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(54) **Title**: COMPOSITIONS AND METHODS FOR MODULATING PKK EXPRESSION

(57) **Abstract**: Disclosed herein are antisense compounds and methods for decreasing PKK mRNA and protein expression. Such methods, compounds, and compositions are useful to treat, prevent, or ameliorate PKK-associated diseases, disorders, and conditions.

COMPOSITIONS AND METHODS FOR MODULATING PKK 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 BIOL0252WOSEQ_ST25.txt created April 27, 2015, which is approximately 636 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are compounds, compositions, and methods for reducing expression of human plasma prekallikrein (PKK) mRNA and protein in an animal. Such compositions and methods are useful to treat, prevent, or ameliorate inflammatory and thromboembolic conditions.

Background

Plasma prekallikrein (PKK) is the precursor of plasma kallikrein (PK), which is encoded by the KLKB1 gene. PKK is a glycoprotein that participates in the surface-dependent activation of blood coagulation, fibrinolysis, kinin generation, and inflammation. PKK is converted to PK by Factor XIIa by the cleavage of an internal Arg-Ile peptide bond. PK liberates kinins from kininogens and also generates plasmin from plasminogen. PK is a member of the kinin-kallikrein pathway, which consists of several proteins that play a role in inflammation, blood pressure control, coagulation, and pain.

Summary

Provided herein are compounds, compositions, and methods for modulating expression of PKK mRNA and protein. In certain embodiments, compounds useful for modulating expression of PKK mRNA and protein are antisense compounds. In certain embodiments, the antisense compounds are antisense oligonucleotides.

In certain embodiments, modulation can occur in a cell or tissue. In certain embodiments, the cell or tissue is in an animal. In certain embodiments, the animal is a human. In certain embodiments, PKK mRNA levels are reduced. In certain embodiments, PKK protein levels are reduced. Such reduction can occur in a time-dependent manner or in a dose-dependent manner.

Also provided are compounds, compositions, and methods useful for preventing, treating, and ameliorating diseases, disorders, and conditions associated with PKK. In certain embodiments, such PKK associated diseases, disorders, and conditions are inflammatory diseases. In certain embodiments, the

inflammatory disease may be an acute or chronic inflammatory disease. In certain embodiments, such inflammatory diseases may include hereditary angioedema (HAE), edema, angioedema, swelling, angioedema of the lids, ocular edema, macular edema, and cerebral edema. In certain embodiments, such PKK associated diseases, disorders, and conditions are thromboembolic diseases. In certain embodiments, such thromboembolic diseases may include thrombosis, embolism, thromboembolism, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and infarct.

Such diseases, disorders, and conditions can have one or more risk factors, causes, or outcomes in common.

Certain risk factors and causes for development of an inflammatory disease include genetic predisposition to an inflammatory disease and environmental factors. In certain embodiments, the subject has a mutated complement 1 esterase inhibitor (C1-INH) gene or mutated Factor 12 gene. In certain embodiments, the subject has taken or is on angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs). In certain embodiments, the subject has had an allergic reaction leading to angioedema. In certain embodiments, the subject has type I HAE. In certain embodiments, the subject has type II HAE. In certain embodiments, the subject has type III HAE.

Certain outcomes associated with development of an inflammatory disease include edema/swelling in various body parts including the extremities (i.e., hands, feet, arms, legs), the intestines (abdomen), the face, the genitals, the larynx (i.e., voice box); vascular permeability; vascular leakage; generalized inflammation; abdominal pain; bloating; vomiting; diarrhea; itchy skin; respiratory (asthmatic) reactions; rhinitis; anaphylaxis; bronchoconstriction; hypotension; coma; and death.

Certain risk factors and causes for development of a thromboembolic disease include genetic predisposition to a thromboembolic disease, immobility, surgery (particularly orthopedic surgery), malignancy, pregnancy, older age, use of oral contraceptives, atrial fibrillation, previous thromboembolic condition, chronic inflammatory disease, and inherited or acquired prothrombotic clotting disorders. Certain outcomes associated with development of a thromboembolic condition include decreased blood flow through an affected vessel, death of tissue, and death.

In certain embodiments, methods of treatment include administering a PKK antisense compound to an individual in need thereof. In certain embodiments, methods of treatment include administering a PKK antisense oligonucleotide to an individual in need thereof.

Listing of Figures

Figure 1 is a Western blot quantification of HMWK from blood samples as described in Example 124.

Figure 2 is a Western blot quantification of HMWK from blood samples as described in Example 127.

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.

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.

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.

Definitions

Unless specific definitions are provided, the nomenclature utilized 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. Where permitted, all patents, applications, published applications and other publications, GENBANK Accession Numbers and associated sequence information obtainable through databases such as National Center for Biotechnology Information (NCBI) and other data referred to throughout in the disclosure herein are incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

Unless otherwise indicated, the following terms have the following meanings:

"2'-O-methoxyethyl" (also 2'-MOE and 2'-OCH_2CH_2-OCH_3 and MOE) refers to an O-methoxyethyl modification of the 2' position of a furanose ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

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

"2'-substituted nucleoside" means a nucleoside comprising a substituent at the 2'-position of the furanose ring other than H or OH. In certain embodiments, 2' substituted nucleosides include nucleosides with bicyclic sugar modifications.

"2'-deoxynucleoside" means a nucleoside comprising a hydrogen at the 2' position of the sugar portion of the nucleoside.

"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 ±7% of a value. For example, if it is stated, "the compounds affected at least about 70% inhibition of PKK", it is implied that the PKK levels are inhibited within a range of 63% and 77%.

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

"Administering" means providing a pharmaceutical agent to an animal, and includes, but is not limited to administering by a medical professional and self-administering.

"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, slowing, stopping, or reversing of at least one indicator of the severity 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 compound" means an oligomeric compound that 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 or 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 mechanisms" are all those mechanisms involving hybridization of a compound with a 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 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.

"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" means a furanose ring modified by the bridging of two atoms. A bicyclic sugar is a modified sugar.

"Bicyclic nucleoside" (also BNA) 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 nucleoside having a 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'.

"cEt modified nucleoside" (also "constrained ethyl 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 nucleosides is chemically distinct from a region having nucleosides 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 compound" means an antisense compound that has at least two 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 "GalNac3-1_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.

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

"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 a 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.

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

"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.

"Expression" includes all the functions by which a gene's coded information is converted into structures present and operating in a cell. Such structures include, but are not limited to the products of transcription 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.

"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 a "gap" and the external regions may be referred to as the "wings."

"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 target nucleic acid. 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 an inflammatory disease" means identifying an animal having been diagnosed with an inflammatory disease or predisposed to develop an inflammatory disease. Individuals predisposed to develop an inflammatory disease include those having one or more risk factors for developing an inflammatory disease including environmental factors, having a personal or family history, or genetic predisposition to one or more inflammatory disease. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments, such as genetic testing.

"Identifying an animal having a PKK associated disease" means identifying an animal having been diagnosed with a PKK associated disease or predisposed to develop a PKK associated disease. Individuals predisposed to develop a PKK associated disease include those having one or more risk factors for developing a PKK associated disease including having a personal or family history, or genetic predisposition of one or more PKK associated diseases. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments, such as genetic testing.

"Identifying an animal having a thromboembolic disease" means identifying an animal having been diagnosed with a thromboembolic disease or predisposed to develop a thromboembolic disease. Individuals predisposed to develop a thromboembolic disease include those having one or more risk factors for developing a thromboembolic disease including having a personal or family history, or genetic predisposition of one or more thromboembolic diseases, immobility, surgery (particularly orthopedic surgery), malignancy, pregnancy, older age, use of oral contraceptives, atrial fibrillation, previous thromboembolic condition, chronic inflammatory disease, and inherited or acquired prothrombotic clotting disorders. Such identification may be accomplished by any method including evaluating an individual's medical history and standard clinical tests or assessments, such as genetic testing.

"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.

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

"Inhibiting PKK" means reducing the level or expression of a PKK mRNA and/or protein. In certain embodiments, PKK mRNA and/or protein levels are inhibited in the presence of an antisense compound targeting PKK, including an antisense oligonucleotide targeting PKK, as compared to expression of PKK mRNA and/or protein levels in the absence of a PKK antisense compound, such as an antisense oligonucleotide.

"Inhibiting the expression or activity" refers to a reduction or 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.

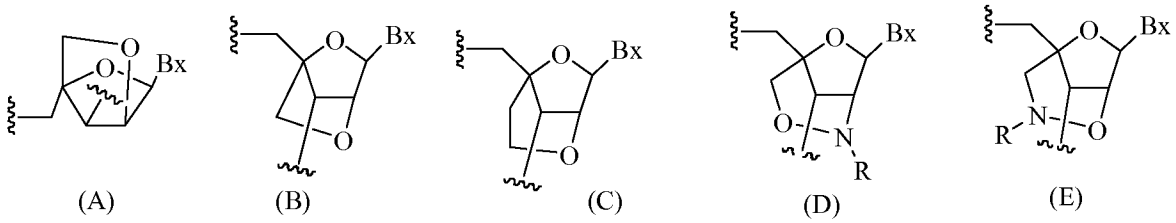
"Internucleoside neutral linking group" means a neutral linking group that directly links two nucleosides.

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

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

"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.

"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 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 (also known as 5-methyluracil), 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, and/or modified nucleobase.

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

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

"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.

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

"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 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, double-stranded nucleic acids, small interfering ribonucleic acids (siRNA), and microRNAs (miRNA).

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

"Nucleobase complementarity" refers to 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 refers to 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.

"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 nucleobase linked to a sugar.

"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" or "oligomer" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of a nucleic acid molecule.

"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 (e.g., bolus 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 molecule 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, an antisense oligonucleotide targeted to PKK is a pharmaceutical agent.

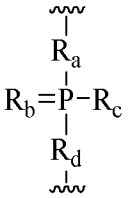
"Pharmaceutical composition" means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an antisense oligonucleotide and a sterile aqueous solution.

"Pharmaceutically acceptable derivative" encompasses pharmaceutically acceptable salts, conjugates, prodrugs or isomers of the compounds described herein.

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

"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.

"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.

"PKK" means mammalian plasma prekallikrein, including human plasma prekallikrein. Plasma prekallikrein (PKK) is the precursor of plasma kallikrein (PK), which is encoded by the KLKB1 gene.

"PKK associated disease" means any disease associated with any PKK nucleic acid or expression product thereof. Such diseases may include an inflammatory disease or a thromboembolic disease. Such diseases may include hereditary angioedema (HAE).

"PKK mRNA" means any messenger RNA expression product of a DNA sequence encoding PKK.

"PKK nucleic acid" means any nucleic acid encoding PKK. For example, in certain embodiments, a PKK nucleic acid includes a DNA sequence encoding PKK, an RNA sequence transcribed from DNA encoding PKK (including genomic DNA comprising introns and exons), and an mRNA sequence encoding PKK. "PKK mRNA" means an mRNA encoding a PKK protein.

"PKK protein" means the polypeptide expression product of a PKK nucleic acid.

"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" or "preventing" refers to delaying or forestalling the onset or development of a disease, disorder, or condition for a period of time from minutes to days, weeks to months, or indefinitely.

"Prodrug" means a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions.

"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 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.

"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 responses attributable to a treatment other than desired effects. In certain embodiments, side effects include, without limitation, injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, and myopathies.

"Single-stranded oligonucleotide" means an oligonucleotide which is not hybridized to a complementary strand.

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

"Specifically hybridizable" or "specifically hybridizes" 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," and "target RNA transcript" and "nucleic acid target" all mean a nucleic acid capable of being targeted by antisense compounds.

"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.

"Treat" or "treating" or "treatment" refers to administering a composition to effect an improvement of the disease or condition.

"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" mean the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (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 toward 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 compounds, compositions, and methods for inhibiting plasma prekallikrein (PKK) mRNA and protein expression. Certain embodiments provide compounds, compositions, and methods for decreasing PKK mRNA and protein levels.

Certain embodiments provide antisense compounds targeted to a plasma prekallikrein (PKK) nucleic acid. In certain embodiments, the PKK nucleic acid is the sequence set forth in GENBANK Accession No. NM_000892.3 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. DC412984.1

(incorporated herein as SEQ ID NO: 2), GENBANK Accession No. CN265612.1 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. AK297672.1 (incorporated herein as SEQ ID NO: 4), GENBANK Accession No. DC413312.1 (incorporated herein as SEQ ID NO: 5), GENBANK Accession No. AV688858.2 (incorporated herein as SEQ ID NO: 6), GENBANK Accession No. CD652077.1 (incorporated herein as SEQ ID NO: 7), GENBANK Accession No. BC143911.1 (incorporated herein as SEQ ID NO: 8), GENBANK Accession No. CB162532.1 (incorporated herein as SEQ ID NO: 9), GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000 (incorporated herein as SEQ ID NO: 10), GENBANK Accession No. NM_008455.2 (incorporated herein as SEQ ID NO: 11), GENBANK Accession No. BB598673.1 (incorporated herein as SEQ ID NO: 12), GENBANK Accession No. NT_039460.7 truncated from nucleobases 6114001 to 6144000 (incorporated herein as SEQ ID NO: 13), GENBANK Accession No. NM_012725.2 (incorporated herein as SEQ ID NO: 14), GENBANK Accession No. NW_047473.1 truncated from nucleobases 10952001 to 10982000 (incorporated herein as SEQ ID NO: 15), GENBANK Accession No. XM_002804276.1 (incorporated herein as SEQ ID NO: 17), and GENBANK Accession No. NW_001118167.1 truncated from nucleobases 2358000 to 2391000 (incorporated herein as SEQ ID NO: 18).

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 30-2226.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases of the nucleobase sequence of SEQ ID NO: 570.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases of the nucleobase sequence of SEQ ID NO: 705.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of the nucleobase sequence of SEQ ID NO: 1666.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has the nucleobase sequence of SEQ ID NO: 570.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has the nucleobase sequence of SEQ ID NO: 705.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 16 linked nucleosides and has the nucleobase sequence of SEQ ID NO: 1666.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 62, 72, 103, 213, 312, 334-339, 344, 345, 346, 348, 349, 351, 369, 373, 381, 382, 383, 385, 387-391, 399, 411, 412, 414, 416, 444, 446-449, 452, 453, 454, 459, 460, 462-472, 473, 476, 477, 479, 480, 481, 484, 489-495, 497, 500, 504, 506, 522, 526, 535, 558, 559, 560, 564, 566, 568-571, 573, 576, 577, 578, 587, 595, 597-604, 607, 608, 610, 613, 615, 618, 619, 622, 623, 624, 633, 635, 636, 638, 639, 640, 642, 643, 645, 652, 655-658, 660, 661, 670, 674-679, 684, 685, 698, 704, 705, 707, 708, 713, 716, 717, 728, 734, 736, 767, 768, 776, 797, 798, 800, 802, 810, 815, 876, 880, 882, 883, 886, 891, 901-905, 908-911, 922, 923, 924, 931, 942, 950-957, 972, 974, 978, 979, 980, 987-991, 1005, 1017-1021, 1025, 1026, 1029, 1030, 1032, 1034, 1035, 1037, 1040, 1041, 1045, 1046, 1051, 1054, 1059, 1060, 1061, 1064, 1065, 1066, 1075, 1076, 1087, 1089, 1111, 1114, 1116, 1117, 1125, 1133, 1153, 1169, 1177, 1181, 1182, 1187, 1196, 1200, 1214, 1222, 1267, 1276, 1277, 1285, 1286, 1289, 1290, 1291, 1303, 1367, 1389, 1393, 1398-1401, 1406, 1407, 1408, 1411, 1419-1422, 1426, 1430, 1431, 1432, 1434-1437, 1439, 1440, 1443, 1444, 1451, 1452, 1471, 1516, 1527, 1535, 1537, 1538, 1539, 1540, 1541, 1563, 1564, 1567, 1568, 1616, 1617, 1623, 1629, 1664, 1665, 1666, 1679, 1687, 1734, 1804, 1876, 1886, 1915, 2008, 2018, 2100, 2101, 2115, and 2116. In certain embodiments, the modified oligonucleotide achieves at least 80% mRNA inhibition of PKK.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 62, 72, 103, 213, 334-339, 344, 346, 348, 349, 351, 381, 382, 383, 385, 389, 390, 391, 446, 448, 452, 453, 454, 466-473, 476, 481, 484, 491, 492, 494, 495, 497, 504, 526, 558, 559, 566, 568-571, 576, 578, 587, 595, 597, 598, 600-604, 607, 610, 613, 618, 619, 624, 635, 638, 639, 645, 652, 656, 657, 658, 660, 674, 675, 676, 684, 698, 704, 705,

707, 713, 716, 768, 876, 880, 901-905, 908-911, 922, 923, 924, 931, 942, 951, 954-957, 972, 974, 978, 979, 987, 988, 990, 1005, 1019, 1020, 1021, 1025, 1032, 1037, 1040, 1041, 1045, 1054, 1059, 1060, 1061, 1064, 1065, 1066, 1075, 1111, 1116, 1117, 1125, 1133, 1153, 1169, 1177, 1200, 1222, 1267, 1285, 1290, 1291, 1303, 1367, 1398, 1399, 1401, 1406, 1408, 1411, 1419, 1420, 1421, 1426, 1430, 1431, 1432, 1434-1437, 1440, 1443, 1444, 1451, 1537-1540, 1563, 1616, 1679, 1687, 1804, 2008, 2101, 2115, and 2116. In certain embodiments, the modified oligonucleotide achieves at least 85% mRNA inhibition of PKK.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 334, 346, 351, 382, 390, 391, 446, 448, 452, 453, 468, 469, 470, 471, 472, 476, 481, 491, 495, 504, 558, 566, 568, 570, 571, 578, 587, 597, 598, 600, 604, 613, 635, 638, 645, 656, 658, 660, 674, 675, 684, 704, 705, 880, 901-905, 909, 922, 931, 951, 954, 956, 990, 1005, 1020, 1032, 1037, 1040, 1041, 1045, 1054, 1075, 1111, 1125, 1133, 1153, 1200, 1267, 1291, 1303, 1398, 1399, 1401, 1406, 1420, 1426, 1430, 1431, 1434, 1435, 1436, 1440, 1443, 1451, 1537-1540, 2115, and 2116. In certain embodiments, the modified oligonucleotide achieves at least 90% mRNA inhibition of PKK.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 334, 391, 448, 468, 469, 568, 570, 598, 635, 658, 674, 684, 705, 901, 903, 904, 922, 990, 1267, 1291, 1420, 1430, 1431, 1434, 1435, 1436, 1537, 1538, and 1540. In certain embodiments, the modified oligonucleotide achieves at least 95% mRNA inhibition of PKK.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 334, 338, 346, 349, 382, 383, 390, 448, 452, 453, 454, 495, 526, 559, 570, 587, 598, 635, 660, 705, 901, 903, 904, 908, 923, 931, 955, 974, 988, 990, 1020, 1039, 1040, 1111, 1117, 1267, 1291, 1349, 1352, 1367, 1389, 1393, 1399, 1401, 1408, 1411, 1426, 1499, 1516, 1535, 1544, 1548, 1563, 1564, 1568, 1569, 1598, 1616, 1617, 1623, 1624, 1643, 1661, 1665, 1666, 1673, 1679, 1695, 1720, 1804, 1817, 1876, 1881, 1886, 1940, 1947, 2008, 2018, 2019, 2031, 2044, 2100, 2101, 2115, and 2116. In certain embodiments, the modified oligonucleotide achieves an IC_{50} (μM) of 0.4 or less.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 334, 346, 349, 382, 453, 454, 495, 526, 570, 587, 598, 635, 660, 901, 903, 904, 931, 955, 990, 1020, 1111, 1267, 1349, 1352, 1367, 1389, 1399, 1408, 1411, 1426, 1516, 1535, 1544, 1548, 1563, 1564, 1568, 1569, 1598, 1616, 1617, 1623, 1643, 1661, 1665, 1666, 1673, 1695, 1804, 1876, 1881, 2019, 2044, 2100, 2101, 2115, and 2116. In certain embodiments, the modified oligonucleotide achieves an IC_{50} (μM) of 0.3 or less.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 334, 346, 382, 453, 495, 526, 570, 587, 598, 635, 901, 904, 931, 955, 1020, 1111, 1349, 1352, 1389, 1426, 1516, 1535, 1544, 1548, 1564, 1569, 1598, 1616, 1617, 1665, 1666, 1804, 1876, 1881, 2019, 2044, 2101, and 2116. In certain embodiments, the modified oligonucleotide achieves an IC_{50} (μM) of 0.2 or less.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 334, 495, 587, 598, 635, 1349, 1352, 1389, 1516, 1544, 1548, 1569, 1598, 1617, 1665, 1666, 1804, 1881, and 2019. In certain embodiments, the modified oligonucleotide achieves an IC_{50} (μM) of less than 0.2.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consistsof 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 27427-27466 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 33183-33242 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14,

at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 30570-30610 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 27427-27520 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 33085-33247 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 30475-30639 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 27362-27524 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 33101-33240 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of nucleobases 30463-30638 of SEQ ID NO: 10.

Certain embodiments provide compounds, comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides and comprises a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases complementary to an equal length portion of exon 9, exon 12, or exon 14 of a PKK nucleic acid.

In certain embodiments the nucleobase sequence of the modified oligonucleotide is 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 SEQ ID NO: 10.

In certain embodiments, the compound consists of a single-stranded modified oligonucleotide.

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: Tes Ges mCes Aes Aes Gds Tds mCds Tds mCds Tds Tds Gds Gds mCds Aes Aes Aes 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.

Certain embodiments provide compounds consisting of a conjugate group and a modified oligonucleotide according to the following formula: mCes mCes mCes mCes mCes Tds Tds mCds Tds Tds Tds Ads Tds Ads Gds mCes mCes Aes Ges mCe; 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.

Certain embodiments provide compounds consisting of a conjugate group and a modified oligonucleotide according to the following formula: mCes Ges Aks Tds Ads Tds mCds Ads Tds Gds Ads Tds Tds mCks mCks mCe; wherein,

A = an adenine,

mC = a 5'-methylcytosine;

G = a guanine,

T = a thymine,

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

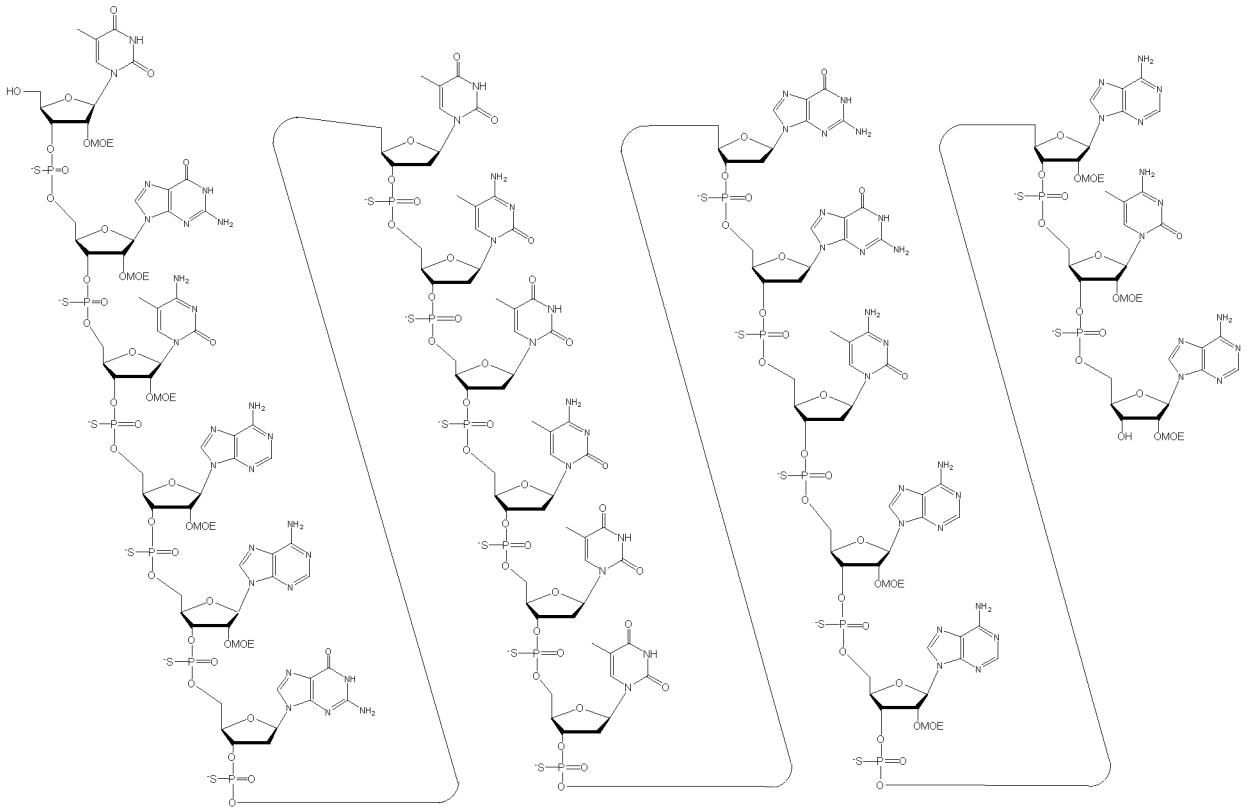
k = a cEt modified nucleoside,

d = a 2'-deoxynucleoside, and

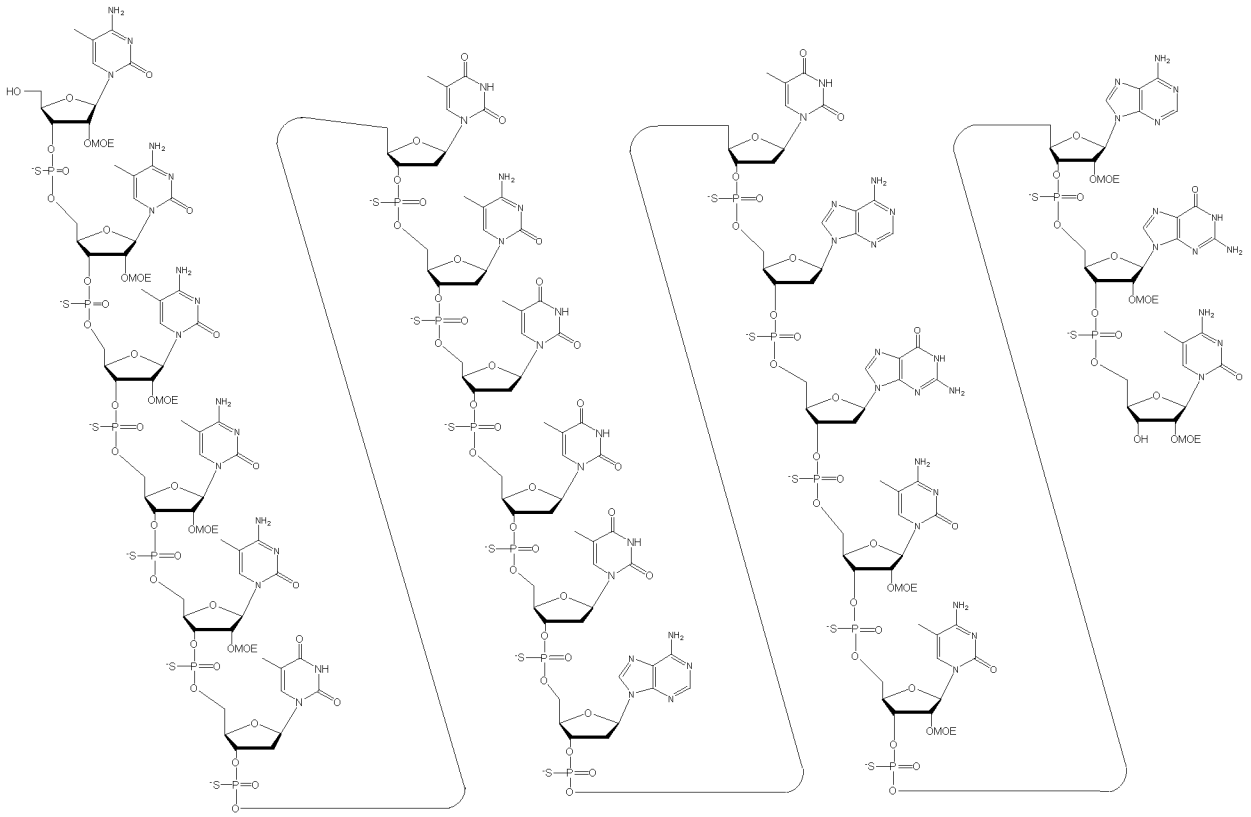
s = a phosphorothioate internucleoside linkage.

