839	TGGTACCTATATTGAGAGGT	Intron 4	46	269052	269071	1264
523840	TTAAGGAAAAATATAGTATA	Intron 4	7	269854	269873	1265
523841	TTATTTATGTGTCAGGGATG	Intron 4	28	270668	270687	1266
523842	CAAAAGTTAAGTGCTTTAGG	Intron 4	10	271468	271487	1267
523843	TTCATAGATGTCTAAGGAAT	Intron 4	32	273341	273360	1268
523844	ACCTGTGATTTACCTATTTC	Exon 5- intron 5 junction	18	274185	274204	1269
523845	TGCCTAGAAAACCACATAAA	Intron 5	38	274985	275004	1270
523846	AAACATCCTCAAAGGTACCT	Intron 5	64	275808	275827	1271
523847	CTTCCCTGAGACACACACAT	Intron 5	35	276617	276636	1272
523848	CTTCTTCAATCTTCTCATAC	Intron 5	33	278288	278307	1273
523849	TACCATTTTCCATTTAGTTT	Exon 6- intron 6 junction	7	279088	279107	1274
523850	ATTGGCATCTTTTTCAGTGG	Intron 6	34	279902	279921	1275
523851	TCAAGCTCACGGTTGGAGAC	Intron 6	36	280799	280818	1276
523852	AAATGAAATCAGTATGTTGA	Intron 6	0	281622	281641	1277
523853	TGATTTATCACAAAGGTGCT	Intron 6	29	282437	282456	1278
523854	AAAACAGTAGAAAAGATTAA	Intron 6	14	284073	284092	1279
523855	CTACATCACAGCAGTCAGAA	Intron 6	23	285187	285206	1280
523856	AAAAGATGTAAGTGTGACAT	Intron 6	28	286349	286368	1281
				286919	286938	
523857	TTACAAGAACTGCTAAAGGG	Intron 6	15	287151	287170	1282
523858	ATAAAGAAAAAGTTAACTGA	Intron 6	9	287982	288001	1283
523859	AGATAATATACTTCTTCTAT	Intron 6	4	288809	288828	1284
523860	CCTTCTTCACATGTAAATTG	Exon 7- intron 7 junction	19	290456	290475	1285
523861	TTTCTATGTAGCTTGTGGTT	Intron 7	30	291258	291277	1286
523862	AGGCAGAGTTTTTATTGATA	Intron 7	19	292058	292077	1287
523863	ATAGTCACCAGCCTAAGCCT	Intron 8	28	292858	292877	1288
523864	AGACTTTTAGCATGCTTGAC	Intron 8	56	293658	293677	1289
523865	TTTACAGCCCTACAGTTCTA	Intron 8	7	294464	294483	1290
523866	CCAGAGAACCTGACTCCAAA	Intron 8	6	295330	295349	1291
523867	CAGAAGAAAATATTAGACAG	Intron 8	10	296993	297012	1292

Table 140

Inhibition of GHR mRNA by 5-10-5 MOE gapmers targeting introns 3-8 of SEQ ID NO: 2

ISIS NO	Sequence	Target Region	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	SEQ ID NO

532531	TATTATACTTCTAAATTCCC	Intron 3	70	236716	236735	1293
532532	TAAAAGCAAGAAAAAGGAAC	Intron 3	52	236889	236908	1294
532533	CCTAATTTATATGAACAAAC	Intron 3	56	237177	237196	1295
532534	TGCAATGCCTTAGCCTAAAA	Intron 3	86	238087	238106	1296
532535	CACCACCATTATTACACTAC	Intron 3	75	238186	238205	1297
532536	AAATAAATCAGATTATTATA	Intron 3	52	238242	238261	1298
532537	CTTAGATCTGTGCTGTCCAA	Intron 3	81	245758	245777	1299
532538	GTTAGTGTTAGATTCTTTGA	Intron 3	67	246152	246171	1300
532539	CATGCTCACGGCTGTGTTAC	Intron 3	66	246248	246267	1301
532540	CCCATCAAATACTGAGTTCT	Intron 3	86	246487	246506	1302
532541	GAAAGTAGTGATTAATGAGA	Intron 3	38	247012	247031	1303
532542	ATTAATCAACAAGTGGCATT	Intron 3	72	247203	247222	1304
532543	TTTAATTTTAGGGTTTAGAG	Intron 3	48	248344	248363	1305
532544	CTTGCTACCACTAGAGCCTT	Intron 3	69	248694	248713	1306
532545	ACCACTGACTTATATCATTT	Intron 3	58	248743	248762	1307
532546	TTCCCCATTGCTAATTTTGT	Intron 3	48	251601	251620	1308
532547	TCCTGAAACTTAGTAGCTGG	Intron 3	83	253147	253166	1309
532548	TGTCTTAAAAAGGAATAAAA	Intron 3	52	253785	253804	1310
532549	CCTATAATAAAGTATTGTCT	Intron 3	70	253800	253819	1311
532550	ATGTAAAATGGTATAGCTAC	Intron 3	50	254040	254059	1312
532551	AACCCTCACACACTTCTGTT	Intron 3	71	254064	254083	1313
532552	ATTCTGCATAAGCAGTGTTT	Intron 3	53	254246	254265	1314
532553	TTACTACCCTGAAGAAGAAC	Intron 3	35	254314	254333	1315
532554	AAGACCTATAACTTACTACC	Intron 3	49	254326	254345	1316
532555	TTTCACAAGATTTACTTGGT	Intron 3	77	254641	254660	1317
532556	CAGTTGTGATTGTCAACCTA	Intron 3	77	257073	257092	1318
532557	AATCTTGCCTCGATGAAAGT	Intron 3	57	257819	257838	1319
532558	TGGCCTAAATGTATCAGTTA	Intron 3	66	259157	259176	1320
532559	AGGCTTTGGGTAAAATCTTT	Intron 3	67	259184	259203	1321
532560	TATGATTTTTAAAGATTAAA	Intron 3	20	261419	261438	1322
532561	GTACAGTGAAAAAGATGTGT	Intron 3	56	263666	263685	1323
532562	GACAGGTATGAAGCAAAACA	Intron 3	64	267033	267052	1324
532563	TGAGCTGAGGGTCTTTGCCG	Intron 3	61	267391	267410	1325
532564	AGGCTGAGTTGTACACAAAC	Intron 4	52	269422	269441	1326
532565	ATGAGGAGGCTGAGTTGTAC	Intron 4	43	269428	269447	1327
532566	TCATAAAGTGGGCCCAGCTT	Intron 4	70	270044	270063	1328
532567	ACTCCTAATCCCTCAGTTTT	Intron 4	62	270492	270511	1329
532568	TTTACATGCAAGGAGCTGAG	Intron 4	61	271047	271066	1330
532569	TAATGCCCTTTCTCCCTACT	Intron 4	60	271215	271234	1331
532570	CCTGTTTAGATTATCCCAAA	Intron 4	62	271763	271782	1332
532571	CATGATTCACAGAATTTCTC	Intron 4	56	271831	271850	1333
532572	AGTTAGAAAACTCAAAGTAT	Intron 4	2	271915	271934	1334
532573	TCAAATGTACTTAGCATAAG	Intron 4	9	271947	271966	1335

532574	ATATCAAATGTACTTAGCAT	Intron 4	59	271950	271969	1336
532575	AAAGTTCAGAAGAGGGAATG	Intron 4	51	273233	273252	1337
532576	AATTCCCATCTGAGTAGTTT	Intron 4	56	273440	273459	1338
532577	GTCCCCTAATTTCAGGCTAA	Intron 4	31	273471	273490	1339
532578	CTATGTCAAATGAAACAAAA	Intron 5	38	274205	274224	1340
532579	TGATTATGCTTTGTGATAAA	Intron 5	42	274624	274643	1341
532580	TCCAGCTGACTAGGAGGGCT	Intron 5	7	275732	275751	1342
532581	CATACCAGTCTCCTCGCTCA	Intron 5	0	276738	276757	1343
532582	ATATAACAGAATCCAACCAT	Intron 5	47	277045	277064	1344
				278361	278380	
532583	TGCAAAATGGCCAAACTACA	Intron 5	56	277577	277596	1345
532584	TCTTCCTAGCCACATGTGAT	Intron 5	32	278227	278246	1346
532585	TACCATGCTCTCTAATTGCC	Intron 6	47	279624	279643	1347
532586	AGTGATCTGTGCCAGGCTGC	Intron 6	65	279848	279867	1348
532587	AAGTTACAGAACAGATATCT	Intron 6	61	280012	280031	1349
532588	GTATTGTGAAAATAGTACTG	Intron 6	45	280226	280245	1350
532589	AAACACTATCAAGCTCACGG	Intron 6	54	280807	280826	1351
532590	TTCAAGAAAAGTCTTCAAAT	Intron 6	24	280831	280850	1352
532591	GGATCATTTCCCCATGCATG	Intron 6	52	280982	281001	1353
532592	ATATTATATTAAGAAAAATG	Intron 6	4	281422	281441	1354
532593	CTCCCATGTTCATTACTTAT	Intron 6	49	281587	281606	1355
532594	CATGACATTGGTTTGGGCAA	Intron 6	43	282229	282248	1356
532595	AATGTTGTTGGGAAAATTGG	Intron 6	42	282383	282402	1357
532596	AGCTGCAGGATACAAAGTCA	Intron 6	49	282986	283005	1358
532597	ATATCCTTTCATGATAAAAA	Intron 6	31	283354	283373	1359
532598	ATGGGCTAATATCTCTGATA	Intron 6	50	283590	283609	1360
532599	ACATTACTAATAATTAGAGA	Intron 6	0	285236	285255	1361
532600	ATAAAAACATATGAAAGTAT	Intron 6	12	287093	287112	1362
532601	TTCTGAATTAAATCTATTAG	Intron 6	16	287408	287427	1363
532602	TTACATTTTTGCAAATTTAT	Intron 6	31	287472	287491	1364
532603	TGAACAGTTGATTAACAAAG	Intron 6	15	287887	287906	1365
532604	AAGTTATTGGTTTACTAGAT	Intron 6	0	288598	288617	1366
532605	TTGGAAAAGGTCCTAGAAAA	Intron 6	24	289808	289827	1367
532606	CATGACAGAAACTTCTTAGA	Intron 7	25	292035	292054	1368
532607	CCATACTTGCTGACAAATAT	Intron 8	39	294389	294408	1369

Example 115: Dose-dependent antisense inhibition of human GHR in Hep3B cells by MOE gapmers

Gapmers from the studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in Hep3B cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in

separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.625 μM, 1.25 μM, 2.50 μM, 5.00 μM and 10.00 μM concentrations of antisense oligonucleotide, as specified in the Tables below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 141

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523271	41	61	73	86	92	0.8
523274	20	36	64	80	92	1.8
523324	35	45	68	91	90	1.2

Table 142

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523604	21	42	68	58	86	2.0
523577	6	22	56	66	91	2.7
523614	14	44	61	84	87	1.9
523564	4	26	48	67	86	2.8
523633	30	43	71	82	84	1.4
523571	2	9	38	55	82	3.9

Table 143

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523570	25	50	64	77	88	1.5
523592	27	42	59	79	88	1.7
523595	21	50	62	76	90	1.6
523596	36	47	62	75	77	1.4
523607	49	62	71	82	84	0.5
523615	20	49	63	83	91	1.6
523630	4	28	54	79	78	2.6
523661	4	34	48	73	79	2.7

523665	4	28	54	73	79	2.7
523687	30	56	61	78	81	1.4
523711	42	66	78	94	95	0.7
523712	6	37	60	72	89	2.3
523713	4	32	55	72	85	2.5
523714	59	75	88	95	97	0.2

Table 144

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523655	26	33	60	67	78	2.1
523656	19	33	45	69	87	2.4
523658	0	42	62	67	79	3.1
523715	78	90	92	93	95	<0.6
523718	30	46	67	84	92	1.4
523723	56	69	83	92	94	0.3
523725	45	64	79	89	95	0.6
523726	32	48	77	88	89	1.2
523736	0	64	75	90	96	1.5
523747	48	64	80	91	92	0.6
523758	25	39	61	74	84	1.9
523766	7	37	66	81	93	2.0
523776	26	54	72	78	83	1.3
523789	62	68	81	85	90	0.2

Table 145

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523719	24	46	65	84	93	1.5
523720	18	49	72	85	93	1.5
523724	43	61	77	91	91	0.7
523735	8	42	63	81	93	2.0
523740	37	58	72	83	88	1.0
523752	9	29	52	72	86	2.5
523763	8	32	57	70	80	2.6
523764	43	52	67	77	79	0.9
523765	24	48	62	88	4	1.5
523767	49	62	67	72	82	0.6
523772	29	39	54	62	61	2.7
523774	28	59	63	88	91	1.2
523778	25	32	63	78	84	1.9

523783	0	22	53	72	88	2.8

Table 146

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532151	57	69	76	85	88	<0.6
532153	23	43	54	80	86	1.8
532158	46	58	81	87	87	0.6
532160	17	26	55	76	92	2.2
532162	14	46	71	83	93	1.7
532164	37	76	82	90	93	0.6
532171	41	81	67	81	83	<0.6
532181	56	81	84	89	93	0.2
532186	26	65	75	83	91	1.1
532188	51	68	80	89	93	<0.6
532189	24	31	52	75	86	2.1
532197	0	40	66	85	93	2.1
532199	24	37	50	73	87	2.1
532222	12	41	67	84	94	1.8

Table 147

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532175	41	54	76	84	89	0.9
532223	53	69	75	88	94	<0.6
532235	43	58	67	77	82	0.8
532241	39	53	62	73	87	1.2
532248	49	65	72	85	93	0.6
532254	52	62	85	87	92	<0.6
532300	20	29	49	66	78	2.7
532304	26	39	66	78	90	1.7
532316	41	66	76	86	94	0.7
532395	32	56	84	93	97	1.0
532401	47	80	92	96	98	<0.6
532411	73	90	94	97	98	<0.6
532420	38	49	82	85	97	1.0
532436	37	58	75	90	96	0.9

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Table 148

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532410	66	83	92	94	97	<0.6
532468	45	68	78	93	94	0.6
532469	0	17	56	76	92	2.8
532470	10	34	62	84	94	2.0
532475	13	36	52	64	87	2.5
532476	34	64	73	79	93	0.9
532480	28	54	67	78	87	1.4
532482	21	39	69	83	92	1.7
532490	42	60	68	84	93	0.9
532500	37	50	63	81	87	1.2
532506	13	41	66	75	89	1.9
532507	47	59	71	86	89	0.7
532508	0	31	73	83	89	2.2
532526	31	56	78	79	88	1.1

Table 149

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532495	59	74	81	87	95	<0.6
532501	49	53	71	83	84	0.7
532534	53	75	85	91	97	<0.6
532535	0	34	61	84	92	2.6
532537	49	67	80	90	94	<0.6
532540	59	70	87	93	95	<0.6
532547	57	71	81	91	92	<0.6
532555	48	36	61	72	85	1.3
532556	33	57	67	86	90	1.1

Table 150

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523421	32	57	81	82	88	1.0
533006	46	43	69	83	91	1.0
533121	53	75	75	88	93	<0.6
533122	65	77	82	90	93	<0.6
533123	39	71	84	91	95	0.6
533125	49	61	81	85	91	0.6

533131	3	57	59	82	90	1.9
533136	32	65	62	81	88	1.1
533139	13	51	72	90	94	1.5
533140	36	66	39	87	92	1.2
533153	50	65	83	89	90	<0.6
533156	43	64	74	85	90	0.7
533160	57	80	87	91	95	<0.6
533161	54	62	81	89	92	<0.6

Table 151

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
533234	50	70	86	93	95	<0.6
533237	5	45	63	84	93	1.9
533233	43	55	76	90	95	0.8
533179	31	63	75	87	87	1.0
533178	53	67	76	89	94	<0.6
533187	5	15	53	79	86	2.7
533188	49	68	83	89	94	<0.6
533271	45	66	85	92	94	0.6
533134	22	45	64	81	89	1.6
533258	52	72	88	93	95	<0.6
533235	50	54	75	82	90	0.7
533262	23	54	78	91	96	1.2
533189	48	66	78	82	88	<0.6
533193	38	53	72	77	91	1.0

Table 152

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
533259	63	78	84	90	92	<0.6
533291	25	57	75	86	96	1.2
533256	67	76	90	95	95	<0.6
533269	42	75	82	94	97	0.6
533265	67	78	91	95	97	<0.6
533318	16	45	77	87	95	1.5
533257	55	84	91	96	96	<0.6
533280	34	62	80	91	91	0.9
533301	52	77	84	93	96	<0.6
533316	41	50	79	93	94	0.9
533270	62	71	88	94	97	<0.6

533330	46	76	93	97	98	<0.6
533317	55	60	82	87	96	<0.6
533315	39	56	82	87	93	0.9

Table 153

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
533364	71	77	92	90	94	<0.6
533925	26	55	61	85	91	1.4
533326	54	77	80	93	95	<0.6
533916	18	62	69	83	93	1.4
533328	52	68	89	94	98	<0.6
533932	42	49	80	86	92	0.9
533352	42	82	88	93	94	<0.6
533917	20	37	57	78	84	2.0
533331	54	83	89	93	96	<0.6
533936	21	46	73	84	88	1.5
533329	56	73	84	92	98	<0.6
533937	26	32	79	86	94	1.5
533908	58	66	81	88	94	<0.6
533898	61	64	84	90	92	<0.6

Table 154

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539371	32	41	82	92	98	1.2
539382	18	58	74	91	97	1.3
539392	34	59	79	94	96	0.9
539398	31	53	89	94	98	1.0
539399	31	72	87	95	97	0.8
539400	36	60	79	93	97	0.9
539405	33	58	74	91	94	1.0
539412	23	61	80	93	95	1.1
539413	53	75	86	92	96	<0.6
539415	47	62	84	91	96	0.6
539416	61	85	94	97	96	<0.6
539430	24	48	68	80	93	1.5
539431	14	40	71	89	95	1.7
539433	46	67	74	92	95	0.6

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Example 116: Dose-dependent antisense inhibition of human GHR in Hep3B cells by MOE gapmers

Gapmers from the studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in Hep3B cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.3125 μM, 0.625 μM, 1.25 μM, 2.50 μM, 5.00 μM and 10.00 μM concentrations of antisense oligonucleotide, as specified in the Tables below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 155

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523814	0	24	48	52	68	82	2.2
523805	13	29	55	0	79	85	1.5
523822	0	19	26	41	65	85	2.8
523820	0	19	29	58	74	86	2.3
523815	3	6	19	37	45	71	4.8
523828	12	19	32	51	64	74	2.7
523801	3	9	31	43	59	76	3.3
523824	12	28	44	63	77	85	1.7
523794	13	21	30	51	66	78	2.5
523810	15	34	55	72	78	86	1.3
523819	0	24	40	60	66	75	2.4

Table 156

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539302	31	56	80	92	97	98	0.5
539314	16	28	49	69	85	95	1.3
539319	8	30	45	71	90	94	1.4
539320	11	42	64	83	92	95	1.0
539321	25	48	64	82	95	97	0.8

539322	19	34	58	72	90	96	1.1
539331	7	14	46	69	88	96	1.6
539355	28	35	67	89	96	98	0.8
539358	12	39	56	80	93	98	1.1
539359	15	23	58	77	93	98	1.2

Table 157

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539318	23	21	56	73	88	94	1.2
539325	14	26	38	74	92	98	1.4
539339	18	23	58	83	92	98	1.1
539341	17	29	62	84	94	95	1.0
539342	20	31	43	71	90	95	1.2
539352	15	23	41	61	89	95	1.5
539356	24	46	62	83	90	97	0.8
539361	37	42	73	88	96	98	0.6
539379	53	66	83	96	96	98	0.2
539380	52	77	91	97	97	99	0.1
539383	34	61	71	89	98	98	0.5

Table 158

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539360	45	60	81	94	97	98	0.3
539362	21	36	72	90	98	99	0.8
539375	23	36	66	85	95	99	0.9
539376	26	35	58	82	95	99	0.9
539377	29	31	43	64	85	89	1.3
539378	37	59	81	93	97	98	0.4
539389	34	61	61	87	95	97	0.5
539401	34	52	63	84	92	95	0.6
539403	52	73	83	94	97	98	0.1
539404	22	55	74	88	94	96	0.6
539432	32	50	75	86	94	96	0.6

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Example 117: Dose-dependent antisense inhibition of human GHR in Hep3B cells by MOE gapmers

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in Hep3B cells. The antisense oligonucleotides were tested in a series of

experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.625 μM, 1.25 μM, 2.50 μM, 5.00 μM and 10.00 μM concentrations of antisense oligonucleotide, as specified in the Tables below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 159

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523271	26	41	80	89	94	1.4
523274	13	35	63	85	95	1.9
523324	26	40	64	88	95	1.6
523577	27	50	72	87	95	1.3
523604	49	66	74	81	87	0.5
523614	43	54	82	92	89	0.8

Table 160

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523564	16	48	69	75	91	1.7
523570	24	52	65	71	88	1.6
523592	6	31	52	65	81	2.8
523595	13	49	60	79	92	1.8
523596	20	49	62	71	75	1.9
523607	38	63	66	74	76	0.8
523615	17	48	60	80	92	1.8
523630	19	42	42	67	80	2.5
523633	41	69	78	79	80	0.6
523665	16	45	56	71	80	2.1
523687	37	59	73	75	78	0.9
523711	33	63	78	91	93	0.9
523712	13	36	61	78	87	2.1
523714	63	85	91	96	96	<0.6

Table 161

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523655	28	42	57	74	76	1.9
523656	33	43	53	74	88	1.7
523661	29	29	66	79	82	1.9
523713	35	45	64	83	87	1.3
523715	83	86	92	93	94	<0.6
523718	27	52	69	84	95	1.3
523723	65	74	86	85	94	<0.6
523725	37	63	78	78	92	0.8
523726	43	57	72	86	89	0.8
523736	39	65	80	88	95	0.8
523747	51	71	83	86	93	<0.6
523766	30	50	70	82	89	1.3
523776	45	59	67	79	84	0.7
523789	63	75	76	83	83	<0.6

Table 162

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523719	18	40	56	73	83	2.1
523720	36	46	59	64	89	1.5
523724	44	60	75	81	87	0.7
523735	11	40	60	78	84	2.1
523740	17	47	61	80	81	1.8
523752	25	31	38	70	84	2.5
523758	23	48	58	72	80	1.8
523763	2	24	48	64	75	3.3
523764	22	49	45	73	75	2.1
523765	42	40	57	79	87	1.4
523767	43	53	56	69	79	1.2
523774	36	52	71	81	89	1.1
523778	15	45	59	75	79	2.0
523783	5	30	48	66	83	2.9

Table 163

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532151	40	45	64	71	82	1.3
532158	28	47	63	70	87	1.6
532164	36	47	64	75	89	1.3
532171	35	47	50	69	89	1.6
532175	27	38	43	75	87	2.1
532181	21	56	63	69	80	1.7
532186	28	49	62	73	91	1.5
532188	40	52	73	75	90	1.0
532223	22	34	53	71	90	2.2
532235	35	31	48	68	73	2.3
532241	6	24	29	51	72	4.5
532248	19	37	47	73	84	2.3
532254	56	56	72	85	90	0.5
532316	32	55	50	78	90	1.5

Table 164

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
532304	44	57	68	78	73	0.7
532395	47	62	82	91	96	0.6
532401	70	83	91	94	96	<0.6
532410	56	71	85	90	96	<0.6
532411	88	93	96	97	98	<0.6
532420	61	67	82	85	96	<0.6
532436	48	49	77	90	97	0.8
532468	42	67	82	89	94	0.6
532476	32	58	75	84	90	1.1
532482	5	26	56	71	87	2.6
532490	18	47	55	69	86	2.0
532501	4	22	43	59	77	3.5
532507	39	63	66	83	89	0.9
532526	30	48	67	82	88	1.4

Table 165

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
533121	59	67	78	83	87	0.2
533122	48	73	78	84	90	0.4

533125	47	61	74	89	89	0.6
533136	5	25	58	79	90	2.4
533156	37	48	69	77	87	1.2
533161	28	67	77	89	90	1.0
533178	30	60	72	90	92	1.1
533179	37	66	76	76	87	0.8
533188	32	64	74	80	90	1.0
533189	49	66	77	81	81	0.4
533193	26	48	69	75	85	1.5
533233	39	60	59	84	93	1.0
533234	45	69	84	91	94	0.5
533235	28	49	69	82	90	1.4

Table 166

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
533256	47	72	86	90	94	<0.6
533257	63	77	88	91	96	<0.6
533258	66	81	88	95	95	<0.6
533259	48	70	84	90	93	<0.6
533262	44	66	79	90	96	0.7
533265	59	74	85	93	96	<0.6
533269	25	55	74	86	87	1.2
533270	34	59	73	86	95	1.0
533271	63	82	88	92	92	<0.6
533291	14	46	64	84	89	1.8
533301	49	61	75	83	91	0.6
533315	22	39	73	76	91	1.7
533317	26	53	68	85	94	1.3
533318	29	40	46	77	91	1.9

Table 167

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
533280	58	64	77	82	87	0.3
533316	35	55	68	87	91	1.1
533326	34	68	76	89	96	0.8
533328	54	55	79	83	92	0.5
533329	46	62	72	83	95	0.7
533330	56	75	83	91	94	0.3
533331	54	61	80	86	89	0.4

533352	54	62	79	83	89	0.4
533364	52	73	83	91	94	0.4
533898	17	47	63	78	87	1.8
533908	35	58	74	82	87	1
533916	22	46	72	78	88	1.6
533932	51	62	70	79	80	0.5
533937	20	40	61	79	85	1.9

Example 118: Dose-dependent antisense inhibition of human GHR in Hep3B cells by MOE gapmers

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in Hep3B cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.3125 μM, 0.625 μM, 1.25 μM, 2.50 μM, 5.00 μM and 10.00 μM concentrations of antisense oligonucleotide, as specified in the Tables below. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 168

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
523577	0	16	33	59	72	94	2.2
523633	15	33	66	73	82	86	1.1
523764	11	33	50	68	78	83	1.5
523794	12	30	33	56	76	82	1.9
523805	21	48	66	78	85	92	0.8
523810	18	36	61	80	89	90	1.0
523814	13	35	52	67	81	88	1.3
523819	11	30	57	72	81	89	1.3
523820	0	15	43	61	84	92	1.8
523824	21	27	59	72	84	90	1.2

Table 169

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539302	34	41	56	83	83	96	0.8
539321	30	32	76	73	80	94	0.8
539322	22	36	57	72	78	94	1.1
539355	23	42	48	72	71	88	1.2
539359	21	38	48	73	78	92	1.2
539320	14	32	53	72	82	91	1.3
539341	3	19	35	56	78	89	2.0
539342	6	18	33	51	70	83	2.3
539356	0	0	21	45	73	94	2.7
539358	0	15	23	50	52	91	2.9

Table 170

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539339	22	37	52	77	90	92	1.0
539360	28	49	72	82	95	97	0.7
539361	36	56	75	86	95	98	0.5
539362	24	26	63	77	91	97	1.0
539375	21	29	39	63	77	91	1.5
539378	8	42	64	85	92	97	1.0
539379	43	59	80	89	96	98	0.3
539380	61	73	90	95	98	98	0.1
539383	30	49	75	87	97	98	0.6
539403	48	55	75	85	94	96	0.3
539432	36	42	69	79	88	95	0.7

Table 171

ISIS No	0.3125 μM	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
539376	34	46	62	82	94	98	0.7
539389	53	58	78	86	94	97	0.2
539392	1	19	26	68	81	94	1.9
539399	27	52	65	78	92	98	0.7
539400	7	26	43	59	88	95	1.6
539401	32	39	77	90	92	95	0.6
539404	22	59	77	87	93	95	0.6
539413	16	33	53	82	86	96	1.1
539415	4	44	56	74	81	94	1.2

539416	37	61	70	85	92	95	0.4
539433	31	52	70	85	87	94	0.6

Example 119: Antisense inhibition of human growth hormone receptor in Hep3B cells by deoxy, MOE and (S)-cEt gapmers

Additional antisense oligonucleotides were designed targeting a growth hormone receptor (GHR) nucleic acid and were tested for their effects on GHR mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured Hep3B cells at a density of 20,000 cells per well were transfected using electroporation with 5,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as deoxy, MOE, and (S)-cEt gapmers. The deoxy, MOE and (S)-cEt oligonucleotides are 16 nucleosides in length wherein the nucleoside have either a MOE sugar modification, an (S)-cEt sugar modification, or a deoxy modification. The 'Chemistry' column describes the sugar modifications of each oligonucleotide. 'k' indicates an (S)-cEt sugar modification; 'd' indicates deoxyribose; and 'e' indicates a MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human GHR mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_000163.4) or the human GHR genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000). 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity. In case the sequence alignment for a target gene in a particular table is not shown, it is understood that none of the oligonucleotides presented in that table align with 100% complementarity with that target gene.