In certain embodiments, the conjugate group is linked to the modified oligonucleotide at the 5' end of the modified oligonucleotide. In certain embodiments, the conjugate group is linked to the modified oligonucleotide at the 3' end of the modified oligonucleotide. In certain embodiments, the conjugate group comprises at least one *N*- Acetylgalactosamine (GalNAc), at least two *N*- Acetylgalactosamines (GalNAcs), or at least three *N*- Acetylgalactosamines (GalNAcs).

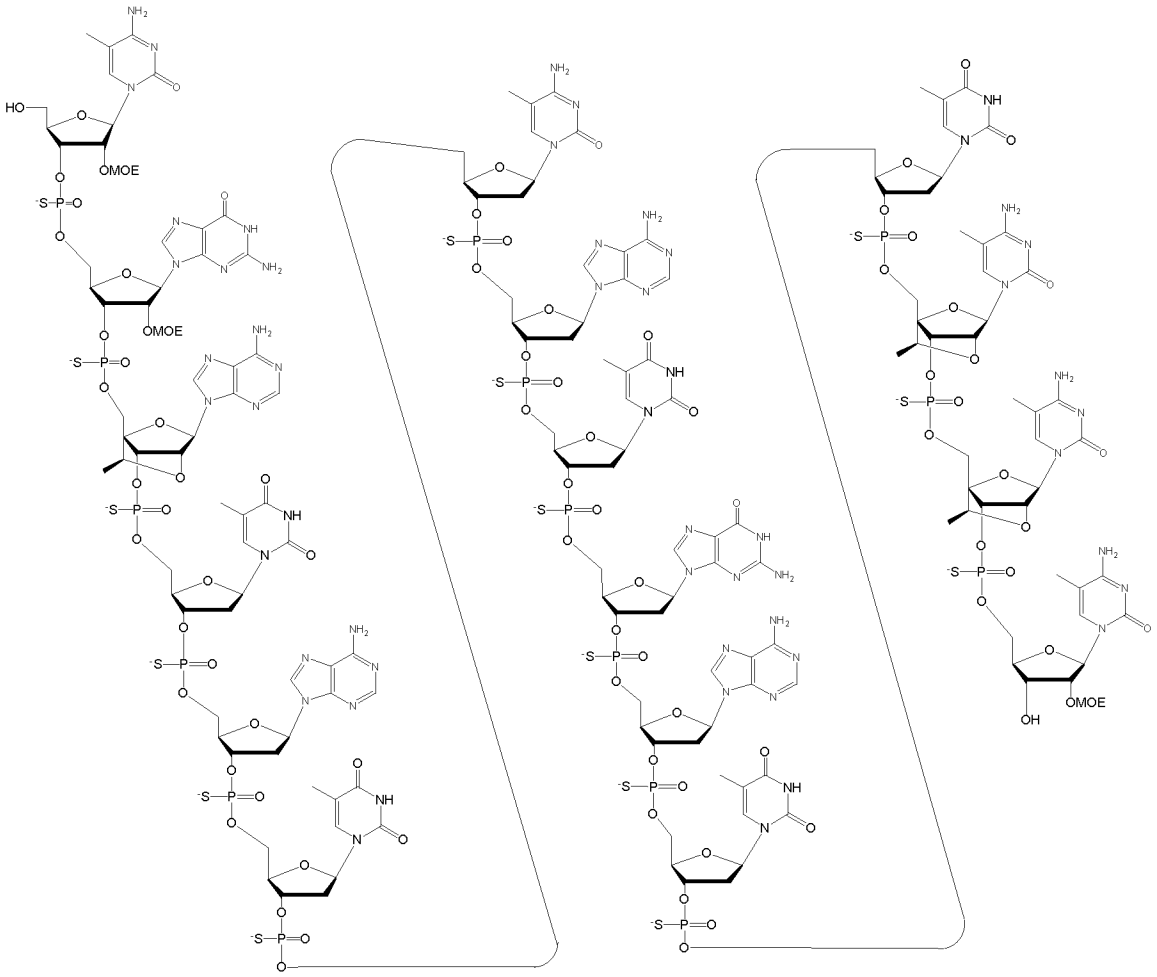
Certain embodiments provide compounds according to the following formula:



Certain embodiments provide compounds according to the following formula:

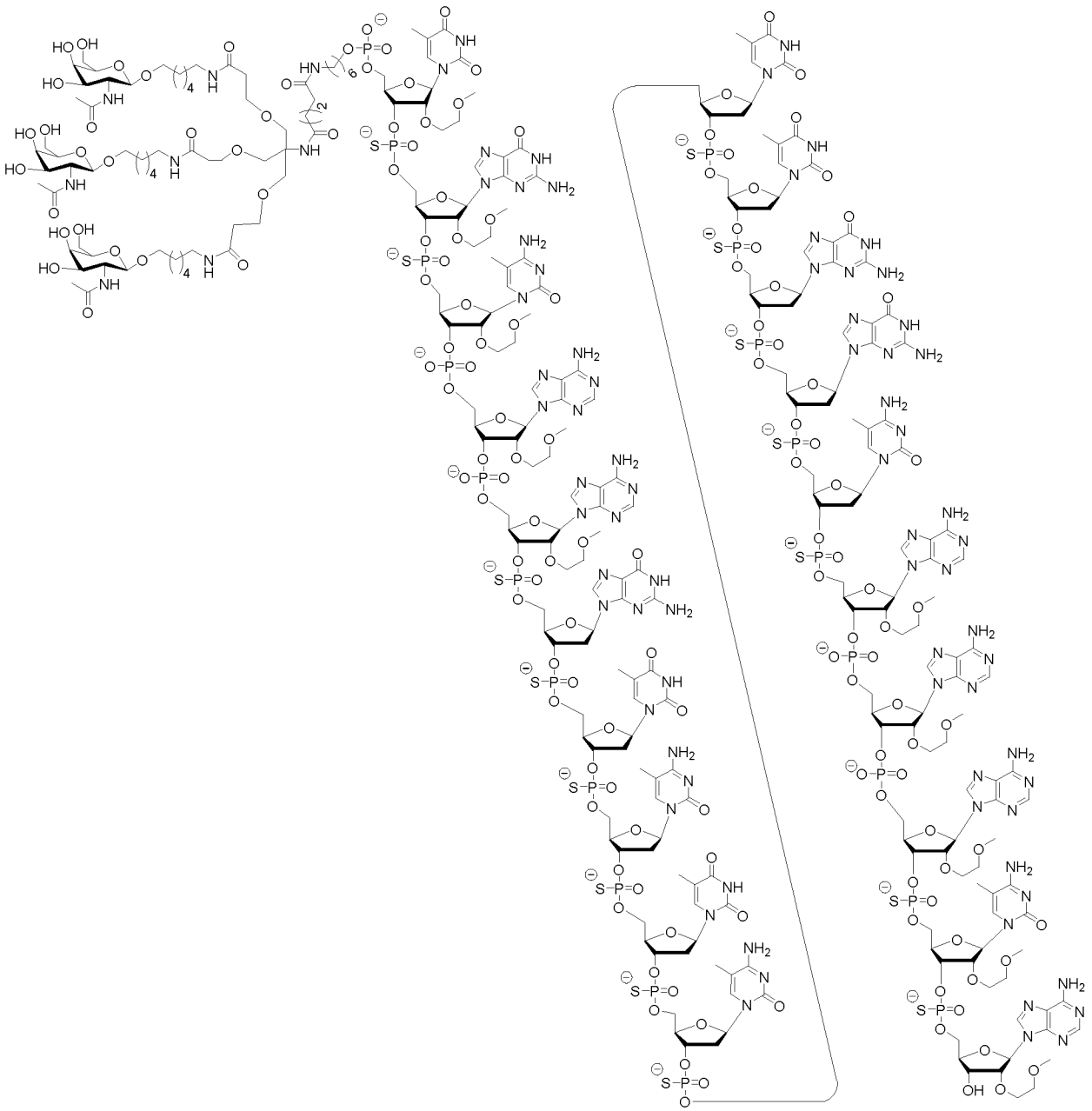


Certain embodiments provide compounds according to the following formula:

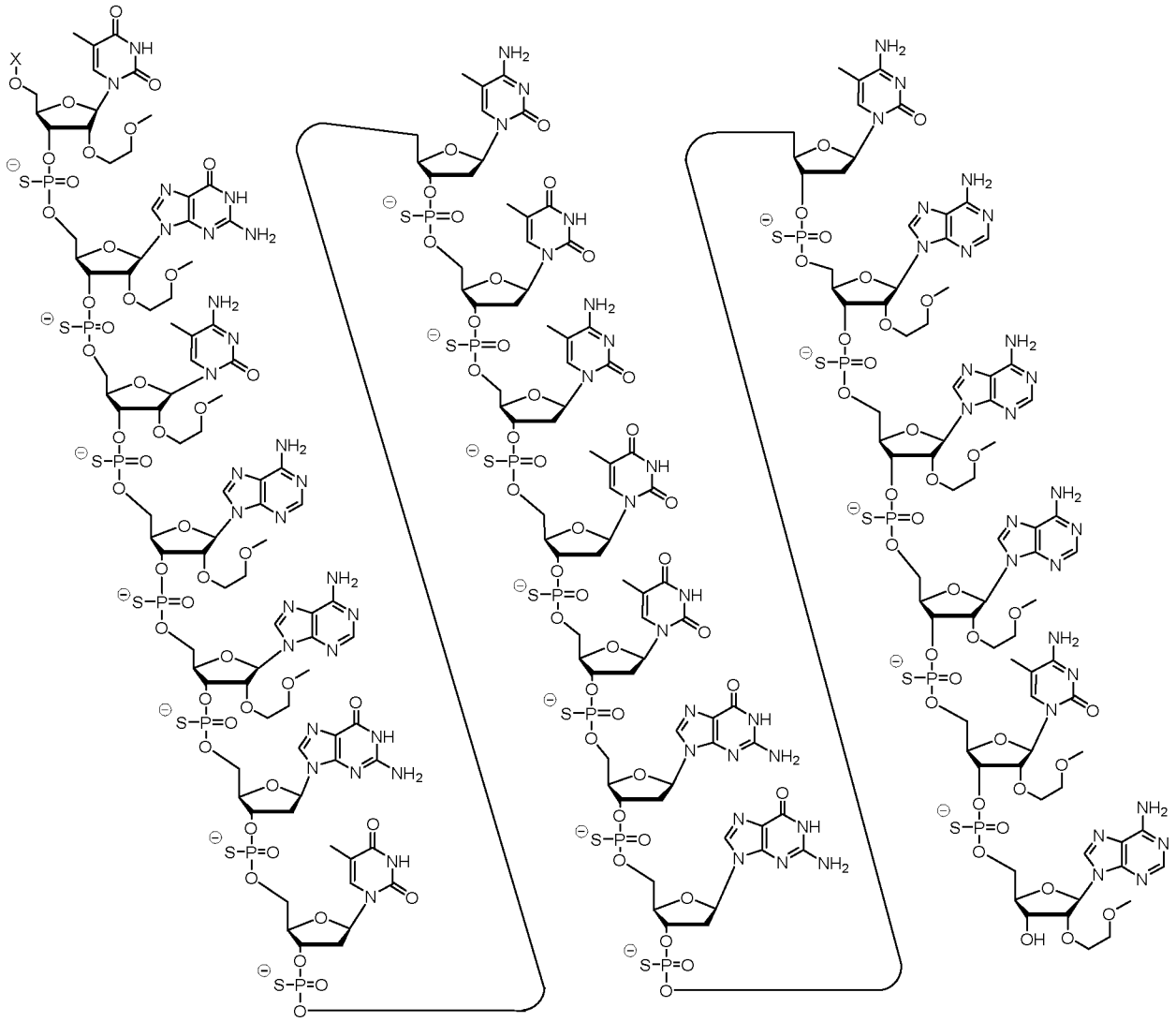


In certain embodiments, a compound can comprise or consist of any modified oligonucleotide described herein and a conjugate group. In certain embodiments, a compound can comprise or consist of a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 consecutive nucleobases of any of the nucleobase sequences of SEQ ID NOs: 30-2226, and a conjugate group.

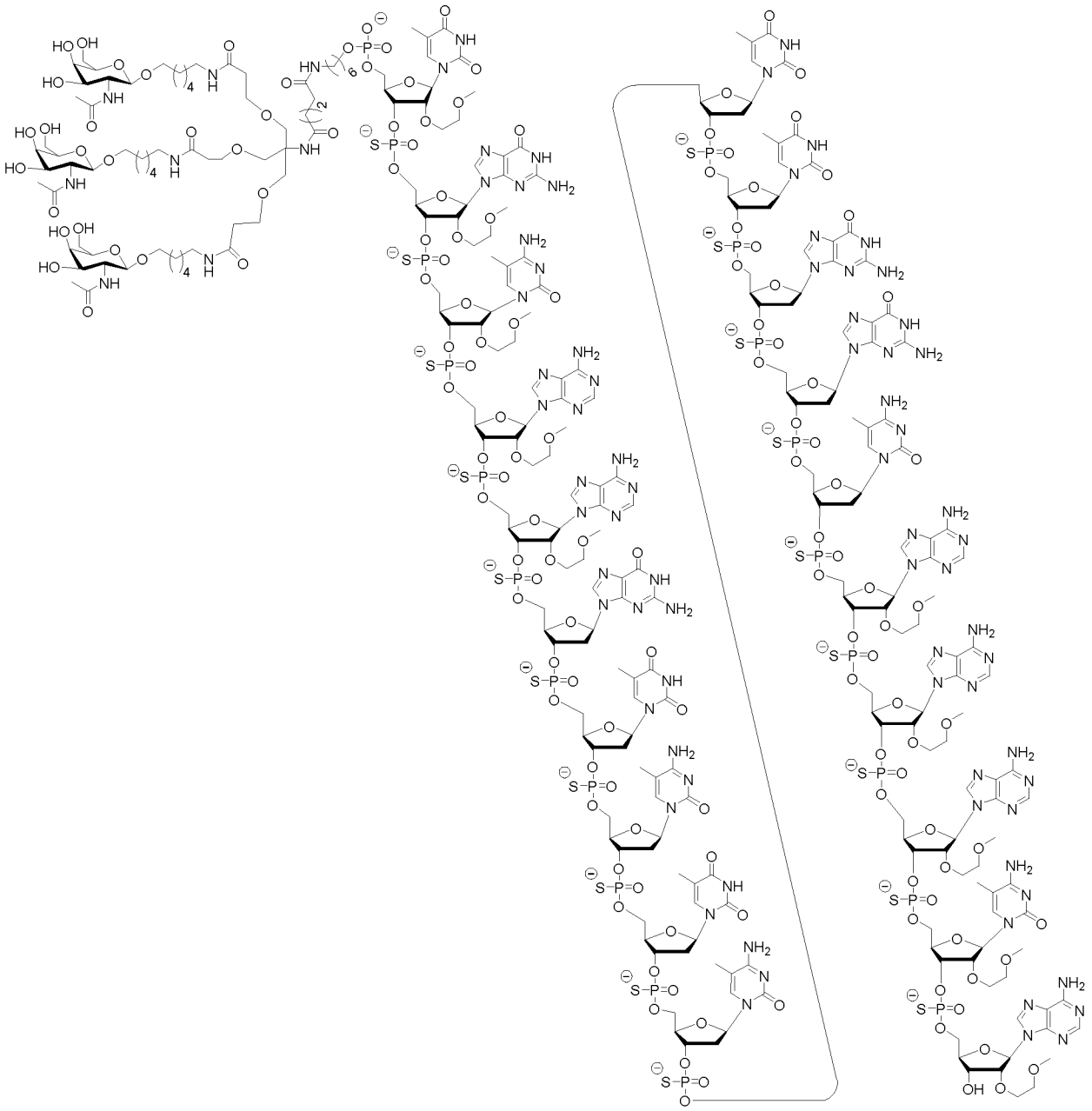
In certain embodiments, a compound having the following chemical structure comprises or consists of ISIS 721744 with a 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:



In certain embodiments, a compound having the following chemical structure comprises or consists of ISIS 546254 with a 5'-X, wherein X is a conjugate group comprising GalNAc as described herein:



Certain embodiments provide a compound comprising or consisting of the following formula:



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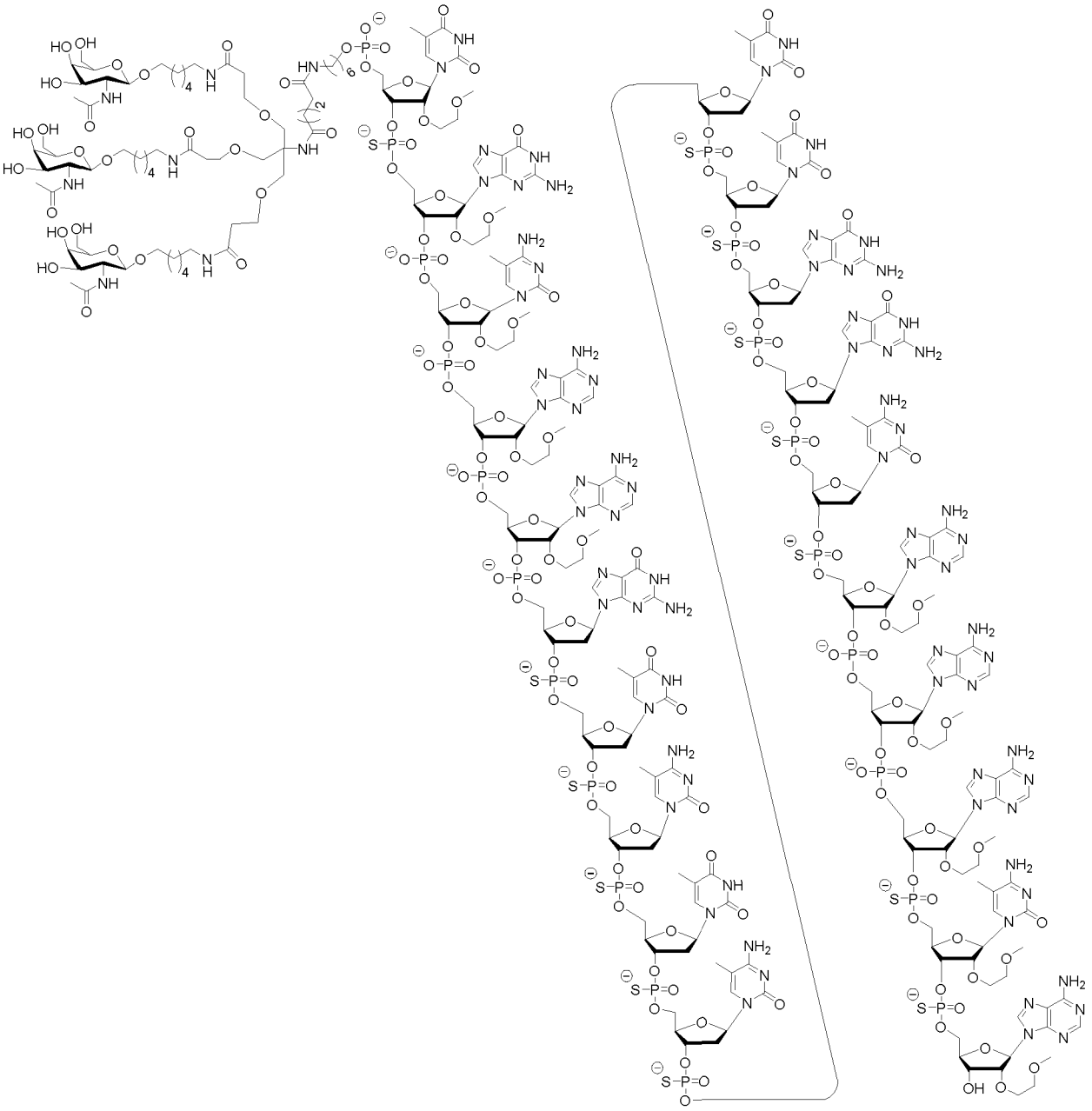
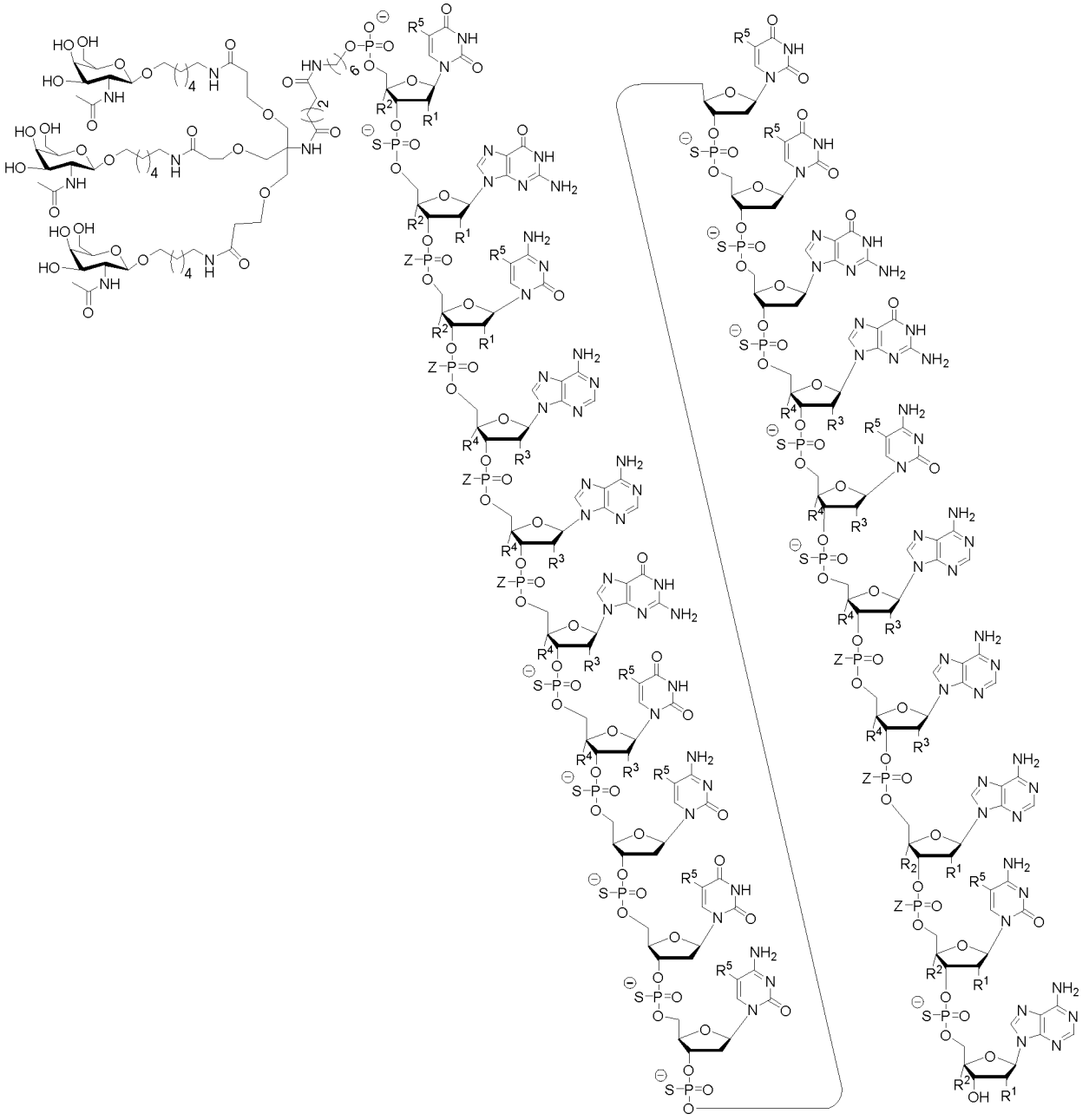
Certain embodiments provide a compound comprising or consisting of the following formula:



Certain embodiments provide a compound comprising or consisting of the following formula:



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^-.