Table 172

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	84	156891	1370
541263	164	Intron 1	CCGAGCTTCGCCTCTG	eekddddddddddkke	89	3040	1371
541264	167	Intron 1	CCTCCGAGCTTCGCCT	eekddddddddddkke	90	3043	1372
541265	170	Junction spanning two exons	GGACCTCCGAGCTTCG	eekddddddddddkke	89	n/a	1373
541266	176	Junction spanning two exons	CCTGTAGGACCTCCGA	eekddddddddddkke	83	n/a	1374
541268	214	Exon 2	CCAGTGCCAAGGTCAA	eekddddddddddkke	87	144998	1375
541269	226	Exon 2	CACTTGATCCTGCCAG	eekddddddddddkke	67	145010	1376
541270	244	Exon 2	CACTTCCAGAAAAAGC	eekddddddddddkke	34	145028	1377
541278	365	Exon 4/Intron 3	GTCTCTCGCTCAGGTG	eekddddddddddkke	77	268028	1378
541279	368	Exon 4/Intron 3	AAAGTCTCTCGCTCAG	eekddddddddddkke	76	268031	1379
541280	373	Exon 4/Intron 3	ATGAAAAAGTCTCTCG	eekddddddddddkke	66	268036	1380
541283	445	exon 2-exon 3 junction	TCCTTCTGGTATAGAA	eekddddddddddkke	37	n/a	1381
541288	554	Exon 5	CAATAAGGTATCCAGA	eekddddddddddkke	49	274114	1382
541289	561	Exon 5	CTTGATACAATAAGGT	eekddddddddddkke	66	274121	1383
541290	569	Exon 5	CTAGTTAGCTTGATAC	eekddddddddddkke	61	274129	1384
541293	628	exon 3-exon 4 junction	GATCTGGTTGCACTAT	eekddddddddddkke	57	n/a	1385
541294	639	Exon 6	GGCAATGGGTGGATCT	eekddddddddddkke	38	278933	1386
541295	648	Exon 6	CCAGTTGAGGGCAATG	eekddddddddddkke	67	278942	1387
541296	654	Exon 6	TAAAGTCCAGTTGAGG	eekddddddddddkke	43	278948	1388
541301	924	Exon 7	TACATAGAGCACCTCA	eekddddddddddkke	86	290422	1389
541302	927	Exon 7	TGTTACATAGAGCACC	eekddddddddddkke	78	290425	1390
541303	930	Exon 7	AAGTGTTACATAGAGC	eekddddddddddkke	59	290428	1391
541304	958	Exon 7	CTTCACATGTAAATTG	eekddddddddddkke	26	290456	1392
541305	981	Exon 8	GAGCCATGGAAAGTAG	eekddddddddddkke	66	292535	1393
541310	1127	Exon 7-exon 8 junction	CCTTCCTTGAGGAGAT	eekddddddddddkke	26	n/a	1394
541320	1317	Exon 10	CTTCACCCCTAGGTTA	eekddddddddddkke	38	297734	1395
541321	1322	Exon 10	CCATCCTTCACCCCTA	eekddddddddddkke	81	297739	1396
541322	1326	Exon 10	GTCGCCATCCTTCACC	eekddddddddddkke	79	297743	1397
541323	1331	Exon 10	CCAGAGTCGCCATCCT	eekddddddddddkke	64	297748	1398
541325	1420	Exon 10	GTGGCTGAGCAACCTC	eekddddddddddkke	79	297837	1399

541326	1434	Exon 10	CCCTTTTAACCTCTGT	eekddddddddddkke	67	297851	1400
541331	1492	Exon 10	CATCATGATAAGGTGA	eekddddddddddkke	16	297909	1401
541332	1526	Exon 10	TGGATAACACTGGGCT	eekddddddddddkke	30	297943	1402
541333	1532	Exon 10	TCTGCTTGGATAACAC	eekddddddddddkke	63	297949	1403
541335	1597	Exon 10	GAATATGGGCAGCTTG	eekddddddddddkke	33	298014	1404
541336	1601	Exon 10	AGCTGAATATGGGCAG	eekddddddddddkke	34	298018	1405
541337	1607	Exon 10	TTGCTTAGCTGAATAT	eekddddddddddkke	39	298024	1406
541338	1611	Exon 10	TGGATTGCTTAGCTGA	eekddddddddddkke	79	298028	1407
541339	1614	Exon 10	ACTTGGATTGCTTAGC	eekddddddddddkke	73	298031	1408

Example 120: Antisense inhibition of human growth hormone receptor in Hep3B cells by deoxy, MOE and (S)-cEt gapmers

Additional antisense oligonucleotides were designed targeting a growth hormone receptor (GHR) nucleic acid and were tested for their effects on GHR mRNA in vitro. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cultured Hep3B cells at a density of 20,000 cells per well were transfected using electroporation with 4,500 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The newly designed chimeric antisense oligonucleotides in the Tables below were designed as deoxy, MOE, and (S)-cEt gapmers. The deoxy, MOE and (S)-cEt oligonucleotides are 16 nucleosides in length wherein the nucleoside have either a MOE sugar modification, an (S)-cEt sugar modification, or a deoxy modification. The 'Chemistry' column describes the sugar modifications of each oligonucleotide. 'k' indicates an (S)-cEt sugar modification; 'd' indicates deoxyribose; and 'e' indicates a MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the human gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to either the human GHR mRNA, designated herein as SEQ ID NO: 1 (GENBANK Accession No. NM_000163.4) or the human GHR genomic sequence, designated herein as SEQ ID NO: 2 (GENBANK Accession No. NT_006576.16 truncated from nucleotides 42411001 to 42714000). 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence with 100% complementarity. In case the sequence alignment for a target gene in a particular table is not shown, it is understood that none of the oligonucleotides presented in that table align with 100% complementarity with that target gene. The oligonucleotides of Table 175 do not target SEQ ID NOs: 1 or 2, but instead target variant gene sequences

SEQ ID NO: 4 (GENBANK Accession No. DR006395.1) or SEQ ID NO: 7 (the complement of GENBANK Accession No. AA398260.1).

Table 173

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	86	156891	1370
541340	1619	Exon 10	AGTGAACTTGGATTGC	eekddddddddddkke	73	298036	1409
541341	1641	Exon 10	GGCATAAAAGTCGATG	eekddddddddddkke	41	298058	1410
541342	1644	Exon 10	CTGGGCATAAAAGTCG	eekddddddddddkke	33	298061	1411
541343	1683	Exon 10	GGAAAGGACCACACTA	eekddddddddddkke	34	298100	1412
541344	1746	Exon 10	GAGTGAGACCATTTCC	eekddddddddddkke	65	298163	1413
541345	1827	Exon 10	GATGTGAGGAGCCACA	eekddddddddddkke	54	298244	1414
541346	1830	Exon 10	CTTGATGTGAGGAGCC	eekddddddddddkke	70	298247	1415
541347	1835	Exon 10	TCAACCTTGATGTGAG	eekddddddddddkke	38	298252	1416
541348	1839	Exon 10	TGATTCAACCTTGATG	eekddddddddddkke	39	298256	1417
541349	1842	Exon 10	GTGTGATTCAACCTTG	eekddddddddddkke	74	298259	1418
541350	1845	Exon 10	TATGTGTGATTCAACC	eekddddddddddkke	58	298262	1419
541351	1949	Exon 10	GGCATCTCAGAACCTG	eekddddddddddkke	41	298366	1420
541352	1965	Exon 10	GGTATAGTCTGGGACA	eekddddddddddkke	18	298382	1421
541353	1969	Exon 10	TGGAGGTATAGTCTGG	eekddddddddddkke	17	298386	1422
541354	1972	Exon 10	GAATGGAGGTATAGTC	eekddddddddddkke	0	298389	1423
541355	1975	Exon 10	TATGAATGGAGGTATA	eekddddddddddkke	0	298392	1424
541356	1978	Exon 10	CTATATGAATGGAGGT	eekddddddddddkke	30	298395	1425
541357	1981	Exon 10	GTACTATATGAATGGA	eekddddddddddkke	43	298398	1426
541358	1987	Exon 10	GGGACTGTACTATATG	eekddddddddddkke	12	298404	1427
541369	2306	Exon 10	TTACATTGCACAATAG	eekddddddddddkke	21	298723	1428
541373	2667	Exon 10	TAGCCATGCTTGAAGT	eekddddddddddkke	34	299084	1429
541374	2686	Exon 10	TGTGTAGTGTAATATA	eekddddddddddkke	10	299103	1430
541375	2690	Exon 10	ACAGTGTGTAGTGTAA	eekddddddddddkke	82	299107	1431
541376	2697	Exon 10	GCAGTACACAGTGTGT	eekddddddddddkke	46	299114	1432
541377	2700	Exon 10	ACTGCAGTACACAGTG	eekddddddddddkke	32	299117	1433
541378	2740	Exon 10	TTAGACTGTAGTTGCT	eekddddddddddkke	25	299157	1434
541379	2746	Exon 10	CCAGCTTTAGACTGTA	eekddddddddddkke	69	299163	1435
541380	2750	Exon 10	TAAACCAGCTTTAGAC	eekddddddddddkke	20	299167	1436
541381	2755	Exon 10	AACATTAAACCAGCTT	eekddddddddddkke	64	299172	1437
541382	2849	Exon 10	ACTACAATCATTTTAG	eekddddddddddkke	0	299266	1438
541383	2853	Exon 10	GATTACTACAATCATT	eekddddddddddkke	0	299270	1439

541384	2859	Exon 10	AATGCAGATTACTACA	eekddddddddddkke	46	299276	1440
541385	2865	Exon 10	TCCAATAATGCAGATT	eekddddddddddkke	52	299282	1441
541386	2941	Exon 10	GTTGATCTGTGCAAAC	eekddddddddddkke	74	299358	1442
541389	3037	Exon 10	TCTACTTCTCTTAGCA	eekddddddddddkke	50	299454	1443
541393	3215	Exon 10	GCTTCTTGTACCTTAT	eekddddddddddkke	84	299632	1444
541394	3237	Exon 10	GATTTGCTTCAACTTA	eekddddddddddkke	47	299654	1445
541395	3305	Exon 10	GGTTATAGGCTGTGAA	eekddddddddddkke	0	299722	1446
541396	3308	Exon 10	TCTGGTTATAGGCTGT	eekddddddddddkke	88	299725	1447
541397	3311	Exon 10	GTGTCTGGTTATAGGC	eekddddddddddkke	56	299728	1448
541398	3316	Exon 10	AGTATGTGTCTGGTTA	eekddddddddddkke	76	299733	1449
541399	3371	Exon 10	GGGACTGAAAACCTTG	eekddddddddddkke	50	299788	1450
541400	3975	Exon 10	AGTATTCTTCACTGAG	eekddddddddddkke	36	300392	1451
541401	4044	Exon 10	GCGATAAATGGGAAAT	eekddddddddddkke	36	300461	1452
541402	4048	Exon 10	GTCTGCGATAAATGGG	eekddddddddddkke	52	300465	1453
541403	4058	Exon 10	CCTAAAAAAGGTCTGC	eekddddddddddkke	51	300475	1454
541404	4072	Exon 10	CATTAAGCTTGCTTCC	eekddddddddddkke	53	300489	1455

Table 174

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NO: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	85	156891	1370
541421	4418	Exon 10	CACAACTAGTCATACT	eekddddddddddkke	42	300835	1456
541422	4428	Exon 10	AACTGCCAGACACAAC	eekddddddddddkke	68	300845	1457
541423	4431	Exon 10	ATAAACTGCCAGACAC	eekddddddddddkke	86	300848	1458
541424	4503	Exon 10	TATCAGGAATCCAAGA	eekddddddddddkke	11	300920	1459
541425	4521	Exon 10	TTGATAACAGAAGCAC	eekddddddddddkke	16	300938	1460
541426	4528	Exon 10	TTGGTGTTTGATAACA	eekddddddddddkke	31	300945	1461
541427	4531	Exon 10	ATGTTGGTGTTTGATA	eekddddddddddkke	32	300948	1462
541429	30	Exon 1	CCGCCACTGTAGCAGC	eekddddddddddkke	77	2906	1463
541430	35	Exon 1	CGCCACCGCCACTGTA	eekddddddddddkke	88	2911	1464
541431	63	Exon 1	GCCGCCCGGGCTCAGC	eekddddddddddkke	86	2939	1465
541432	67	Exon 1	CGCCGCCGCCCGGGCT	eekddddddddddkke	61	2943	1466
541433	144	Exon 1	GAGAGCGCGGGTTCGC	eekddddddddddkke	57	3020	1467
541434	n/a	Exon 1/Intron 1	CTACTGACCCCAGTTC	eekddddddddddkke	80	3655	1468
541435	n/a	Exon 1/Intron 1	TCACTCTACTGACCCC	eekddddddddddkke	90	3660	1469
541436	n/a	Exon 1/Intron 1	TCATGCGGACTGGTGG	eekddddddddddkke	56	3679	1470
541437	n/a	Exon 3/Intron 3	ATGTGAGCATGGACCC	eekddddddddddkke	82	225438	1471
541438	n/a	Exon 3/Intron 3	TCTTGATATGTGAGCA	eekddddddddddkke	93	225445	1472

541439	n/a	Exon 3/Intron 3	TTCAAGTTGGTGAGCT	eekddddddddddkke	72	226788	1473
541440	n/a	Exon 3/Intron 3	TGCTTCCTTCAAGTTG	eekddddddddddkke	68	226795	1474
541441	n/a	Exon 3/Intron 3	TGTAATTTCATTCATG	eekddddddddddkke	62	226809	1475
541442	n/a	Exon 3/Intron 3	CCTTTTGCCAAGAGCA	eekddddddddddkke	85	226876	1476
541443	n/a	Exon 3/Intron 3	GATCCTTTTGCCAAGA	eekddddddddddkke	77	226879	1477
541444	n/a	Exon 3/Intron 3	GCTAGTAATGTTACAT	eekddddddddddkke	68	238331	1478
541445	n/a	Exon 3/Intron 3	GCAACTTGCTAGTAAT	eekddddddddddkke	65	238338	1479
541446	n/a	Exon 3/Intron 3	TGTGCAACTTGCTAGT	eekddddddddddkke	44	238341	1480
541447	n/a	Exon 3/Intron 3	GGATTTCAGTTTGAAT	eekddddddddddkke	0	238363	1481
541448	n/a	Exon 3/Intron 3	CTCAGAGCCTTGGTAG	eekddddddddddkke	65	238428	1482
541449	n/a	Exon 1/Intron 1	CAAACGCGCAAAAGAC	eekddddddddddkke	1	3608	1483
541450	n/a	Exon 1/Intron 1	GCCCGCACAAACGCGC	eekddddddddddkke	11	3615	1484
541451	n/a	Exon 1/Intron 1	GGTTAAAGAAGTTGCT	eekddddddddddkke	60	93190	1485
541452	n/a	Exon 1/Intron 1	CCCAGTGAATTCAGCA	eekddddddddddkke	85	93245	1486
541453	n/a	Exon 1/Intron 1	GCGCCCAGTGAATTCA	eekddddddddddkke	74	93248	1487
541454	n/a	Exon 1/Intron 1	AAGATGCGCCCAGTGA	eekddddddddddkke	71	93253	1488
541455	n/a	Exon 1/Intron 1	TGTAAGATGCGCCCAG	eekddddddddddkke	75	93256	1489
541456	n/a	Exon 1/Intron 1	AATTACTTGTAAGATG	eekddddddddddkke	15	93263	1490
541457	n/a	Exon 1/Intron 1	CCCAGAAGGCACTTGT	eekddddddddddkke	61	93302	1491
541458	n/a	Exon 1/Intron 1	TTGCAGAACAAATCTT	eekddddddddddkke	3	93333	1492
541459	n/a	Exon 1/Intron 1	CATGGAAGATTTGCAG	eekddddddddddkke	17	93343	1493
541460	n/a	Exon 1/Intron 1	GGTCATGGAAGATTTG	eekddddddddddkke	57	93346	1494
541461	n/a	Exon 1/Intron 1	GACCTTGGTCATGGAA	eekddddddddddkke	51	93352	1495
541462	n/a	Exon 1/Intron 1	TGCCAATCCAAAGAGG	eekddddddddddkke	34	93369	1496
541463	n/a	Exon 1/Intron 1	GGGTCTGCCAATCCAA	eekddddddddddkke	67	93374	1497
541464	n/a	Exon 1/Intron 1	TCCCTGGGTCTGCCAA	eekddddddddddkke	82	93379	1498
541465	n/a	Exon 1/Intron 1	AAGTGTGAATTTATCT	eekddddddddddkke	16	93408	1499
541466	n/a	Exon 1/Intron 1	GGAGATCTCAACAAGG	eekddddddddddkke	38	93428	1500
541468	n/a	Exon 1/Intron 1	TCGCCCATCACTCTTC	eekddddddddddkke	43	93989	1501
541469	n/a	Exon 1/Intron 1	CCTGTCGCCCATCACT	eekddddddddddkke	61	93993	1502
541470	n/a	Exon 1/Intron 1	TCACCTGTCGCCCATC	eekddddddddddkke	70	93996	1503
541471	n/a	Exon 1/Intron 1	CCATCACCTGTCGCCC	eekddddddddddkke	89	93999	1504
541472	n/a	Exon 1/Intron 1	TCACCATCACCTGTCG	eekddddddddddkke	72	94002	1505
541473	n/a	Exon 1/Intron 1	TAATAGTTGTCACCAT	eekddddddddddkke	42	94011	1506
541474	n/a	Exon 1/Intron 1	TTCAGATCTTATTAAT	eekddddddddddkke	0	94023	1507
541475	n/a	Exon 1/Intron 1	TTGCAAATTCAGTCTG	eekddddddddddkke	32	94096	1508
541477	n/a	Exon 2/Intron 2	CGTTCTCTTGGAAGTA	eekddddddddddkke	78	198766	1509
541478	n/a	Exon 2/Intron 2	TCTTGAATAAATTTCG	eekddddddddddkke	25	198780	1510
541479	n/a	Exon 2/Intron 2	AAGCTCACTCTTCAAT	eekddddddddddkke	60	198810	1511
541480	n/a	Exon 2/Intron 2	TCCAAGCTCACTCTTC	eekddddddddddkke	49	198813	1512
541481	n/a	Exon 2/Intron 2	GCTCCTGCCACTCTGT	eekddddddddddkke	75	198837	1513
541482	n/a	Exon 2/Intron 2	ATGGGCAAAGGCATCT	eekddddddddddkke	60	198874	1514
541483	n/a	5' UTR	AGTCTTCCCGGCGAGG	eekddddddddddkke	32	2571	1515

541484	n/a	5' and overlappig with exon 1	CCGCCGCTCCCTAGCC	eekddddddddddkke	73	2867	1516
541485	n/a	Intron 1	GCCCGCAACTCCCTGC	eekddddddddddkke	37	3341	1517
541486	n/a	Intron 1	CGCCTCCCCAGGCGCA	eekddddddddddkke	34	4024	1518
541487	n/a	Intron 1	GAGTGTCTTCCCAGGC	eekddddddddddkke	86	4446	1519
541488	n/a	Intron 1	CTGAAGACTCCTTGAA	eekddddddddddkke	39	4721	1520
541489	n/a	Intron 1	GGCTAGCCAAGTTGGA	eekddddddddddkke	54	5392	1521
541490	n/a	Intron 1	TGACTCCAGTCTTACC	eekddddddddddkke	76	5802	1522
541491	n/a	Intron 1	ATTCATTGTGGTCAGC	eekddddddddddkke	91	6128	1523
541492	n/a	Intron 1	GAAGTGGGTTTTTCCC	eekddddddddddkke	86	6543	1524
541493	n/a	Intron 1	GCCTTGGTTCAGGTGA	eekddddddddddkke	79	6786	1525

Table 175

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting SEQ ID NO: 4 and 7

ISIS NO	Target Start Site	Target SEQ ID NO	Sequence	Chemistry	% inhibition	SEQ ID NO
541428	66	4	CCACTGTAGCAGCCGC	eekddddddddddkke	92	1526
541476	263	7	TAGGTATTTCAGAGCC	eekddddddddddkke	80	1527

Table 176

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic regions of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 2 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	541277	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	80	1370
541494	7231	541509	Intron 1	GTCCAGGCAGAGTTGT	eekddddddddddkke	30	1528
541495	7570	541510	Intron 1	AGCCAAATGTTGGTCA	eekddddddddddkke	19	1529
541496	8395	541511	Intron 1	GAGGGCGAGTTTTTCC	eekddddddddddkke	71	1530
541497	9153	541512	Intron 1	GTGGCATTGGCAAGCC	eekddddddddddkke	81	1531
541498	9554	541513	Intron 1	ACCCCACTGCACCAAG	eekddddddddddkke	67	1532
541499	9931	541514	Intron 1	TCCAAGTACTTGCCAA	eekddddddddddkke	83	1533
541500	10549	541515	Intron 1	AGTGCCTGGCCTAAGG	eekddddddddddkke	75	1534
541501	11020	541516	Intron 1	GCGCTTCTTCCCTAGG	eekddddddddddkke	71	1535
541502	11793	541517	Intron 1	CATCTTGCCCAGGGAT	eekddddddddddkke	84	1536
541503	12214	541518	Intron 1	CCATCTTGCTCCAAGT	eekddddddddddkke	93	1537
541504	12474	541519	Intron 1	CTTACATCCTGTAGGC	eekddddddddddkke	71	1538
541505	12905	541520	Intron 1	CGCCTCCTGGTCCTCA	eekddddddddddkke	97	1539
541506	13400	541521	Intron 1	CCCTATGCACTACCTA	eekddddddddddkke	49	1540
541507	13717	541522	Intron 1	GAGGGACTGTGGTGCT	eekddddddddddkke	65	1541
541508	14149	541523	Intron 1	GCCCAATATGTGCCAG	eekddddddddddkke	60	1542