Certain embodiments provide compositions comprising the compound of any preceding claim or salt thereof and at least one of a pharmaceutically acceptable carrier or diluent.

Certain embodiments provide methods comprising administering to an animal the compound or composition of any preceding claim.

In certain embodiments, the animal is a human.

In certain embodiments, administering the compound prevents, treats, or ameliorates a PKK associated disease, disorder or condition.

In certain embodiments, the PKK associated disease, disorder or condition is a hereditary angioedema (HAE), edema, angioedema, swelling, angioedema of the lids, ocular edema, macular edema, cerebral edema, thrombosis, embolism, thromboembolism, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, or infarct.

Certain embodiments provide use of the compound or composition of any preceding claim for the manufacture of a medicament for treating an inflammatory disease or a thromboembolic disease.

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 targeted to a PKK nucleic acid is 12 to 30 subunits in length. In certain embodiments, an antisense compound targeted to PKK nucleic acid is 12 to 25 subunits in length. In certain embodiments, an antisense compound targeted to PKK nucleic acid is 12 to 22 subunits in length. In certain embodiments, an antisense compound targeted to PKK nucleic acid is 14 to 20 subunits in length. In certain embodiments, an antisense compound targeted to PKK nucleic acid is 15 to 25 subunits

in length. In certain embodiments, an antisense compound targeted to PKK nucleic acid is 18 to 22 subunits in length. In certain embodiments, an antisense compound targeted to PKK nucleic acid is 19 to 21 subunits in length. In certain 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 30, 18 to 50, 19 to 30, 19 to 50, or 20 to 30 linked subunits in length.

In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 12 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 13 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 14 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 15 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 16 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 17 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 18 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 19 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 20 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 21 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 22 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 23 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 24 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 25 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 26 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 27 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 28 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 29 subunits in length. In certain embodiments, an antisense compound targeted to a PKK nucleic acid is 30 subunits in length. In certain embodiments, the antisense compound targeted to a PKK nucleic acid is 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 certain embodiments the antisense compound is an antisense oligonucleotide, and the linked subunits are nucleosides.

In certain embodiments antisense oligonucleotides targeted to a PKK nucleic acid 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 PKK 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.

Antisense Compound Motifs

In certain embodiments, antisense compounds targeted to a PKK nucleic acid 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 optionally serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

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 4'-(CH_2)n-O-2' bridge, where n=1 or n=2 and 4'-CH_2-O-CH_2-2'). In certain embodiments, wings may include several modified sugar moieties, including, for example 2'-MOE. In certain embodiments, wings may include several modified and unmodified sugar moieties. In certain embodiments, wings may include various combinations of 2'-MOE 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, gapmers provided herein include, for example 20-mers having a motif of 5-10-5.

Target Nucleic Acids, Target Regions and Nucleotide Sequences

Nucleotide sequences that encode human plasma prekallikrein (PKK) include, without limitation, the following: GENBANK Accession No. NM_000892.3 (incorporated herein as SEQ ID NO: 1), GENBANK Accession No. DC412984.1 (incorporated herein as SEQ ID NO: 2), GENBANK Accession No. CN265612.1 (incorporated herein as SEQ ID NO: 3), GENBANK Accession No. AK297672.1 (incorporated

herein as SEQ ID NO: 4), GENBANK Accession No. DC413312.1 (incorporated herein as SEQ ID NO: 5), GENBANK Accession No. AV688858.2 (incorporated herein as SEQ ID NO: 6), GENBANK Accession No. CD652077.1 (incorporated herein as SEQ ID NO: 7), GENBANK Accession No. BC143911.1 (incorporated herein as SEQ ID NO: 8), GENBANK Accession No. CB162532.1 (incorporated herein as SEQ ID NO: 9), GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000 (incorporated herein as SEQ ID NO: 10), GENBANK Accession No. NM_008455.2 (incorporated herein as SEQ ID NO: 11), GENBANK Accession No. BB598673.1 (incorporated herein as SEQ ID NO: 12), GENBANK Accession No. NT_039460.7 truncated from nucleobases 6114001 to 6144000 (incorporated herein as SEQ ID NO: 13), GENBANK Accession No. NM_012725.2 (incorporated herein as SEQ ID NO: 14), GENBANK Accession No. NW_047473.1 truncated from nucleobases 10952001 to 10982000 (incorporated herein as SEQ ID NO: 15), GENBANK Accession No. XM_002804276.1 (incorporated herein as SEQ ID NO: 17), and GENBANK Accession No. NW_001118167.1 truncated from nucleobases 2358000 to 2391000 (incorporated herein as SEQ ID NO: 18).

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.

In certain embodiments, a target region is a structurally defined region of the target nucleic acid. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, an exon/intron junction, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. The structurally defined regions for PKK can be obtained by accession number from sequence databases such as NCBI and such information is incorporated herein by reference. In certain embodiments, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the same target region.

Targeting includes determination of at least one target segment to which an antisense compound hybridizes, such that a desired effect occurs. In certain embodiments, the desired effect is a reduction in mRNA target nucleic acid levels. In certain embodiments, the desired effect is reduction of levels of protein encoded by the target nucleic acid or a phenotypic change associated with the target nucleic acid.

A target region may contain one or more target segments. Multiple target segments within a target region may be overlapping. Alternatively, they may be non-overlapping. In certain embodiments, target segments within a target region are separated by no more than about 300 nucleotides. In certain emodiments, target segments within a target region are separated by a number of nucleotides that is, is about, is no more than, is no more than about, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10 nucleotides on the target

nucleic acid, or is a range defined by any two of the preceeding values. In certain embodiments, target segments within a target region are separated by no more than, or no more than about, 5 nucleotides on the target nucleic acid. In certain embodiments, target segments are contiguous. Contemplated are target regions defined by a range having a starting nucleic acid that is any of the 5' target sites or 3' target sites listed herein.

Suitable target segments may be found within a 5' UTR, a coding region, a 3' UTR, an intron, an exon, or an exon/intron junction. Target segments containing a start codon or a stop codon are also suitable target segments. A suitable target segment may specifcally exclude a certain structurally defined region such as the start codon or stop codon.

The determination of suitable target segments may include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm may be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that may hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

There may be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within an active target region. In certain embodiments, reductions in PKK mRNA levels are indicative of inhibition of PKK expression. Reductions in levels of a PKK protein are also indicative of inhibition of target mRNA expression. Further, phenotypic changes are indicative of inhibition of PKK expression. For example, reduced or prevented inflammation can be indicative of inhibition of PKK expression. In another example, reduced or prevented edema/swelling can be indicative of inhibition of PKK expression. In another example, reduced or prevented vascular permeability can be indicative of inhibition of PKK expression. In another example, reduced or prevented vascular leakage can be indicative of inhibition of PKK expression. In certain embodiments, vascular permeability is measured by quanification of a dye, such as Evans Blue.

Hybridization

In some embodiments, hybridization occurs between an antisense compound disclosed herein and a target 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 target 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 PKK nucleic acid).

Non-complementary nucleobases between an antisense compound and a PKK 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 PKK 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%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an PKK 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 plasma prekallikrein 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 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 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 plasma prekallikrein 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 2009/100320. 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;

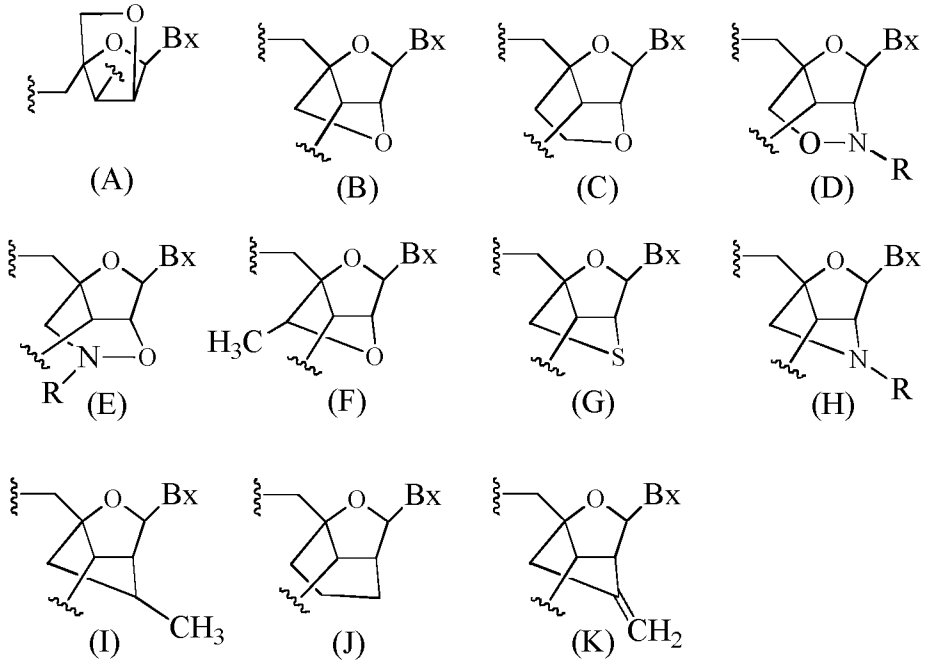
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C_1-C_{12} alkyl, substituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, substituted C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted C_2-C_{12} alkynyl, C_5-C_{20} aryl, substituted C_5-C_{20} aryl, heterocycle radical, substituted heterocycle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

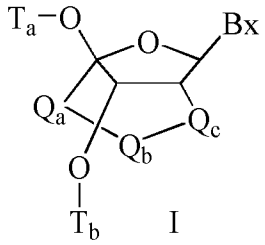
In certain embodiments, bicyclic nucleosides are further defined by isomeric configuration. For example, a nucleoside comprising a 4'-2' methylene-oxy bridge, may be in the α-L configuration or in the β-D configuration. Previously, α-L-methyleneoxy (4'-CH_2-O-2') BNA's have been incorporated into antisense 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:

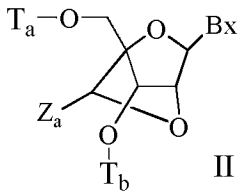
Bx is a heterocyclic base moiety;

$-Q_a-Q_b-Q_c-$ 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:

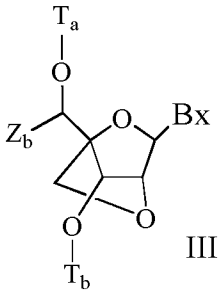
Bx is a heterocyclic base moiety;

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

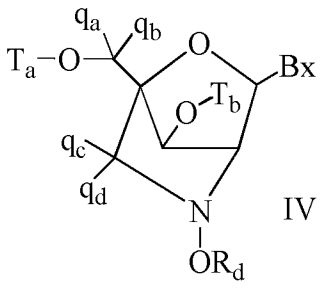
wherein:

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:

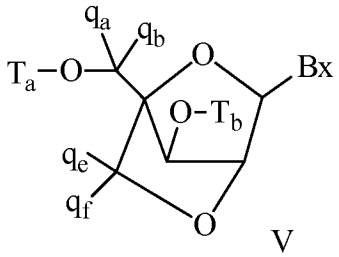
Bx is a heterocyclic base moiety;

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 $N(H)C(=S)NJ_jJ_k$;

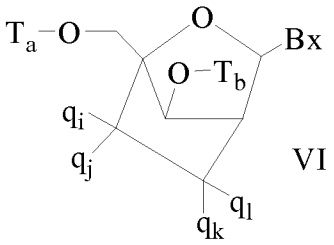
or q_e and q_f together are $=C(q_g)(q_h)$;

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.

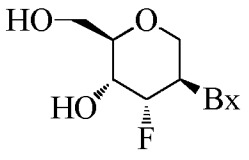
One carbocyclic bicyclic nucleoside having a 4'-$(CH_2)_3$-2' bridge and the alkenyl analog bridge 4'-CH=CH-CH_2-2' have been described (Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443 and Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740). The synthesis and preparation of carbocyclic 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).

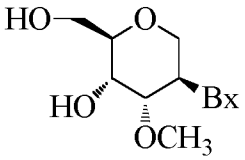
As used herein, "4'-2' bicyclic nucleoside" or "4' to 2' bicyclic nucleoside" refers to a bicyclic nucleoside comprising a furanose ring comprising a bridge connecting two carbon atoms of the furanose ring connects the 2' carbon atom and the 4' carbon atom of the sugar ring.

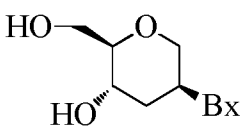
As used herein, "monocylic nucleosides" refer to nucleosides comprising modified sugar moieties that are not bicyclic sugar moieties. In certain embodiments, the sugar moiety, or sugar moiety analogue, of a nucleoside may be modified or substituted at any position.

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).

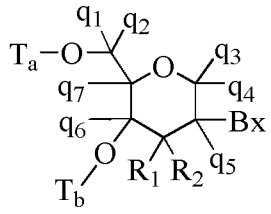
As used herein, a "modified tetrahydropyran nucleoside" or "modified THP nucleoside" means a nucleoside having a six-membered tetrahydropyran "sugar" substituted in for the pentofuranosyl residue in normal nucleosides (a sugar surrogate). Modified THP nucleosides include, but are not limited to, what 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*, 841-1954) 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:

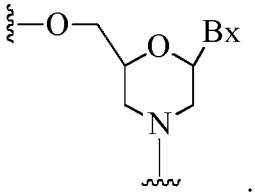
Bx is a heterocyclic base moiety;

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.

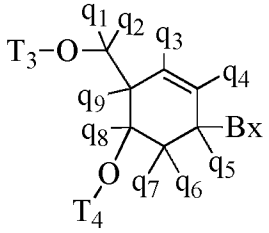
In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example nucleosides comprising morpholino sugar moieties and their use in oligomeric compounds has been reported (see for example: Braasch *et al.*, *Biochemistry*, 2002, *41*, 4503-4510; 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*, 841-1954). 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.

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.

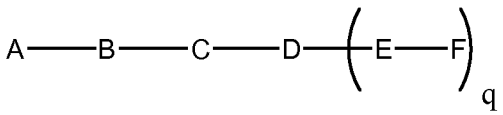
In certain embodiments, conjugation allows one to alter antisense compounds in ways that have less attractive consequences in the absence of conjugation. For example, in certain embodiments, replacing one or more phosphorothioate linkages of a fully phosphorothioate antisense compound with phosphodiester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

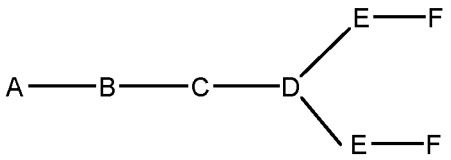
each E is a tether;

each F is a ligand; and

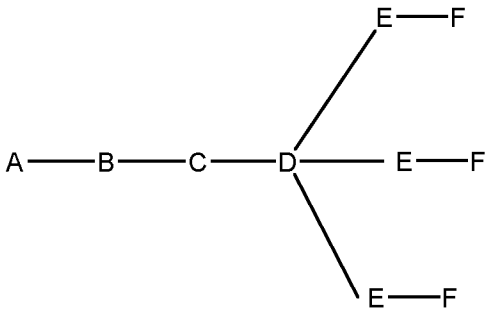
q is an integer between 1 and 5.

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:

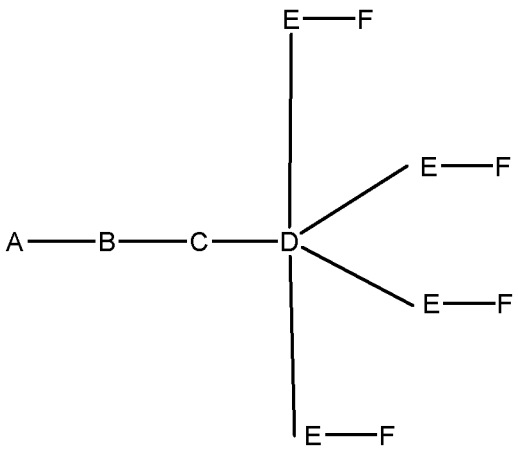
where q = 2, the formula is:



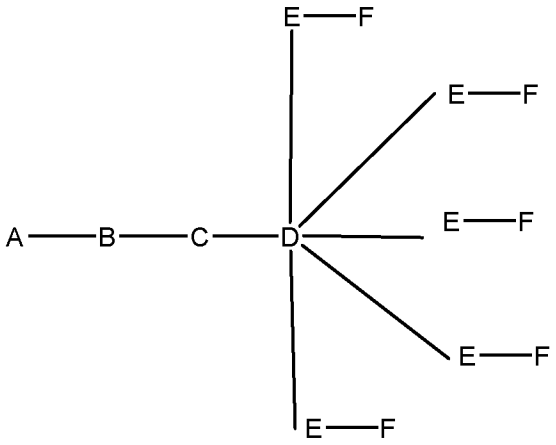
where q = 3, the formula is:



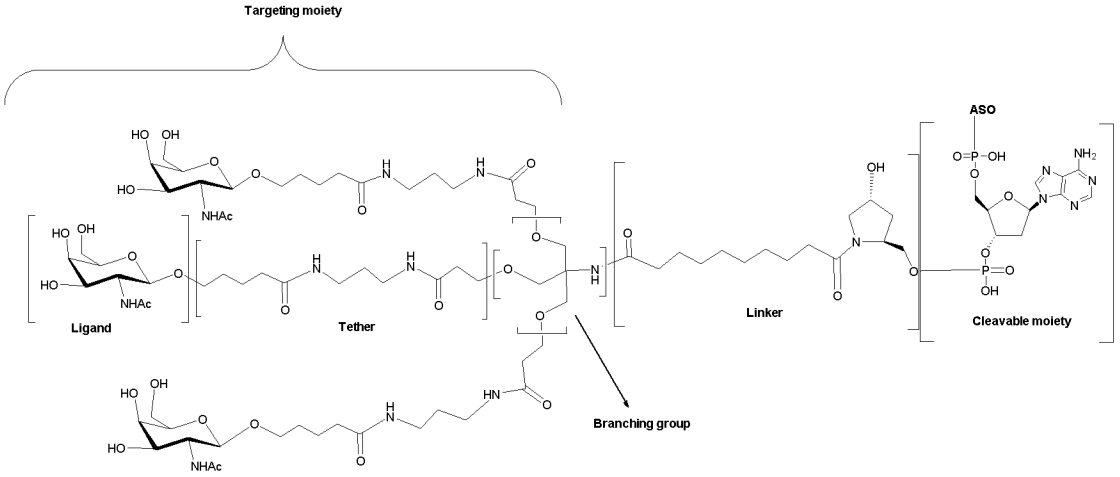
where q = 4, the formula is:



where q = 5, the formula is:



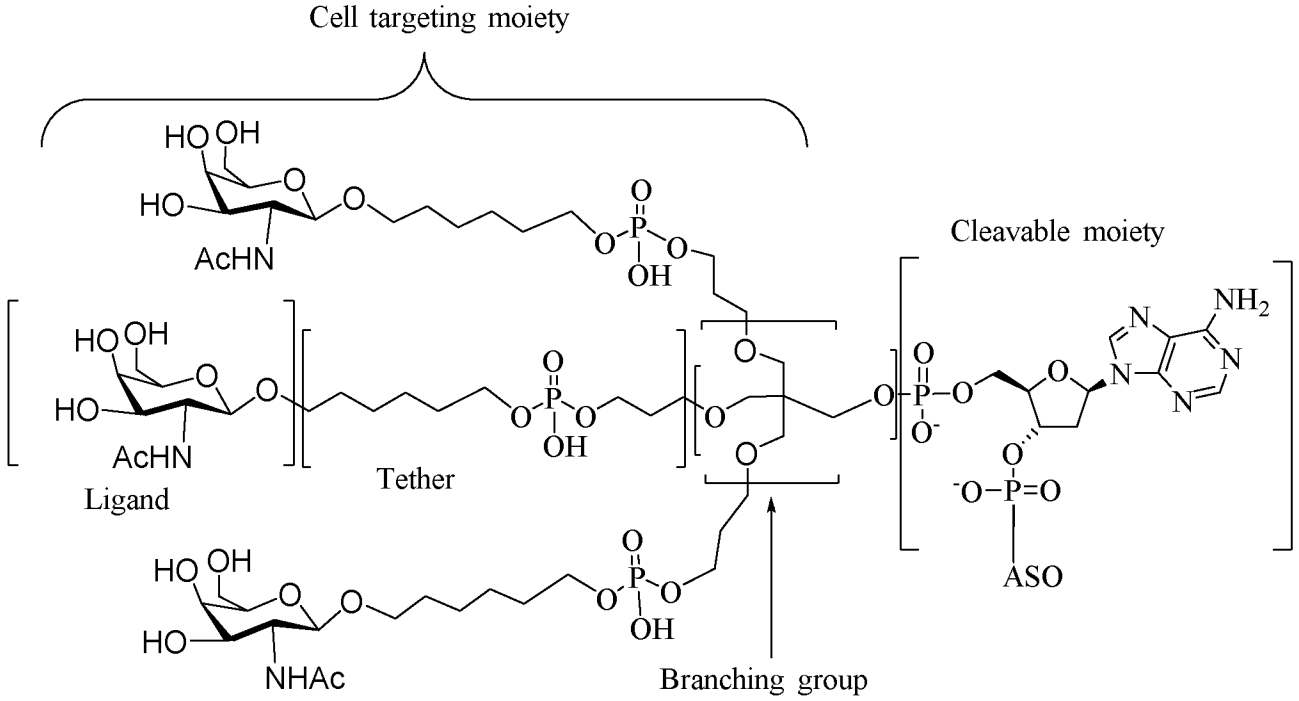
In certain embodiments, conjugated antisense compounds are provided having the structure:



.