541509	14540	541524	Intron 1	GCTCTCTCATCGCTGG	eekddddddddddkke	90	1543
541510	15264	541525	Intron 1	CTCAAGGCTATGTGCC	eekddddddddddkke	67	1544
541511	15849	541526	Intron 1	TCCACATCCCTCATGT	eekddddddddddkke	68	1545
541512	16530	541527	Intron 1	AGGACTGAAGGCCCAT	eekddddddddddkke	49	1546
541513	17377	541528	Intron 1	GTGCGACTTACCAGCT	eekddddddddddkke	85	1547
541514	17581	541529	Intron 1	TCGCTAAAGCCACACA	eekddddddddddkke	89	1548
541515	17943	541530	Intron 1	GCTCTGGCTGATGGTC	eekddddddddddkke	92	1549
541516	18353	541531	Intron 1	TTCCCATGAGGATTTC	eekddddddddddkke	70	1550
541517	18636	541532	Intron 1	TTGGGCTTAAGCACTA	eekddddddddddkke	71	1551
541518	19256	541533	Intron 1	GCTAGCACCTAGTCCA	eekddddddddddkke	71	1552
541519	19814	541534	Intron 1	CCTCTGGCCTACAACA	eekddddddddddkke	64	1553
541520	20365	541535	Intron 1	ACCCCTCATCAGCACC	eekddddddddddkke	93	1554
541521	20979	541536	Intron 1	GGCCACCCCTGATCCT	eekddddddddddkke	66	1555
541522	21566	541537	Intron 1	GAAGCTCCCTTGCCCA	eekddddddddddkke	96	1556
541523	22150	541538	Intron 1	AGTGTTGCCCCTCCAA	eekddddddddddkke	83	1557
541524	22803	541539	Intron 1	GGGTCTCCAACCTACT	eekddddddddddkke	70	1558
541525	29049	541540	Intron 1	GGGATGTAGGTTTACC	eekddddddddddkke	74	1559
541526	29554	541541	Intron 1	GCAACCGATATCACAG	eekddddddddddkke	60	1560
541527	30245	541542	Intron 1	TGCCCTGGAACAAATT	eekddddddddddkke	13	1561
541528	30550	541543	Intron 1	AGTCTAGGAGTAGCTA	eekddddddddddkke	50	1562
541529	30915	541544	Intron 1	GCTGTTGTCAAGAGAC	eekddddddddddkke	55	1563
541530	31468	541545	Intron 1	CACCTAGACACTCAGT	eekddddddddddkke	47	1564
541531	32366	541546	Intron 1	GTCAAGGGATCCCTGC	eekddddddddddkke	34	1565
541532	32897	541547	Intron 1	TCCCCCTGGCACTCCA	eekddddddddddkke	79	1566
541533	33187	541548	Intron 1	GCCTGGTAACTCCATT	eekddddddddddkke	56	1567
541534	33780	541549	Intron 1	GGGCTCACCAACTGTG	eekddddddddddkke	39	1568
541535	34407	541550	Intron 1	CCACAGGATCATATCA	eekddddddddddkke	37	1569
541536	34846	541551	Intron 1	CTCCAGCAGAAGTGTC	eekddddddddddkke	10	1570
541537	35669	541552	Intron 1	AGCCCAACTGTTGCCT	eekddddddddddkke	79	1571
541538	36312	541553	Intron 1	TGCCAGGCAGTTGCCA	eekddddddddddkke	75	1572
541539	36812	541554	Intron 1	GCCAGTAAGCACCTTG	eekddddddddddkke	93	1573
541540	37504	541555	Intron 1	CTAGCTTCCCAGCCCC	eekddddddddddkke	46	1574
541541	38841	541556	Intron 1	TCAAGCCCAGCTAGCA	eekddddddddddkke	39	1575
541542	39108	541557	Intron 1	CCTCACAGGCCCTAAT	eekddddddddddkke	4	1576
541543	39408	541558	Intron 1	ACCTGCTTACATGGTA	eekddddddddddkke	21	1577
541544	40250	541559	Intron 1	CCTTTGCTAGGACCCA	eekddddddddddkke	52	1578
541545	40706	541560	Intron 1	GGGACTGCCACCAAGG	eekddddddddddkke	27	1579
541546	40922	541561	Intron 1	GCTAGATGTTCAGGCC	eekddddddddddkke	34	1580
541547	41424	541562	Intron 1	CCTATGGCCATGCTGA	eekddddddddddkke	32	1581
541548	41999	541563	Intron 1	GTATGCTAGTTCCCAT	eekddddddddddkke	83	1582
541549	42481	541564	Intron 1	CCCTCATAATCTTGGG	eekddddddddddkke	13	1583
541550	42700	541565	Intron 1	GTCCAACCACTACCAC	eekddddddddddkke	74	1584
541551	43291	541566	Intron 1	ACTTGCAGATAGCTGA	eekddddddddddkke	73	1585

541552	43500	541567	Intron 1	GCATGACCCCACTGCC	eekddddddddddkke	72	1586
541553	43947	541568	Intron 1	GAGGGTCACATTCCCT	eekddddddddddkke	23	1587
541554	44448	541569	Intron 1	TCTCTTACTGGTGGGT	eekddddddddddkke	90	1588
541555	45162	541570	Intron 1	GCCCCCTTCCTGGATA	eekddddddddddkke	28	1589
541556	46010	541571	Intron 1	CCTCATGCGACACCAC	eekddddddddddkke	71	1590
541557	46476	541572	Intron 1	AGCCCTCTGCCTGTAA	eekddddddddddkke	67	1591
541558	47447	541573	Intron 1	CTCCCAGCTATAGGCG	eekddddddddddkke	38	1592
541559	47752	541574	Intron 1	GCTAGCTGCGCAAGGA	eekddddddddddkke	5	1593
541560	48001	541575	Intron 1	GCGCAGCCCGCTGCAA	eekddddddddddkke	18	1594
541561	48423	541576	Intron 1	TGCATGATCCACCCCA	eekddddddddddkke	65	1595
541562	50195	541577	Intron 1	GCTTAGTGCTGGCCCA	eekddddddddddkke	72	1596
541563	50470	541578	Intron 1	CCTTCCAGTCCTCATA	eekddddddddddkke	81	1597
541564	51104	541579	Intron 1	ATAGTGTCAAGGCCCA	eekddddddddddkke	91	1598
541565	51756	541580	Intron 1	AGGCCTTAGTCACCCA	eekddddddddddkke	88	1599
541566	52015	541581	Intron 1	TAACCAACCTAAGGGA	eekddddddddddkke	11	1600
541567	52230	541582	Intron 1	ATTCTGGTGATGCCCT	eekddddddddddkke	66	1601
541568	52588	541583	Intron 1	GTGTTCACTGCCATGA	eekddddddddddkke	67	1602
541569	53532	541584	Intron 1	GGTAGAGCACACTGCC	eekddddddddddkke	47	1603
541570	54645	541585	Intron 1	CCACTTTAATGCCACC	eekddddddddddkke	76	1604

Table 177

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic regions of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	156906	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	88	1370
541571	54886	54901	Intron 1	GTCAAATGCTGTTGGG	eekddddddddddkke	91	1605
541572	55900	55915	Intron 1	CATCCCCTATCAGGGT	eekddddddddddkke	53	1606
541573	62266	62281	Intron 1	CTCGAATCCCTTGAGC	eekddddddddddkke	73	1607
541574	62733	62748	Intron 1	GATTCCCTCCCCTAAC	eekddddddddddkke	27	1608
541575	63173	63188	Intron 1	ATCCATCCATGTGCTG	eekddddddddddkke	92	1609
541576	63751	63766	Intron 1	GAGCATGCCTCAGTGG	eekddddddddddkke	81	1610
541577	63964	63979	Intron 1	CAGAAGGACTGCCTCT	eekddddddddddkke	50	1611
541578	64213	64228	Intron 1	ACAATGCTCAACAGCC	eekddddddddddkke	75	1612
541579	64576	64591	Intron 1	GTTGGATCTGGCATGC	eekddddddddddkke	80	1613
541580	65027	65042	Intron 1	CGGCTGAGAGCAAGGG	eekddddddddddkke	88	1614
541581	65363	65378	Intron 1	GAGAGGGTTCAGCCTG	eekddddddddddkke	62	1615
541582	65600	65615	Intron 1	ACTTAGTTCCTAGCCA	eekddddddddddkke	91	1616
541583	66087	66102	Intron 1	GTGAACCAGATGTGCT	eekddddddddddkke	86	1617
541584	66566	66581	Intron 1	GGAGTGACAGCTAAGT	eekddddddddddkke	98	1618
541585	66978	66993	Intron 1	AAGTGTTCAGAGCCAC	eekddddddddddkke	97	1619

541586	67662	67677	Intron 1	AACCCTGCCAAGGTAC	eekddddddddddkke	45	1620
541587	67914	67929	Intron 1	GATGGTGAGCACTACC	eekddddddddddkke	78	1621
541588	68278	68293	Intron 1	GGCAGGATAGGACAGA	eekddddddddddkke	11	1622
541589	68727	68742	Intron 1	GCAAAGTGATGAGCCT	eekddddddddddkke	81	1623
541590	69207	69222	Intron 1	CTATCCACACCATTCC	eekddddddddddkke	93	1624
541591	69605	69620	Intron 1	GGATCATGGGCCCCTA	eekddddddddddkke	70	1625
541592	70130	70145	Intron 1	GTGAATTTGCTGGGCC	eekddddddddddkke	94	1626
541593	70569	70584	Intron 1	GTGATGGGCCCAAGGC	eekddddddddddkke	67	1627
541594	71056	71071	Intron 1	TCCTCAGTCGGCTTGC	eekddddddddddkke	69	1628
541595	71314	71329	Intron 1	CAGCCTTTTGCCAGAT	eekddddddddddkke	93	1629
541596	71620	71635	Intron 1	CCTCCCTAGGATTACC	eekddddddddddkke	42	1630
541597	72226	72241	Intron 1	ACGCCCCAATCACTCA	eekddddddddddkke	79	1631
541598	72655	72670	Intron 1	GCATGACCCATTATGT	eekddddddddddkke	94	1632
541599	73061	73076	Intron 1	TCCCTCCAAGAGCTCA	eekddddddddddkke	83	1633
541600	73708	73723	Intron 1	GATGCCTGTGGCTGAC	eekddddddddddkke	84	1634
541601	74107	74122	Intron 1	GGCTAGCATGTTGCCT	eekddddddddddkke	19	1635
541602	74542	74557	Intron 1	TAACCCACTAGGCTGG	eekddddddddddkke	84	1636
541603	74947	74962	Intron 1	TGGCCCAAAACTAATC	eekddddddddddkke	34	1637
541604	75192	75207	Intron 1	GGAGCAGTCTGGCACC	eekddddddddddkke	85	1638
541605	75699	75714	Intron 1	TATTCTGTGGGACAAG	eekddddddddddkke	51	1639
541606	75979	75994	Intron 1	GTGTCTAGTTCCAGCC	eekddddddddddkke	86	1640
541607	76410	76425	Intron 1	TACTATCATGTAGCGC	eekddddddddddkke	87	1641
541608	76701	76716	Intron 1	TGCCCTTGTAGTGAGA	eekddddddddddkke	31	1642
541609	76980	76995	Intron 1	TCCCCAACCTACAAGC	eekddddddddddkke	41	1643
541610	77292	77307	Intron 1	GCTCTAGGCATATGAA	eekddddddddddkke	63	1644
541611	77555	77570	Intron 1	TACCTCCCTTGTAGGG	eekddddddddddkke	27	1645
541612	77854	77869	Intron 1	GGTTCCCTTGCAGAGA	eekddddddddddkke	62	1646
541613	78311	78326	Intron 1	GTGCCCTCTTCATGCC	eekddddddddddkke	68	1647
541614	79006	79021	Intron 1	CCTGTGTGCAACTGGC	eekddddddddddkke	85	1648
541615	79490	79505	Intron 1	CTGAGTCATTTGCCTG	eekddddddddddkke	93	1649
541616	79829	79844	Intron 1	GGCCTTAGTAGGCCAG	eekddddddddddkke	0	1650
541617	80277	80292	Intron 1	GTCCTTGCAGTCAACC	eekddddddddddkke	77	1651
541618	80575	80590	Intron 1	GCTGGGCCAAGTCCAT	eekddddddddddkke	77	1652
541619	80895	80910	Intron 1	TAGGGCACTTTTTGCC	eekddddddddddkke	31	1653
541620	81207	81222	Intron 1	GCTGAGGTCCCTCTCT	eekddddddddddkke	34	1654
541621	81761	81776	Intron 1	CTTTGGTCCCATTGCC	eekddddddddddkke	83	1655
541622	82233	82248	Intron 1	GGAACATGCCAAGGGC	eekddddddddddkke	91	1656
541623	82738	82753	Intron 1	AGGTGGTCTCCCTTCA	eekddddddddddkke	74	1657
541624	83056	83071	Intron 1	TCCCAAAGCTCCCCTC	eekddddddddddkke	53	1658
541625	83401	83416	Intron 1	CCTGGCCTAGCAAGCT	eekddddddddddkke	47	1659
541626	84048	84063	Intron 1	TCTTAGCCCTGGGCTA	eekddddddddddkke	12	1660
541627	84388	84403	Intron 1	GACTTGGACTGGGCTC	eekddddddddddkke	81	1661
541628	85261	85276	Intron 1	GGCCTAGGATCTAGGA	eekddddddddddkke	0	1662

541629	85714	85729	Intron 1	GTCAGGCTAGAGGGAC	eekddddddddddkke	41	1663
541630	86220	86235	Intron 1	GGAAGTTCTCCCAGCC	eekddddddddddkke	47	1664
541631	86640	86655	Intron 1	CCTGACTGATGTACAC	eekddddddddddkke	35	1665
541632	86903	86918	Intron 1	CTCTGGCCTAGCCTAT	eekddddddddddkke	54	1666
541633	87247	87262	Intron 1	GGCTGCTGTCAGATGC	eekddddddddddkke	79	1667
541634	88293	88308	Intron 1	TCTCAGGTGTAGGCAG	eekddddddddddkke	59	1668
541635	88605	88620	Intron 1	GGTCACTGAGACTGGG	eekddddddddddkke	88	1669
541636	88952	88967	Intron 1	ACCCACTAGCAGCTAG	eekddddddddddkke	61	1670
541637	89160	89175	Intron 1	CGGATGAGGCAGTTAG	eekddddddddddkke	42	1671
541638	89855	89870	Intron 1	TGGTAGGCCCTCTGGC	eekddddddddddkke	28	1672
541639	90240	90255	Intron 1	GTCACAAGGTGGGTGC	eekddddddddddkke	28	1673
541640	90513	90528	Intron 1	GTCTTGCCCTCACGGA	eekddddddddddkke	73	1674
541641	91073	91088	Intron 1	GCAGTCTGTGGACTTA	eekddddddddddkke	93	1675
541642	91647	91662	Intron 1	TGCTCTCTGGTCACAC	eekddddddddddkke	75	1676
541643	92069	92084	Intron 1	TATCCCCCAGAGCCAT	eekddddddddddkke	68	1677
541644	92356	92371	Intron 1	AAGGTGAGAGGGCACT	eekddddddddddkke	75	1678
541645	92904	92919	Intron 1	GTTTTAACCTCACCCT	eekddddddddddkke	0	1679
541646	93846	93861	Intron 1	CCTTCCACTGACCTTC	eekddddddddddkke	56	1680
541647	94374	94389	Intron 1	GACACTAGCCTAAGCC	eekddddddddddkke	37	1681

Table 178

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic regions of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	156906	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	94	1370
541648	94638	94653	Intron 1	GGTTAGCCCTCAGCCT	eekddddddddddkke	61	1682
541649	94839	94854	Intron 1	TATGAAGGTTGGACCA	eekddddddddddkke	69	1683
541650	95509	95524	Intron 1	CAACCAGCTCACCTGA	eekddddddddddkke	37	1684
541651	95829	95844	Intron 1	GGGCTCCAAGGCTCTC	eekddddddddddkke	75	1685
541652	96158	96173	Intron 1	AGCTGTTACATGCCAA	eekddddddddddkke	93	1686
541653	96488	96503	Intron 1	GGCCCAGAGGTTATAG	eekddddddddddkke	30	1687
541654	96991	97006	Intron 1	GTCCTTAGACCCCTCA	eekddddddddddkke	70	1688
541655	97539	97554	Intron 1	GCCCTGGCTAGAGACA	eekddddddddddkke	39	1689
541656	98132	98147	Intron 1	CATCCAGCAGCTGGAC	eekddddddddddkke	35	1690
541657	98833	98848	Intron 1	GACTGAGGTCATCACA	eekddddddddddkke	60	1691
541658	99258	99273	Intron 1	GGCCAGGCACATCATG	eekddddddddddkke	45	1692
541659	99843	99858	Intron 1	GGAGCTCATTGAGCCA	eekddddddddddkke	36	1693
541660	100406	100421	Intron 1	GTGCCCATTGCTGTGT	eekddddddddddkke	70	1694
541661	100742	100757	Intron 1	CCAAGTGTGGCTTCAG	eekddddddddddkke	54	1695
541662	101305	101320	Intron 1	CCACCCTTTATACGCA	eekddddddddddkke	87	1696
541663	101788	101803	Intron 1	CAGTAACCCCAAGGGA	eekddddddddddkke	12	1697

541664	102649	102664	Intron 1	CCCCACCTTATATGGG	eekddddddddddkke	9	1698
541665	103034	103049	Intron 1	AGGCCCTTTTTACATG	eekddddddddddkke	9	1699
541666	103316	103331	Intron 1	TCAATAAGTCCCTAGG	eekddddddddddkke	20	1700
541667	104277	104292	Intron 1	GGCATTGAGTGACTGC	eekddddddddddkke	51	1701
541668	104679	104694	Intron 1	ATAATGCCTTCTCAGC	eekddddddddddkke	62	1702
541669	106349	106364	Intron 1	GTGAGGCATTTAGCCC	eekddddddddddkke	35	1703
541670	106632	106647	Intron 1	GCTCTTGTGTTGGGTA	eekddddddddddkke	89	1704
541671	107084	107099	Intron 1	TGTGCAGGAGGTCTCA	eekddddddddddkke	60	1705
541672	107949	107964	Intron 1	TGGAGAGTCTTGTCTC	eekddddddddddkke	17	1706
541673	108773	108788	Intron 1	GTGACCCACCCAAGAG	eekddddddddddkke	34	1707
541674	109336	109351	Intron 1	GTTGTAGCTAGTGTTC	eekddddddddddkke	74	1708
541675	109849	109864	Intron 1	GCCTTAGTTTGTGCCA	eekddddddddddkke	78	1709
541676	110427	110442	Intron 1	GCCCCAGCTGAGAATT	eekddddddddddkke	29	1710
541677	110701	110716	Intron 1	ACAACAATCCAGGGTG	eekddddddddddkke	61	1711
541678	110959	110974	Intron 1	CTCCCCTGGAAGTCAC	eekddddddddddkke	59	1712
541679	111307	111322	Intron 1	GCCCTCATGGCTCAAG	eekddddddddddkke	60	1713
541680	112499	112514	Intron 1	TCAGCAGATAGGGAGC	eekddddddddddkke	61	1714
541681	113896	113911	Intron 1	GAATGCGGTGATCAGG	eekddddddddddkke	29	1715
541682	117477	117492	Intron 1	CTGAGAGAATTGGCCC	eekddddddddddkke	5	1716
541683	117740	117755	Intron 1	AGGCACATTGTTACCA	eekddddddddddkke	26	1717
541684	118229	118244	Intron 1	GGGAGGCACTAGAGAA	eekddddddddddkke	13	1718
541685	119269	119284	Intron 1	TACAGTAACACATCCC	eekddddddddddkke	78	1719
541686	119688	119703	Intron 1	GAAGCTCAGCCTGATC	eekddddddddddkke	45	1720
541687	120376	120391	Intron 1	CTTGCCTGACAACCTA	eekddddddddddkke	53	1721
541688	120738	120753	Intron 1	GCCTACCTGCTTTTGC	eekddddddddddkke	10	1722
541689	121242	121257	Intron 1	TTTCCCAACCACTTAG	eekddddddddddkke	7	1723
541690	121615	121630	Intron 1	TCTCCTATTTCAGTTA	eekddddddddddkke	23	1724
541691	121823	121838	Intron 1	GGGTGATGGATGAACT	eekddddddddddkke	40	1725
541692	122345	122360	Intron 1	ACACTGCTGGTAGTGA	eekddddddddddkke	0	1726
541693	122588	122603	Intron 1	ACCCAACTAGCCTGTC	eekddddddddddkke	35	1727
541694	123152	123167	Intron 1	GAGACCTGCTGCCTGA	eekddddddddddkke	80	1728
541695	123671	123686	Intron 1	ACATCTCTTGGGAGGT	eekddddddddddkke	78	1729
541696	124040	124055	Intron 1	ACATAGTACCCCTCCA	eekddddddddddkke	35	1730
541697	124430	124445	Intron 1	CTCTCAAGTACCTGCC	eekddddddddddkke	72	1731
541698	124824	124839	Intron 1	TTTGTACCCAACCCCC	eekddddddddddkke	15	1732
541699	125032	125047	Intron 1	AGGCCCACATAAATGC	eekddddddddddkke	21	1733
541700	125533	125548	Intron 1	GAGCATCCCCTACACT	eekddddddddddkke	12	1734
541701	126357	126372	Intron 1	GCTGGGCCTTTAGCTG	eekddddddddddkke	66	1735
541702	126736	126751	Intron 1	TTGGTCAATTGGGCAG	eekddddddddddkke	79	1736
541703	127179	127194	Intron 1	GTCTCATGAGGCCTAT	eekddddddddddkke	60	1737
541704	127454	127469	Intron 1	GGAGGTGGGATCCCAC	eekddddddddddkke	35	1738
541705	128467	128482	Intron 1	GCCCACTACCTAGCAC	eekddddddddddkke	30	1739
541706	129096	129111	Intron 1	CCCAGCTGGCTGGTCG	eekddddddddddkke	50	1740

541707	129312	129327	Intron 1	GCACCAGGTCTCCTGT	eekddddddddddkke	7	1741
541708	129516	129531	Intron 1	GTCTAGAAGCCTAGGG	eekddddddddddkke	23	1742
541709	129976	129991	Intron 1	GCCGGGTGTTGGTGCA	eekddddddddddkke	50	1743
541710	130308	130323	Intron 1	TTGGTGCCTGTGTTGC	eekddddddddddkke	49	1744
541711	130767	130782	Intron 1	TGCTTCTGATCCCTAC	eekddddddddddkke	18	1745
541712	131286	131301	Intron 1	GTTCCCAGGAGGCTTA	eekddddddddddkke	56	1746
541713	131676	131691	Intron 1	AGGCCCCTAGAGTCTA	eekddddddddddkke	41	1747
541714	132292	132307	Intron 1	TGGTGTGCCCAGACTT	eekddddddddddkke	60	1748
541715	132730	132745	Intron 1	GATGGCTAACCCACTG	eekddddddddddkke	14	1749
541716	133101	133116	Intron 1	CCCCCAAAAGTTGCCC	eekddddddddddkke	12	1750
541717	133522	133537	Intron 1	TAGGGTGTTCCAGATC	eekddddddddddkke	44	1751
541718	133724	133739	Intron 1	GTACCATGAAGCTCTG	eekddddddddddkke	67	1752
541719	134086	134101	Intron 1	CTTGGACTTGGACCAT	eekddddddddddkke	42	1753
541720	134441	134456	Intron 1	GTGCATAGGGCCTGTC	eekddddddddddkke	42	1754
541721	135015	135030	Intron 1	CCTCACCTGAACACCC	eekddddddddddkke	23	1755
541722	135859	135874	Intron 1	ATGCCTCCCCGCAACT	eekddddddddddkke	27	1756
541723	136287	136302	Intron 1	TTGTGCTTGGGTGTAC	eekddddddddddkke	39	1757
541724	137000	137015	Intron 1	AGGCTTCATGTGAGGT	eekddddddddddkke	86	1758

Table 179

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting introns 1 and 2 of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	156906	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	95	1370
541725	137372	137387	Intron 1	TGTAAAAGGTCCTCCC	eekddddddddddkke	53	1759
541726	137750	137765	Intron 1	GACCTGTGCAGCAGGT	eekddddddddddkke	32	1760
541727	138783	138798	Intron 1	TCCTCTTGGAGATCCA	eekddddddddddkke	44	1761
541728	139825	139840	Intron 1	AGGTCATAGGACTGCT	eekddddddddddkke	73	1762
541729	140343	140358	Intron 1	GAAGGTCAGACTAGGG	eekddddddddddkke	53	1763
541730	140686	140701	Intron 1	TCTGTAGACTGCCCAG	eekddddddddddkke	87	1764
541731	141116	141131	Intron 1	GTCCCTCTATTCCCCT	eekddddddddddkke	57	1765
541732	141591	141606	Intron 1	AATTGCCATGCTCCCA	eekddddddddddkke	56	1766
541733	142113	142128	Intron 1	GATGACCTTCCTCCAA	eekddddddddddkke	15	1767
541734	142327	142342	Intron 1	GTTTCCAGTAGCACCT	eekddddddddddkke	82	1768
541735	143118	143133	Intron 1	GGCCTTGAGCTGATGG	eekddddddddddkke	11	1769
541736	143836	143851	Intron 1	TATCCCTAATCAGGCT	eekddddddddddkke	40	1770
541737	144094	144109	Intron 1	GGTGTCCACATCCCGG	eekddddddddddkke	58	1771
541738	144558	144573	Intron 1	AGCTGGACAGGCCATA	eekddddddddddkke	27	1772
541740	145510	145525	Intron 2	GGTAATCACCCAGAGA	eekddddddddddkke	90	1773
541741	145937	145952	Intron 2	GCGCTAAGTCTGCTGT	eekddddddddddkke	92	1774
541742	146320	146335	Intron 2	CCTCAAATCTTGCCCA	eekddddddddddkke	96	1775