5

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



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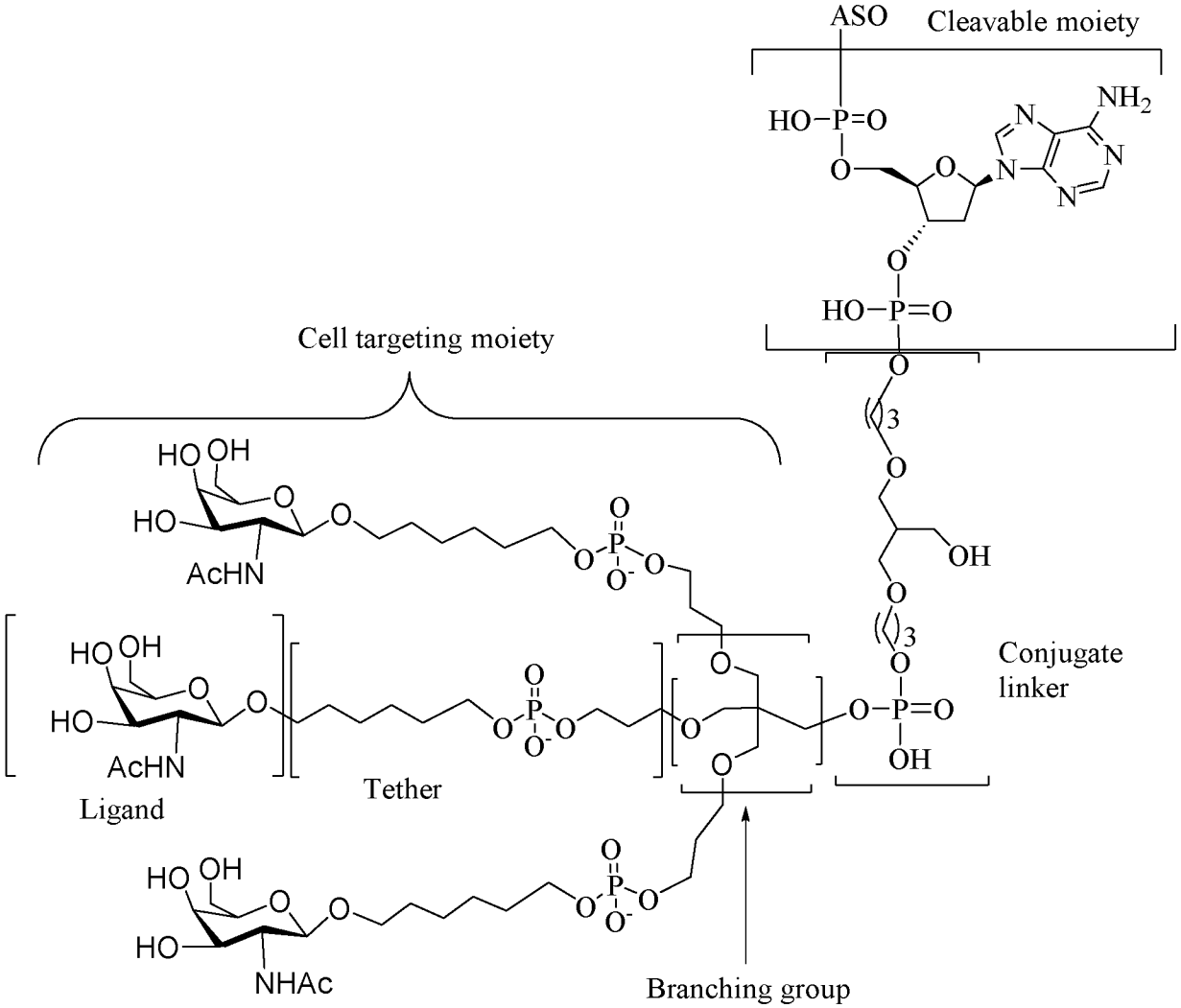
In certain embodiments, conjugated antisense compounds are provided having the structure:



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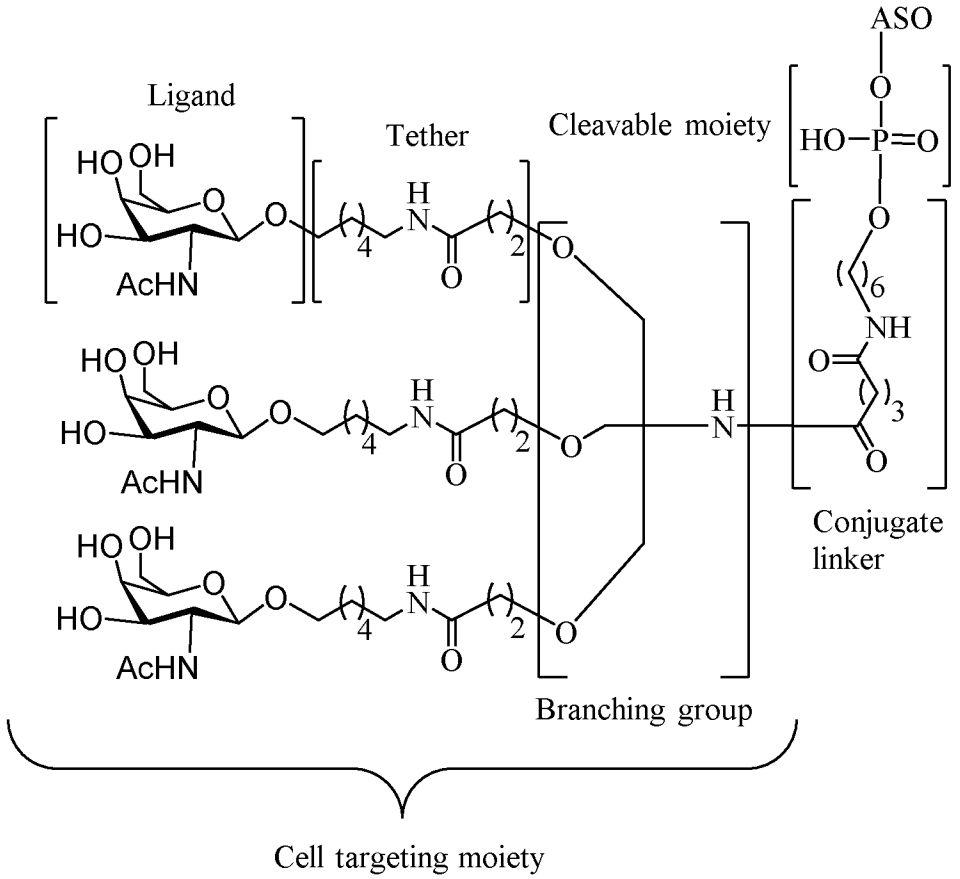
In certain embodiments, conjugated antisense compounds are provided having the structure:



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.

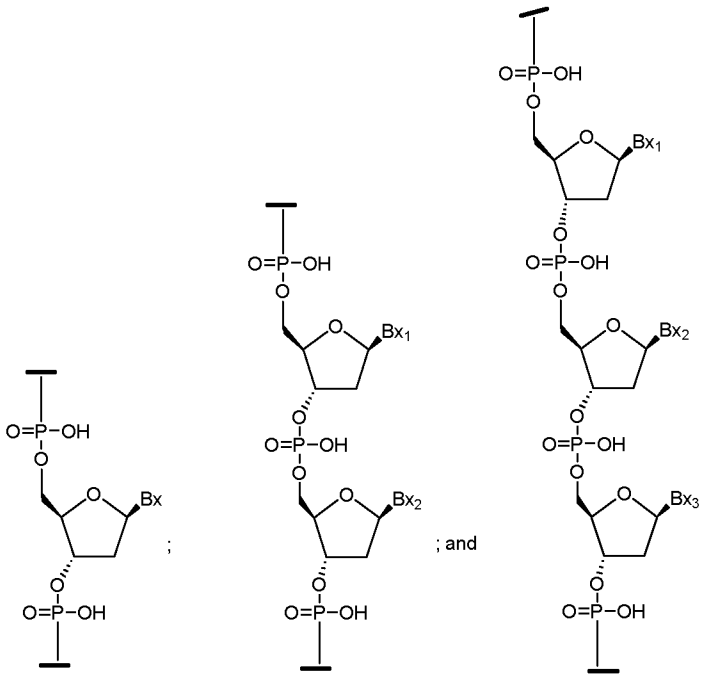
i. Certain Cleavable Moieties

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

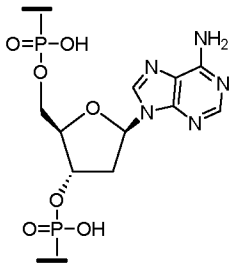
purine, pyrimidine or substituted pyrimidine. In certain embodiments, the cleavable moiety is a nucleoside comprising an optionally protected heterocyclic base selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methylcytosine, 4-N-benzoyl-5-methylcytosine, adenine, 6-N-benzoyladenine, guanine 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:



5

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.

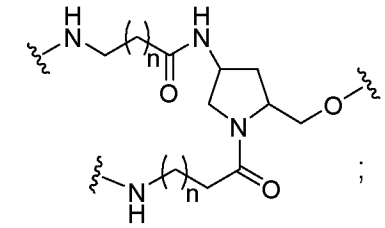
In certain embodiments, the linker includes at least a linear group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether (-S-) and hydroxylamino (-O-N(H)-) groups. In certain embodiments, the linear group comprises groups selected from alkyl, amide and ether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

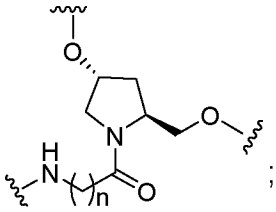
In certain embodiments, the linker includes the linear group covalently attached to a scaffold group. In certain embodiments, the scaffold includes a branched aliphatic group comprising groups selected from alkyl, amide, disulfide, polyethylene glycol, ether, thioether and hydroxylamino groups. In certain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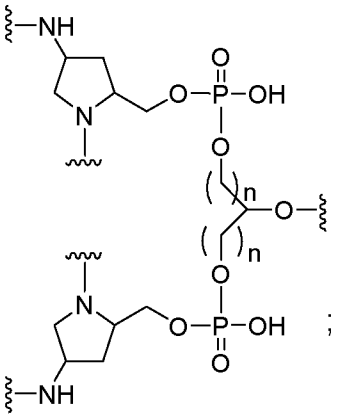
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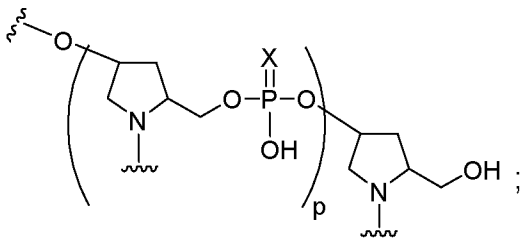
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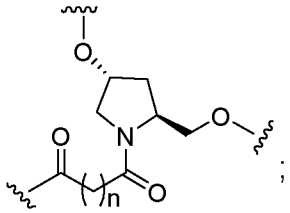
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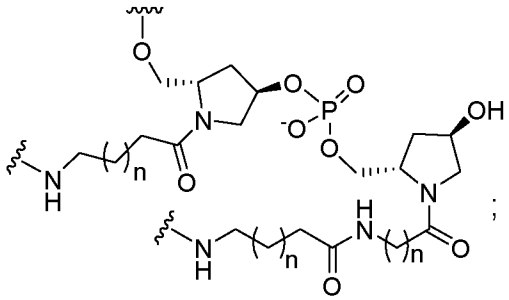
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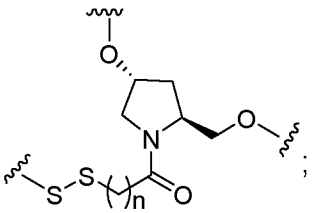
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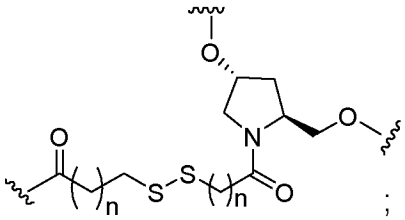
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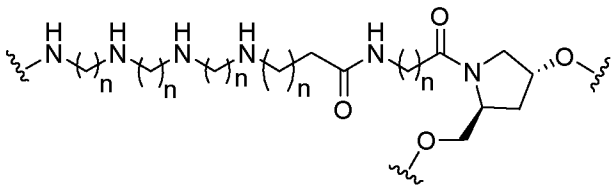
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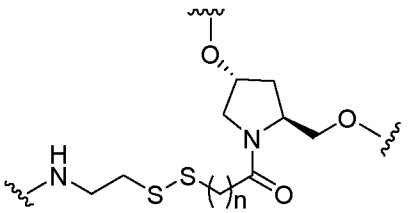
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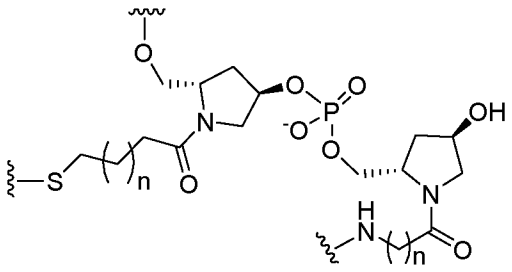
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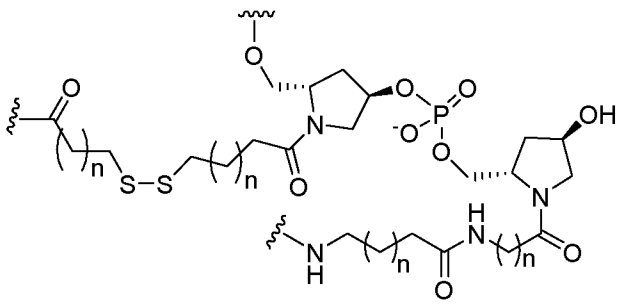
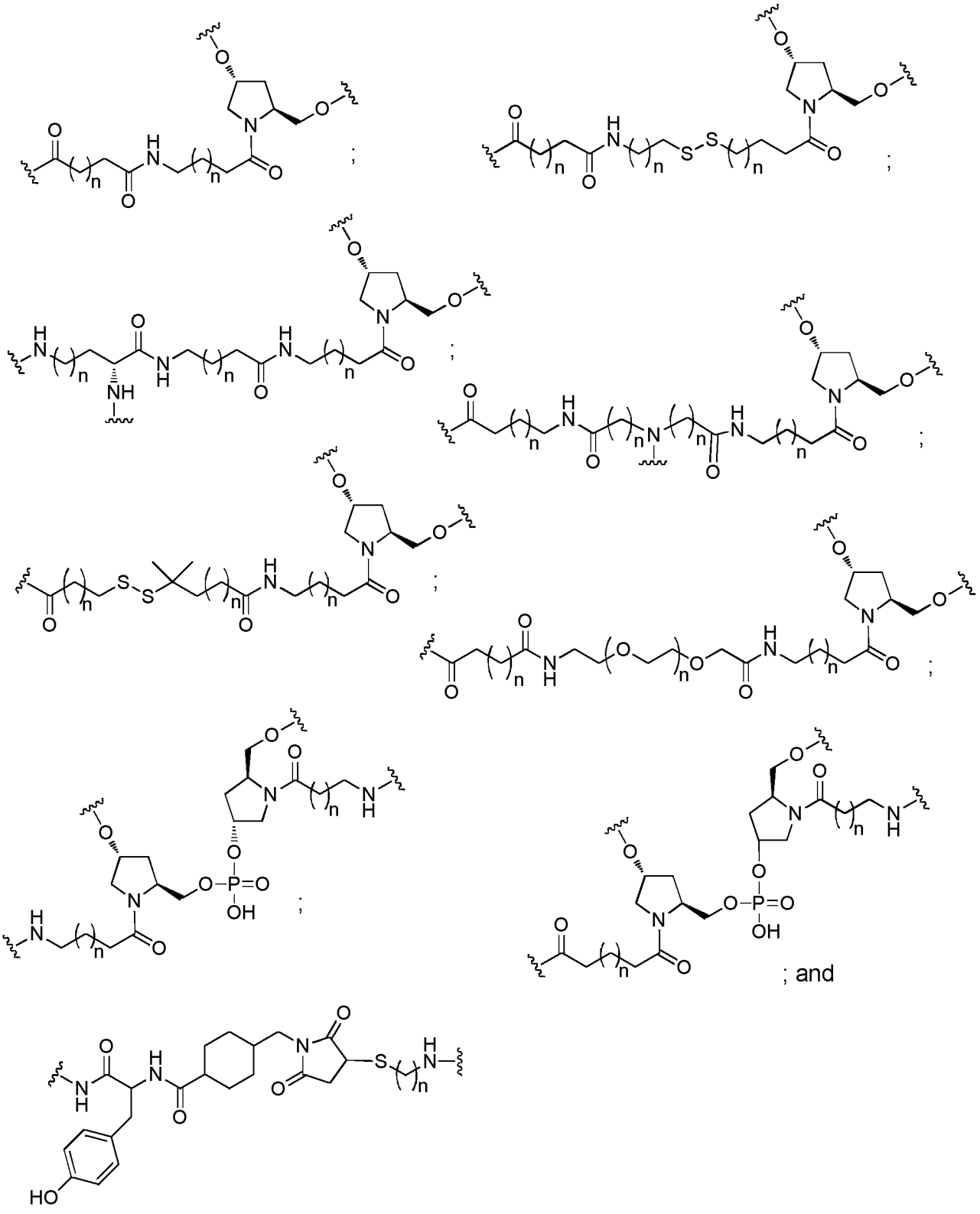


wherein each n is, independently, from 1 to 20; and p is from 1 to 6.

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

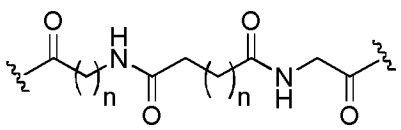


; and

5

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

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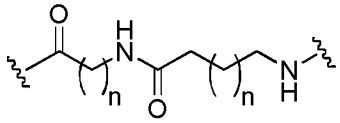
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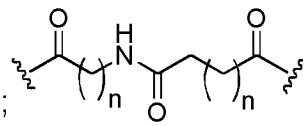
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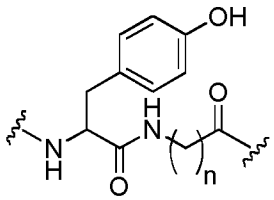
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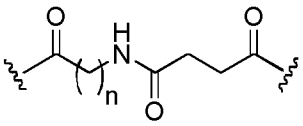
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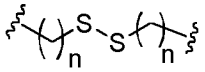
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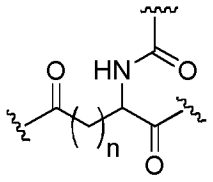
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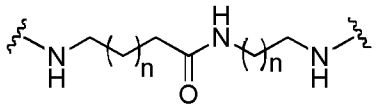
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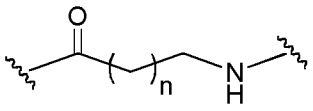
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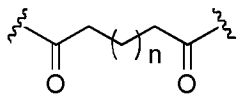
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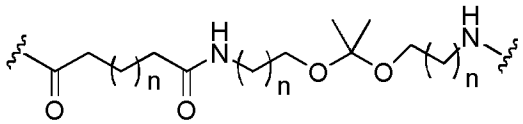
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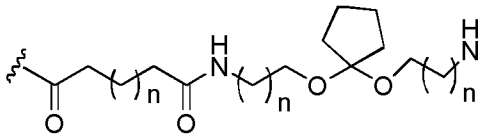
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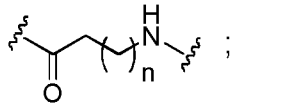
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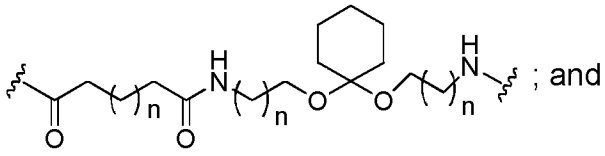
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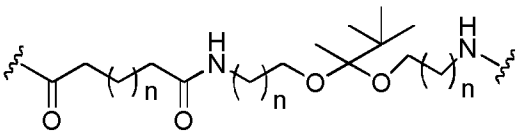
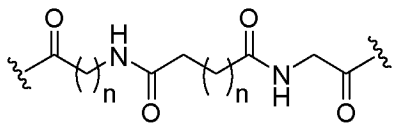


wherein n is from 1 to 20.

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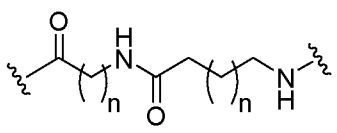
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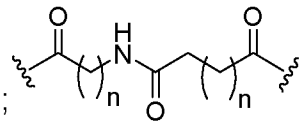
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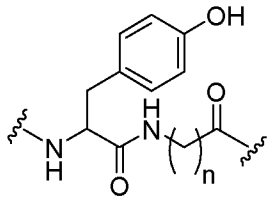
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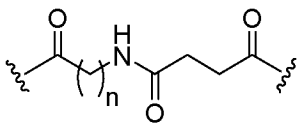
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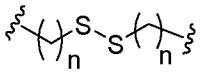
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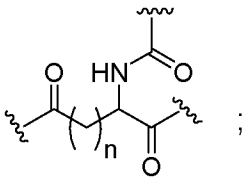
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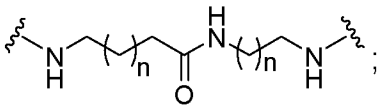
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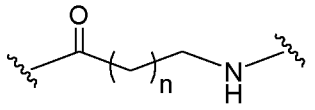
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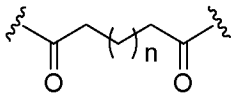
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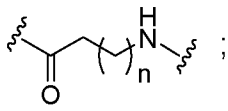
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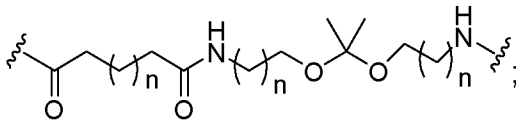
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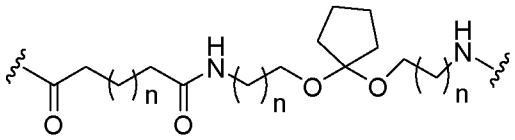
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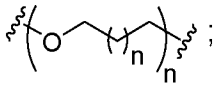
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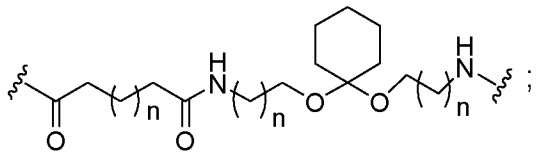
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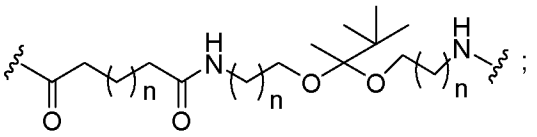
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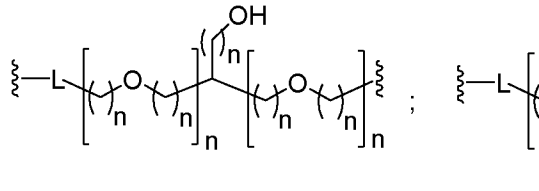
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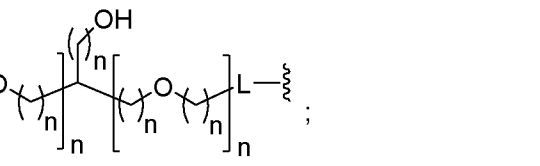
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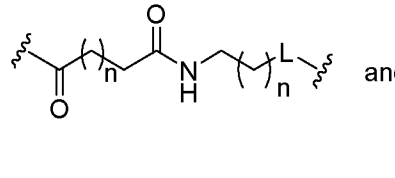
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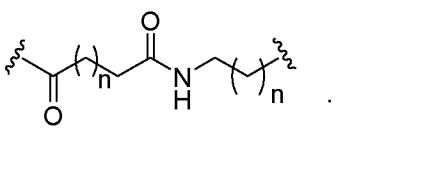
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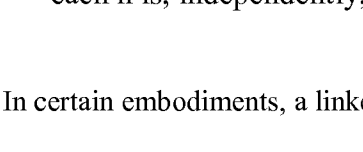
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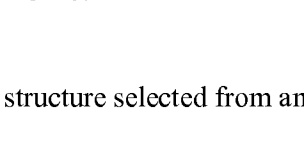
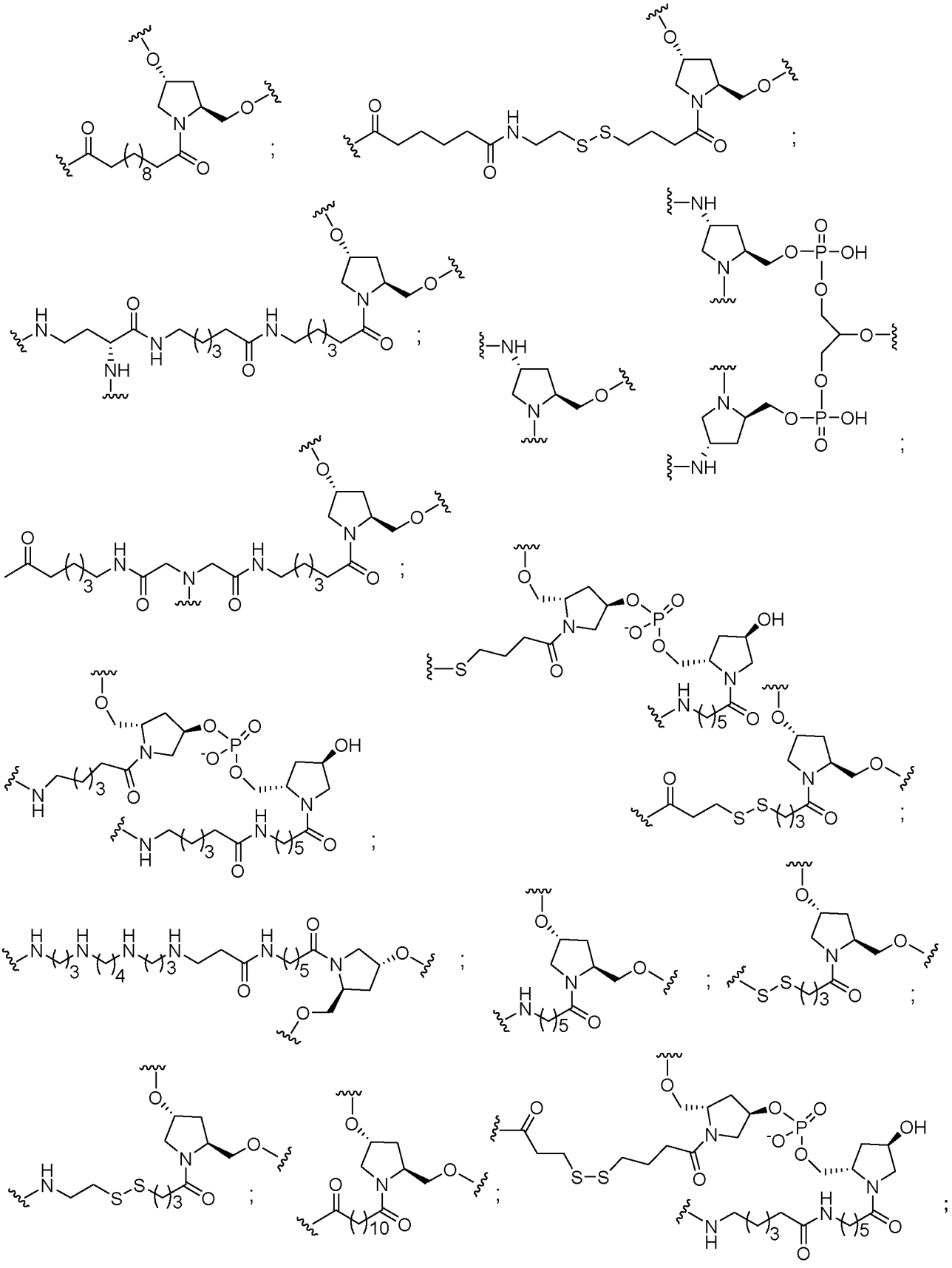
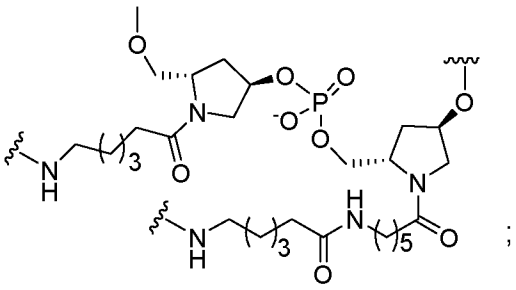

.