541743	147028	147043	Intron 2	ATCCAGACCTGGCAGA	eekddddddddddkke	84	1776
541744	147262	147277	Intron 2	ATCCCTGCTCAAGTGC	eekddddddddddkke	89	1777
541745	147671	147686	Intron 2	CAGGCACTCCTTGGAA	eekddddddddddkke	93	1778
541746	148139	148154	Intron 2	AGCTGAGGTATCCCTC	eekddddddddddkke	94	1779
541747	148564	148579	Intron 2	GGGCCCAGCAAGTCTT	eekddddddddddkke	33	1780
541748	149069	149084	Intron 2	GTTTTGTCAGTGTGCA	eekddddddddddkke	98	1781
541749	149491	149506	Intron 2	GTGACCTGCTGAACTC	eekddddddddddkke	95	1782
541750	150236	150251	Intron 2	GGCTGAACTGTGCACC	eekddddddddddkke	95	1783
541751	150748	150763	Intron 2	GGGTGGTCCCACTCCT	eekddddddddddkke	91	1784
541752	151124	151139	Intron 2	GAGGAATCCTGGGCCC	eekddddddddddkke	94	1785
541753	151373	151388	Intron 2	ATGACAAGCTAGGTGC	eekddddddddddkke	81	1786
541754	151644	151659	Intron 2	TTGCCAGACAGGGCAC	eekddddddddddkke	18	1787
541755	152373	152388	Intron 2	AGACCCCTCCCACTAT	eekddddddddddkke	43	1788
541756	152617	152632	Intron 2	GGTGCTGGGTGACCGG	eekddddddddddkke	91	1789
541757	153349	153364	Intron 2	GGCCAAACGGTGCCCT	eekddddddddddkke	23	1790
541758	153918	153933	Intron 2	TGGGTGAATAGCAACC	eekddddddddddkke	85	1791
541759	154171	154186	Intron 2	GCCCCCAAGGAAGTGA	eekddddddddddkke	76	1792
541760	154813	154828	Intron 2	CAGGCTTCATGTGTGG	eekddddddddddkke	92	1793
541761	155289	155304	Intron 2	CTGTCAGTGCTTTGGT	eekddddddddddkke	52	1794
541762	156233	156248	Intron 2	GAGTACCCTGGCAGGT	eekddddddddddkke	58	1795
541763	156847	156862	Intron 2	TAGCTAGCACCTGGGT	eekddddddddddkke	90	1796
541764	157552	157567	Intron 2	GGCAAACCTTTGAGCC	eekddddddddddkke	27	1797
541765	157927	157942	Intron 2	GCTATCATTGGAGCAG	eekddddddddddkke	94	1798
541766	158542	158557	Intron 2	CCTCTGAGTACTCCCT	eekddddddddddkke	96	1799
541767	159252	159267	Intron 2	AGCTGAAGGCAACCAG	eekddddddddddkke	97	1800
541768	159539	159554	Intron 2	GGGCAGTTTTCCATAG	eekddddddddddkke	89	1801
541769	159778	159793	Intron 2	GGTCCTACCTCTGACA	eekddddddddddkke	82	1802
541770	160352	160367	Intron 2	GGCTGCCTTAGGGTGG	eekddddddddddkke	90	1803
541771	160812	160827	Intron 2	CGCACCTCCCCCACTA	eekddddddddddkke	15	1804
541772	161461	161476	Intron 2	GCTTATTGGTCCATGG	eekddddddddddkke	93	1805
541773	161821	161836	Intron 2	AACCGCAGAGCCCCCA	eekddddddddddkke	76	1806
541774	162132	162147	Intron 2	GGGCTTGTTCTGCCAA	eekddddddddddkke	33	1807
541775	162639	162654	Intron 2	GGGACCTGCGCTGACT	eekddddddddddkke	86	1808
541776	163024	163039	Intron 2	CTTTCACCTGGTGACT	eekddddddddddkke	83	1809
541777	163542	163557	Intron 2	AGCTTGAGGGAGTATA	eekddddddddddkke	52	1810
541778	164144	164159	Intron 2	GCCTGCTCAATTGAGG	eekddddddddddkke	32	1811
541779	164570	164585	Intron 2	ATAGCAGCTGGCTGCC	eekddddddddddkke	24	1812
541780	165419	165434	Intron 2	AAAAGCTTGGCACCCC	eekddddddddddkke	91	1813
541781	165859	165874	Intron 2	CCTGGCAAGAAGGGCC	eekddddddddddkke	65	1814
541782	166435	166450	Intron 2	TTAGCCCATCTATCCC	eekddddddddddkke	82	1815
541783	166837	166852	Intron 2	GTGGTCTCCCTGTGCC	eekddddddddddkke	90	1816
541784	167107	167122	Intron 2	AGCCCTCTCTGGCAAA	eekddddddddddkke	38	1817
541785	168004	168019	Intron 2	TTACTGTGGCCCGAGT	eekddddddddddkke	94	1818

541786	169062	169077	Intron 2	GTAGACTCCTAGGGTC	eekddddddddddkke	90	1819
541787	169696	169711	Intron 2	CCTCCAGTTAGTGTGC	eekddddddddddkke	91	1820
541788	170081	170096	Intron 2	GTGGGTGGCCAACAGG	eekddddddddddkke	91	1821
541789	170799	170814	Intron 2	GGGATTCCCTGGTAGC	eekddddddddddkke	77	1822
541790	171021	171036	Intron 2	GTGAGACCGGCCTTTG	eekddddddddddkke	23	1823
541791	171530	171545	Intron 2	ACTGGCACCCACTTGG	eekddddddddddkke	54	1824
541792	172447	172462	Intron 2	ATTGGCCTAATGCCCC	eekddddddddddkke	76	1825
541793	172733	172748	Intron 2	AGGCTATACATTCCAG	eekddddddddddkke	94	1826
541794	173045	173060	Intron 2	GGTGGCAGCTAGGTGG	eekddddddddddkke	80	1827
541795	173677	173692	Intron 2	TCCACAGTTGGCACTG	eekddddddddddkke	77	1828
541796	174128	174143	Intron 2	TGGGCCTTAGATTGTA	eekddddddddddkke	69	1829
541797	174521	174536	Intron 2	TGTCTTCCTGGTGGCC	eekddddddddddkke	97	1830
541798	174870	174885	Intron 2	CCCGCCTCTCCAGCAA	eekddddddddddkke	89	1831
541799	175275	175290	Intron 2	GCAGCAGCCAATAAGT	eekddddddddddkke	76	1832
541800	175691	175706	Intron 2	TTGTATCCTGGCCCCT	eekddddddddddkke	80	1833
541801	176038	176053	Intron 2	GCCTCATGGGCCTTAC	eekddddddddddkke	66	1834

Table 180

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting introns 2 and 3 of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	156906	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	97	1370
541802	176619	176634	Intron 2	GGATGCCAGTCTTGGC	eekddddddddddkke	48	1835
541803	176835	176850	Intron 2	CTGCTCTCAGTACCTC	eekddddddddddkke	87	1836
541804	177300	177315	Intron 2	ACCCAAGAAGTCACCT	eekddddddddddkke	93	1837
541805	177551	177566	Intron 2	GCCTCAAGCCCTACCC	eekddddddddddkke	73	1838
541806	178066	178081	Intron 2	AGCTCCAGCCTATAGA	eekddddddddddkke	81	1839
541807	178361	178376	Intron 2	GGTCCACATGGCCCTA	eekddddddddddkke	90	1840
541808	178895	178910	Intron 2	CAGGCCCAGGATTGTC	eekddddddddddkke	81	1841
541809	179444	179459	Intron 2	GGGCCTGCTTTGCAGC	eekddddddddddkke	81	1842
541810	179863	179878	Intron 2	ACTCCTCTCTTTAGGC	eekddddddddddkke	87	1843
541811	180524	180539	Intron 2	CTGGGTAACAGTCCTC	eekddddddddddkke	98	1844
541812	181528	181543	Intron 2	ACTGTATGGTTTCCAC	eekddddddddddkke	83	1845
541813	182103	182118	Intron 2	GCCAAAGATAGCTCTT	eekddddddddddkke	94	1846
541814	182978	182993	Intron 2	GGCATTGGAAGTTGGT	eekddddddddddkke	87	1847
541815	183193	183208	Intron 2	CCCTTCCTGACCTTAC	eekddddddddddkke	55	1848
541816	183658	183673	Intron 2	TTACCCTCTATTCACC	eekddddddddddkke	65	1849
541818	184501	184516	Intron 2	GGCACCCCAGGCCGGG	eekddddddddddkke	25	1850
541819	185080	185095	Intron 2	CAGCAGCTAGTTCCCC	eekddddddddddkke	96	1851
541820	185327	185342	Intron 2	GTGGGCACTAGTGTGT	eekddddddddddkke	75	1852
541821	185682	185697	Intron 2	TGCCCTTGTCAGGGCA	eekddddddddddkke	20	1853

541822	186025	186040	Intron 2	GCAGATAGGCTCAGCA	eekddddddddddkke	98	1854
541823	186570	186585	Intron 2	CCCTAGCCCTTAGCAC	eekddddddddddkke	44	1855
541824	186841	186856	Intron 2	ACTGGAATGGCCCTCT	eekddddddddddkke	86	1856
541825	187176	187191	Intron 2	TTTGCTCATGCTCACA	eekddddddddddkke	96	1857
541826	187629	187644	Intron 2	GCCTTTGTGTGTCACT	eekddddddddddkke	99	1858
541827	187857	187872	Intron 2	TATGTGGTAGCATGTC	eekddddddddddkke	96	1859
541828	188442	188457	Intron 2	CCCCAGGAAGTTGGCC	eekddddddddddkke	68	1860
541829	189086	189101	Intron 2	TAGCTGTCAAGGCCCT	eekddddddddddkke	90	1861
541830	189534	189549	Intron 2	CCTAGTCAGCCACTAG	eekddddddddddkke	20	1862
541831	189889	189904	Intron 2	AGACTCCCCATCAGCC	eekddddddddddkke	74	1863
541832	190172	190187	Intron 2	GTGAAGGGCCTTCATC	eekddddddddddkke	68	1864
541833	190961	190976	Intron 2	GGTTGAGAGTCCAATG	eekddddddddddkke	95	1865
541834	191404	191419	Intron 2	CAGCTAATTCCCTCAT	eekddddddddddkke	79	1866
541835	191614	191629	Intron 2	TTGTGTCTCAACCCAC	eekddddddddddkke	95	1867
541836	191999	192014	Intron 2	GGCTATGCTGCATGCT	eekddddddddddkke	91	1868
541837	192860	192875	Intron 2	CCCCATACCCAGTGGA	eekddddddddddkke	71	1869
541838	193460	193475	Intron 2	GGTGGTTTTCCTCCCT	eekddddddddddkke	95	1870
541839	194144	194159	Intron 2	GAGCCTGCCCAACTTT	eekddddddddddkke	90	1871
541840	194425	194440	Intron 2	TGATGCCCAAGAGTGA	eekddddddddddkke	85	1872
541841	194953	194968	Intron 2	TTCCCTCTGCGAACAT	eekddddddddddkke	96	1873
541842	195428	195443	Intron 2	GTTCCATCTCAATCCA	eekddddddddddkke	94	1874
541843	196858	196873	Intron 2	ACGGCCACTCCACTGG	eekddddddddddkke	44	1875
541844	197326	197341	Intron 2	TGGAAGTGGTTCCAGA	eekddddddddddkke	90	1876
541845	197946	197961	Intron 2	TTGCCCCAGACCAACA	eekddddddddddkke	47	1877
541846	198366	198381	Intron 2	GAGGTTGTGGAGGTGC	eekddddddddddkke	26	1878
541847	198715	198730	Intron 2	GAGTTGCTGTGTGTGA	eekddddddddddkke	83	1879
541848	198939	198954	Intron 2	CATGTCAGAGGTGTCC	eekddddddddddkke	93	1880
541849	199506	199521	Intron 2	AGGTAAGGATCATGGC	eekddddddddddkke	87	1881
541850	199816	199831	Intron 2	GTTCAGTTGCATCACG	eekddddddddddkke	90	1882
541851	200249	200264	Intron 2	GCCCAGCTAGCCACCC	eekddddddddddkke	68	1883
541852	201258	201273	Intron 2	CCTTAGCAGCCAGGCC	eekddddddddddkke	86	1884
541853	202079	202094	Intron 2	GCACTTAGGGTTTTGC	eekddddddddddkke	94	1885
541854	202382	202397	Intron 2	GTTGAACTTTCCCTAC	eekddddddddddkke	53	1886
541855	202702	202717	Intron 2	TGACTCCTTGAGACAG	eekddddddddddkke	83	1887
541856	203098	203113	Intron 2	TGCGCTGGCTTAGCAA	eekddddddddddkke	59	1888
541857	203464	203479	Intron 2	GGCCTAACATCAGCAG	eekddddddddddkke	88	1889
541858	204212	204227	Intron 2	ACTCCTCCCAGTTAGC	eekddddddddddkke	70	1890
541859	205630	205645	Intron 2	ACCAGTGGCCAATGTC	eekddddddddddkke	92	1891
541861	206422	206437	Intron 2	GCCTAGACACAGTAGG	eekddddddddddkke	70	1892
541862	206749	206764	Intron 2	TATTCTCCCCCTAGGG	eekddddddddddkke	42	1893
541863	207517	207532	Intron 2	GACGGCCTTGGGCACA	eekddddddddddkke	96	1894
	210196	210211					
541865	208659	208674	Intron 3	GCAGGCTGTATTAGCA	eekddddddddddkke	15	1895

541867	209999	210014	Intron 3	ACCCCCTATCCTGCAC	eekddddddddddkke	58	1896
541868	210281	210296	Intron 3	TCCTCCATACCTAGAG	eekddddddddddkke	61	1897
	211033	211048					
541869	210502	210517	Intron 3	GATAGGTGCCCACTGT	eekddddddddddkke	80	1898
541870	210920	210935	Intron 3	GTCAGTTCTGGCTAGG	eekddddddddddkke	97	1899
541871	211269	211284	Intron 3	GCCTGAACTTACAAGC	eekddddddddddkke	68	1900
541872	211836	211851	Intron 3	ACCCTGGGCTGACCTT	eekddddddddddkke	92	1901
541873	212606	212621	Intron 3	GGACCTGGACAAGCAA	eekddddddddddkke	97	1902
541874	213099	213114	Intron 3	CTCCTTGCGAGAGAGG	eekddddddddddkke	7	1903
541875	213425	213440	Intron 3	AGAGTTGACATGGGCA	eekddddddddddkke	96	1904
541876	213846	213861	Intron 3	CACTAGGTCCCTGACC	eekddddddddddkke	37	1905
541877	214483	214498	Intron 3	CACTCTCTTGGGCTGT	eekddddddddddkke	94	1906
541878	214884	214899	Intron 3	AGGGACCTGCATTCCA	eekddddddddddkke	72	1907

Table 181

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting introns 2 and 3 of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	156906	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	91	1370
541879	215493	215508	Intron 3	TTCACCACCCATTGGG	eekddddddddddkke	63	1908
541880	216192	216207	Intron 3	ATCTGGTCTGAGGGCC	eekddddddddddkke	92	1909
541881	216458	216473	Intron 3	GACATGCAATTGACCC	eekddddddddddkke	98	1910
541882	217580	217595	Intron 3	GTGTGCAGCAGACTGT	eekddddddddddkke	92	1911
541883	218233	218248	Intron 3	GACAGTCCAGCTGCAA	eekddddddddddkke	84	1912
541884	218526	218541	Intron 3	CCTGCGGCAGTGAAGA	eekddddddddddkke	85	1913
541885	218734	218749	Intron 3	CTCTGAGGATAACCCT	eekddddddddddkke	76	1914
541886	219342	219357	Intron 3	GTTCCCAGCTCCCCAA	eekddddddddddkke	68	1915
541887	219618	219633	Intron 3	TAGGGTCAGTGTCCCA	eekddddddddddkke	79	1916
541888	220039	220054	Intron 3	GGCGAGCCTCTCAGCC	eekddddddddddkke	52	1917
541889	220393	220408	Intron 3	GACTCATCCAGGCAGT	eekddddddddddkke	91	1918
541890	220665	220680	Intron 3	TCCCTCCCTTAGGCAC	eekddddddddddkke	71	1919
541891	221044	221059	Intron 3	GAGGAGCCAGGCATAT	eekddddddddddkke	80	1920
541892	221562	221577	Intron 3	CACCAACGAAGTCCCC	eekddddddddddkke	89	1921
541893	221947	221962	Intron 3	GCTGGCAGTCACCAAA	eekddddddddddkke	90	1922
541894	222569	222584	Intron 3	GCCCACACCATTGAGC	eekddddddddddkke	70	1923
541895	222983	222998	Intron 3	AGTGAGATGCCCTGGT	eekddddddddddkke	92	1924
541896	223436	223451	Intron 3	CACTGGCAGTTAGACC	eekddddddddddkke	88	1925
541897	224107	224122	Intron 3	ACTCTGGCCACTAGTA	eekddddddddddkke	80	1926
541898	224731	224746	Intron 3	GGTAGGGTGGCCACAT	eekddddddddddkke	78	1927
541899	225133	225148	Intron 3	GAGCCATGTCTAGGCA	eekddddddddddkke	18	1928
541900	225465	225480	Intron 3	CAGACTGAAACCCACC	eekddddddddddkke	86	1929

541901	225671	225686	Intron 3	TATGGTCCAGCCACCA	eekddddddddddkke	76	1930
541902	226110	226125	Intron 3	TACCTCCTCTGTTGGT	eekddddddddddkke	36	1931
541903	227025	227040	Intron 3	ACACCTCAGTCATGAT	eekddddddddddkke	92	1932
541904	227236	227251	Intron 3	AACAGGCTTCAAGAGG	eekddddddddddkke	91	1933
541905	227485	227500	Intron 3	GTACTACTGGCCATGT	eekddddddddddkke	73	1934
541906	227914	227929	Intron 3	CTGCAGGCGGTTGCTA	eekddddddddddkke	60	1935
541907	228718	228733	Intron 3	GTCTGTTGCCAAGAGC	eekddddddddddkke	95	1936
541908	229174	229189	Intron 3	CCCTGGGTCACTTAAG	eekddddddddddkke	44	1937
541909	229423	229438	Intron 3	CCTGTCCTTGCTTGCA	eekddddddddddkke	96	1938
541910	230042	230057	Intron 3	GCCCAGCTTATCCTAA	eekddddddddddkke	78	1939
541911	230313	230328	Intron 3	AGTAGAGCCTTTGCCT	eekddddddddddkke	75	1940
541912	230580	230595	Intron 3	CTGTCTCTTGGCCCAT	eekddddddddddkke	80	1941
541913	231330	231345	Intron 3	GGCCCAAATCTTGAGT	eekddddddddddkke	67	1942
541914	231817	231832	Intron 3	GCTTGTTACAGCACTA	eekddddddddddkke	92	1943
541915	232088	232103	Intron 3	ACTTTGGCCCAGAGAT	eekddddddddddkke	51	1944
541916	232884	232899	Intron 3	GCAGTCAGGTCAGCTG	eekddddddddddkke	75	1945
541917	233210	233225	Intron 3	GCCTTGTCCTACTACC	eekddddddddddkke	65	1946
541918	233657	233672	Intron 3	GGCTCTGCTATTGGCC	eekddddddddddkke	59	1947
541919	233998	234013	Intron 3	CTTATAGAGCCTTGCC	eekddddddddddkke	59	1948
541920	234296	234311	Intron 3	GGAAGGGCCCAAATAT	eekddddddddddkke	15	1949
541921	234903	234918	Intron 3	GATCTACTCCTACTGC	eekddddddddddkke	65	1950
541922	235313	235328	Intron 3	GTCAGCCTGTGTCTGA	eekddddddddddkke	45	1951
541923	235770	235785	Intron 3	AGCTTCCTCCTTACAC	eekddddddddddkke	54	1952
541924	236198	236213	Intron 3	CTGCTAAGCCCCTACC	eekddddddddddkke	59	1953
541925	236684	236699	Intron 3	AGAGGTCAGGTGCATA	eekddddddddddkke	77	1954
541926	237055	237070	Intron 3	TTCAGCCTGGTTGGGA	eekddddddddddkke	71	1955
541927	237585	237600	Intron 3	GATTGATTGAGCTCCT	eekddddddddddkke	86	1956
541928	237949	237964	Intron 3	ATGGACTCCCTAGGCT	eekddddddddddkke	61	1957
541929	238542	238557	Intron 3	TACTCAAGGGCCCCTC	eekddddddddddkke	67	1958
541930	245319	245334	Intron 3	GGCATATGTAGCTTGC	eekddddddddddkke	91	1959
541931	245765	245780	Intron 3	GAGCTTAGATCTGTGC	eekddddddddddkke	73	1960
541932	246251	246266	Intron 3	ATGCTCACGGCTGTGT	eekddddddddddkke	81	1961
541933	246500	246515	Intron 3	ATTGAAAGGCCCATCA	eekddddddddddkke	45	1962
541934	246936	246951	Intron 3	CAACCCAGTTTGCCGG	eekddddddddddkke	71	1963
541935	247225	247240	Intron 3	CAGCTATTCCCTGTTT	eekddddddddddkke	53	1964
541936	247644	247659	Intron 3	GCTGTGTCACACTTCC	eekddddddddddkke	98	1965
541937	248223	248238	Intron 3	GTCCAAGGATCACAGC	eekddddddddddkke	86	1966
541938	248695	248710	Intron 3	GCTACCACTAGAGCCT	eekddddddddddkke	81	1967
541939	249494	249509	Intron 3	GTTTCAGGGCTTATGT	eekddddddddddkke	63	1968
541940	250693	250708	Intron 3	TCCCACACCTATTGAA	eekddddddddddkke	51	1969
541941	251622	251637	Intron 3	ACTGACTAGAGAGTCC	eekddddddddddkke	81	1970
541942	251950	251965	Intron 3	TCCAAGGCTGATGTCC	eekddddddddddkke	85	1971
541943	252665	252680	Intron 3	TCCCATGGTGGACATG	eekddddddddddkke	39	1972

541944	253140	253155	Intron 3	AGTAGCTGGCAGAAGG	eekddddddddddkke	85	1973
541945	253594	253609	Intron 3	CTGGGAGTGACTACTA	eekddddddddddkke	77	1974
541946	254036	254051	Intron 3	TGGTATAGCTACTGGG	eekddddddddddkke	84	1975
541947	254905	254920	Intron 3	CTGTGGTTTGGCAGGT	eekddddddddddkke	90	1976
541948	255407	255422	Intron 3	GTTCTCACCTGAACTA	eekddddddddddkke	65	1977
541949	255618	255633	Intron 3	ATAGGCTACTGGCAGG	eekddddddddddkke	89	1978
541950	255992	256007	Intron 3	CCCAGCTAGCTGGAGT	eekddddddddddkke	50	1979
541951	256428	256443	Intron 3	GGCTGGCTCTCAAAGG	eekddddddddddkke	61	1980
541952	256689	256704	Intron 3	TGGTGATACTGTGGCA	eekddddddddddkke	94	1981
541953	257317	257332	Intron 3	GCTGATTTTGGTGCCA	eekddddddddddkke	92	1982
541954	257826	257841	Intron 3	GCTAATCTTGCCTCGA	eekddddddddddkke	52	1983
541955	258407	258422	Intron 3	CACTGGTGGCTTTCAA	eekddddddddddkke	31	1984

Table 182

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	93	156891	1370
541956	n/a	Intron 3	GTCCCCTTCTTAAGCA	eekddddddddddkke	56	258980	1985
541957	n/a	Intron 3	GCCAGGCCAACTGTGG	eekddddddddddkke	53	259290	1986
541958	n/a	Intron 3	GGCCCGTTATGGTGGA	eekddddddddddkke	72	259500	1987
541959	n/a	Intron 3	CCTAAAGTCCAACTCC	eekddddddddddkke	76	261641	1988
541960	n/a	Intron 3	CCCTATCCAGCCTTCA	eekddddddddddkke	77	262021	1989
541961	n/a	Intron 3	AAGCATGGCCTCTGGC	eekddddddddddkke	23	262453	1990
541962	n/a	Intron 3	TACCCTGCACCCTCCT	eekddddddddddkke	71	262764	1991
541963	n/a	Intron 3	TCCTTAGTAGAATGCC	eekddddddddddkke	82	263342	1992
541964	n/a	Intron 3	TTAGCCCTGGGAGCAC	eekddddddddddkke	78	263913	1993
541965	n/a	Intron 3	GCTGGGTCAGGTAGCG	eekddddddddddkke	71	266503	1994
541966	n/a	Intron 3	GGGAGGCTCTCAATCT	eekddddddddddkke	75	266861	1995
541967	n/a	Intron 3	GTAAGTGCAGAATGCC	eekddddddddddkke	87	267116	1996
541968	n/a	Intron 3	TGCCGAGGCAGGCACC	eekddddddddddkke	33	267380	1997
541969	n/a	Intron 3	TCCGTGTCTAGGAGGT	eekddddddddddkke	84	267865	1998
541970	n/a	Intron 4	GTCTCCCTGCATTGGA	eekddddddddddkke	31	268366	1999
541971	n/a	Intron 4	CCATATCACTCTCCTC	eekddddddddddkke	79	268786	2000
541972	n/a	Intron 4	CGAACACCTTGAGCCA	eekddddddddddkke	90	269252	2001
541973	n/a	Intron 4	GGCCCAGCTTAAGAGG	eekddddddddddkke	59	270038	2002
541974	n/a	Intron 4	CTGATACTCCTAATCC	eekddddddddddkke	70	270501	2003
541975	n/a	Intron 4	GCCTGTAGGGCTGTGC	eekddddddddddkke	82	270817	2004
541976	n/a	Intron 4	TGCCCTTTCTCCCTAC	eekddddddddddkke	87	271216	2005
541977	n/a	Intron 4	AGTGCATGTCAGTACC	eekddddddddddkke	75	271812	2006

541978	n/a	Intron 4	TGCTCCTCAGCTGTTG	eekddddddddddkke	44	272631	2007
541979	n/a	Intron 4	GTTTGGGACCATCCCT	eekddddddddddkke	41	272834	2008
541980	n/a	Intron 4	AGTGCTCTCTAGGGTC	eekddddddddddkke	87	273257	2009
541981	n/a	Intron 4	TACAGAGAATCACCCC	eekddddddddddkke	82	273651	2010
541982	n/a	Intron 4	GTCCAAGTAAGGTGCT	eekddddddddddkke	57	273947	2011
541983	n/a	Intron 5	GACCTTGCAGGCTTCC	eekddddddddddkke	87	274244	2012
541984	n/a	Intron 5	GGGCAAAGGATCCTCT	eekddddddddddkke	71	274758	2013
541985	n/a	Intron 5	CCCATTCTGCTATCCC	eekddddddddddkke	92	275198	2014
541986	n/a	Intron 5	GCTGACTAGGAGGGCT	eekddddddddddkke	62	275732	2015
541987	n/a	Intron 5	CCTGTGAGGTAGTACC	eekddddddddddkke	83	276309	2016
541988	n/a	Intron 5	GTCCCCCTCCAGTCTA	eekddddddddddkke	50	276932	2017
541989	n/a	Intron 5	GAGGACTCAATTCCTC	eekddddddddddkke	0	277149	2018
541990	n/a	Intron 5	GACAAGGTCCTTTTGG	eekddddddddddkke	43	277391	2019
541991	n/a	Intron 5	GCTCTTGTGTGCACCC	eekddddddddddkke	90	277730	2020
541992	n/a	Intron 5	TCACCGCCTGCACCAC	eekddddddddddkke	75	278342	2021
541993	n/a	Intron 5	GGTTGCACTGTGCAAT	eekddddddddddkke	26	278917	2022
541994	n/a	Intron 6	TTCCACAGGCCTCCAT	eekddddddddddkke	64	279303	2023
541995	n/a	Intron 6	GCTGAGTTCCATATGC	eekddddddddddkke	72	279679	2024
541996	n/a	Intron 6	GAACCGCCACCTCAGG	eekddddddddddkke	38	280157	2025
541997	n/a	Intron 6	GCTCACGGTTGGAGAC	eekddddddddddkke	42	280799	2026
541998	n/a	Intron 6	TGGGCTCCCATGTTCA	eekddddddddddkke	45	281595	2027
541999	n/a	Intron 6	TCACTCTACCAACCTC	eekddddddddddkke	33	282572	2028
542000	n/a	Intron 6	TCCTTGCTTACAGATG	eekddddddddddkke	33	283079	2029
542001	n/a	Intron 6	TGATGCTAGCATTACC	eekddddddddddkke	37	283653	2030
542002	n/a	Intron 6	TGGGTAACTGGCTAGT	eekddddddddddkke	47	285711	2031
542003	n/a	Intron 6	AACCATTCCTCACCAA	eekddddddddddkke	53	287181	2032
542004	n/a	Intron 6	GCCCTGAACAGTTGAT	eekddddddddddkke	37	287895	2033
542005	n/a	Intron 6	GGCTCCTATCATACCT	eekddddddddddkke	38	288943	2034
542006	n/a	Intron 6	TAGGTCTCACAACCCT	eekddddddddddkke	10	289638	2035
542007	n/a	Intron 6	GTGCATTAGTCTTCCA	eekddddddddddkke	74	290035	2036
542008	n/a	Intron 7	CAAAAGCCAGGTTAGC	eekddddddddddkke	13	290503	2037
542009	n/a	Intron 7	CTGCTGTTGACTACCT	eekddddddddddkke	50	290924	2038
542010	n/a	Intron 7	GTACCTGCCAGCTACT	eekddddddddddkke	35	291807	2039
542011	n/a	Exon 8-intron 8 junction	CCTACCTTTGCTGTTT	eekddddddddddkke	12	292611	2040
542012	n/a	Intron 8	AGTCACCAGCCTAAGC	eekddddddddddkke	47	292860	2041
542013	n/a	Intron 8	AGGCAACCTGGGAGTG	eekddddddddddkke	52	293377	2042
542014	n/a	Intron 8	TGGCCTTCACAATGGC	eekddddddddddkke	33	294052	2043
542015	n/a	Intron 8	GGTGAAGTGGGTTGGA	eekddddddddddkke	27	294536	2044
542016	n/a	Intron 8	GCTGGTTGTCTGCTGC	eekddddddddddkke	60	294931	2045
542017	n/a	Intron 8	AGTTTGTGACCCCTGC	eekddddddddddkke	81	295475	2046
542018	n/a	Intron 8	CCACTCAGTGTGAATG	eekddddddddddkke	85	295955	2047

542019	n/a	Intron 8	CTGGCCTCAGGGCAAT	eekddddddddddkke	51	296186	2048
542020	n/a	Intron 8	GTAGACTTGGGTAGGT	eekddddddddddkke	53	296680	2049
542022	n/a	3'UTR	TGGTGCTAAGCTCTCC	eekddddddddddkke	67	301009	2050
542023	n/a	3'UTR	CATGCTCAAGCTGGAA	eekddddddddddkke	47	301280	2051
542024	206	Exon 2	AAGGTCAACAGCAGCT	eekddddddddddkke	93	144990	2052
542025	207	Exon 2	CAAGGTCAACAGCAGC	eekddddddddddkke	85	144991	2053
542026	208	Exon 2	CCAAGGTCAACAGCAG	eekddddddddddkke	82	144992	2054
542027	209	Exon 2	GCCAAGGTCAACAGCA	eekddddddddddkke	84	144993	2055

Table 183

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	86	156891	1370
542034	870	Exon 7	TCTCACACGCACTTCA	eekddddddddddkke	49	290368	2056
542035	871	Exon 7	ATCTCACACGCACTTC	eekddddddddddkke	39	290369	2057
542036	872	Exon 7	GATCTCACACGCACTT	eekddddddddddkke	50	290370	2058
542049	n/a	Intron 1	CTTTCATGAATCAAGC	eekddddddddddkke	85	17928	2059
542050	n/a	Intron 1	TCTTTCATGAATCAAG	eekddddddddddkke	54	17929	2060
542051	n/a	Intron 1	GTCTTTCATGAATCAA	eekddddddddddkke	96	17930	2061
542052	n/a	Intron 1	GGTCTTTCATGAATCA	eekddddddddddkke	98	17931	2062
542053	n/a	Intron 1	ATGGTCTTTCATGAAT	eekddddddddddkke	94	17933	2063
542054	n/a	Intron 1	GATGGTCTTTCATGAA	eekddddddddddkke	73	17934	2064
542055	n/a	Intron 1	TGATGGTCTTTCATGA	eekddddddddddkke	83	17935	2065
542056	n/a	Intron 1	TATATCAATATTCTCC	eekddddddddddkke	75	21821	2066
542057	n/a	Intron 1	TTATATCAATATTCTC	eekddddddddddkke	23	21822	2067
542058	n/a	Intron 1	GTTATATCAATATTCT	eekddddddddddkke	87	21823	2068
542059	n/a	Intron 1	TTTCTTTAGCAATAGT	eekddddddddddkke	85	22519	2069
542060	n/a	Intron 1	CTTTCTTTAGCAATAG	eekddddddddddkke	81	22520	2070
542061	n/a	Intron 1	GCTTTCTTTAGCAATA	eekddddddddddkke	68	22521	2071
542062	n/a	Intron 1	CTCCATTAGGGTTCTG	eekddddddddddkke	91	50948	2072
542063	n/a	Intron 1	TCTCCATTAGGGTTCT	eekddddddddddkke	88	50949	2073
542064	n/a	Intron 1	TTCTCCATTAGGGTTC	eekddddddddddkke	85	50950	2074
542065	n/a	Intron 1	GTTCTCCATTAGGGTT	eekddddddddddkke	84	50951	2075
542066	n/a	Intron 1	AGGTTGGCAGACAGAC	eekddddddddddkke	92	53467	2076
542067	n/a	Intron 1	CAGGTTGGCAGACAGA	eekddddddddddkke	93	53468	2077
542068	n/a	Intron 1	GCAGGTTGGCAGACAG	eekddddddddddkke	91	53469	2078
542069	n/a	Intron 1	CTTCTTGTGAGCTGGC	eekddddddddddkke	95	64885	2079
542070	n/a	Intron 1	TCTTCTTGTGAGCTGG	eekddddddddddkke	89	64886	2080

542071	n/a	Intron 1	GTCTTCTTGTGAGCTG	eekddddddddddkke	96	64887	2081
542072	n/a	Intron 1	AGTCTTCTTGTGAGCT	eekddddddddddkke	81	64888	2082
542073	n/a	Intron 1	TCTTCCACTCACATCC	eekddddddddddkke	89	65991	2083
542074	n/a	Intron 1	CTCTTCCACTCACATC	eekddddddddddkke	79	65992	2084
542075	n/a	Intron 1	TCTCTTCCACTCACAT	eekddddddddddkke	86	65993	2085
542076	n/a	Intron 1	GTCTCTTCCACTCACA	eekddddddddddkke	92	65994	2086
542077	n/a	Intron 1	ATAGATTTTGACTTCC	eekddddddddddkke	86	72108	2087
542078	n/a	Intron 1	CATAGATTTTGACTTC	eekddddddddddkke	42	72109	2088
542079	n/a	Intron 1	GCATAGATTTTGACTT	eekddddddddddkke	66	72110	2089
542080	n/a	Intron 1	AAATGTCAACAGTGCA	eekddddddddddkke	97	80639	2090
542081	n/a	Intron 1	CATGACTATGTTCTGG	eekddddddddddkke	68	125595	2091
542082	n/a	Intron 1	ACATGACTATGTTCTG	eekddddddddddkke	66	125596	2092
542083	n/a	Intron 1	CACATGACTATGTTCT	eekddddddddddkke	74	125597	2093
542084	n/a	Intron 2	GAATTCTGAGCTCTGG	eekddddddddddkke	91	145430	2094
542085	n/a	Intron 2	TGAATTCTGAGCTCTG	eekddddddddddkke	94	145431	2095
542086	n/a	Intron 2	CTGAATTCTGAGCTCT	eekddddddddddkke	94	145432	2096
542087	n/a	Intron 2	CCTGAATTCTGAGCTC	eekddddddddddkke	93	145433	2097
542088	n/a	Intron 2	GCCTGAATTCTGAGCT	eekddddddddddkke	87	145434	2098
542089	n/a	Intron 2	AGCCTGAATTCTGAGC	eekddddddddddkke	84	145435	2099
542090	n/a	Intron 2	ATATTGTAATTCTTGG	eekddddddddddkke	47	148060	2100
542091	n/a	Intron 2	GATATTGTAATTCTTG	eekddddddddddkke	61	148061	2101
542092	n/a	Intron 2	TGATATTGTAATTCTT	eekddddddddddkke	0	148062	2102
542093	n/a	Intron 2	CTGATATTGTAATTCT	eekddddddddddkke	58	148063	2103
542094	n/a	Intron 2	CCTGATATTGTAATTC	eekddddddddddkke	95	148064	2104
542095	n/a	Intron 2	GCCTGATATTGTAATT	eekddddddddddkke	85	148065	2105
542096	n/a	Intron 2	TGCCTGATATTGTAAT	eekddddddddddkke	86	148066	2106
542097	n/a	Intron 2	ATTATGTGCTTTGCCT	eekddddddddddkke	86	148907	2107
542098	n/a	Intron 2	AATTATGTGCTTTGCC	eekddddddddddkke	75	148908	2108
542099	n/a	Intron 2	CAATTATGTGCTTTGC	eekddddddddddkke	88	148909	2109
542100	n/a	Intron 2	TCAATTATGTGCTTTG	eekddddddddddkke	78	148910	2110
542101	n/a	Intron 2	GTCAATTATGTGCTTT	eekddddddddddkke	97	148911	2111
542102	n/a	Intron 2	GCCATCACCAAACACC	eekddddddddddkke	97	150973	2112
542103	n/a	Intron 2	TGCCATCACCAAACAC	eekddddddddddkke	90	150974	2113
542104	n/a	Intron 2	TTGCCATCACCAAACA	eekddddddddddkke	89	150975	2114
542105	n/a	Intron 2	TGGTGACTCTGCCTGA	eekddddddddddkke	98	151388	2115
542106	n/a	Intron 2	CTGGTGACTCTGCCTG	eekddddddddddkke	96	151389	2116
542107	n/a	Intron 2	GCTGGTGACTCTGCCT	eekddddddddddkke	98	151390	2117
542108	n/a	Intron 2	TGCTGGTGACTCTGCC	eekddddddddddkke	97	151391	2118
542109	n/a	Intron 2	CTGCTGGTGACTCTGC	eekddddddddddkke	93	151392	2119

Table 184

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting introns 2 and 3 of SEQ ID NO: 2

ISIS NO	SEQ ID NO: 2 Start Site	SEQ ID NO: 2 Stop Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO
541262	156891	156906	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	95	1370
542110	153002	153017	Intron 2	AGTAGTCAATATTATT	eekddddddddddkke	74	2120
542111	153003	153018	Intron 2	CAGTAGTCAATATTAT	eekddddddddddkke	55	2121
542112	153004	153019	Intron 2	CCAGTAGTCAATATTA	eekddddddddddkke	97	2122
542113	153922	153937	Intron 2	CCTTTGGGTGAATAGC	eekddddddddddkke	90	2123
542114	153923	153938	Intron 2	ACCTTTGGGTGAATAG	eekddddddddddkke	71	2124
542115	153924	153939	Intron 2	CACCTTTGGGTGAATA	eekddddddddddkke	78	2125
542116	155595	155610	Intron 2	CAACTTGAGGACAATA	eekddddddddddkke	89	2126
542118	155597	155612	Intron 2	CTCAACTTGAGGACAA	eekddddddddddkke	98	2127
542119	156395	156410	Intron 2	CAGGAAGAAAGGAACC	eekddddddddddkke	95	2128
542120	156396	156411	Intron 2	CCAGGAAGAAAGGAAC	eekddddddddddkke	83	2129
542121	156397	156412	Intron 2	ACCAGGAAGAAAGGAA	eekddddddddddkke	90	2130
542122	156595	156610	Intron 2	TGCAGTCATGTACACA	eekddddddddddkke	97	2131
542123	156596	156611	Intron 2	CTGCAGTCATGTACAC	eekddddddddddkke	90	2132
542124	156597	156612	Intron 2	TCTGCAGTCATGTACA	eekddddddddddkke	81	2133
542125	156890	156905	Intron 2	TGGTTTGTCAATCCTT	eekddddddddddkke	97	2134
542126	156892	156907	Intron 2	CTTGGTTTGTCAATCC	eekddddddddddkke	99	2135
542127	157204	157219	Intron 2	GCTACAATGCACAGGA	eekddddddddddkke	98	2136
542128	157205	157220	Intron 2	TGCTACAATGCACAGG	eekddddddddddkke	98	2137
542129	158008	158023	Intron 2	GATATTTATTGCTGTA	eekddddddddddkke	61	2138
542130	158009	158024	Intron 2	TGATATTTATTGCTGT	eekddddddddddkke	41	2139
542131	158010	158025	Intron 2	CTGATATTTATTGCTG	eekddddddddddkke	86	2140
542132	162752	162767	Intron 2	AGGGTCTTTACAAAGT	eekddddddddddkke	69	2141
542133	162753	162768	Intron 2	CAGGGTCTTTACAAAG	eekddddddddddkke	71	2142
542134	162754	162769	Intron 2	CCAGGGTCTTTACAAA	eekddddddddddkke	93	2143
542135	166353	166368	Intron 2	TTCTGCAGTATCCTAG	eekddddddddddkke	84	2144
542136	166354	166369	Intron 2	TTTCTGCAGTATCCTA	eekddddddddddkke	88	2145
542137	166355	166370	Intron 2	GTTTCTGCAGTATCCT	eekddddddddddkke	95	2146
542138	166356	166371	Intron 2	AGTTTCTGCAGTATCC	eekddddddddddkke	92	2147
542139	166357	166372	Intron 2	CAGTTTCTGCAGTATC	eekddddddddddkke	93	2148
542140	172747	172762	Intron 2	CAAATTCCAGTCCTAG	eekddddddddddkke	73	2149
542141	172748	172763	Intron 2	CCAAATTCCAGTCCTA	eekddddddddddkke	91	2150
542142	172749	172764	Intron 2	TCCAAATTCCAGTCCT	eekddddddddddkke	90	2151
542143	175372	175387	Intron 2	ACCCATTTCATCCATT	eekddddddddddkke	94	2152
542144	175373	175388	Intron 2	AACCCATTTCATCCAT	eekddddddddddkke	93	2153
542145	175374	175389	Intron 2	GAACCCATTTCATCCA	eekddddddddddkke	97	2154

542146	175375	175390	Intron 2	GGAACCCATTTCATCC	eekddddddddddkke	96	2155
542147	175376	175391	Intron 2	AGGAACCCATTTCATC	eekddddddddddkke	68	2156
542148	189120	189135	Intron 2	GCTTCATGTCTTTCTA	eekddddddddddkke	90	2157
542149	189121	189136	Intron 2	TGCTTCATGTCTTTCT	eekddddddddddkke	96	2158
542150	189122	189137	Intron 2	GTGCTTCATGTCTTTC	eekddddddddddkke	97	2159
542151	189485	189500	Intron 2	TGAGCTTAGCAGTCAC	eekddddddddddkke	92	2160
542152	189486	189501	Intron 2	ATGAGCTTAGCAGTCA	eekddddddddddkke	95	2161
542153	189487	189502	Intron 2	CATGAGCTTAGCAGTC	eekddddddddddkke	95	2162
542154	191143	191158	Intron 2	TACAGACATAGCTCTA	eekddddddddddkke	91	2163
542155	191144	191159	Intron 2	ATACAGACATAGCTCT	eekddddddddddkke	74	2164
542156	191145	191160	Intron 2	GATACAGACATAGCTC	eekddddddddddkke	91	2165
542157	191146	191161	Intron 2	GGATACAGACATAGCT	eekddddddddddkke	94	2166
542158	198149	198164	Intron 2	TGTGGCTTTAATTCAC	eekddddddddddkke	71	2167
542159	198150	198165	Intron 2	ATGTGGCTTTAATTCA	eekddddddddddkke	81	2168
542160	198151	198166	Intron 2	TATGTGGCTTTAATTC	eekddddddddddkke	78	2169
542161	199817	199832	Intron 2	TGTTCAGTTGCATCAC	eekddddddddddkke	91	2170
542162	199818	199833	Intron 2	GTGTTCAGTTGCATCA	eekddddddddddkke	89	2171
542163	199819	199834	Intron 2	TGTGTTCAGTTGCATC	eekddddddddddkke	90	2172
542164	210562	210577	Intron 3	CATCTGGATGTGAGGC	eekddddddddddkke	90	2173
542165	210563	210578	Intron 3	ACATCTGGATGTGAGG	eekddddddddddkke	78	2174
542166	210564	210579	Intron 3	CACATCTGGATGTGAG	eekddddddddddkke	55	2175
542167	219020	219035	Intron 3	TCAGGTAATTTCTGGA	eekddddddddddkke	82	2176
542168	219021	219036	Intron 3	CTCAGGTAATTTCTGG	eekddddddddddkke	73	2177
542169	219022	219037	Intron 3	TCTCAGGTAATTTCTG	eekddddddddddkke	40	2178
542170	225568	225583	Intron 3	TGCTTATTTACCTGGG	eekddddddddddkke	90	2179
542171	225569	225584	Intron 3	TTGCTTATTTACCTGG	eekddddddddddkke	90	2180
542172	225570	225585	Intron 3	TTTGCTTATTTACCTG	eekddddddddddkke	79	2181
542173	225571	225586	Intron 3	TTTTGCTTATTTACCT	eekddddddddddkke	32	2182
542174	229619	229634	Intron 3	ATGATGTTACTACTAC	eekddddddddddkke	63	2183
542175	229620	229635	Intron 3	AATGATGTTACTACTA	eekddddddddddkke	53	2184
542176	229621	229636	Intron 3	CAATGATGTTACTACT	eekddddddddddkke	12	2185
542177	232827	232842	Intron 3	CCCCTAGAGCAATGGT	eekddddddddddkke	76	2186
542178	232828	232843	Intron 3	CCCCCTAGAGCAATGG	eekddddddddddkke	83	2187
542179	232829	232844	Intron 3	TCCCCCTAGAGCAATG	eekddddddddddkke	49	2188
542180	237676	237691	Intron 3	TCAATTGCAGATGCTC	eekddddddddddkke	88	2189
542181	237677	237692	Intron 3	CTCAATTGCAGATGCT	eekddddddddddkke	90	2190
542182	237678	237693	Intron 3	GCTCAATTGCAGATGC	eekddddddddddkke	81	2191
542183	237679	237694	Intron 3	AGCTCAATTGCAGATG	eekddddddddddkke	85	2192
542184	248232	248247	Intron 3	GTATATTCAGTCCAAG	eekddddddddddkke	90	2193
542185	248233	248248	Intron 3	AGTATATTCAGTCCAA	eekddddddddddkke	94	2194
542186	248234	248249	Intron 3	CAGTATATTCAGTCCA	eekddddddddddkke	97	2195

Table 185

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	93	156891	1370
545316	168	exon 1- intron 1 junction	ACCTCCGAGCTTCGCC	eekddddddddddkke	80	3044	2196
545317	173	exon-exon junction	GTAGGACCTCCGAGCT	eekddddddddddkke	74	n/a	2197
545318	177	exon-exon junction	ACCTGTAGGACCTCCG	eekddddddddddkke	70	n/a	2198
545321	213	Exon 2	CAGTGCCAAGGTCAAC	eekddddddddddkke	77	144997	2199
545322	225	Exon 2	ACTTGATCCTGCCAGT	eekddddddddddkke	36	145009	2200
545332	361	Exon 4/ Intron 3	CTCGCTCAGGTGAACG	eekddddddddddkke	57	268024	2201
545333	366	Exon 4/ Intron 3	AGTCTCTCGCTCAGGT	eekddddddddddkke	88	268029	2202
545337	444	Exon 4-intron 4 junction	CCTTCTGGTATAGAAC	eekddddddddddkke	21	268107	2203
545340	570	Exon 5	GCTAGTTAGCTTGATA	eekddddddddddkke	39	274130	2204
545343	626	exon 3- exon 4 junction	TCTGGTTGCACTATTT	eekddddddddddkke	34	n/a	2205
545344	629	exon 3- exon 4 junction	GGATCTGGTTGCACTA	eekddddddddddkke	30	n/a	2206
545345	632	Exon 6	GGTGGATCTGGTTGCA	eekddddddddddkke	18	278926	2207
545346	638	Exon 6	GCAATGGGTGGATCTG	eekddddddddddkke	50	278932	2208
545347	647	Exon 6	CAGTTGAGGGCAATGG	eekddddddddddkke	71	278941	2209
545348	651	Exon 6	AGTCCAGTTGAGGGCA	eekddddddddddkke	58	278945	2210
545349	655	Exon 6	GTAAAGTCCAGTTGAG	eekddddddddddkke	34	278949	2211
545350	660	Exon 6	GTTCAGTAAAGTCCAG	eekddddddddddkke	52	278954	2212
545351	685	Exon 6	CTGCATGAATCCCAGT	eekddddddddddkke	77	278979	2213
545355	923	Exon 7	ACATAGAGCACCTCAC	eekddddddddddkke	38	290421	2214
545356	926	Exon 7	GTTACATAGAGCACCT	eekddddddddddkke	79	290424	2215
545357	929	Exon 7	AGTGTTACATAGAGCA	eekddddddddddkke	70	290427	2216
545362	1124	Exon 7- exon 8 junction	TCCTTGAGGAGATCTG	eekddddddddddkke	3	n/a	2217
545363	1170	Exon 10	GCTATCATGAATGGCT	eekddddddddddkke	69	297587	2218
545364	1180	Exon 10	CGGGTTTATAGCTATC	eekddddddddddkke	58	297597	2219
545369	1320	Exon 10	ATCCTTCACCCCTAGG	eekddddddddddkke	46	297737	2220
545370	1328	Exon 10	GAGTCGCCATCCTTCA	eekddddddddddkke	60	297745	2221
545371	1332	Exon 10	TCCAGAGTCGCCATCC	eekddddddddddkke	51	297749	2222
545373	1418	Exon 10	GGCTGAGCAACCTCTG	eekddddddddddkke	80	297835	2223
545374	1422	Exon 10	CTGTGGCTGAGCAACC	eekddddddddddkke	63	297839	2224

545380	1524	Exon 10	GATAACACTGGGCTGC	eekddddddddddkke	60	297941	2225
545381	1530	Exon 10	TGCTTGGATAACACTG	eekddddddddddkke	76	297947	2226
545382	1533	Exon 10	CTCTGCTTGGATAACA	eekddddddddddkke	60	297950	2227
545386	1600	Exon 10	GCTGAATATGGGCAGC	eekddddddddddkke	29	298017	2228
545387	1613	Exon 10	CTTGGATTGCTTAGCT	eekddddddddddkke	59	298030	2229
545388	1645	Exon 10	CCTGGGCATAAAAGTC	eekddddddddddkke	47	298062	2230
545392	1832	Exon 10	ACCTTGATGTGAGGAG	eekddddddddddkke	44	298249	2231

Table 186

Inhibition of GHR mRNA by deoxy, MOE and (S)-cEt gapmers targeting intronic and exonic regions of SEQ ID NOs: 1 and 2