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

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

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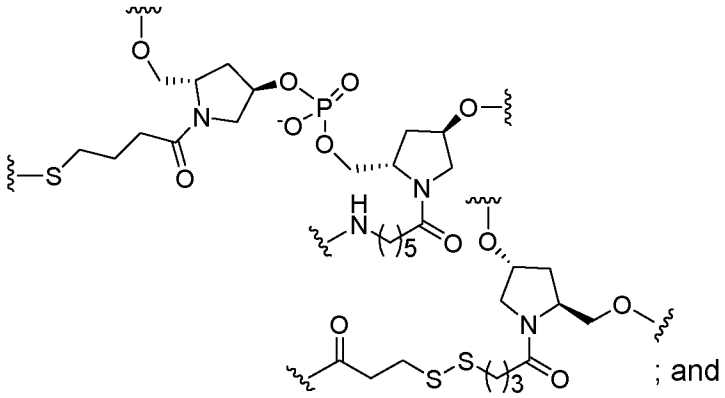
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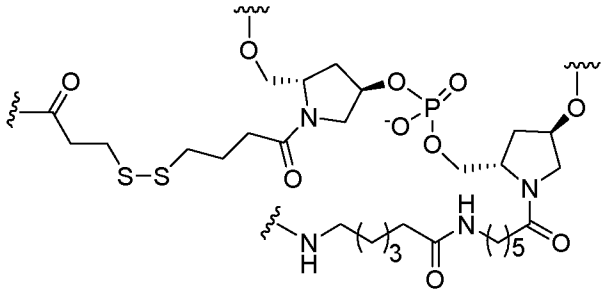
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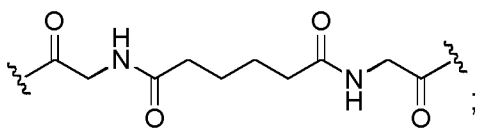
In certain embodiments, a linker has a structure selected from among: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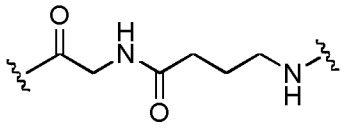
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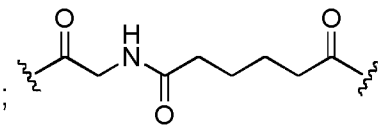
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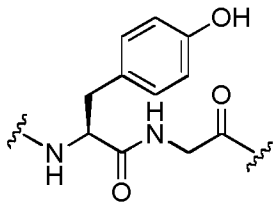
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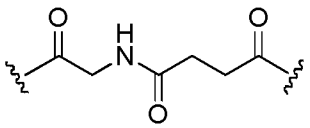
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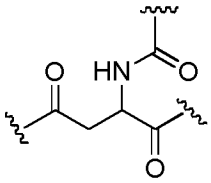
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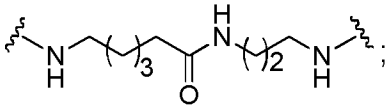
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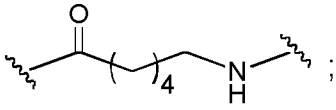
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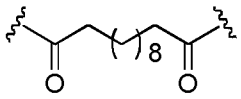
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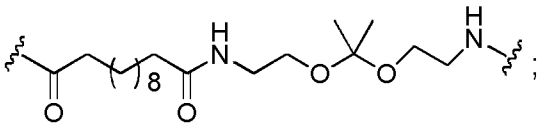
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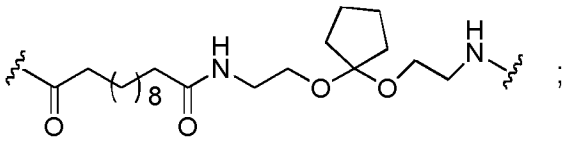
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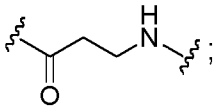
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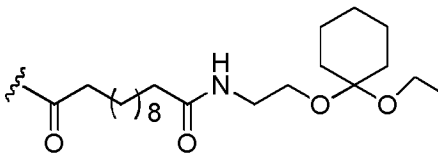
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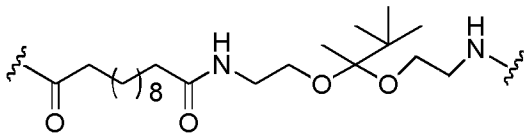
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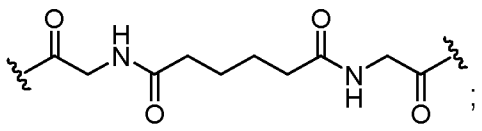
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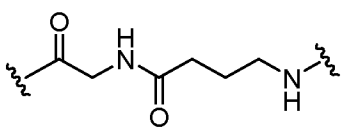
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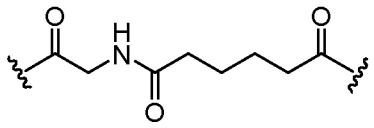
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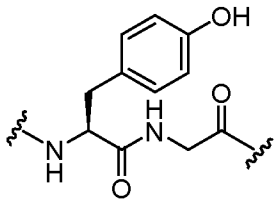
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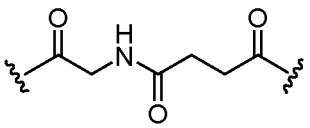
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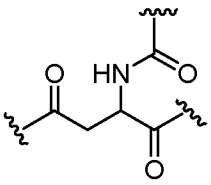
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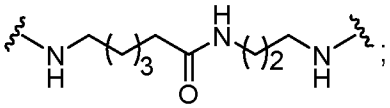
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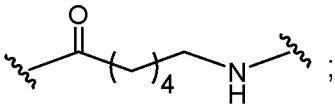
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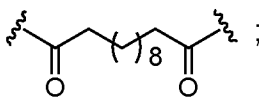
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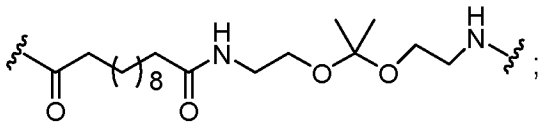
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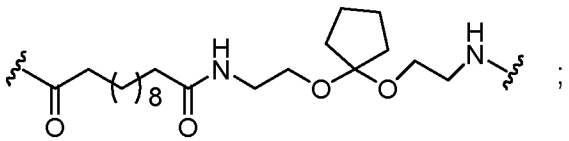
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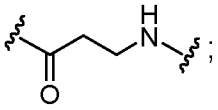
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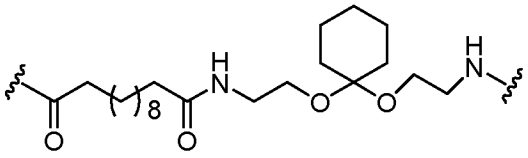

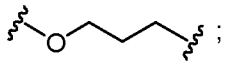
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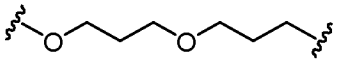
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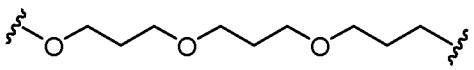
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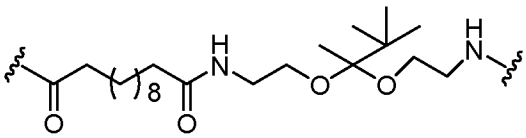
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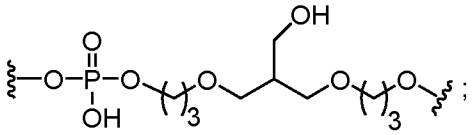
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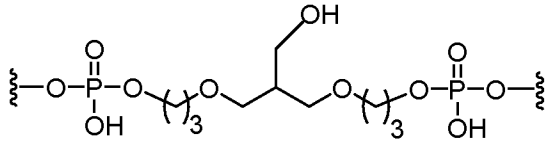
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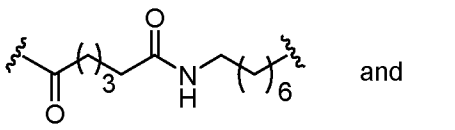
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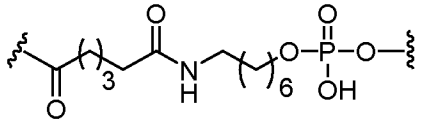
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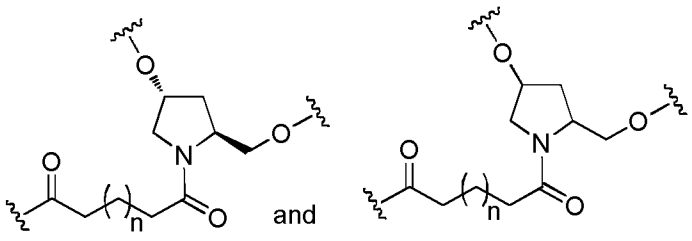
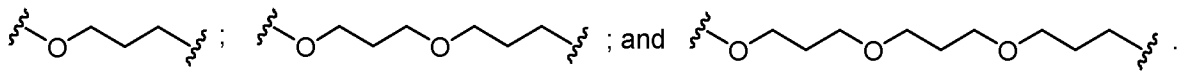
In certain embodiments, a linker has a structure selected from among:

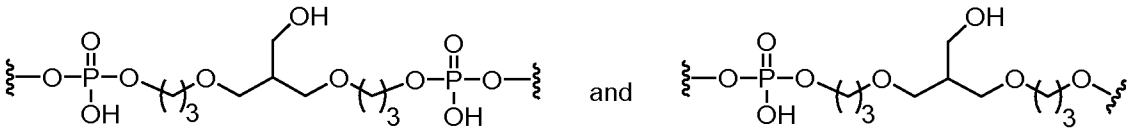


wherein n is from 1 to 20.

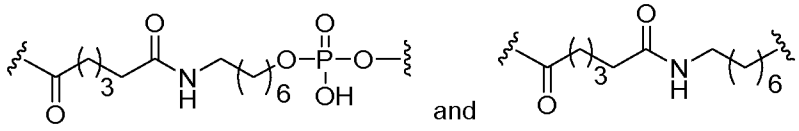
In certain embodiments, a linker has a structure selected from among:



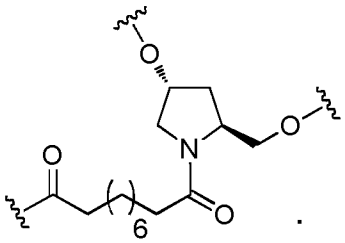
In certain embodiments, a linker has a structure selected from among:



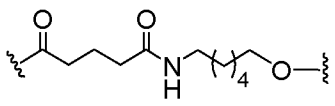
In certain embodiments, a linker has a structure selected from among:



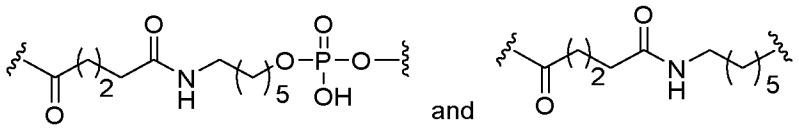
In certain embodiments, the conjugate linker has the structure:



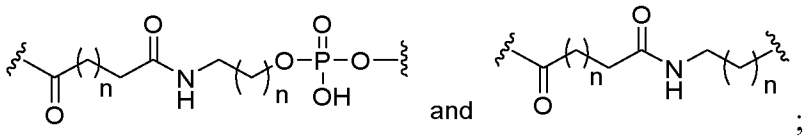
In certain embodiments, the conjugate linker has the structure:



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



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



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

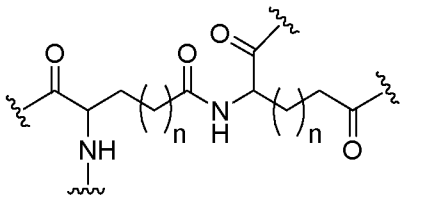
iii. Certain Cell-Targeting Moieties

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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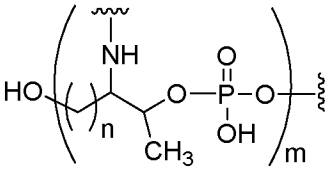
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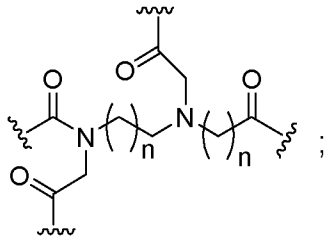
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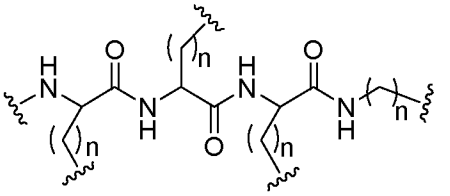
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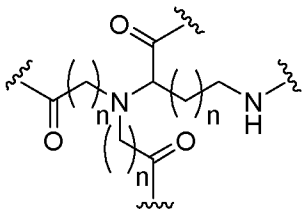
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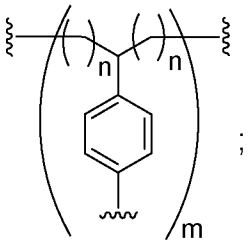
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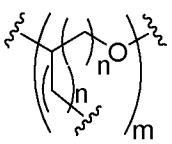
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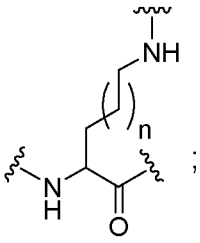
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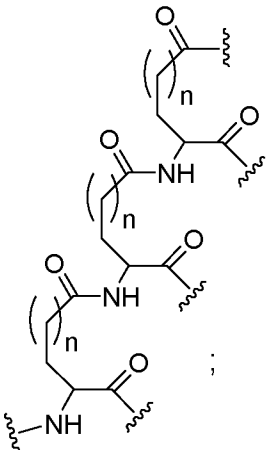
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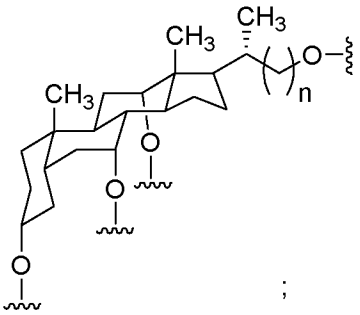
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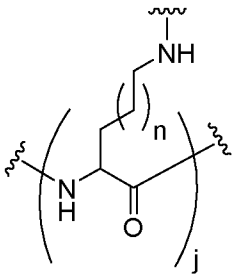
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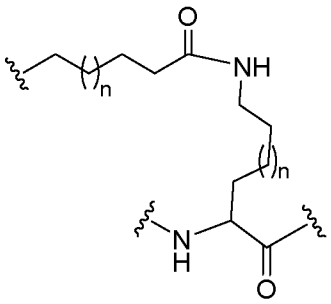
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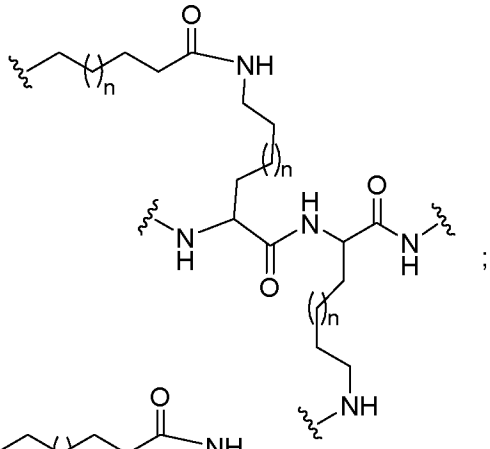
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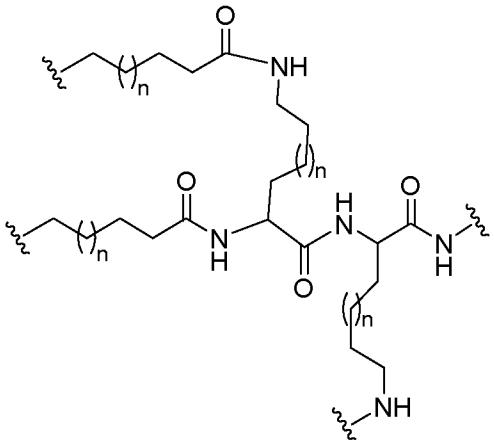
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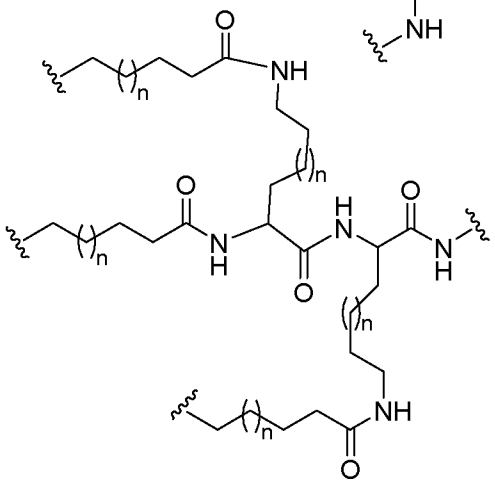
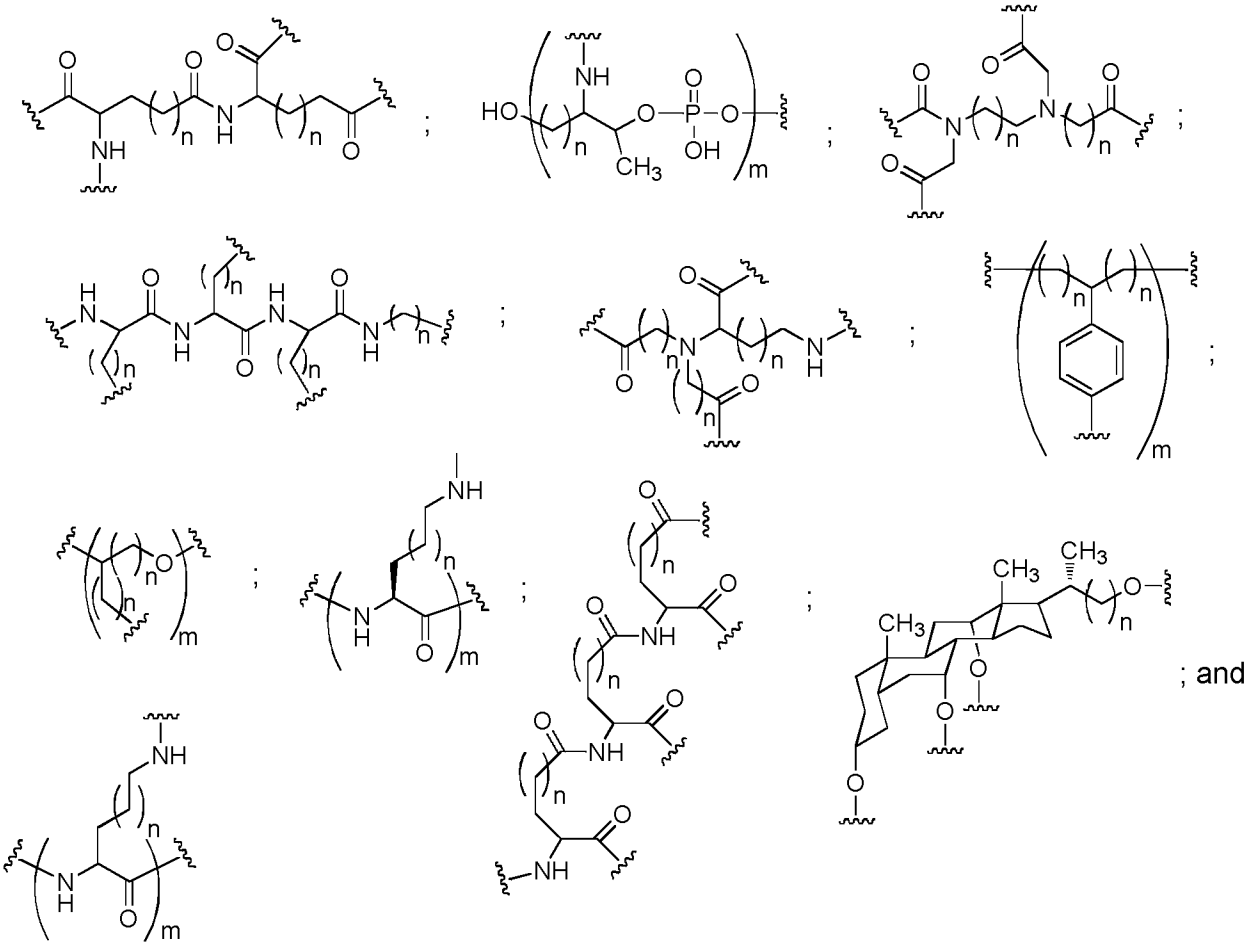

.

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

j is from 1 to 3; and

m is from 2 to 6.

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

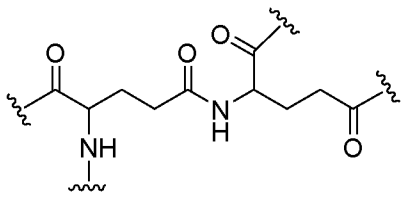


; and

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: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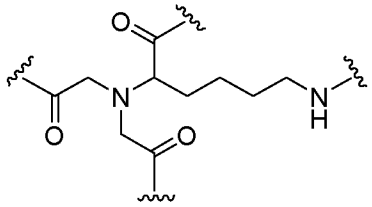
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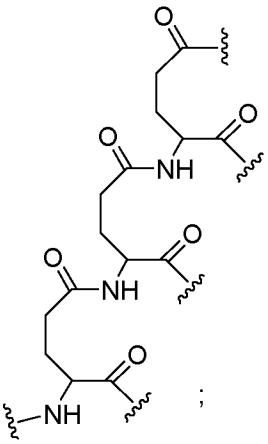
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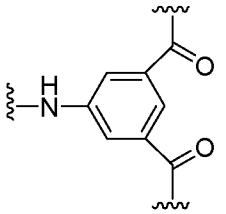
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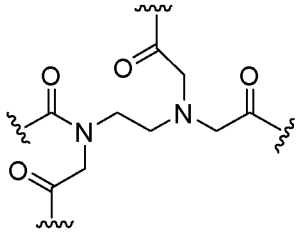
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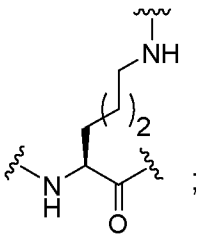
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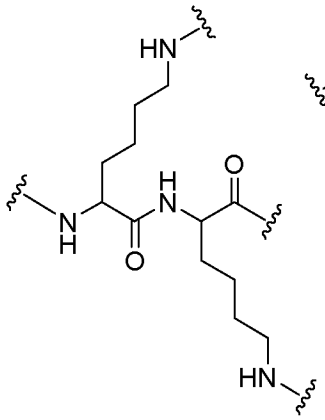
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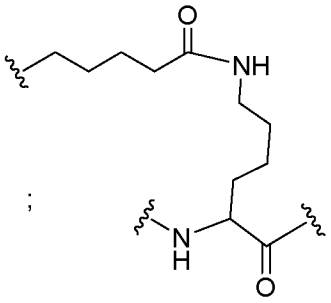
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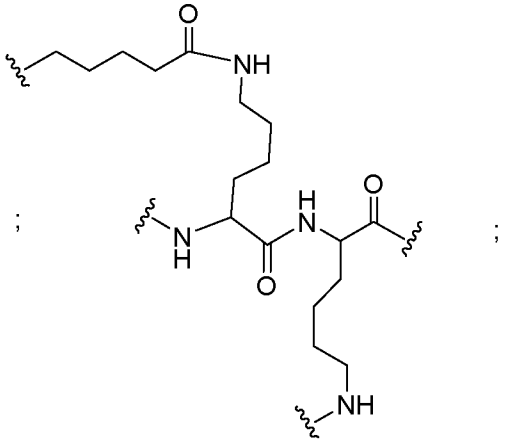
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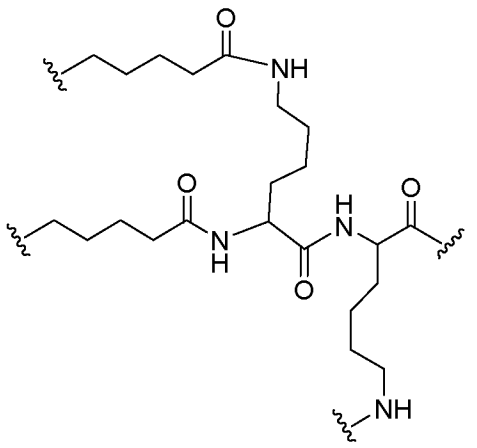
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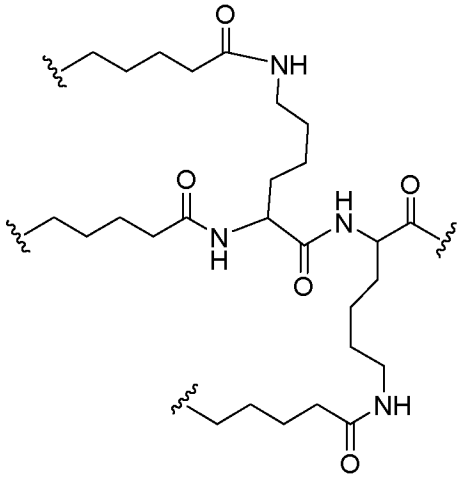
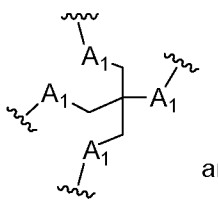
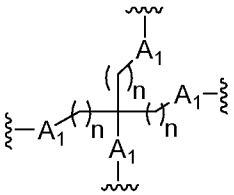

.