ISIS NO	SEQ ID NO: 1 Start Site	Target Region	Sequence	Chemistry	% inhibition	SEQ ID NO: 2 Start Site	SEQ ID NO
541262	n/a	Intron 2	TTGGTTTGTCAATCCT	eekddddddddddkke	89	156891	1370
545393	1838	Exon 10	GATTCAACCTTGATGT	eekddddddddddkke	40	298255	2232
545394	1844	Exon 10	ATGTGTGATTCAACCT	eekddddddddddkke	80	298261	2233
545395	1956	Exon 10	TGGGACAGGCATCTCA	eekddddddddddkke	29	298373	2234
545396	1961	Exon 10	TAGTCTGGGACAGGCA	eekddddddddddkke	48	298378	2235
545397	1968	Exon 10	GGAGGTATAGTCTGGG	eekddddddddddkke	61	298385	2236
545398	1986	Exon 10	GGACTGTACTATATGA	eekddddddddddkke	48	298403	2237
545401	2077	Exon 10	TCAGTTGGTCTGTGCT	eekddddddddddkke	60	298494	2238
545402	2095	Exon 10	GCTAAGGCATGATTTT	eekddddddddddkke	53	298512	2239
545406	2665	Exon 10	GCCATGCTTGAAGTCT	eekddddddddddkke	87	299082	2240
545407	2668	Exon 10	ATAGCCATGCTTGAAG	eekddddddddddkke	70	299085	2241
545408	2692	Exon 10	ACACAGTGTGTAGTGT	eekddddddddddkke	60	299109	2242
545409	2699	Exon 10	CTGCAGTACACAGTGT	eekddddddddddkke	31	299116	2243
545410	2704	Exon 10	ACCAACTGCAGTACAC	eekddddddddddkke	57	299121	2244
545411	2739	Exon 10	TAGACTGTAGTTGCTA	eekddddddddddkke	53	299156	2245
545412	2747	Exon 10	ACCAGCTTTAGACTGT	eekddddddddddkke	56	299164	2246
545413	2945	Exon 10	GTAAGTTGATCTGTGC	eekddddddddddkke	79	299362	2247
545414	2963	Exon 10	TACTTCTTTTGGTGCC	eekddddddddddkke	82	299380	2248
545416	3212	Exon 10	TCTTGTACCTTATTCC	eekddddddddddkke	73	299629	2249
545417	3306	Exon 10	TGGTTATAGGCTGTGA	eekddddddddddkke	90	299723	2250
545418	3309	Exon 10	GTCTGGTTATAGGCTG	eekddddddddddkke	88	299726	2251
545419	3313	Exon 10	ATGTGTCTGGTTATAG	eekddddddddddkke	68	299730	2252
545420	3317	Exon 10	GAGTATGTGTCTGGTT	eekddddddddddkke	84	299734	2253
545421	4049	Exon 10	GGTCTGCGATAAATGG	eekddddddddddkke	69	300466	2254
545429	4424	Exon 10	GCCAGACACAACTAGT	eekddddddddddkke	59	300841	2255
545430	31	Exon 1	ACCGCCACTGTAGCAG	eekddddddddddkke	76	2907	2256

545431	36	Exon 1	CCGCCACCGCCACTGT	eekddddddddddkke	94	2912	2257
545432	103	Exon 1	GGGCCTCCGGCCCGCG	eekddddddddddkke	22	2979	2258
545433	143	Exon 1	AGAGCGCGGGTTCGCG	eekddddddddddkke	61	3019	2259
545434	n/a	Intron 1/Exon 1	TACTGACCCCAGTTCC	eekddddddddddkke	68	3654	2260
545435	n/a	Intron 1/Exon 1	ACTCTACTGACCCCAG	eekddddddddddkke	70	3658	2261
545436	n/a	Intron 1/Exon 1	GTCACTCTACTGACCC	eekddddddddddkke	83	3661	2262
545437	n/a	Intron 1/Exon 1	TTCATGCGGACTGGTG	eekddddddddddkke	68	3680	2263
545438	n/a	Intron 3/Exon 3	GTGAGCATGGACCCCA	eekddddddddddkke	94	225436	2264
545439	n/a	Intron 3/Exon 3	TGATATGTGAGCATGG	eekddddddddddkke	88	225442	2265
545440	n/a	Intron 3/Exon 3	AAGTTGGTGAGCTTCT	eekddddddddddkke	85	226785	2266
545441	n/a	Intron 3/Exon 3	CCTTCAAGTTGGTGAG	eekddddddddddkke	88	226790	2267
545442	n/a	Intron 3/Exon 3	GTAAGATCCTTTTGCC	eekddddddddddkke	70	226883	2268
545443	n/a	Intron 3/Exon 3	CAGCTGTGCAACTTGC	eekddddddddddkke	50	238345	2269
545444	n/a	Intron 3/Exon 3	GCCTTGGTAGGTAGGG	eekddddddddddkke	68	238422	2270
545445	n/a	Intron 3/Exon 3	AGAGCCTTGGTAGGTA	eekddddddddddkke	85	238425	2271
545446	n/a	Intron 1/Exon 1	CCCGCACAAACGCGCA	eekddddddddddkke	10	3614	2272
545447	n/a	Intron 1/Exon 1	GTCTTCAAGGTCAGTT	eekddddddddddkke	92	93208	2273
545448	n/a	Intron 1/Exon 1	GCCCAGTGAATTCAGC	eekddddddddddkke	76	93246	2274
545449	n/a	Intron 1/Exon 1	AGATGCGCCCAGTGAA	eekddddddddddkke	60	93252	2275
545450	n/a	Intron 1/Exon 1	GTAAGATGCGCCCAGT	eekddddddddddkke	78	93255	2276
545451	n/a	Intron 1/Exon 1	CCAGAAGGCACTTGTA	eekddddddddddkke	42	93301	2277
545452	n/a	Intron 1/Exon 1	GGAAGATTTGCAGAAC	eekddddddddddkke	15	93340	2278
545453	n/a	Intron 1/Exon 1	CCTTGGTCATGGAAGA	eekddddddddddkke	35	93350	2279
545454	n/a	Intron 1/Exon 1	TGACCTTGGTCATGGA	eekddddddddddkke	55	93353	2280
545455	n/a	Intron 1/Exon 1	GAGGTGACCTTGGTCA	eekddddddddddkke	70	93357	2281
545456	n/a	Intron 1/Exon 1	ATCCAAAGAGGTGACC	eekddddddddddkke	41	93364	2282
545457	n/a	Intron 1/Exon 1	GCCAATCCAAAGAGGT	eekddddddddddkke	56	93368	2283

545458	n/a	Intron 1/Exon 1	GGTCTGCCAATCCAAA	eekddddddddddkke	79	93373	2284
545459	n/a	Intron 1/Exon 1	CCCTGGGTCTGCCAAT	eekddddddddddkke	68	93378	2285
545460	n/a	Intron 1/Exon 1	GAGATCTCAACAAGGG	eekddddddddddkke	52	93427	2286
545461	n/a	Intron 1/Exon 1	CGCCCATCACTCTTCC	eekddddddddddkke	68	93988	2287
545462	n/a	Intron 1/Exon 1	CACCTGTCGCCCATCA	eekddddddddddkke	67	93995	2288
545463	n/a	Intron 1/Exon 1	CATCACCTGTCGCCCA	eekddddddddddkke	78	93998	2289
545464	n/a	Intron 1/Exon 1	CACCATCACCTGTCGC	eekddddddddddkke	74	94001	2290
545465	n/a	Intron 1/Exon 1	AATAGTTGTCACCATC	eekddddddddddkke	76	94010	2291
545466	n/a	Intron 1/Exon 1	GCCACCTTTCATGAGA	eekddddddddddkke	58	94048	2292
545467	n/a	Intron 2/Exon 2	CTCTTGGAAGTAGGTA	eekddddddddddkke	89	198762	2293
545468	n/a	Intron 2/Exon 2	GTTCTCTTGGAAGTAG	eekddddddddddkke	80	198765	2294
545469	n/a	Intron 2/Exon 2	TAAACAGGTTGGTCTG	eekddddddddddkke	68	198854	2295

Example 121: Dose-dependent antisense inhibition of human GHR in Hep3B cells by deoxy, MOE and (S)-cEt gapmers

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in Hep3B cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.625 μM, 1.25 μM, 2.50 μM, 5.00 μM and 10.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 187

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541396	30	51	68	74	67	1.4
541262	55	87	90	94	97	0.2
541393	30	38	52	66	81	2.1
541375	41	45	54	64	79	1.6
541438	44	49	75	80	91	0.9
541428	35	32	56	78	88	1.8
541491	13	46	67	55	95	2.0
541435	21	46	55	72	94	1.9
541471	11	49	50	77	89	2.0
541430	24	44	56	57	79	2.2
541492	32	40	65	80	85	1.5
541431	22	46	73	84	92	1.5

Table 188

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541487	36	46	66	85	92	1.3
541423	33	55	64	80	93	1.2
541452	37	60	79	87	94	0.9
541505	51	75	86	92	97	0.4
541522	54	76	81	90	95	0.3
541539	65	76	85	94	98	0.2
541503	54	65	80	93	97	0.5
541520	43	61	86	94	96	0.7
541515	57	72	85	92	94	0.3
541564	57	72	88	90	97	0.3
541554	43	65	81	89	93	0.7
541509	11	8	19	6	8	>10
541584	59	65	84	91	96	0.3
541585	70	80	93	92	98	0.1

Table 189

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541598	26	43	75	80	76	1.5
541592	35	48	67	85	95	1.2
541641	22	63	70	91	93	1.2

541590	27	59	70	94	95	1.2
541615	40	65	84	88	94	0.7
541595	35	57	73	84	95	1.0
541575	49	60	79	84	95	0.6
541571	41	50	76	80	94	1.0
541582	0	10	25	50	82	4.4
541262	66	79	93	94	99	<0.6
541652	1	44	80	82	87	1.9
541670	29	40	63	79	89	1.6
541662	17	13	45	62	84	3.1
541724	37	47	72	85	95	1.2

Table 190

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541748	86	94	96	98	98	<0.6
541767	83	91	95	96	98	<0.6
541797	78	89	93	97	99	<0.6
541766	59	82	92	97	99	<0.6
541742	65	87	93	95	99	<0.6
541750	80	86	96	96	99	<0.6
541262	79	88	93	97	97	<0.6
541749	71	84	93	95	98	<0.6
541793	71	88	94	97	98	<0.6
541785	56	79	89	93	98	<0.6
541746	34	61	85	94	97	0.9
541752	49	72	88	93	93	<0.6
541826	86	94	95	99	98	<0.6
541811	66	87	93	97	98	<0.6

Table 191

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541822	83	88	95	96	96	<0.6
541870	77	87	95	97	98	<0.6
541262	85	93	96	97	98	<0.6
541873	32	77	93	94	97	0.7
541819	60	91	97	97	99	<0.6
541841	86	91	95	96	97	<0.6
541825	78	88	95	98	98	<0.6
541863	63	77	87	93	97	<0.6

541827	42	80	87	94	97	<0.6
541875	77	84	93	96	97	<0.6
541835	56	73	90	95	98	<0.6
541838	72	90	93	98	97	<0.6
541833	52	69	83	92	97	<0.6
541813	47	75	86	95	97	<0.6

Table 192

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541853	74	79	88	93	91	<0.6
541842	69	85	91	97	99	<0.6
541877	79	91	93	98	97	<0.6
541848	58	90	96	98	98	0.7
541804	23	81	89	95	95	0.8
541881	87	94	98	98	99	<0.6
541936	91	96	98	99	98	<0.6
541909	56	80	89	95	97	<0.6
541907	75	91	95	97	98	<0.6
541952	68	81	93	97	98	<0.6
541953	68	80	94	97	98	<0.6
541914	60	78	94	97	97	<0.6
541880	56	74	89	94	95	<0.6
541903	37	74	87	96	98	0.6

Table 193

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541895	47	72	85	93	94	<0.6
541882	60	67	89	93	97	<0.6
541889	63	80	87	94	97	<0.6
541904	26	78	23	89	93	1.4
545418	0	81	91	94	95	1.7
541930	58	71	82	88	92	<0.6
545439	67	87	93	96	98	<0.6
542024	15	58	78	87	90	1.4
541985	59	81	88	93	97	<0.6
541972	47	58	83	90	92	0.6
541991	57	64	88	92	83	<0.6
541980	33	50	76	72	93	1.2

Table 194

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
541264	26	44	64	79	89	1.6
541265	29	32	62	79	91	1.8
541263	25	40	62	78	93	1.7
541268	57	73	85	90	95	0.3
541266	15	33	46	66	90	2.5
542107	93	97	98	98	98	<0.6
542052	93	96	97	96	98	<0.6
542105	80	92	96	98	97	<0.6
542102	94	96	96	97	98	<0.6
542108	90	92	94	97	99	<0.6
542080	87	93	95	95	97	<0.6

Table 195

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
542101	90	97	97	97	95	<0.6
542051	89	96	95	98	97	<0.6
542106	83	93	96	96	98	<0.6
542071	84	91	94	97	97	<0.6
542094	85	92	94	97	98	<0.6
542069	89	94	97	95	98	<0.6
542086	83	94	96	97	98	<0.6
542085	85	92	96	97	97	<0.6
542053	64	83	94	98	97	<0.6
542087	69	84	99	95	98	<0.6
542109	87	94	96	98	98	<0.6
542126	96	98	99	98	98	<0.6
542127	94	96	97	98	97	<0.6
542128	90	96	98	98	97	<0.6

Table 196

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
542118	97	97	98	95	43	<0.6
542186	93	96	98	99	98	<0.6
542150	95	97	98	99	99	<0.6

542122	90	94	98	98	99	<0.6
542125	88	97	98	98	99	<0.6
542145	90	96	98	99	99	<0.6
542112	86	94	99	99	99	<0.6
542149	88	93	99	98	99	<0.6
542146	79	93	96	97	98	<0.6
542153	87	94	97	98	99	<0.6
542119	64	84	93	97	98	<0.6
542137	76	91	97	97	98	<0.6
542152	84	94	96	96	97	<0.6
542157	83	95	98	99	98	<0.6

Table 197

ISIS No	0.625 μM	1.250 μM	2.50 μM	5.00 μM	10.00 μM	IC_{50} (μM)
542185	82	93	96	96	94	<0.6
542143	81	91	96	98	98	<0.6
542144	77	93	95	96	99	<0.6
542139	87	93	98	98	98	<0.6
542134	83	90	90	95	96	<0.6
545333	68	85	91	96	98	<0.6
545373	57	73	86	92	97	<0.6
545438	84	96	98	97	99	<0.6
545431	77	91	93	97	98	<0.6
545447	70	85	96	96	97	<0.6
545417	62	82	90	93	95	<0.6
545467	77	88	91	94	95	<0.6
545441	63	82	92	94	96	<0.6

Example 122: Dose-dependent antisense inhibition of human GHR in Hep3B cells by deoxy, MOE and (S)-cEt gapmers

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in Hep3B cells. The antisense oligonucleotides were tested in a series of experiments that had similar culture conditions. The results for each experiment are presented in separate tables shown below. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.04 μM, 0.11 μM, 0.33 μM, 1.00 μM, and 3.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB

was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 198

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	11	16	57	93	98	0.2
541724	0	27	71	66	83	0.3
541748	28	40	71	90	97	0.1
541767	19	38	54	87	98	0.2
541797	23	46	70	88	97	0.1
541766	15	26	49	82	96	0.3
541742	17	28	41	80	95	0.3
541750	33	27	60	89	98	0.2
541749	27	16	62	84	82	0.2
541793	0	14	44	77	96	0.4
541785	4	11	39	75	95	0.4
541752	14	6	45	70	94	0.4
541826	8	34	74	94	99	0.2
541811	6	4	45	79	97	0.4
541822	9	29	67	89	97	0.2

Table 199

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	0	16	47	82	98	0.4
541819	3	12	50	76	94	0.3
541841	0	19	47	80	95	0.3
541825	0	6	40	74	96	0.4
541827	5	26	48	76	95	0.3
541835	7	11	33	74	93	0.4
541838	21	26	61	90	97	0.2
541833	0	9	41	63	89	0.5
541813	0	17	28	65	92	0.5
541842	5	15	30	72	90	0.4
541804	0	12	3	49	79	1.1
542024	0	0	26	54	76	1.0

542107	15	45	78	92	99	0.1
542105	2	14	55	88	98	0.3
542102	10	16	73	88	98	0.2

Table 200

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	4	18	50	86	95	0.3
542108	15	13	65	86	97	0.2
542101	17	40	68	92	98	0.2
542106	4	23	56	88	98	0.3
542094	0	30	51	86	96	0.3
542086	13	38	50	84	97	0.2
542085	0	27	57	90	98	0.3
542087	7	3	49	80	92	0.4
542109	17	10	56	88	98	0.3
542126	40	63	91	96	99	<0.03
542127	27	47	69	93	97	0.1
542128	11	30	66	90	98	0.2
542118	14	42	77	95	98	0.1
542150	31	46	72	94	98	0.1
542122	13	14	59	90	97	0.3

Table 201

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	0	2	50	86	97	0.4
542125	31	32	69	89	96	0.1
542145	15	29	64	91	97	0.2
542112	14	38	61	87	96	0.2
542149	9	37	63	90	97	0.2
542146	13	33	59	82	95	0.2
542153	22	26	63	86	96	0.2
542119	10	20	34	70	87	0.4
542137	3	19	47	77	95	0.3
542152	0	9	47	82	96	0.4
542157	0	26	56	84	96	0.3
542143	8	12	44	81	95	0.3
542144	0	21	42	75	95	0.4
542139	0	14	46	82	97	0.4
542134	3	23	43	72	92	0.4

Table 202

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	0	9	64	85	97	0.3
541870	7	15	48	80	92	0.3
541262	0	29	63	90	98	0.2
541863	0	26	40	82	93	0.4
541875	6	30	71	84	91	0.2
541853	0	13	39	67	91	0.5
541877	0	26	41	79	94	0.4
541881	0	30	54	87	94	0.3
541936	20	41	73	93	98	0.1
541909	0	16	34	64	90	0.5
541907	6	31	59	84	96	0.2
541952	0	0	50	72	92	0.5
541953	0	22	50	80	92	0.4
541914	0	0	46	76	93	0.4
541880	0	13	48	79	89	0.4

Table 203

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	0	5	53	78	94	0.4
541903	12	20	26	62	88	0.5
541895	3	12	29	66	92	0.5
541882	2	0	27	65	86	0.7
541889	12	12	47	68	87	0.4
541930	0	6	40	59	85	0.6
541985	0	16	41	66	93	0.4
542031	1	0	22	55	80	0.8
541972	0	1	23	46	83	0.9
541991	4	35	42	67	89	0.4
542052	5	28	70	92	98	0.2
542080	0	18	54	87	96	0.3
542051	0	18	52	86	97	0.3
542071	5	3	51	74	95	0.4
542069	0	7	56	85	94	0.3

Table 204

ISIS No	0.04 μM	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
539380	11	20	54	89	92	0.3
542053	6	14	38	69	74	0.6
542186	14	43	70	90	98	0.2
542185	0	26	48	80	96	0.3
545333	0	4	27	65	90	0.6
545336	0	15	24	43	79	0.9
545373	0	2	9	42	86	1.0
545438	0	24	56	81	92	0.3
545431	0	18	50	73	91	0.4
545447	0	15	34	78	93	0.4
545417	0	11	39	66	87	0.5
545467	12	16	37	76	93	0.4
545441	21	15	20	60	87	0.6
545439	17	24	49	82	91	0.3

Example 123: Dose-dependent antisense inhibition of rhesus monkey GHR in LLC-MK2 cells

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested for their potency for rhesus GHR mRNA in LLC-MK2 cells. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.12 μM, 0.37 μM, 1.11 μM, 3.33 μM, and 10.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 205

ISIS No	Chemistry	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
541262	Deoxy, MOE and (S)-cEt	9	25	42	85	91	1.1
541742	Deoxy, MOE and (S)-cEt	0	24	19	58	77	3.2

541767	Deoxy, MOE and (S)-cEt	6	10	30	68	88	2.0
541875	Deoxy, MOE and (S)-cEt	7	19	64	84	96	0.9
541881	Deoxy, MOE and (S)-cEt	6	24	59	79	91	1.0
542101	Deoxy, MOE and (S)-cEt	0	5	38	71	81	2.0
542112	Deoxy, MOE and (S)-cEt	5	17	33	67	76	2.0
542118	Deoxy, MOE and (S)-cEt	1	6	35	68	86	2.0
542125	Deoxy, MOE and (S)-cEt	0	12	57	83	93	1.0
542127	Deoxy, MOE and (S)-cEt	1	0	30	68	84	2.4
542128	Deoxy, MOE and (S)-cEt	12	0	26	58	83	2.7
542153	Deoxy, MOE and (S)-cEt	4	0	0	36	59	6.6
542185	Deoxy, MOE and (S)-cEt	4	0	25	56	87	2.5
542186	Deoxy, MOE and (S)-cEt	15	23	51	73	90	1.1
542051	Deoxy, MOE and (S)-cEt	5	19	40	81	94	1.2

Table 206

ISIS No	Chemistry	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
523723	5-10-5 MOE	23	14	31	43	71	3.5
532254	5-10-5 MOE	29	35	42	69	87	0.8
532401	5-10-5 MOE	27	28	46	73	88	1.2
533932	5-10-5 MOE	10	24	48	70	92	1.2
539376	3-10-4 MOE	21	8	8	35	81	4.3
539399	3-10-4 MOE	2	10	14	18	57	8.3
539404	3-10-4 MOE	39	12	25	27	57	7.7
539416	3-10-4 MOE	24	35	44	79	89	1.0
539432	3-10-4 MOE	9	29	42	73	89	1.2
541262	Deoxy, MOE and (S)-cEt	0	43	63	88	94	0.8
541742	Deoxy, MOE and (S)-cEt	3	19	35	56	85	1.9
541767	Deoxy, MOE and (S)-cEt	3	24	39	64	86	1.6
545439	Deoxy, MOE and (S)-cEt	19	15	43	74	80	1.7

545447	Deoxy, MOE and (S)-cEt	25	34	58	80	90	0.6

Example 124: Dose-dependent antisense inhibition of GHR in cynomolgus primary hepatocytes

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested for their potency for GHR mRNA in cynomolgus monkey primary hepatocytes. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.12 μM, 0.37 μM, 1.11 μM, 3.33 μM, and 10.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 207

ISIS No	Chemistry	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
541262	Deoxy, MOE and (S)-cEt	40	52	75	92	98	0.3
541742	Deoxy, MOE and (S)-cEt	40	57	51	91	96	0.2
541767	Deoxy, MOE and (S)-cEt	36	59	60	78	91	0.4
541875	Deoxy, MOE and (S)-cEt	54	76	88	95	95	<0.1
541881	Deoxy, MOE and (S)-cEt	53	75	85	98	98	<0.1
542101	Deoxy, MOE and (S)-cEt	38	55	78	89	97	0.2
542112	Deoxy, MOE and (S)-cEt	28	50	74	89	96	0.4
542118	Deoxy, MOE and (S)-cEt	20	45	69	84	91	0.5
542125	Deoxy, MOE and (S)-cEt	33	62	77	92	97	0.3
542127	Deoxy, MOE and (S)-cEt	30	50	65	86	92	0.4
542128	Deoxy, MOE and (S)-cEt	25	40	52	80	93	0.7
542153	Deoxy, MOE and (S)-cEt	10	31	51	73	85	1.0

542185	Deoxy, MOE and (S)-cEt	12	45	65	85	93	0.6
542186	Deoxy, MOE and (S)-cEt	36	54	74	90	96	0.3
542051	Deoxy, MOE and (S)-cEt	9	29	32	32	42	>10

Table 208

ISIS No	Chemistry	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
523435	5-10-5 MOE	35	47	61	74	85	0.5
523723	5-10-5 MOE	4	16	40	66	86	1.8
532254	5-10-5 MOE	14	15	24	16	9	>10
532401	5-10-5 MOE	37	54	73	88	94	0.3
533932	5-10-5 MOE	23	40	69	78	86	0.6
539376	3-10-4 MOE	3	0	44	65	91	2.0
539399	3-10-4 MOE	0	0	9	42	67	5.0
539404	3-10-4 MOE	0	0	26	52	71	3.5
539416	3-10-4 MOE	8	29	62	89	93	0.7
539432	3-10-4 MOE	0	24	55	85	93	0.9
541262	Deoxy, MOE and (S)-cEt	23	52	73	92	96	0.4
541742	Deoxy, MOE and (S)-cEt	15	51	73	86	97	0.5
541767	Deoxy, MOE and (S)-cEt	19	20	39	68	81	1.8
545439	Deoxy, MOE and (S)-cEt	0	0	30	61	90	2.4
545447	Deoxy, MOE and (S)-cEt	0	17	17	19	27	>10

Example 125: Dose-dependent antisense inhibition of GHR in Hep3B cells

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested for their potency for GHR mRNA at various doses in Hep3B cells. Cells were plated at a

density of 20,000 cells per well and transfected using electroporation with 0.12 μM, 0.37 μM, 1.11 μM, 3.33 μM, and 10.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 209

ISIS No	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
541262	25	43	76	85	94	0.5
541742	32	55	76	88	97	0.3
541767	29	56	83	89	97	0.3
541875	38	68	84	93	94	0.1
541881	32	57	81	94	97	0.3
542051	34	66	83	95	98	0.2
542101	25	55	85	95	98	0.3
542112	18	56	83	95	98	0.4
542118	42	61	88	95	97	0.1
542125	30	63	87	95	98	0.2
542127	50	70	91	91	98	0.1
542128	38	63	88	96	98	0.2
542153	37	59	85	94	97	0.2
542185	44	51	76	89	96	0.2
542186	46	59	84	95	97	0.1

Table 210

ISIS No	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
523435	9	26	49	78	93	1.0
523723	7	16	39	72	90	1.4
532254	36	46	69	86	94	0.4
532401	25	54	71	86	91	0.4
533932	8	47	69	80	94	0.7
539376	26	31	54	73	86	0.8
539399	23	43	72	89	94	0.5

539404	30	60	88	95	98	0.2
539416	30	59	84	93	98	0.3
539432	35	62	88	95	98	0.2
541262	43	60	84	89	98	0.2
541742	23	53	73	84	97	0.4
541767	22	49	74	85	92	0.4
545439	41	69	88	95	96	0.1
545447	31	47	63	74	82	0.5

Example 126: Dose-dependent antisense inhibition of GHR in cynomolgus primary hepatocytes

Gapmers from studies described above exhibiting significant *in vitro* inhibition of GHR mRNA were selected and tested at various doses in cynomolgous monkey primary hepatocytes. Cells were plated at a density of 35,000 cells per well and transfected using electroporation with 0.04 μM, 0.12 μM, 0.37 μM, 1.11 μM, 3.33 μM, and 10.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. GHR mRNA levels were significantly reduced in a dose-dependent manner in antisense oligonucleotide treated cells.