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



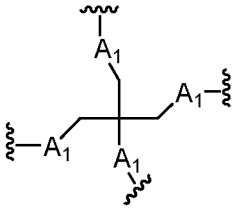
and



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

each n is, independently, from 1 to 20.

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



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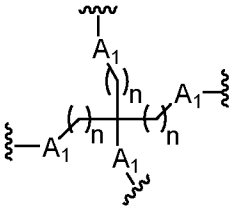
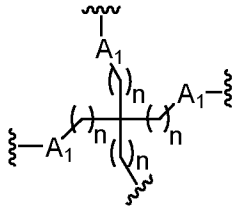


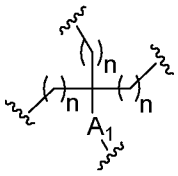
and



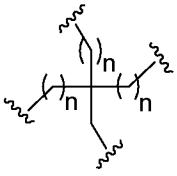
wherein each A_1 is independently, O, S, C=O or NH; and

each n is, independently, from 1 to 20.

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



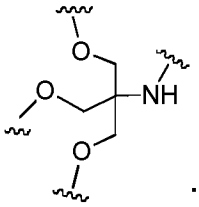
and



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

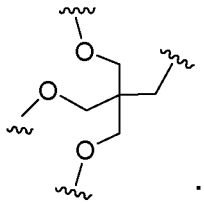
each n is, independently, from 1 to 20.

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

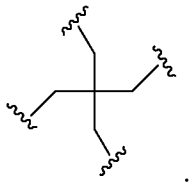


.

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



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



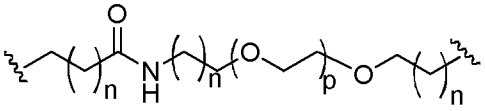
2. Certain Tethers

In certain embodiments, conjugate groups comprise one or more tethers covalently attached to the branching group. In certain embodiments, conjugate groups comprise one or more tethers covalently attached to the linking group. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether, thioether, disulfide, amide and polyethylene glycol groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, substituted alkyl, ether, thioether, disulfide, amide, phosphodiester and polyethylene glycol groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, ether and amide groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl, substituted alkyl, phosphodiester, ether and amide groups in any combination. In certain embodiments, each tether is a linear aliphatic group comprising one or more groups selected from alkyl and phosphodiester in any combination. In certain embodiments, each tether comprises at least one phosphorus linking group or neutral linking group.

In certain embodiments, the tether includes one or more cleavable bond. In certain embodiments, the tether is attached to the branching group through either an amide or an ether group. In certain embodiments, the tether is attached to the branching group through a phosphodiester group. In certain embodiments, the tether is attached to the branching group through a phosphorus linking group or neutral linking group. In certain embodiments, the tether is attached to the branching group through an ether group. In certain embodiments, the tether is attached to the ligand through either an amide or an ether group. In certain embodiments, the tether is attached to the ligand through an ether group. In certain embodiments, the tether is attached to the ligand through either an amide or an ether group. In certain embodiments, the tether is attached to the ligand through an ether group.

In certain embodiments, each tether comprises from about 8 to about 20 atoms in chain length between the ligand and the branching group. In certain embodiments, each tether group comprises from about 10 to about 18 atoms in chain length between the ligand and the branching group. In certain embodiments, each tether group comprises about 13 atoms in chain length.

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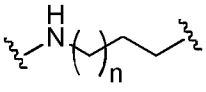
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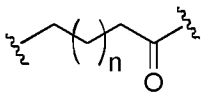
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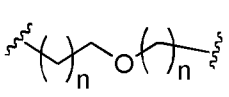
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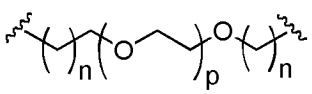
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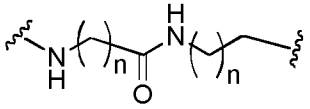
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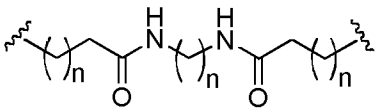
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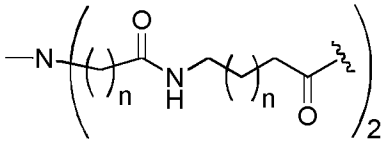
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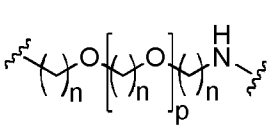
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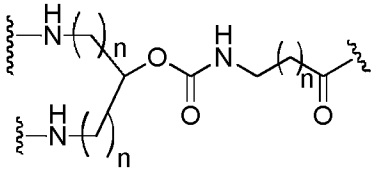
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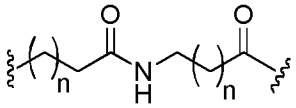
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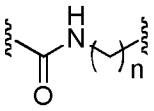
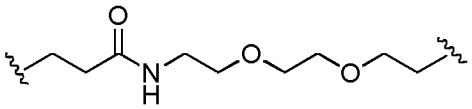
; and


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

each p is from 1 to about 6.

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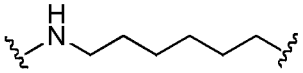
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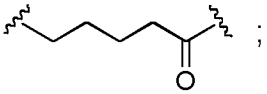
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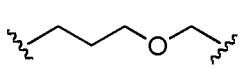
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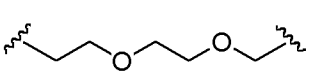
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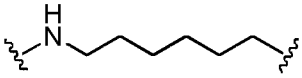
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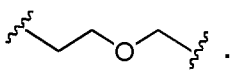
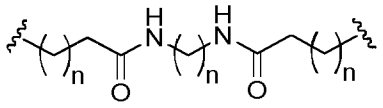
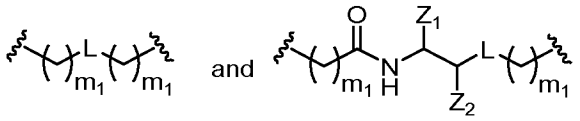

.

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;

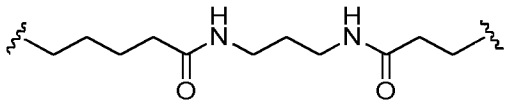
Z_1 is C(=O)O-R_2;

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

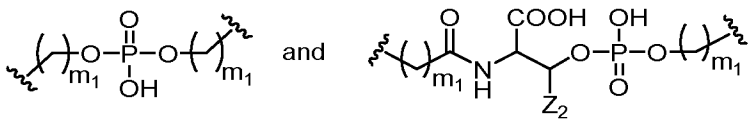
each m_1 is, independently, from 0 to 20 wherein at least one m_1 is greater than 0 for each tether.

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



.

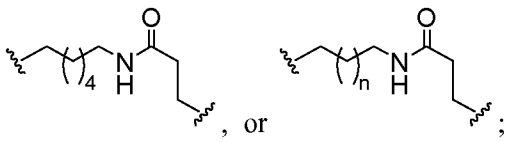
In certain embodiments, a tether has a structure selected from among:



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.

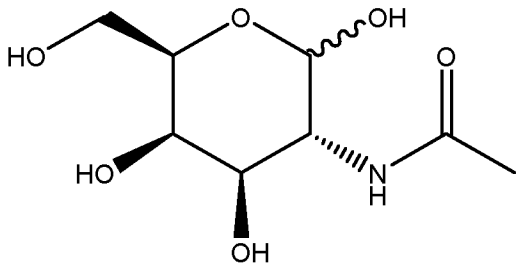
3. Certain Ligands

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.

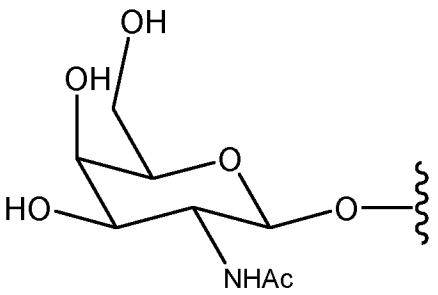
In certain embodiments, the ligand is a carbohydrate, carbohydrate derivative, modified carbohydrate, multivalent carbohydrate cluster, polysaccharide, modified polysaccharide, or polysaccharide derivative. In certain embodiments, the ligand is an amino sugar or a thio sugar. For example, amino sugars 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,

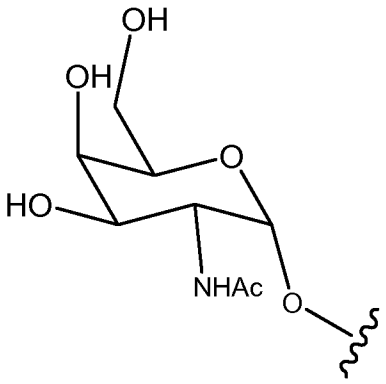
"GalNac" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose. In certain embodiments, "GalNac" or "Gal-NAc" refers to 2-(Acetylamino)-2-deoxy-D-galactopyranose, which includes both the β-form: 2-(Acetylamino)-2-deoxy-β-D-galactopyranose and α-form: 2-(Acetylamino)-2-deoxy-D-galactopyranose. 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

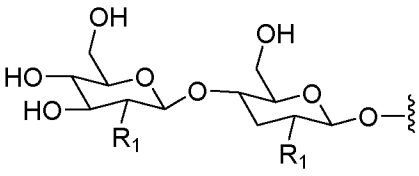


2-(Acetylamino)-2-deoxy-β-D-galactopyranose

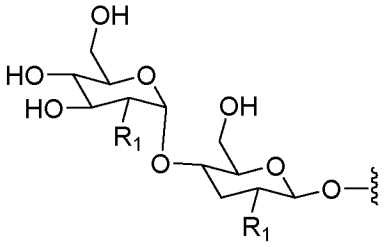


2-(Acetylamino)-2-deoxy-α-D-galactopyranose

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

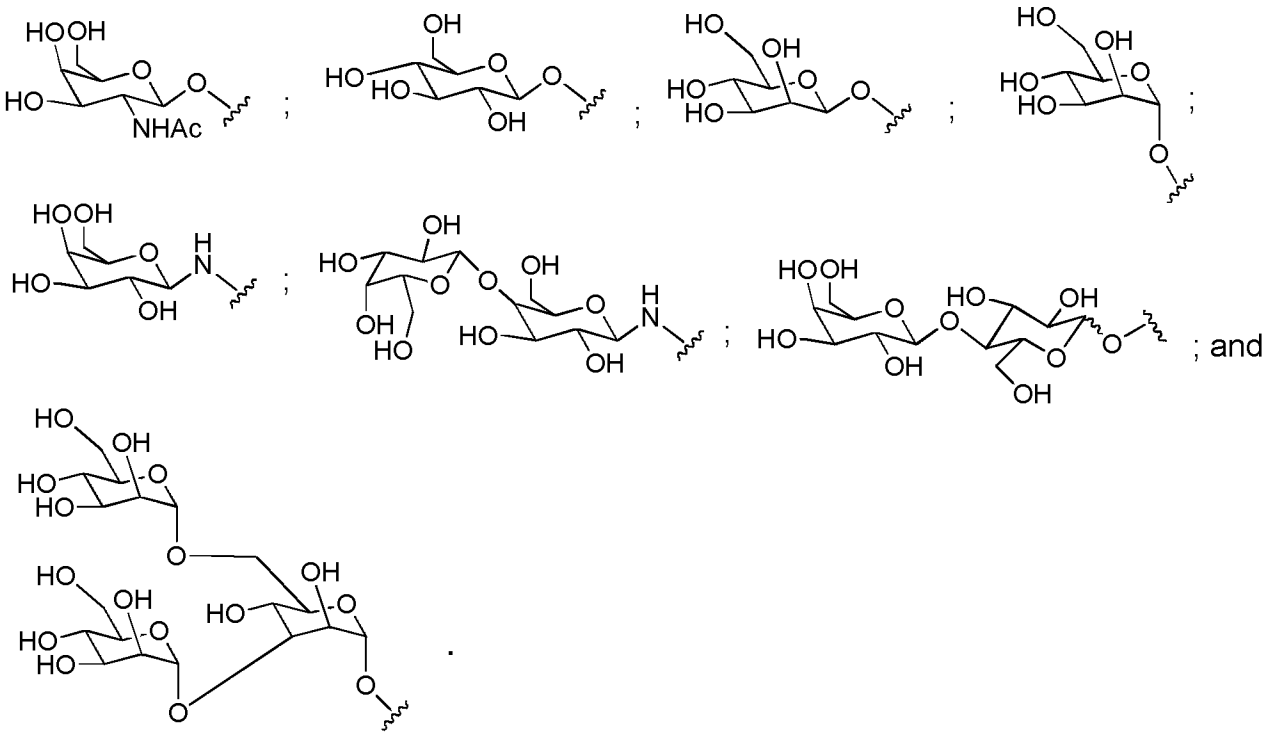


and

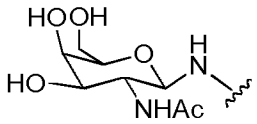


wherein each R_1 is selected from OH and NHCOOH.

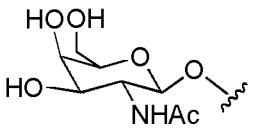
In certain embodiments one or more ligand has a structure selected from among:



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

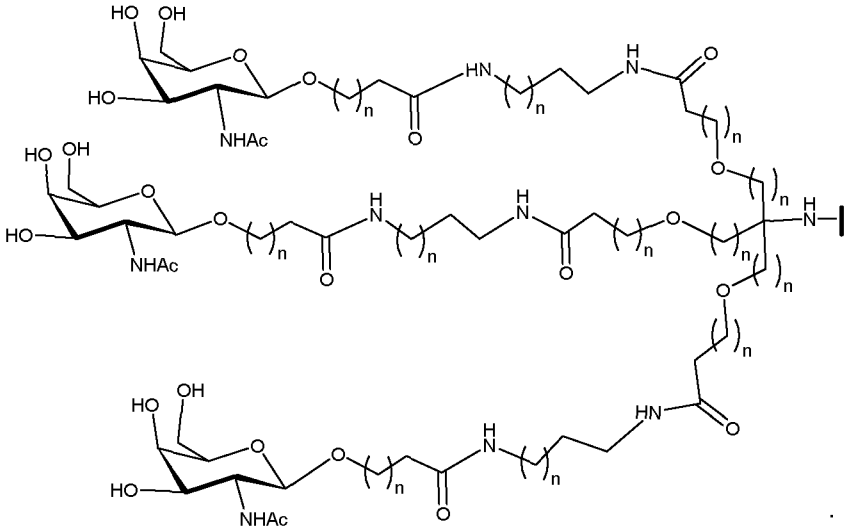


In certain embodiments one or more ligand has a structure selected from among:



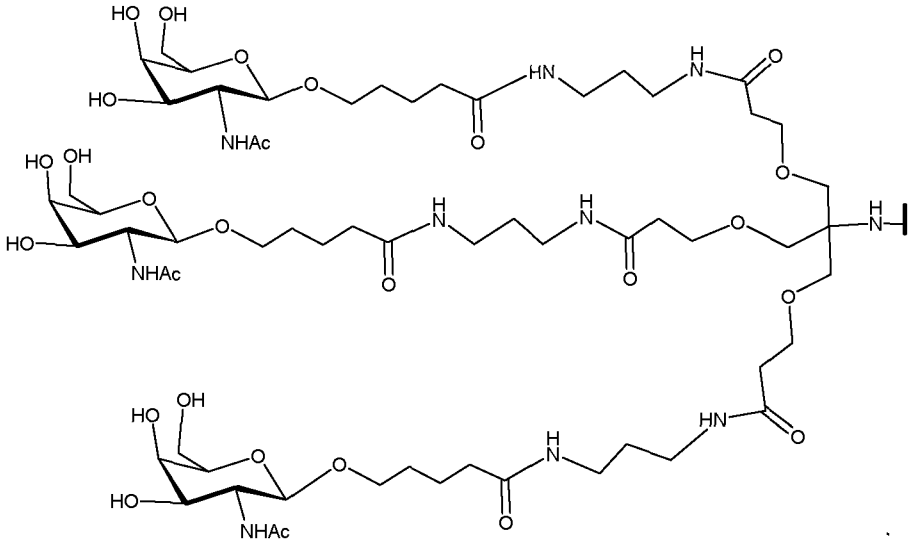
i. Certain Conjugates

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

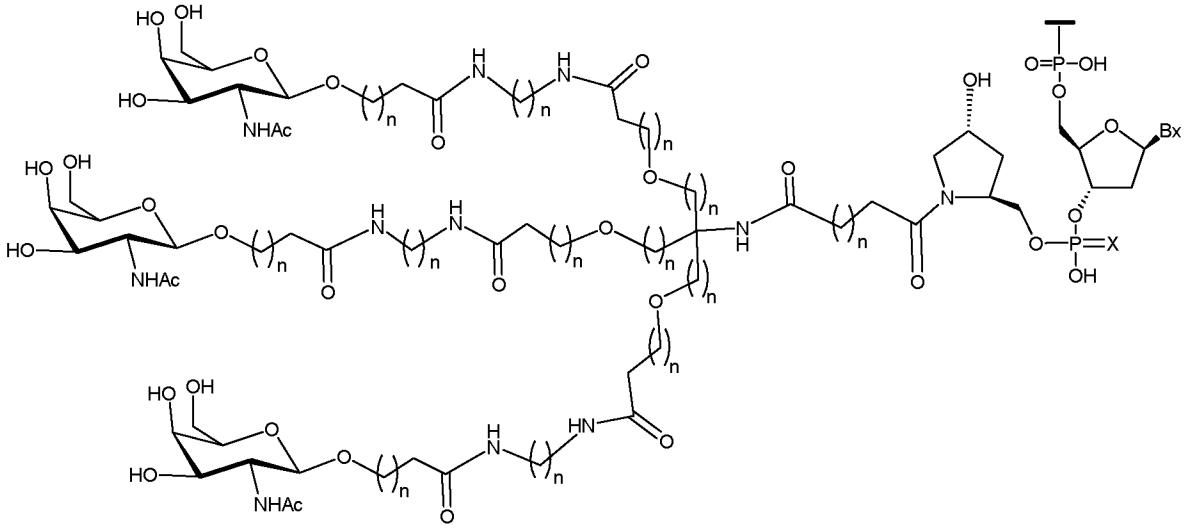


wherein each n is, independently, from 1 to 20.

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;

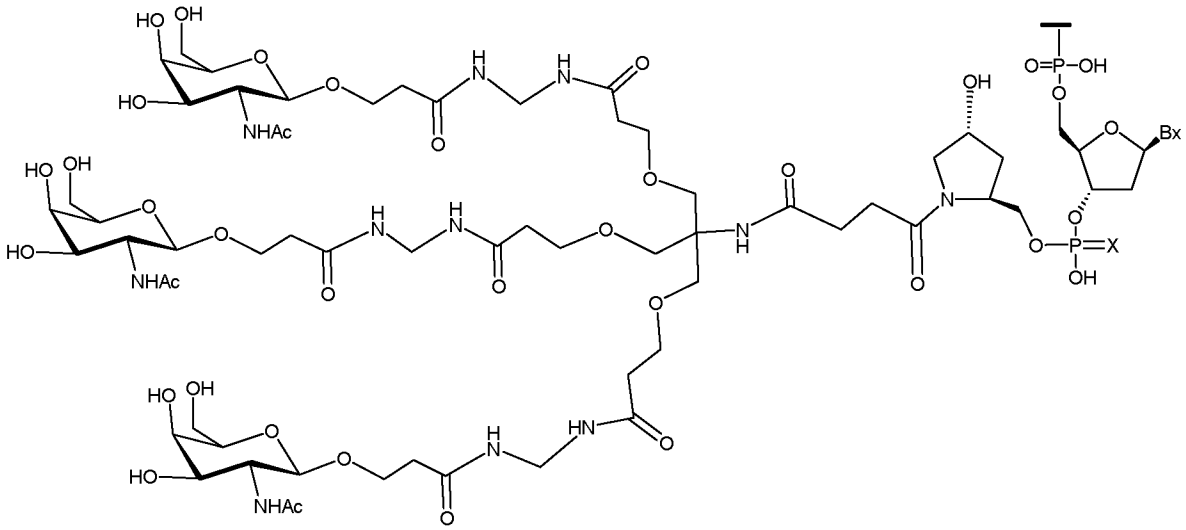
Z is H or a linked solid support;

Q is an antisense compound;

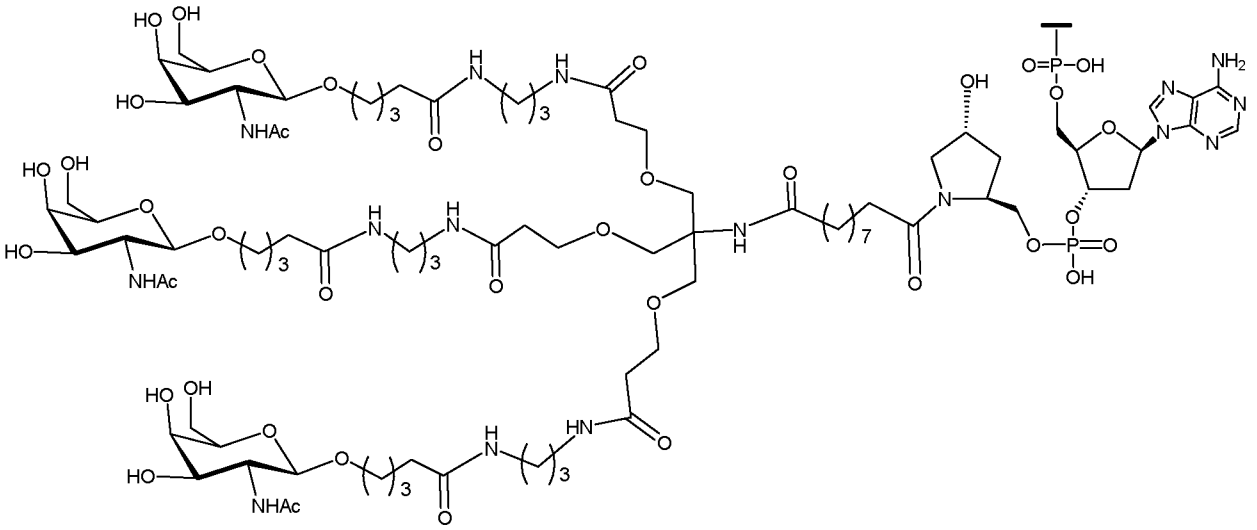
X is O or S; and

Bx is a heterocyclic base moiety.