Table 211

ISIS No	0.04 μM	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
541767	8	17	29	48	59	58	0.4
541875	20	39	48	51	55	58	0.2
541881	23	36	49	60	56	58	0.1
542112	23	21	35	42	54	68	0.5
542118	19	14	26	38	54	59	0.8
542153	17	20	27	39	46	52	2.2
542185	20	23	27	46	39	56	2.0
532254	1	20	23	11	1	23	>10
532401	0	15	24	39	47	55	1.6
523723	0	0	7	24	49	54	2.0

Example 127: Comparative analysis of dose-dependent antisense inhibition of GHR in Hep3B cells

ISIS 532401 was compared with specific antisense oligonucleotides disclosed in US 2006/0178325 by testing at various doses in Hep3B cells. The oligonucleotides were selected based on the potency demonstrated in studies described in the application. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.11 μM, 0.33 μM, 1.00 μM, 1.11 μM, 3.00 μM, and 9.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and GHR mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3437_MGB was used to measure mRNA levels. GHR mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. Results are presented as percent inhibition of GHR, relative to untreated control cells.

The half maximal inhibitory concentration (IC_{50}) of each oligonucleotide is also presented. The results indicate that ISIS 532401 was markedly more potent than the most potent oligonucleotides of US 2006/0178325.

Table 212

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM	9.00 μM	IC_{50} (μM)
227452	11	12	46	73	92	1.4
227488	26	25	39	76	88	1.2
272309	16	14	39	66	91	1.6
272322	13	20	44	70	86	1.4
272328	22	20	24	43	56	5.7
272338	22	24	52	71	85	1.1
532401	34	53	72	87	94	0.3

Example 128: Tolerability of 5-10-5 MOE gapmers targeting human GHR in CD1 mice

CD1® mice (Charles River, MA) are a multipurpose mice model, frequently utilized for safety and efficacy testing. The mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of eight- to ten-week old male CD1 mice were injected subcutaneously twice a week for 6 weeks with 50 mg/kg of ISIS oligonucleotides (100 mg/kg/week dose). One group of male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 213. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 213

Plasma chemistry markers in CD1 mice plasma at week 6

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	31	50	0.28	0.15	28
ISIS 523271	366	285	0.18	0.11	29
ISIS 523324	222	139	0.19	0.10	31
ISIS 523604	2106	1157	0.41	0.06	48
ISIS 532254	66	84	0.11	0.10	27
ISIS 533121	176	155	0.19	0.09	27
ISIS 533161	1094	904	0.23	0.07	29
ISIS 533178	78	83	0.18	0.08	28
ISIS 533234	164	147	0.21	0.09	26

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and platelets, and total hemoglobin content. The results are presented in Table 214. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 214

Hematology markers in CD1 mice plasma at week 6

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	45	13	8.2	4.1	689
ISIS 523271	42	12	7.9	4.5	1181
ISIS 523324	39	11	7.5	7.9	980
ISIS 523604	33	10	6.9	14.1	507
ISIS 532254	35	10	6.9	7.2	861
ISIS 533121	39	12	7.9	8.4	853
ISIS 533161	49	14	9.3	9.0	607

ISIS 533178	44	13	8.5	6.9	765
ISIS 533234	42	12	7.8	9.2	1045

Example 129: Tolerability of 5-10-5 MOE gapmers targeting human GHR in CD1 mice

CD1® mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of eight- to ten-week old male CD1 mice were injected subcutaneously twice a week for 6 weeks with 50 mg/kg of ISIS oligonucleotide (100 mg/kg/week dose). One group of male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 215. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 215

Plasma chemistry markers in CD1 mice plasma at week 6

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	30	59	0.26	0.14	20
ISIS 523715	636	505	0.24	0.14	22
ISIS 523723	57	80	0.20	0.16	23
ISIS 523726	165	167	0.18	0.15	23
ISIS 523736	140	177	0.20	0.15	23
ISIS 523747	96	108	0.17	0.14	23
ISIS 523789	45	74	0.20	0.15	22
ISIS 532395	64	111	0.23	0.12	21
ISIS 532401	47	88	0.21	0.17	22
ISIS 532411	225	426	0.17	0.16	22
ISIS 532420	60	99	0.21	0.12	25
ISIS 532468	319	273	0.15	0.14	21
ISIS 533932	62	81	0.18	0.14	21

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WB), RBC, and platelets, and total hemoglobin content. The results are presented in Table 216. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 216

Hematology markers in CD1 mice plasma at week 6

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	43	13	8.1	3.3	1047
ISIS 523715	40	12	8.1	4.2	1153
ISIS 523723	35	11	6.8	2.9	1154
ISIS 523726	32	10	6.8	5.8	1056
ISIS 523736	35	11	7.1	3.6	1019
ISIS 523747	37	11	7.7	2.8	1146
ISIS 523789	37	11	7.3	2.5	1033
ISIS 532395	37	11	7.4	4.5	890
ISIS 532401	36	11	7.1	3.7	1175
ISIS 532411	27	8	5.3	3.2	641
ISIS 532420	35	11	7.0	3.3	1101
ISIS 532468	36	11	7.4	4.0	1043
ISIS 533932	36	11	7.2	3.8	981

Example 130: Tolerability of 3-10-4 MOE gapmers targeting human GHR in CD1 mice

CD1® mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of eight- to ten-week old male CD1 mice were injected subcutaneously twice a week for 6 weeks with 50 mg/kg of ISIS oligonucleotide (100 mg/kg/week dose). One group of male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 217. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 217

Plasma chemistry markers in CD1 mice plasma at week 6

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	48	63	0.20	0.13	28
ISIS 539302	204	192	0.15	0.15	24
ISIS 539321	726	455	0.17	0.12	27
ISIS 539360	3287	2495	0.58	0.13	22
ISIS 539361	310	226	0.17	0.11	21
ISIS 539376	77	75	0.14	0.12	27
ISIS 539379	134	136	0.16	0.13	24
ISIS 539380	180	188	0.14	0.12	23
ISIS 539383	80	81	0.15	0.12	25
ISIS 539399	119	127	0.13	0.12	24
ISIS 539401	1435	1172	0.24	0.11	24
ISIS 539403	1543	883	0.18	0.12	26
ISIS 539404	75	109	0.16	0.13	23
ISIS 539416	100	107	0.19	0.15	26
ISIS 539432	55	64	0.20	0.14	22
ISIS 539433	86	91	0.12	0.13	22

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and platelets, and total hemoglobin content. The results are presented in Table 218. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 218

Hematology markers in CD1 mice plasma at week 6

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	46	13	8.5	6	954
ISIS 539302	40	11	8.1	13	830
ISIS 539321	39	11	7.8	16	723
ISIS 539360	49	14	9.0	14	671
ISIS 539361	45	13	8.5	9	893
ISIS 539376	42	12	7.7	6	988
ISIS 539379	42	12	8.1	7	795
ISIS 539380	38	10	7.7	8	950
ISIS 539383	45	12	8.4	8	795
ISIS 539399	41	12	8.0	10	895
ISIS 539401	41	11	8.2	9	897
ISIS 539403	33	9	6.2	13	1104
ISIS 539404	42	12	8.4	7	641
ISIS 539416	41	11	7.5	5	686
ISIS 539432	44	12	8.0	6	920
ISIS 539433	40	11	7.4	6	987

Example 131: Tolerability of deoxy, MOE and (S)-cEt gapmers targeting human GHR in CD1 mice

CD1® mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of eight- to ten-week old male CD1 mice were injected subcutaneously twice a week for 6 weeks with 25 mg/kg of ISIS oligonucleotide (50 mg/kg/week dose). One group of male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 219. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 219

Plasma chemistry markers in CD1 mice plasma at week 6

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	36	71	0.22	0.18	22
ISIS 541262	115	133	0.21	0.18	21
ISIS 541724	543	531	0.34	0.17	21
ISIS 541742	44	71	0.18	0.16	21
ISIS 541748	269	582	0.16	0.15	22
ISIS 541749	626	491	0.20	0.20	22
ISIS 541750	1531	670	0.20	0.18	23
ISIS 541766	2107	1139	0.21	0.21	23
ISIS 541767	42	62	0.21	0.17	20
ISIS 541822	493	202	0.13	0.16	22
ISIS 541826	889	398	0.21	0.14	17
ISIS 541838	266	172	0.16	0.15	20
ISIS 541870	445	272	0.23	0.16	23
ISIS 541875	103	114	0.20	0.15	20
ISIS 541907	940	725	0.16	0.19	35
ISIS 541991	1690	1733	0.31	0.20	23

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and platelets, and total hemoglobin content. The results are presented in Table 220. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 220

Hematology markers in CD1 mice plasma at week 6

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	37	11	7	3	1083
ISIS 541262	38	11	7	6	1010
ISIS 541724	52	16	10	9	940
ISIS 541742	47	14	9	6	1134
ISIS 541748	41	12	8	7	941
ISIS 541749	41	12	8	5	1142
ISIS 541750	42	12	8	4	1409
ISIS 541766	39	11	7	7	989

ISIS 541767	46	14	9	2	994
ISIS 541822	42	12	8	3	1190
ISIS 541826	41	12	8	10	1069
ISIS 541838	44	13	8	6	1005
ISIS 541870	38	11	7	8	1020
ISIS 541875	44	13	8	6	1104
ISIS 541907	40	11	8	9	1271
ISIS 541991	34	10	6	6	1274

Example 132: Tolerability of deoxy, MOE and (S)-cEt gapmers targeting human GHR in CD1 mice

CD1® mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers. The 3-10-4 MOE gapmer ISIS 539376 was also included in the study.

Treatment

Groups of eight- to ten-week old male CD1 mice were injected subcutaneously twice a week for 6 weeks with 25 mg/kg of ISIS oligonucleotide (50 mg/kg/week dose). One group of male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 221. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 221

Plasma chemistry markers in CD1 mice plasma at week 6

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	43	66	0.21	0.11	20
ISIS 541881	63	109	0.28	0.13	23
ISIS 541936	3260	2108	0.40	0.13	24
ISIS 542051	97	119	0.23	0.12	23
ISIS 542052	454	236	0.23	0.12	25
ISIS 542069	293	211	0.23	0.13	27
ISIS 542085	91	87	0.18	0.10	21
ISIS 542086	137	133	0.24	0.10	23

ISIS 542094	86	143	0.23	0.13	21
ISIS 542101	46	74	0.19	0.10	21
ISIS 542102	4920	2432	2.30	0.15	29
ISIS 542105	1255	575	0.35	0.13	21
ISIS 542106	3082	2295	3.42	0.17	23
ISIS 542107	4049	3092	0.50	0.14	20
ISIS 542108	1835	859	0.32	0.11	21
ISIS 539376	40	79	0.27	0.08	22

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and total hemoglobin content. The results are presented in Table 222. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 222

Hematology markers in CD1 mice plasma at week 6

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)
PBS	46	13	8	6
ISIS 541881	53	15	10	7
ISIS 541936	41	11	8	18
ISIS 542051	49	14	9	8
ISIS 542052	46	13	9	9
ISIS 542069	43	13	8	7
ISIS 542085	38	11	7	5
ISIS 542086	49	14	9	9
ISIS 542094	36	10	6	5
ISIS 542101	44	13	9	5
ISIS 542102	27	7	5	25
ISIS 542105	42	12	8	7
ISIS 542106	37	10	7	14
ISIS 542107	41	12	7	17
ISIS 542108	51	14	8	10
ISIS 539376	49	14	10	5

Example 133: Tolerability of deoxy, MOE and (S)-cEt gapmers targeting human GHR in CD1 mice

CD1® mice were treated with ISIS antisense oligonucleotides selected from studies described above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Groups of eight- to ten-week old male CD1 mice were injected subcutaneously twice a week for 6 weeks with 25 mg/kg of ISIS oligonucleotide (50 mg/kg/week dose). One group of male CD1 mice was injected subcutaneously twice a week for 6 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine, and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in Table 223. ISIS oligonucleotides that caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 223

Plasma chemistry markers in CD1 mice plasma at week 6

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	51	63	0.3	0.14	27
ISIS 542109	3695	2391	0.8	0.19	24
ISIS 542112	119	104	0.3	0.16	28
ISIS 542118	66	86	0.3	0.15	26
ISIS 542122	1112	350	0.3	0.16	27
ISIS 542125	79	92	0.2	0.13	26
ISIS 542126	381	398	0.5	0.14	23
ISIS 542127	54	85	0.3	0.16	26
ISIS 542128	55	89	0.2	0.12	24
ISIS 542145	834	671	0.3	0.11	24
ISIS 542146	163	107	0.2	0.14	30
ISIS 542149	974	752	0.3	0.12	26
ISIS 542150	2840	2126	2.4	0.17	23
ISIS 542153	53	75	0.2	0.14	28
ISIS 542157	137	122	0.3	0.13	25
ISIS 542185	57	72	0.2	0.11	23
ISIS 542186	62	84	0.2	0.12	24
ISIS 545431	2622	1375	3.0	0.15	28
ISIS 545438	1710	1000	0.3	0.14	26

ISIS 545439	70	117	0.2	0.12	28
ISIS 545447	141	108	0.3	0.13	26

Hematology assays

Blood obtained from all mice groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and total hemoglobin content. The results are presented in Table 224. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 224

Hematology markers in CD1 mice plasma at week 6

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	40	12	7	6	1210
ISIS 542109	47	13	9	16	1244
ISIS 542112	50	13	8	7	1065
ISIS 542118	42	12	8	8	1120
ISIS 542122	37	11	7	7	1064
ISIS 542125	42	13	8	7	1063
ISIS 542126	34	10	7	9	1477
ISIS 542127	41	12	7	7	1144
ISIS 542128	40	12	7	6	1196
ISIS 542145	42	12	8	8	1305
ISIS 542146	45	13	8	7	1310
ISIS 542149	33	10	6	12	903
ISIS 542150	27	7	5	18	1202
ISIS 542153	46	13	8	5	1130
ISIS 542157	44	12	9	6	791
ISIS 542185	45	13	8	3	1031
ISIS 542186	44	12	8	6	985
ISIS 545431	28	7	6	13	2609
ISIS 545438	40	11	8	8	1302
ISIS 545439	48	13	9	4	857
ISIS 545447	45	13	9	9	964

Example 134: Tolerability of MOE gapmers targeting human GHR in Sprague-Dawley rats

Sprague-Dawley rats are a multipurpose model used for safety and efficacy evaluations. The rats were treated with ISIS antisense oligonucleotides from the studies described in the Examples above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Male Sprague-Dawley rats were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously twice a week for 6 weeks with 50 mg/kg of ISIS oligonucleotide (100 mg/kg weekly dose). Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT (alanine transaminase) and AST (aspartate transaminase) were measured and the results are presented in Table 225 expressed in IU/L. Plasma levels of bilirubin were also measured using the same clinical chemistry analyzer and the results are also presented in Table 225 expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 225

Liver function markers in Sprague-Dawley rats

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)
PBS	69	90	0.15
ISIS 523723	79	123	0.12
ISIS 523789	71	105	0.15
ISIS 532254	67	97	0.14
ISIS 532401	61	77	0.12
ISIS 532420	102	127	0.17
ISIS 533178	157	219	0.34
ISIS 533234	71	90	0.11
ISIS 533932	58	81	0.12
ISIS 539376	75	101	0.14
ISIS 539380	86	128	0.16
ISIS 539383	64	94	0.14
ISIS 539399	52	95	0.14
ISIS 539404	88	118	0.13
ISIS 539416	63	104	0.14
ISIS 539432	63	90	0.13
ISIS 539433	69	92	0.13

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in Table 226, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 226

Kidney function markers (mg/dL) in Sprague-Dawley rats

	BUN	Creatinine
PBS	24	0.32
ISIS 523723	20	0.39
ISIS 523789	19	0.37
ISIS 532254	21	0.43
ISIS 532401	17	0.36
ISIS 532420	20	0.31
ISIS 533178	20	0.43
ISIS 533234	22	0.41
ISIS 533932	19	0.43
ISIS 539376	19	0.36
ISIS 539380	18	0.35
ISIS 539383	19	0.35
ISIS 539399	18	0.39
ISIS 539404	23	0.39
ISIS 539416	17	0.39
ISIS 539432	20	0.39
ISIS 539433	20	0.34

Hematology assays

Blood obtained from all rat groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and total hemoglobin content. The results are presented in Table 227. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 227

Hematology markers in Sprague-Dawley rats

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	46	15	8	11	1078
ISIS 523723	38	12	7	19	626
ISIS 523789	38	12	8	12	702
ISIS 532254	36	12	7	11	547
ISIS 532401	42	14	8	12	858
ISIS 532420	37	12	7	17	542
ISIS 533178	37	12	7	15	1117
ISIS 533234	38	12	7	8	657
ISIS 533932	40	13	7	9	999
ISIS 539376	43	14	9	8	910
ISIS 539380	33	11	5	6	330
ISIS 539383	39	13	7	10	832
ISIS 539399	37	11	7	4	603
ISIS 539404	37	12	7	6	639
ISIS 539416	33	11	6	9	601
ISIS 539432	44	14	9	10	810
ISIS 539433	38	12	7	9	742

Organ weights

Liver, heart, spleen and kidney weights were measured at the end of the study, and are presented in Table 228. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 228

Organ weights (g)

	Heart	Liver	Spleen	Kidney
PBS	0.35	3.6	0.2	0.8
ISIS 523723	0.31	4.9	0.7	0.8
ISIS 523789	0.34	4.8	0.6	0.8
ISIS 532254	0.32	5.0	0.6	1.0
ISIS 532401	0.32	3.8	0.4	0.8
ISIS 532420	0.29	4.6	0.7	1.0
ISIS 533178	0.34	5.2	0.7	0.9
ISIS 533234	0.30	4.4	0.6	1.0
ISIS 533932	0.31	3.9	0.5	0.9
ISIS 539376	0.29	4.4	0.4	0.8

ISIS 539380	0.31	6.3	1.6	1.2
ISIS 539383	0.31	4.5	0.6	1.0
ISIS 539399	0.31	4.5	0.8	1.0
ISIS 539404	0.34	4.9	0.6	1.0
ISIS 539416	0.32	4.7	0.7	0.9
ISIS 539432	0.30	3.8	0.4	0.8
ISIS 539433	0.28	4.1	0.7	1.0

Example 135: Tolerability of deoxy, MOE, and (S)-cEt gapmers targeting human GHR in Sprague-Dawley rats

Sprague-Dawley rats were treated with ISIS antisense oligonucleotides from the studies described in the Examples above and evaluated for changes in the levels of various plasma chemistry markers.

Treatment

Male Sprague-Dawley rats were maintained on a 12-hour light/dark cycle and fed ad libitum with Purina normal rat chow, diet 5001. Groups of 4 Sprague-Dawley rats each were injected subcutaneously once a week for 6 weeks with 50 mg/kg of ISIS oligonucleotide (50 mg/kg weekly dose). Two groups of rats were injected subcutaneously once a week for 6 weeks with PBS. Forty eight hours after the last dose, rats were euthanized and organs and plasma were harvested for further analysis.

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, plasma levels of transaminases were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Plasma levels of ALT and AST were measured and the results are presented in Table 229 expressed in IU/L. Plasma levels of bilirubin were also measured using the same clinical chemistry analyzer and the results are also presented in Table 229 expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any markers of liver function outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 229

Liver function markers in Sprague-Dawley rats

	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)
PBS	34	56	0.08
PBS	37	54	0.09
ISIS 541881	53	77	0.12
ISIS 542051	61	96	0.09
ISIS 542101	64	214	0.10

ISIS 542112	46	72	0.10
ISIS 542118	42	60	0.08
ISIS 542125	39	67	0.10
ISIS 542127	56	75	0.12
ISIS 542128	45	71	0.12
ISIS 542153	44	69	0.11
ISIS 542185	44	93	0.09
ISIS 542186	51	107	0.12
ISIS 545439	41	73	0.10
ISIS 545447	103	114	0.10
ISIS 541262	106	133	0.12
ISIS 541742	56	102	0.11
ISIS 541767	53	69	0.09
ISIS 541875	70	133	0.08

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, plasma levels of blood urea nitrogen (BUN) and creatinine were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Results are presented in Table 230, expressed in mg/dL. ISIS oligonucleotides that caused changes in the levels of any of the kidney function markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 230

Kidney function markers (mg/dL) in Sprague-Dawley rats

	BUN	Creatinine
PBS	16	0.2
PBS	15	0.2
ISIS 541881	22	0.3
ISIS 542051	18	0.2
ISIS 542101	22	0.3
ISIS 542112	18	0.2
ISIS 542118	18	0.3
ISIS 542125	18	0.3
ISIS 542127	19	0.3
ISIS 542128	18	0.3
ISIS 542153	17	0.3
ISIS 542185	19	0.3
ISIS 542186	19	0.3
ISIS 545439	16	0.2
ISIS 545447	16	0.2

ISIS 541262	21	0.4
ISIS 541742	19	0.2
ISIS 541767	15	0.2
ISIS 541875	16	0.2

Hematology assays

Blood obtained from all rat groups were sent to Antech Diagnostics for hematocrit (HCT) measurements and analysis, as well as measurements of the various blood cells, such as WBC, RBC, and total hemoglobin content. The results are presented in Table 231. ISIS oligonucleotides that caused changes in the levels of any of the hematology markers outside the expected range for antisense oligonucleotides were excluded in further studies.

Table 231

Hematology markers in Sprague-Dawley rats

	HCT (%)	Hemoglobin (g/dL)	RBC (10^6/μL)	WBC (10^3/μL)	Platelets (10^3/μL)
PBS	43	14	7	7	775
PBS	49	15	8	8	1065
ISIS 541881	41	13	8	6	553
ISIS 542051	39	13	7	9	564
ISIS 542101	37	12	7	15	603
ISIS 542112	45	14	8	10	587
ISIS 542118	47	15	8	7	817
ISIS 542125	41	13	7	7	909
ISIS 542127	44	14	8	10	872
ISIS 542128	44	14	8	7	679
ISIS 542153	48	15	8	7	519
ISIS 542185	44	14	8	9	453
ISIS 542186	44	14	8	12	433
ISIS 545439	40	12	7	11	733
ISIS 545447	43	13	8	9	843
ISIS 541262	46	14	8	17	881
ISIS 541742	47	15	8	10	813
ISIS 541767	53	16	9	9	860
ISIS 541875	42	13	7	9	840

Organ weights

Liver, heart, spleen and kidney weights were measured at the end of the study, and are presented in Table 232. ISIS oligonucleotides that caused any changes in organ weights outside the expected range for antisense oligonucleotides were excluded from further studies.

Table 232

Organ weights (g)

	Heart	Liver	Spleen	Kidney
PBS	0.4	3.7	0.2	0.9
PBS	0.3	3.2	0.2	0.7
ISIS 541881	0.4	3.4	0.4	0.9
ISIS 542051	0.4	3.8	0.4	1.0
ISIS 542101	0.3	4.2	0.6	1.1
ISIS 542112	0.3	3.7	0.4	0.8
ISIS 542118	0.4	3.6	0.2	0.8
ISIS 542125	0.4	3.7	0.3	1.1
ISIS 542127	0.3	4.2	0.3	0.8
ISIS 542128	0.3	3.5	0.3	0.8
ISIS 542153	0.3	3.5	0.3	0.8
ISIS 542185	0.4	3.8	0.4	0.9
ISIS 542186	0.3	3.8	0.6	0.9
ISIS 545439	0.4	4.1	0.3	0.9
ISIS 545447	0.4	3.4	0.3	1.1
ISIS 541262	0.3	3.4	0.3	2.0
ISIS 541742	0.3	3.8	0.3	0.8
ISIS 541767	0.3	3.4	0.2	0.8
ISIS 541875	0.3	5.2	0.4	1.0

Example 136: Effect of ISIS antisense oligonucleotides targeting human GHR in cynomolgus monkeys

Cynomolgus monkeys were treated with ISIS antisense oligonucleotides selected from studies described in the Examples above. Antisense oligonucleotide efficacy and tolerability, as well as their pharmacokinetic profile in the liver and kidney, were evaluated.

At the time this study was undertaken, the cynomolgus monkey genomic sequence was not available in the National Center for Biotechnology Information (NCBI) database; therefore, cross-reactivity with the cynomolgus monkey gene sequence could not be confirmed. Instead, the sequences of the ISIS antisense oligonucleotides used in the cynomolgus monkeys was compared to a rhesus monkey sequence for homology. It is expected that ISIS oligonucleotides with homology to the rhesus monkey sequence are fully

cross-reactive with the cynomolgus monkey sequence as well. The human antisense oligonucleotides tested are cross-reactive with the rhesus genomic sequence (GENBANK Accession No. NW_001120958.1 truncated from nucleotides 4410000 to 4720000, designated herein as SEQ ID NO: 2332). The greater the complementarity between the human oligonucleotide and the rhesus monkey sequence, the more likely the human oligonucleotide can cross-react with the rhesus monkey sequence. The start and stop sites of each oligonucleotide to SEQ ID NO: 2332 is presented in Table 233. "Start site" indicates the 5'-most nucleotide to which the gapmer is targeted in the rhesus monkey gene sequence.

Table 233

Antisense oligonucleotides complementary to the rhesus GHR genomic sequence (SEQ ID NO: 2332)

ISIS No	Target Start Site	Target Stop Site	Chemistry	SEQ ID NO
523723	149071	149090	5-10-5 MOE	918
532254	64701	64720	5-10-5 MOE	479
532401	147560	147579	5-10-5 MOE	703
541767	152700	152715	Deoxy, MOE and (S)-cEt	1800
541875	210099	210114	Deoxy, MOE and (S)-cEt	1904
542112	146650	146665	Deoxy, MOE and (S)-cEt	2122
542118	149074	149089	Deoxy, MOE and (S)-cEt	2127
542185	245782	245797	Deoxy, MOE and (S)-cEt	2194

Treatment

Prior to the study, the monkeys were kept in quarantine during which the animals were observed daily for general health. The monkeys were 2-4 years old and weighed between 2 and 4 kg. Nine groups of 5 randomly assigned male cynomolgus monkeys each were injected subcutaneously with ISIS oligonucleotide or PBS using a stainless steel dosing needle and syringe of appropriate size into the intracapsular region and outer thigh of the monkeys. The monkeys were dosed three times (days 1, 4, and 7) for the first week, and then subsequently once a week for 12 weeks with 40 mg/kg of ISIS oligonucleotide. A control group of 5 cynomolgus monkeys was injected with PBS in a similar manner and served as the control group.

During the study period, the monkeys were observed twice daily for signs of illness or distress. Any animal experiencing more than momentary or slight pain or distress due to the treatment, injury or illness was treated by the veterinary staff with approved analgesics or agents to relieve the pain after consultation with

the Study Director. Any animal in poor health or in a possible moribund condition was identified for further monitoring and possible euthanasia. Scheduled euthanasia of the animals was conducted on day 86 by exsanguination after ketamine/xylazine-induced anesthesia and administration of sodium pentobarbital. The protocols described in the Example were approved by the Institutional Animal Care and Use Committee (IACUC).

Hepatic Target Reduction

RNA analysis

On day 86, RNA was extracted from liver, white adipose tissue (WAT) and kidney for real-time PCR analysis of measurement of mRNA expression of GHR. Results are presented as percent change of mRNA, relative to PBS control, normalized with RIBOGREEN®. 'n.d.' indicates that the data for that particular oligonucleotide was not measured. As shown in Table 234, treatment with ISIS antisense oligonucleotides resulted in significant reduction of GHR mRNA in comparison to the PBS control. Specifically, treatment with ISIS 532401 resulted in significant reduction of mRNA expression in all tissues.

Table 234

Percent inhibition of GHR mRNA in the cynomolgus monkey liver relative to the PBS control

ISIS No	Liver	Kidney	WAT
532401	60	47	59
532254	63	65	n.d.
523723	38	0	n.d.
542112	61	60	36
542118	0	22	27
542185	66	53	n.d.
541767	0	14	n.d.
541875	34	77	n.d.

Protein analysis

Approximately 1 mL of blood was collected from all available animals at day 85 and placed in tubes containing the potassium salt of EDTA. The tubes were centrifuged (3000 rpm for 10 min at room temperature) to obtain plasma. Plasma levels of IGF-1 and GH were measured in the plasma. The results are presented in Table 235. The results indicate that treatment with ISIS oligonucleotides resulted in reduced IGF-1 protein levels.

Table 235

Plasma protein levels in the cynomolgus monkey

	IGF-1 (% baseline)	GH (ng/mL)
PBS	121	19
532401	57	39
532254	51	26
523723	77	16
542112	46	48
542118	97	6
542185	59	32
541767	101	22
541875	45	47

Tolerability studies

Body and organ weight measurements

To evaluate the effect of ISIS oligonucleotides on the overall health of the animals, body and organ weights were measured. Body weights were measured on day 84 and are presented in Table 236. Organ weights were measured on day 86 and the data is also presented in Table 236. The results indicate that effect of treatment with antisense oligonucleotides on body and organ weights was within the expected range for antisense oligonucleotides. Specifically, treatment with ISIS 532401 was well tolerated in terms of the body and organ weights of the monkeys.

Table 236

Final body and organ weights in cynomolgus monkey

	Body Wt (kg)	Spleen (g)	Kidney (g)	Liver (g)
PBS	2.7	2.8	12.3	56.7
532401	2.6	4.0	11.5	58.5
532254	2.6	4.8	15.4	69.5
523723	2.8	3.1	14.8	69.4
542112	2.6	3.5	13.6	60.0
542118	2.7	2.7	11.9	58.6
542185	2.6	5.5	17.2	68.5
541767	2.8	5.1	11.7	65.1
541875	2.8	5.5	13.2	55.0

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, blood samples were collected from all the study groups. The blood samples were collected via femoral venipuncture, 48 hrs post-dosing. The monkeys were fasted overnight prior to blood collection. Blood was collected in tubes containing K_2-EDTA anticoagulant, which were centrifuged to obtain plasma. Levels of various liver function markers were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan). Plasma levels of ALT and AST and bilirubin were measured. The results indicate that antisense oligonucleotides had no effect on liver function outside the expected range for antisense oligonucleotides. Specifically, treatment with ISIS 532401 was well tolerated in terms of the liver function in monkeys.

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, blood samples were collected from all the study groups. The blood samples were collected via femoral venipuncture, 48 hrs post-dosing. The monkeys were fasted overnight prior to blood collection. Blood was collected in tubes containing K_2-EDTA anticoagulant, which were centrifuged to obtain plasma. Levels of BUN and creatinine were measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan).

The plasma chemistry data indicate that most of the ISIS oligonucleotides did not have any effect on the kidney function outside the expected range for antisense oligonucleotides. Specifically, treatment with ISIS 532401 was well tolerated in terms of the kidney function of the monkeys.

Hematology

To evaluate any effect of ISIS oligonucleotides in cynomolgus monkeys on hematologic parameters, blood samples of approximately 1.3 mL of blood was collected from each of the available study animals in tubes containing K_2-EDTA. Samples were analyzed for red blood cell (RBC) count, white blood cells (WBC) count, individual white blood cell counts, such as that of monocytes, neutrophils, lymphocytes, as well as for platelet count, hemoglobin content and hematocrit, using an ADVIA120 hematology analyzer (Bayer, USA).

The data indicate the oligonucleotides did not cause any changes in hematologic parameters outside the expected range for antisense oligonucleotides at this dose. Specifically, treatment with ISIS 532401 was well tolerated in terms of the hematologic parameters of the monkeys.

C-reactive protein level analysis

To evaluate any inflammatory effect of ISIS oligonucleotides in cynomolgus monkeys, blood samples were taken for analysis. The monkeys were fasted overnight prior to blood collection. Approximately 1.5 mL of blood was collected from each animal and put into tubes without anticoagulant for

serum separation. The tubes were kept at room temperature for a minimum of 90 min and then centrifuged at 3,000 rpm for 10 min at room temperature to obtain serum. C-reactive protein (CRP), which is synthesized in the liver and which serves as a marker of inflammation, was measured using a Toshiba 200FR NEO chemistry analyzer (Toshiba Co., Japan). The results indicate that treatment with ISIS 532401 did not cause inflammation in monkeys.

Example 137: Measurement of viscosity of ISIS antisense oligonucleotides targeting human GHR

The viscosity of select antisense oligonucleotides from the study described in the Examples above was measured with the aim of screening out antisense oligonucleotides which have a viscosity more than 40 cP. Oligonucleotides having a viscosity greater than 40 cP would be too viscous to be administered to any subject.

ISIS oligonucleotides (32-35 mg) were weighed into a glass vial, 120 µL of water was added and the antisense oligonucleotide was dissolved into solution by heating the vial at 50^0C. Part of (75 µL) the pre-heated sample was pipetted to a micro-viscometer (Cambridge). The temperature of the micro-viscometer was set to 25^0C and the viscosity of the sample was measured. Another part (20 µL) of the pre-heated sample was pipetted into 10 mL of water for UV reading at 260 nM at 85^0C (Cary UV instrument). The results are presented in Table 237 and indicate that all the antisense oligonucleotides solutions are optimal in their viscosity under the criterion stated above.

Table 237

Viscosity of ISIS antisense oligonucleotides targeting human GHR

ISIS No.	Chemistry	Viscosity (cP)
523723	5-10-5 MOE	8
532254	5-10-5 MOE	22
532401	5-10-5 MOE	12
541767	Deoxy, MOE and (S)-cEt	13
541875	Deoxy, MOE and (S)-cEt	33
542112	Deoxy, MOE and (S)-cEt	10
542118	Deoxy, MOE and (S)-cEt	14
542185	Deoxy, MOE and (S)-cEt	17

Example 138: Effect of ISIS oligonucleotides conjugated with GalNAc3-7 vs. unconjugated in a mouse model.

ISIS oligonucleotides targeting murine GHR and that were either unconjugated or conjugated with GalNAc3-7 were tested in BALB/c mice for efficacy and tolerability. BALB/c mice are a multipurpose mice model, frequently utilized for safety and efficacy testing.

The oligonucleotides are all 5-10-5 MOE gapmers, which are 20 nucleosides in length, wherein the central gap segment comprises of ten 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising five nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-MOE modification. The internucleoside linkages throughout each gapmer are phosphorothioate (P=S) linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. "Start site" indicates the 5'-most nucleoside to which the gapmer is targeted in the murine gene sequence. "Stop site" indicates the 3'-most nucleoside to which the gapmer is targeted human gene sequence. Each gapmer listed in the Tables below is targeted to murine GHR mRNA, designated herein as SEQ ID NO: 2333 (GENBANK Accession No. NM_010284.2). The oligonucleotides are described in detail in the Table below.

Table 238

ISIS antisense oligonucleotides targeting murine GHR and conjugated with GalNAc3-7 or unconjugated

ISIS No.	Sequence	Conjugated	Target Start Site	SEQ ID NO
563179	TGCCAACTCACTTGGATGTC	No	772	2334
739949	TGCCAACTCACTTGGATGTC	Yes	772	2334
563223	GAGACTTTTCCTTGTACACA	No	3230	2335
706937	GAGACTTTTCCTTGTACACA	Yes	3230	2335

Treatment

Two groups of seven-week old female BALB/c mice were injected subcutaneously for 4 weeks with 10 mg/kg/week, 25 mg/kg/week, or 50 mg/kg/week of ISIS 563223 or ISIS 563179. Two groups of seven-week old female BALB/c mice were injected subcutaneously for 4 weeks with 1 mg/kg/week, 5 mg/kg/week, or 10 mg/kg/week of ISIS 706937 or ISIS 739949. One group of female BALB/c mice was injected subcutaneously for 4 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Target reduction

To evaluate the efficacy of the ISIS oligonucleotides, plasma IGF-1 levels and mRNA expression levels of IGF-1 and GHR in liver, as well as mRNA expression levels of GHR in fat and kidney tissues, were measured. The results are presented in the Tables below.

The results indicate that the GalNAc3-7 -conjugated oligonucleotides, ISIS 706937 and ISIS 739949, are 7-8 times more potent than the parent oligonucleotides with the same sequence, ISIS 563223 and ISIS 563179, in reducing GHR liver mRNA levels and were 6- to 8-fold more potent in reducing liver and plasma IGF-1 levels. Expression of GHR levels in the kidney and fat tissues were not decreased with GalNAc3-7 -conjugated oligonucleotides, since the GalNAc3-7 conjugate group targeted the oligonucleotide specifically to the liver. This loss in fat and kidney reduction with GalNAc3-7-conjugated oligonucleotides did not affect reduction of IGF-1.

Table 239

Liver mRNA expression levels (% inhibition) at week 4

	mg/kg/wk	GHR	ED_{50}	IGF-1	ED_{50}
ISIS 563223	10	62	4.2	15	19.4
	25	97		69	
	50	99		77	
ISIS 706937	1	59	0.6	24	3.4
	5	97		63	
	10	98		69	
ISIS 563179	10	50	9.6	22	49.4
	25	67		31	
	50	93		50	
ISIS 739949	1	39	1.2	18	6.4
	5	89		57	
	10	94		45	

Table 240

Plasma IGF-1 levels (% inhibition) at week 4

	mg/kg/wk	Week 2	Week 4
PBS	-	0	0
ISIS 563223	10	13	22
	25	40	60
	50	43	71
ISIS 706937	1	20	31
	5	46	64
	10	61	67
ISIS 563179	10	19	25
	25	10	24
	50	25	46
ISIS 739949	1	11	24
	5	29	41

	10	37	31

Table 241

GHR mRNA expression levels (% inhibition) in fat and kidney at week 4

	mg/kg/wk	Fat	Kidney
ISIS 563223	10	21	45
	25	30	66
	50	62	65
ISIS 706937	1	0	5
	5	0	0
	10	0	14
ISIS 563179	10	4	38
	25	14	40
	50	20	41
ISIS 739949	1	4	11
	5	0	1
	10	0	8

Plasma chemistry markers

To evaluate the effect of ISIS oligonucleotides on liver and kidney function, plasma levels of transaminases, bilirubin, glucose, cholesterol, and triglycerides were measured using an automated clinical chemistry analyzer (Beckman Coulter AU480, Brea, CA). The results are presented in the Table below. None of the ISIS oligonucleotides caused changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides. The GalNAc3-7-conjugated oligonucleotides had a slightly improved profile over the parent oligonucleotides.

Table 242

Plasma chemistry markers in BALB/c mice plasma at week 4

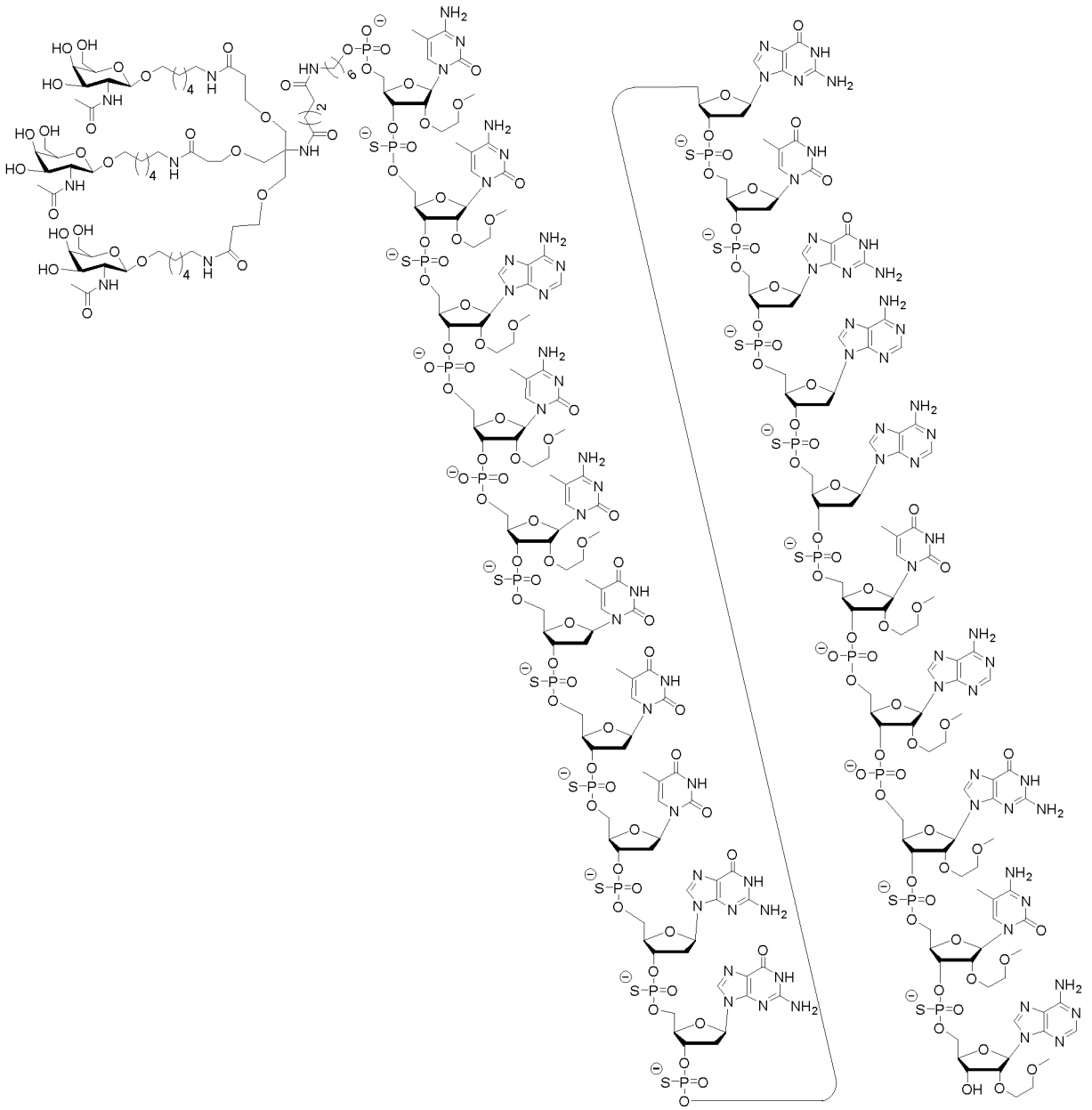
	mg/kg/wk	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Glucose (mg/dL)	Cholesterol (mg/dL)	Triglycerides (mg/dL)
PBS	-	26	58	0.2	165	70	123
ISIS 563223	10	23	69	0.3	157	74	186
	25	39	91	0.3	165	62	160
	50	49	118	0.3	159	56	115
ISIS 706937	1	25	62	0.2	152	64	167
	5	28	64	0.2	180	53	140
	10	27	65	0.2	165	56	133
ISIS 563179	10	28	78	0.4	156	65	131
	25	28	95	0.2	152	59	118

	50	63	108	0.3	157	80	143
ISIS 739949	1	24	66	0.2	156	66	114
	5	29	80	0.2	153	76	161
	10	31	59	0.3	174	78	155

The results taken together indicate that oligonucleotides targeting GHR mRNA expression when conjugated with GalNAc3-7 had tenfold greater potency and similar or improved tolerability profiles compared to the parent oligonucleotides.

Example 139: Tolerability study of an ISIS oligonucleotide conjugated with GalNAc3-7 and targeting human GHR in mice.

ISIS 766720 was designed with the same sequence as ISIS 532401, a potent and tolerable oligonucleotide targeting human GHR and described in the studies above. ISIS 766720 is a 5-10-5 MOE gapmer with mixed backbone chemistry and conjugated with GalNAc3-7. The chemical structure of ISIS 766720 without the GalNAc3-7 conjugate group is denoted as mCes mCes Aeo mCeo mCes Tds Tds Tds Gds Gds Gds Tds Gds Ads Ads Teo Aeo Ges mCes Ae (SEQ ID NO: 703) and is fully denoted as:



Treatment

Groups of six-week old male CD-1 mice were injected subcutaneously for 6 weeks with 25 mg/kg/week, 50 mg/kg/week, or 100 mg/kg/week of ISIS 766720. One group of mice was injected subcutaneously for 6 weeks (days 1, 5, 15, 22, 29, 36, and 43) with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

Plasma chemistry markers

To evaluate the effect of ISIS 766720 on liver and kidney function, plasma levels of transaminases, bilirubin, creatinine and BUN were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). The results are presented in the Table below. ISIS 766720 did not cause changes in the levels of any of the liver or kidney function markers outside the expected range for antisense oligonucleotides and was deemed very tolerable.

Table 243

Plasma chemistry markers in CD-1 mice plasma at week 6

	mg/kg/wk	ALT (IU/L)	AST (IU/L)	Bilirubin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
PBS	-	44	79	0.3	0.2	29
ISIS 766720	25	29	47	0.2	0.2	34
	50	38	56	0.2	0.2	35
	100	29	45	0.2	0.2	31

Body and organ weights

Body and organ weights were measured at the end of the study. The results are presented in the Table below. ISIS 766720 did not cause changes in weights outside the expected range for antisense oligonucleotides and was deemed very tolerable.

Table 244

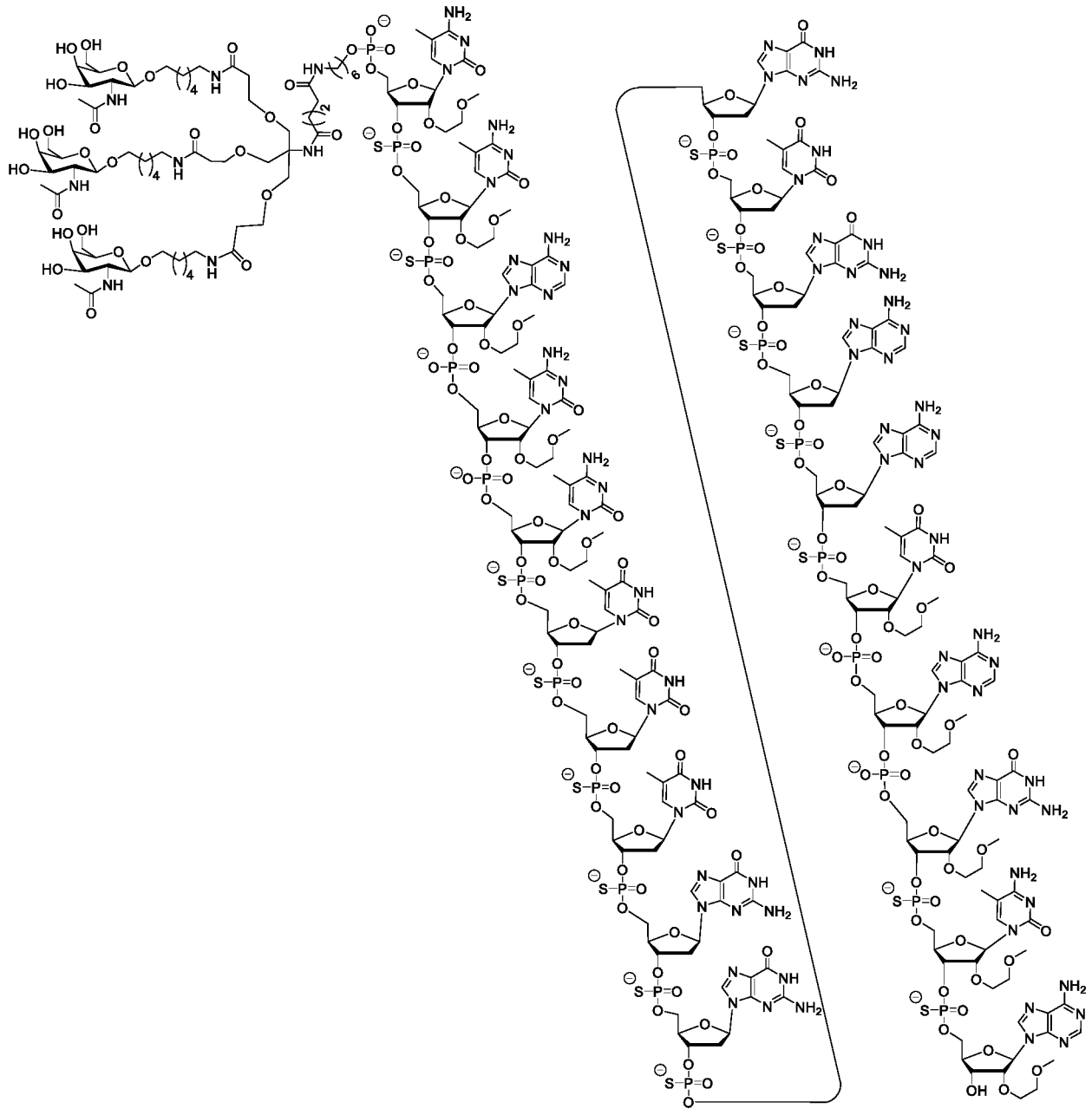
Weights of CD-1 mice at week 6

	mg/kg/wk	Body (g)	Liver (% body)	Kidney (% body)	Spleen (% body)
PBS	-	40	3.0	1.0	0.2
ISIS 766720	25	41	3.4	0.8	0.2
	50	41	3.3	0.8	0.2
	100	40	4.8	0.8	0.2

2015252841 25 Feb 2020

WHAT IS CLAIMED:

1. A compound consisting of a conjugate group and a modified oligonucleotide according to the following formula:



2. A composition comprising the compound of claim 1, or a salt thereof and at least one of a pharmaceutically acceptable carrier or diluent.

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3. The compound of claim 1, or the composition of claim 2, for use in therapy.

4. A therapeutically effective amount of the compound of claim 1, or the composition of claim 2, for use in a method of treating a disease associated with excess growth hormone in a human, wherein the use comprises administering to the human the therapeutically effective amount, thereby treating the disease associated with excess growth hormone, optionally wherein (a) the disease associated with excess growth hormone is acromegaly and/or (b) the treatment reduces IGF-1 levels.

5. A therapeutically effective amount of the compound of claim 1, or the composition of claim 2, for use in a method of reducing growth hormone receptor (GHR) levels in a human, wherein the use comprises administering to the human the therapeutically effective amount, thereby reducing GHR levels in the human, optionally wherein (a) the human has a disease associated with excess growth hormone and/or (b) the disease associated with excess growth hormone is acromegaly.

6. The compound of claim 1, or the composition of claim 2, when used in therapy.

7. A therapeutically effective amount of the compound of claim 1, or the composition of claim 2, when used in a method of treating a disease associated with excess growth hormone in a human, wherein the use comprises administering to the human the therapeutically effective amount, thereby treating the disease associated with excess growth hormone, optionally wherein (a) the disease associated with excess growth hormone is acromegaly and/or (b) the treatment reduces IGF-1 levels.

8. A therapeutically effective amount of the compound of claim 1, or the composition of claim 2, when used in a method of reducing growth hormone receptor (GHR) levels in a human, wherein the use comprises administering to the human the therapeutically effective amount, thereby reducing GHR levels in the human, optionally wherein (a) the human has a disease associated with excess growth hormone and/or (b) the disease associated with excess growth hormone is acromegaly.

9. A method of treating a disease associated with excess growth hormone in a human, wherein the method comprises administering to the human the compound of claim 1, or the composition of claim 2, thereby treating the disease associated with excess growth hormone, optionally wherein (a) the disease associated with excess growth hormone is acromegaly and/or (b) the treatment reduces IGF-1 levels.

10. Use of the compound of claim 1, or the composition of claim 2, in the manufacture of a medicament for treating a disease associated with excess growth hormone in a human, optionally wherein (a) the disease associated with excess growth hormone is acromegaly and/or (b) administering the medicament reduces IGF-1 levels.

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11. A method of reducing growth hormone receptor (GHR) levels in a human, wherein the method comprises administering to the human the compound of claim 1, or the composition of claim 2, thereby reducing GHR levels in the human, optionally wherein (a) the human has a disease associated with excess growth hormone and/or (b) the disease associated with excess growth hormone is acromegaly.

12. Use of the compound of claim 1, or the composition of claim 2, in the manufacture of a medicament for reducing growth hormone receptor (GHR) levels in a human, optionally wherein (a) the human has a disease associated with excess growth hormone and/or (b) the disease associated with excess growth hormone is acromegaly.

SEQUENCE LISTING

<110> Isis Pharmaceuticals

<120> COMPOSITIONS AND METHODS FOR MODULATING GROWTH HORMONE RECEPTOR EXPRESSION

<130> BIOL0253WO

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<151> 2014-05-01

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<151> 2014-10-01

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