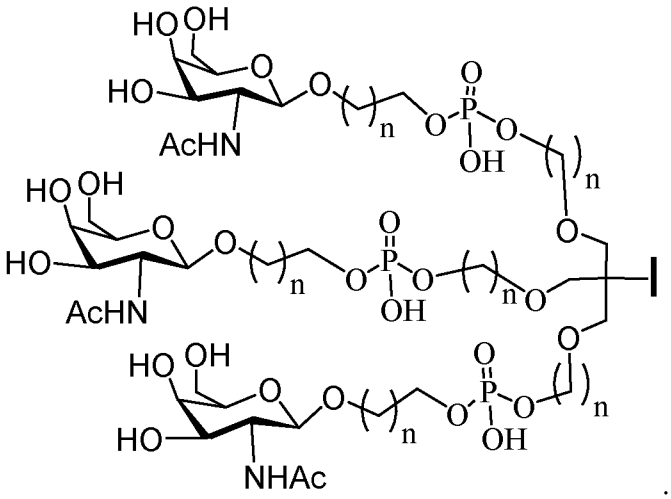
In certain such embodiments, conjugate groups have the following structure:



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

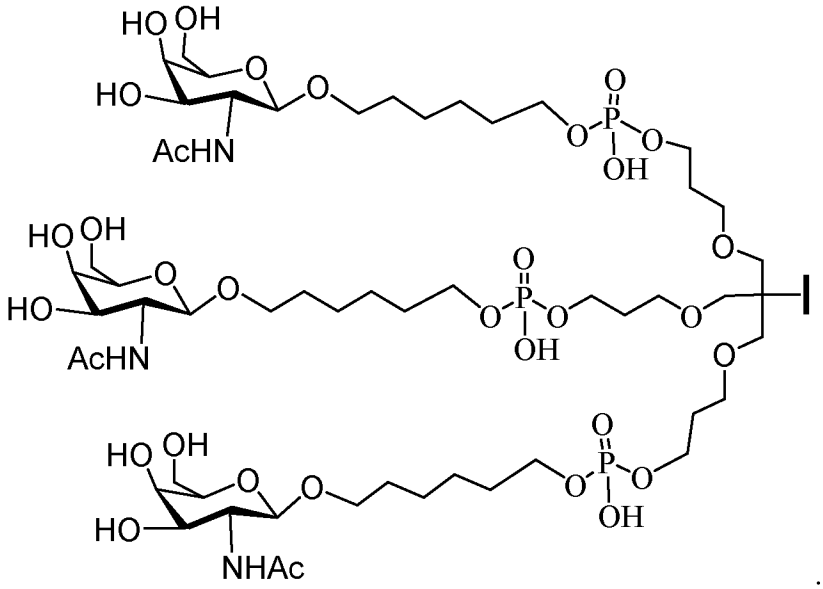


In certain such embodiments, conjugate groups have the following structure:

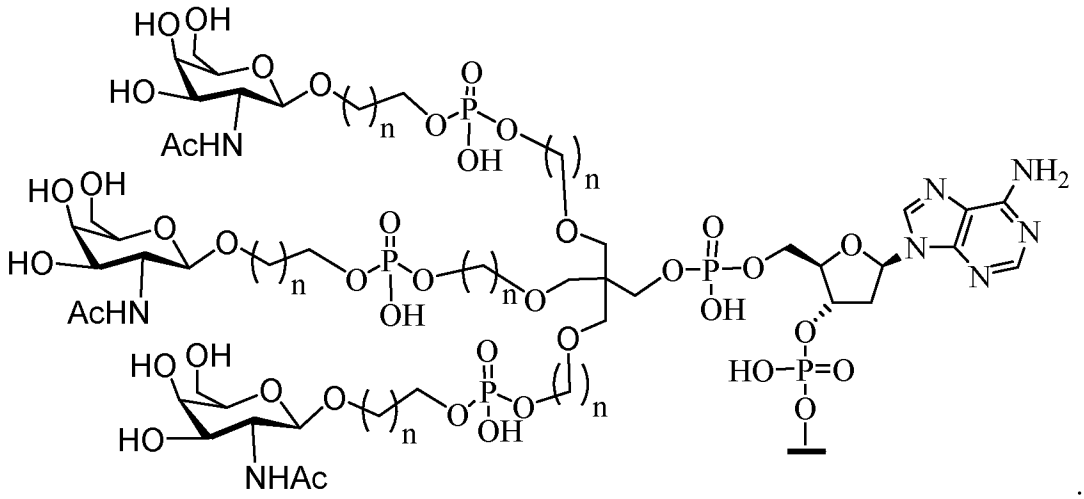


.

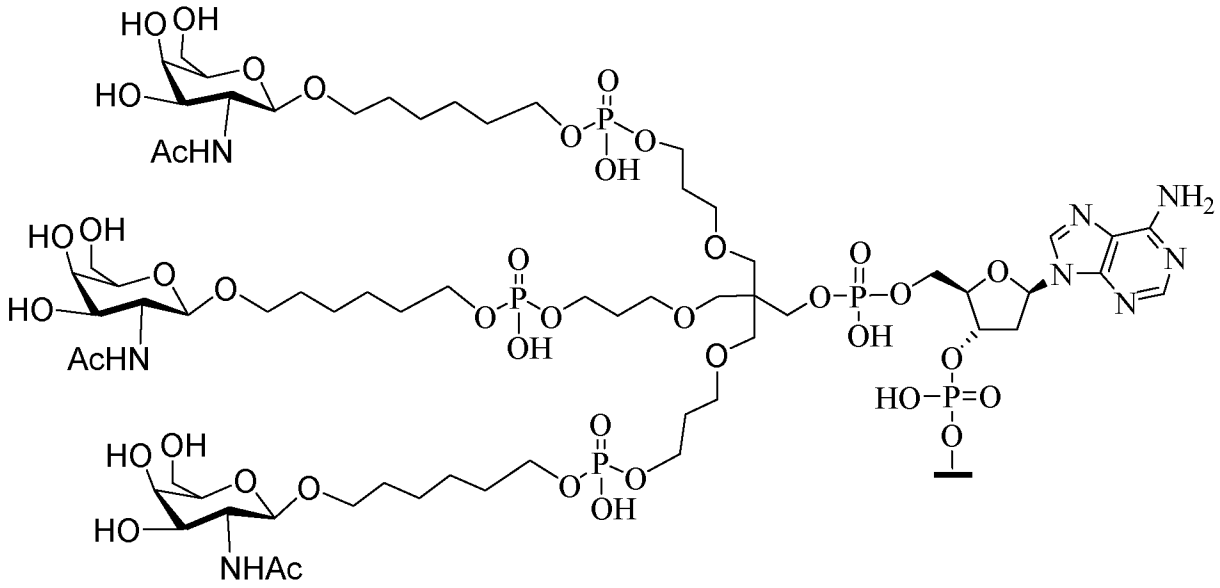
In certain such embodiments, conjugate groups have the following structure:



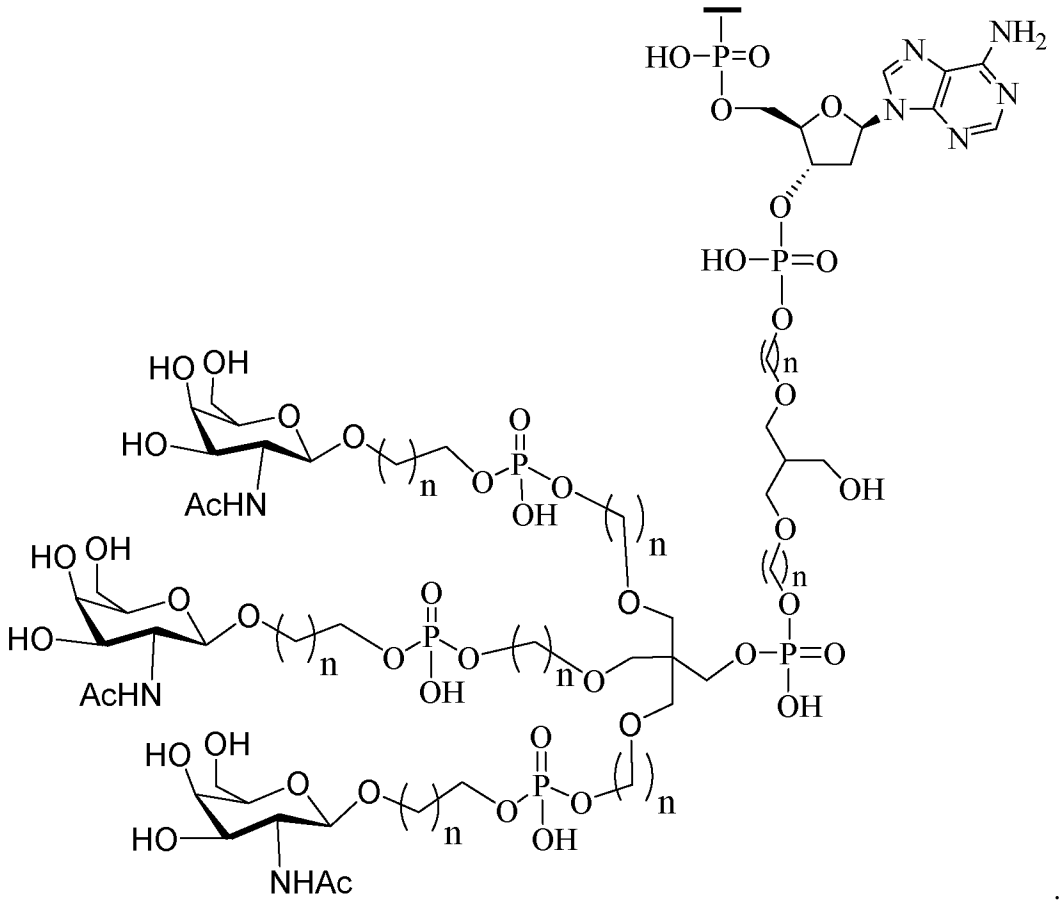
In certain such embodiments, conjugate groups have the following structure:



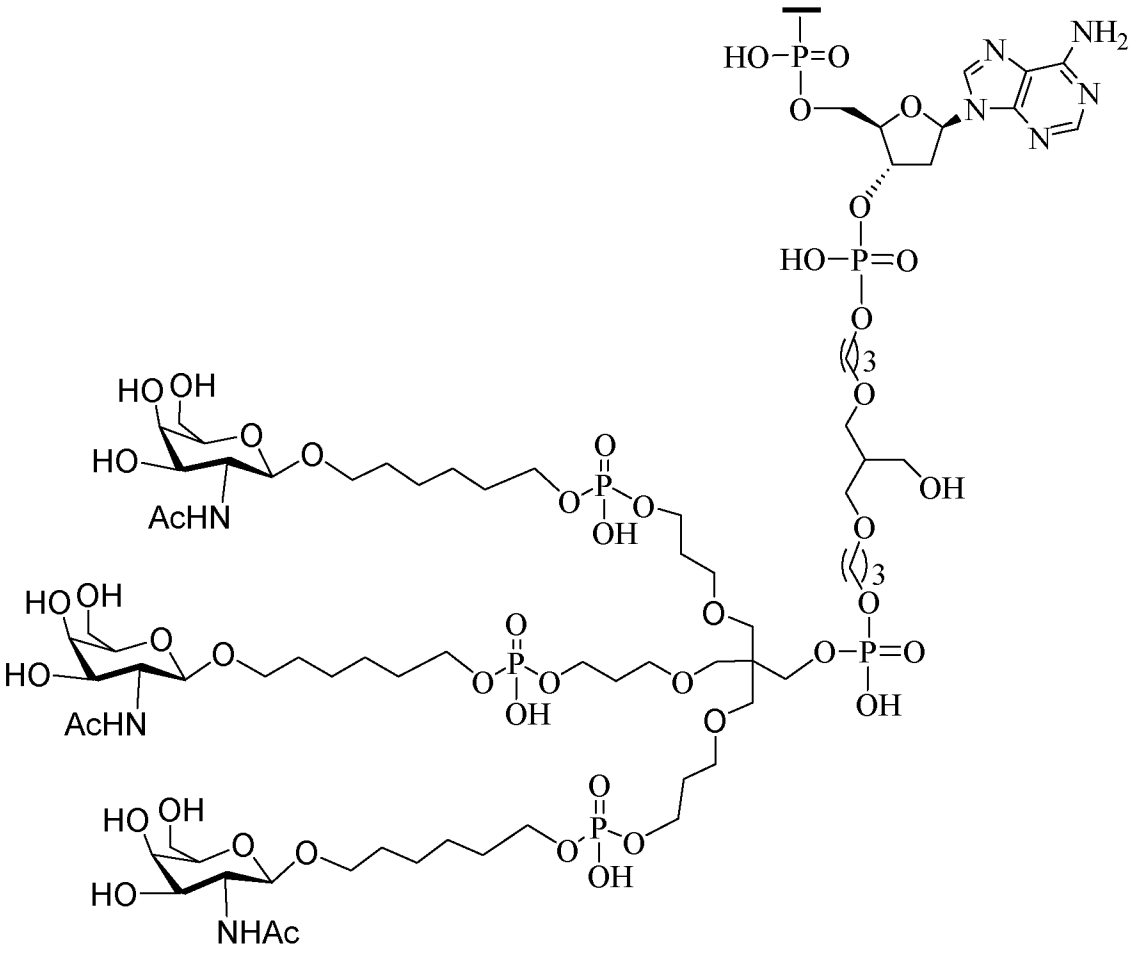
In certain such embodiments, conjugate groups have the following structure:



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

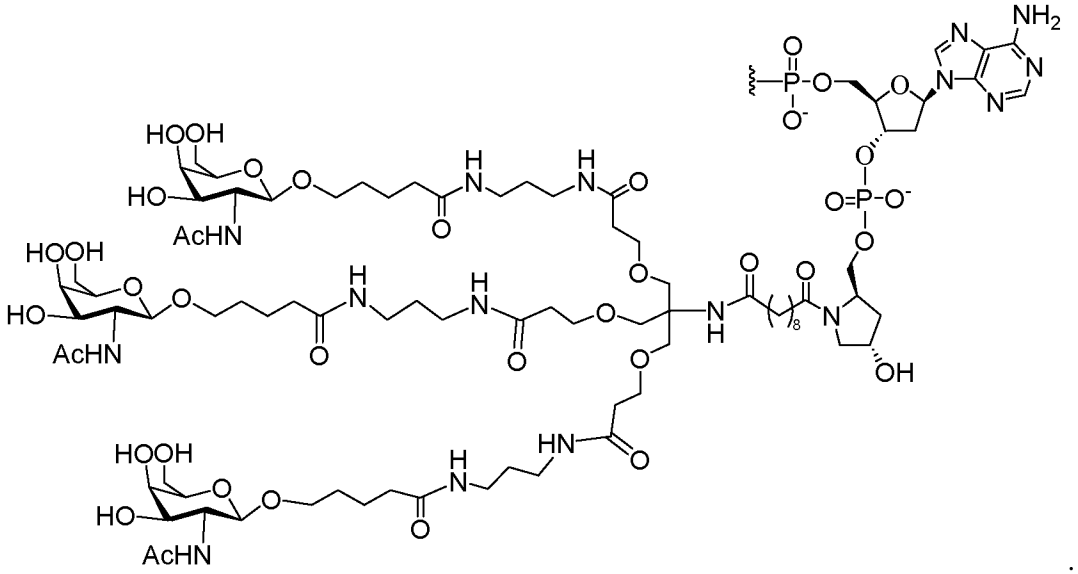


In certain such embodiments, conjugate groups have the following structure:

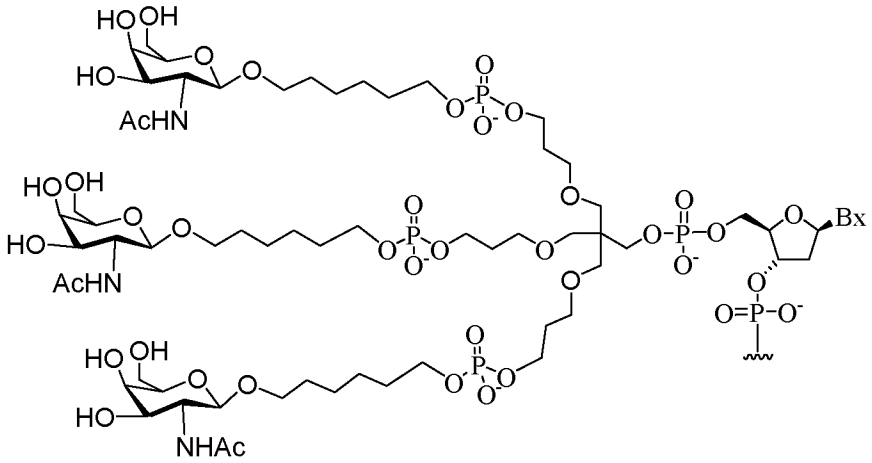


In certain embodiments, conjugates do not comprise a pyrrolidine.

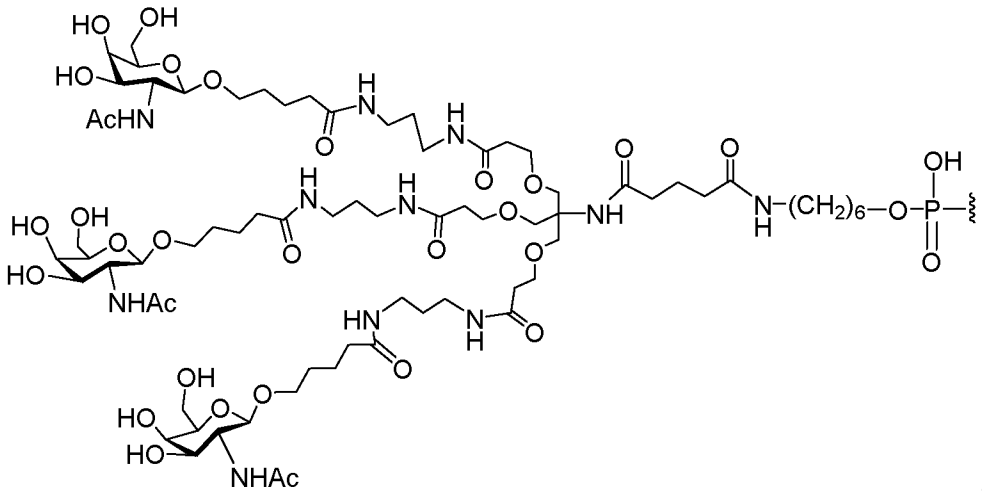
In certain such embodiments, conjugate groups have the following structure:



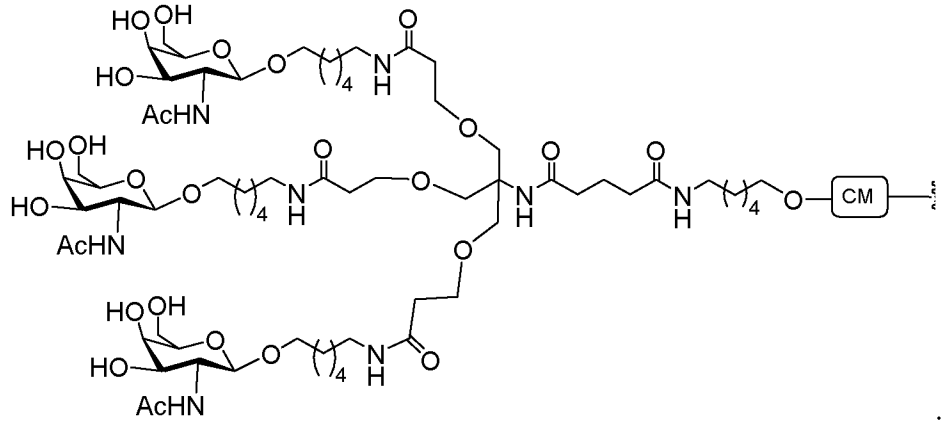
In certain such embodiments, conjugate groups have the following structure:



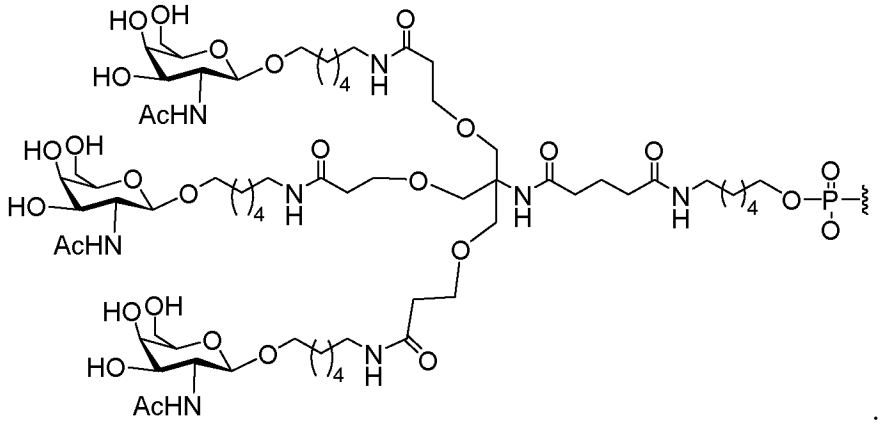
In certain such embodiments, conjugate groups have the following structure:



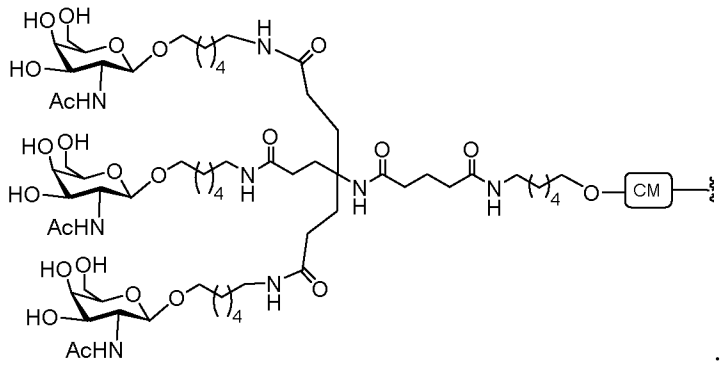
In certain such embodiments, conjugate groups have the following structure:



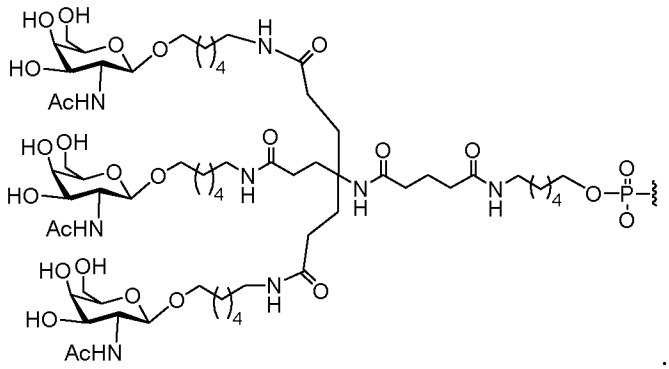
In certain such embodiments, conjugate groups have the following structure:



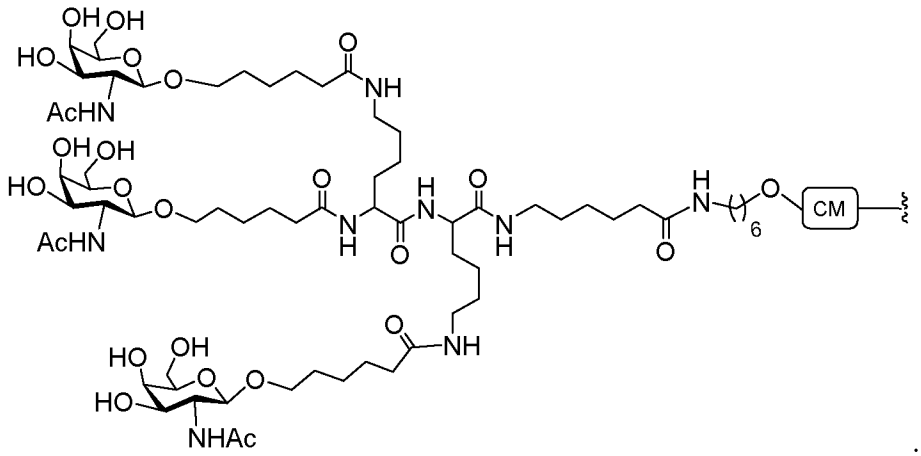
In certain such embodiments, conjugate groups have the following structure:



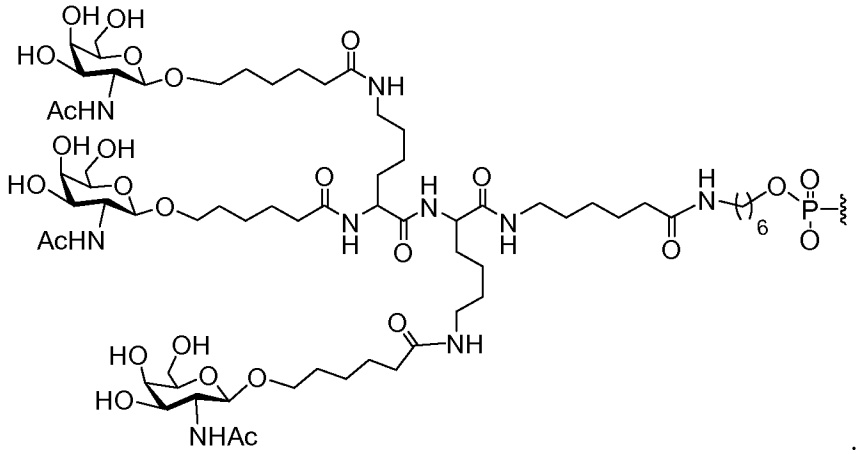
In certain such embodiments, conjugate groups have the following structure:



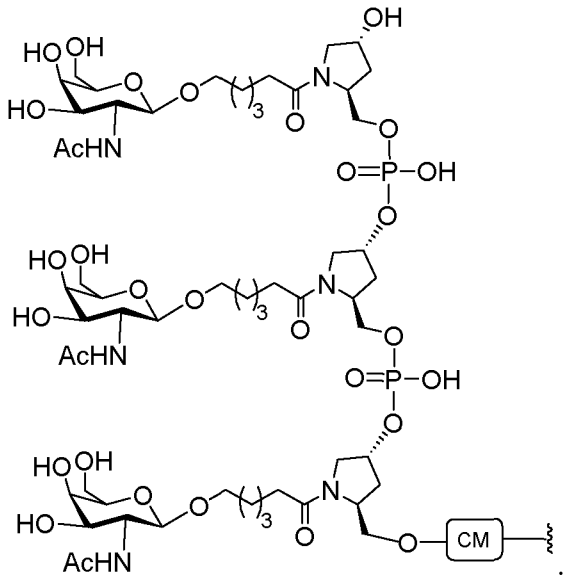
In certain such embodiments, conjugate groups have the following structure:



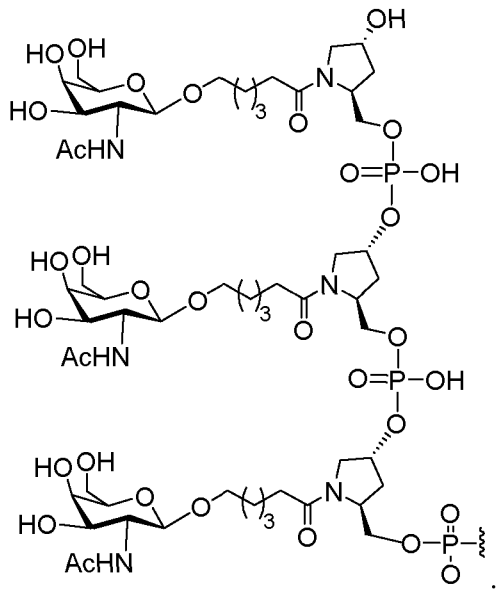
In certain such embodiments, conjugate groups have the following structure:



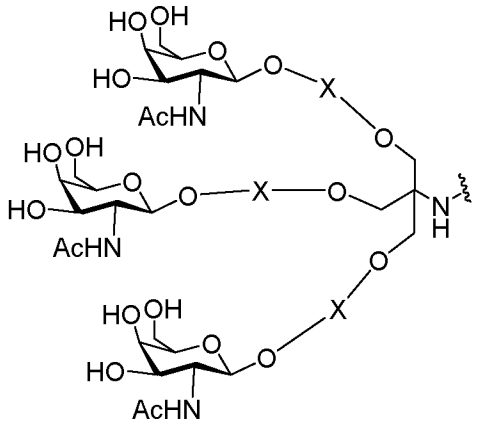
In certain such embodiments, conjugate groups have the following structure:



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

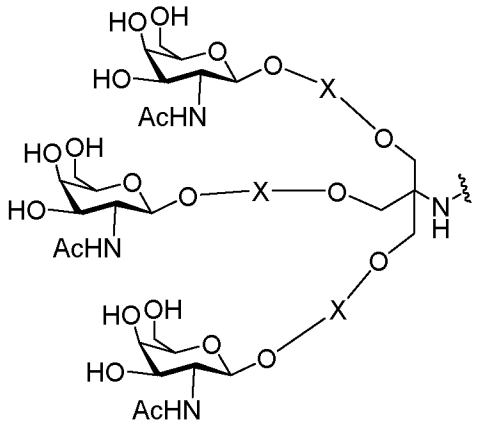


In certain embodiments, the cell-targeting moiety of the conjugate group has the following structure:



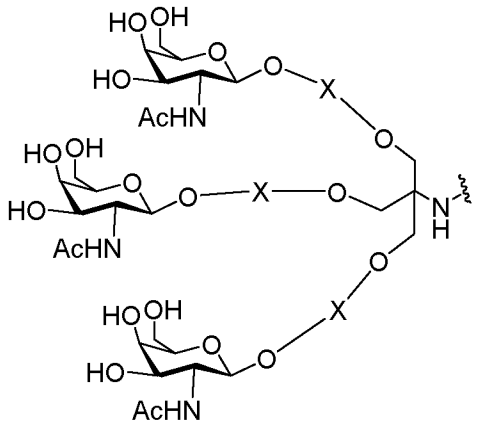
wherein X is a substituted or unsubstituted tether of six to eleven consecutively bonded atoms.

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



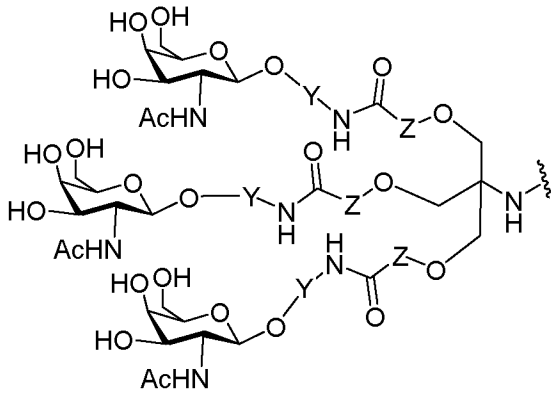
wherein X is a substituted or unsubstituted tether of ten consecutively bonded atoms.

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



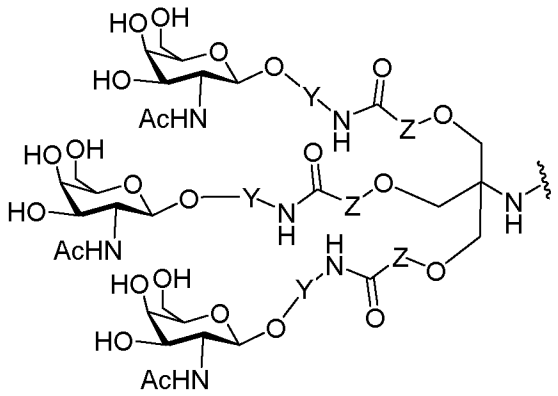
wherein X is a substituted or unsubstituted tether of four to eleven consecutively bonded atoms and wherein the tether comprises exactly one amide bond.

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



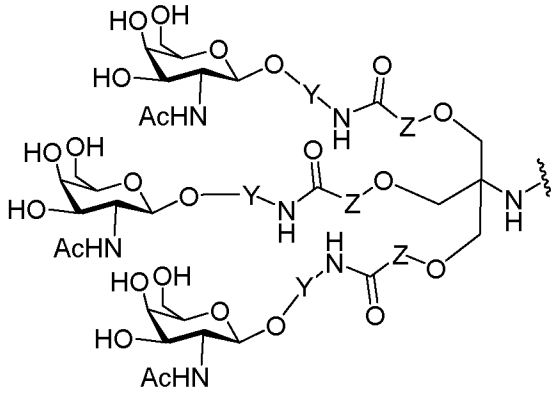
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine,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

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



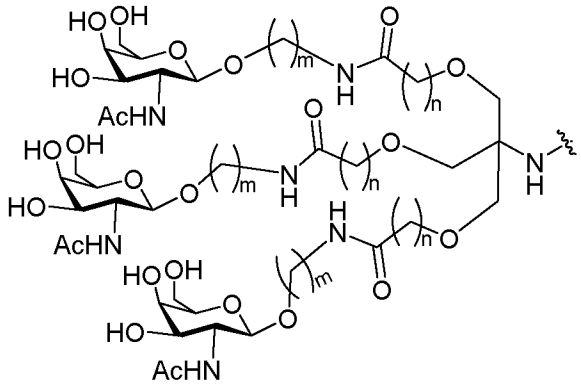
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising exactly one ether or exactly two ethers, an amide, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

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



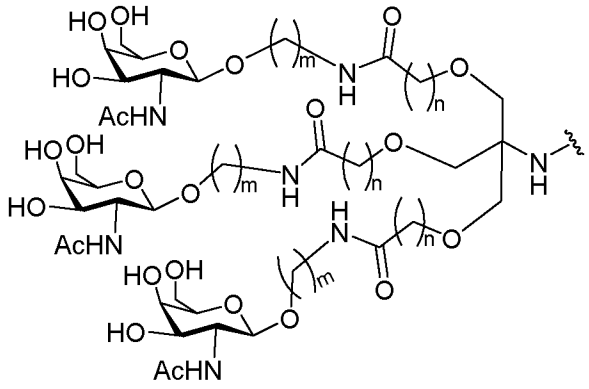
wherein Y and Z are independently selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

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



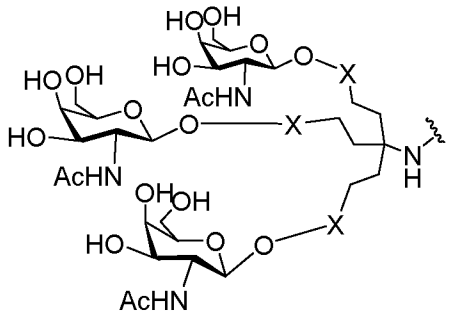
wherein m and n are independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

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



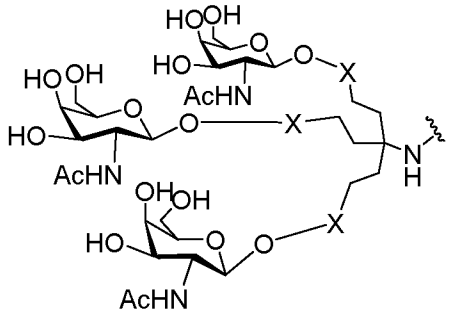
wherein m is 4, 5, 6, 7, or 8, and n is 1, 2, 3, or 4.

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



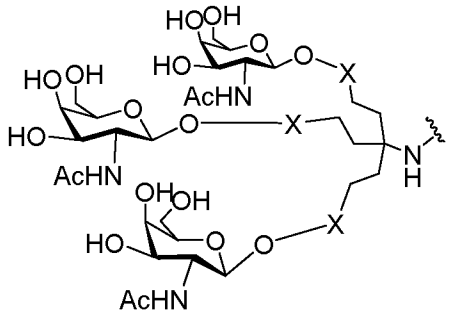
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein X does not comprise an ether group.

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



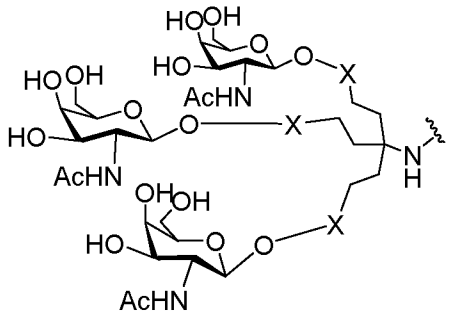
wherein X is a substituted or unsubstituted tether of eight consecutively bonded atoms, and wherein X does not comprise an ether group.

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



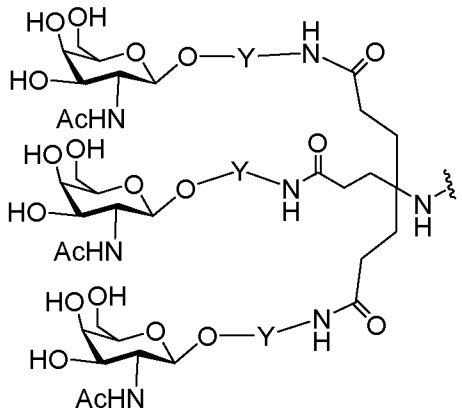
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms, and wherein the tether comprises exactly one amide bond, and wherein X does not comprise an ether group.

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



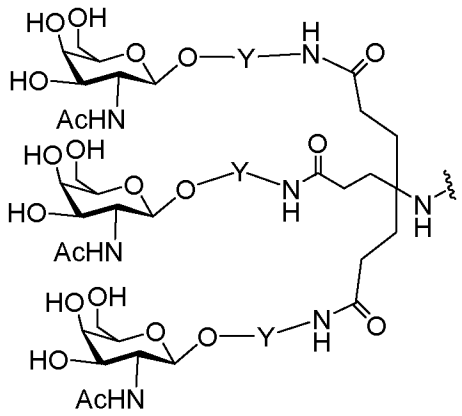
wherein X is a substituted or unsubstituted tether of four to thirteen consecutively bonded atoms and wherein the tether consists of an amide bond and a substituted or unsubstituted C_2-C_{11} alkyl group.

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



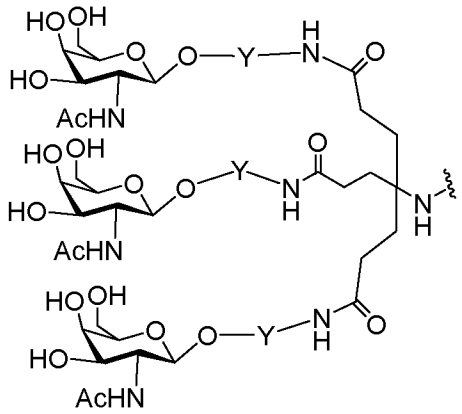
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or a group comprising an ether, a ketone, an amide, an ester, a carbamate, an amine, a piperidine, a phosphate, a phosphodiester, a phosphorothioate, a triazole, a pyrrolidine, a disulfide, or a thioether.

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



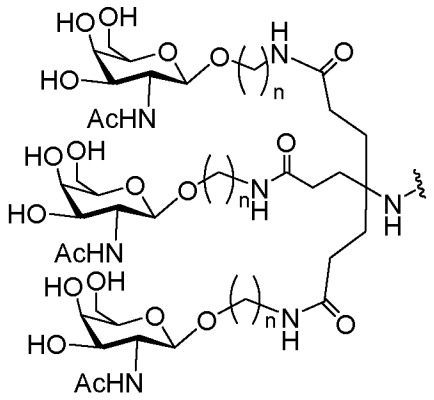
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group, or a group comprising an ether, an amine, a piperidine, a phosphate, a phosphodiester, or a phosphorothioate.

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



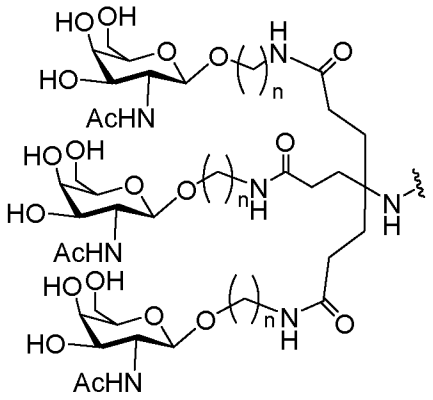
wherein Y is selected from a C_1-C_{12} substituted or unsubstituted alkyl group.

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.

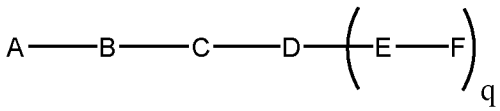
In certain such embodiments, the cell-targeting moiety of the conjugate group has the following structure:



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

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

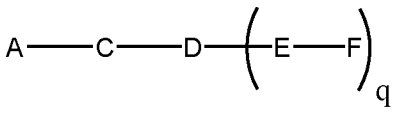
D is the branching group

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.

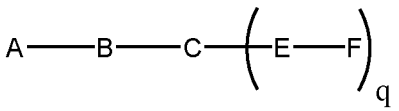
In certain such embodiments, the conjugate linker comprises at least one cleavable bond.

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

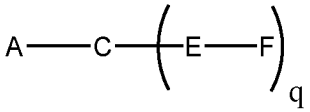
C is the conjugate linker

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;

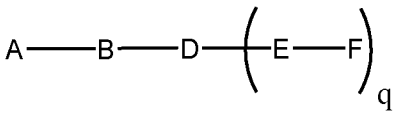
C is the conjugate linker

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

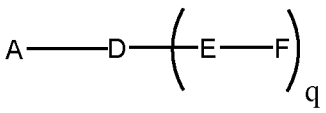
D is the branching group

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;

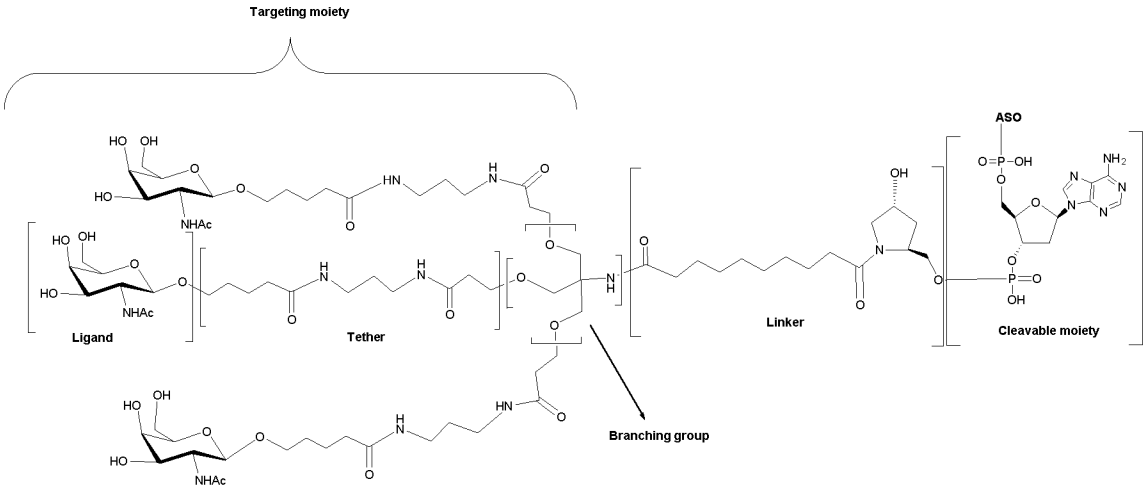
each F is a ligand; and

q is an integer between 1 and 5.

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

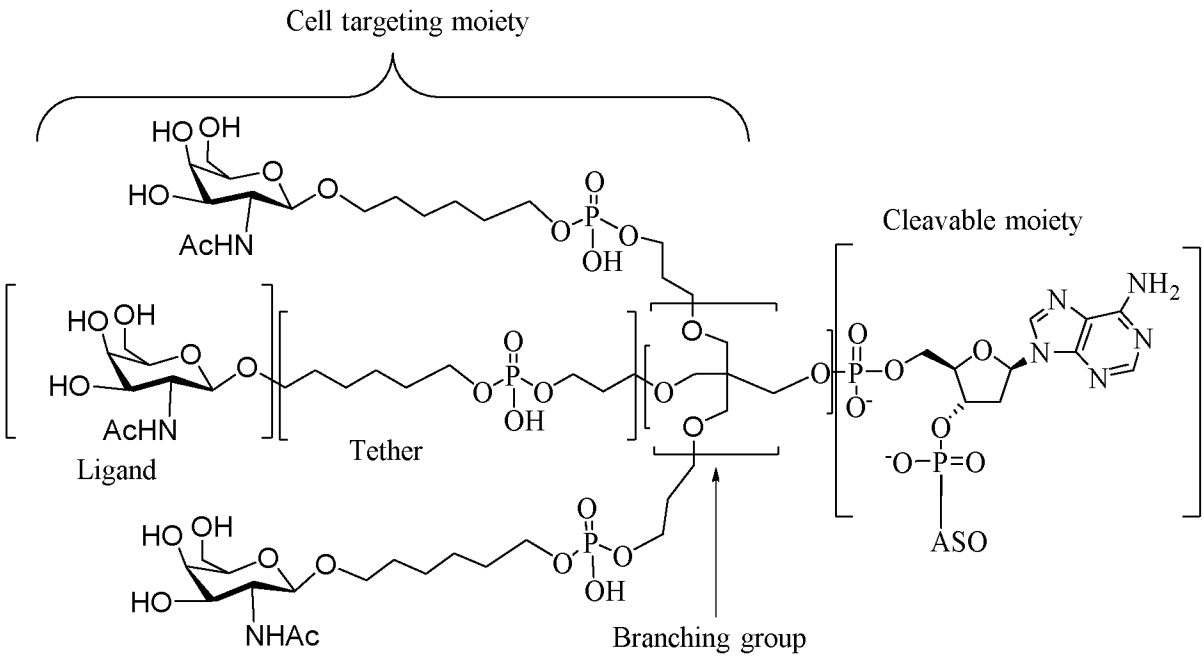
In certain embodiments each tether comprises at least one cleavable bond.

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



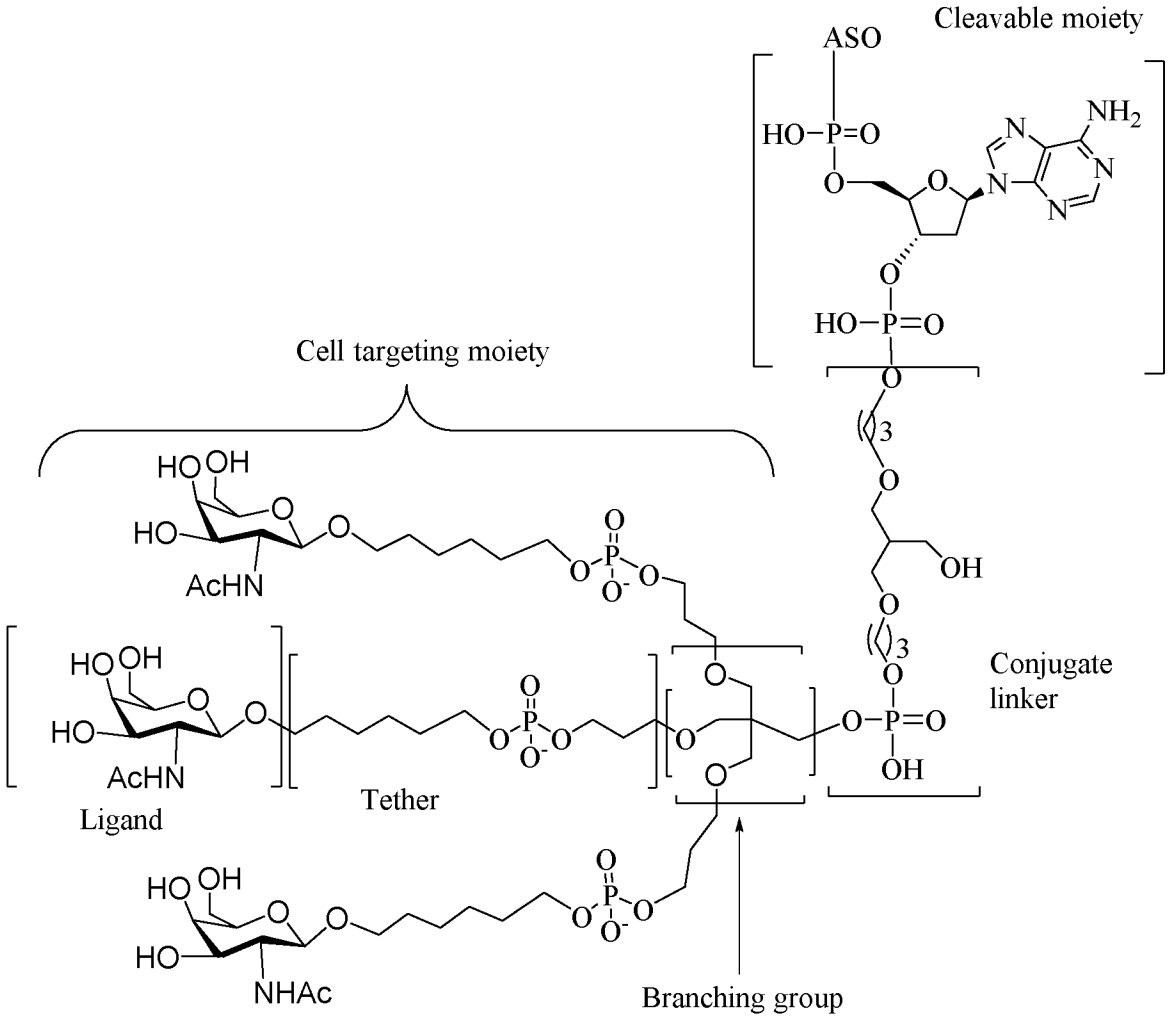
.

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:



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.

Cell culture and antisense compounds treatment

The effects of antisense compounds on the level, activity, or expression of PKK nucleic acids can be tested in vitro in a variety of cell types. Cell types used for such analyses are available from commercial vendors (e.g., American Type Culture Collection, Manassus, VA; Zen-Bio, Inc., Research Triangle Park, NC; Clonetics Corporation, Walkersville, MD) and are cultured according to the vendor's instructions using commercially available reagents (e.g., Life Technologies, Carlsbad, CA). Illustrative cell types include, but are not limited to, HepaRG™T cells and mouse primary hepatocytes.

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 (Life Technologies, Carlsbad, CA). Antisense oligonucleotides may be mixed with LIPOFECTIN in OPTI-MEM 1 (Life Technologies, 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 (Life Technologies, Carlsbad, CA). Antisense oligonucleotide is mixed with LIPOFECTAMINE in OPTI-MEM 1 reduced serum medium (Life Technologies, 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 (Life Technologies, Carlsbad, CA) according to the manufacturer's recommended protocols.

Analysis of inhibition of target levels or expression

Inhibition of levels or expression of a PKK nucleic acid can be assayed in a variety of ways known in the art. For example, target nucleic acid levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitaive real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. Northern

blot analysis is also routine in the art. Quantitative real-time PCR can be conveniently accomplished using the commercially available ABI PRISM 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions.

Quantitative Real-Time PCR Analysis of Target RNA Levels

Quantitation of target RNA levels may be accomplished by quantitative real-time PCR using the ABI PRISM 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

Prior to real-time PCR, the isolated RNA is subjected to a reverse transcriptase (RT) reaction, which produces complementary DNA (cDNA) that is then used as the substrate for the real-time PCR amplification. The RT and real-time PCR reactions are performed sequentially in the same sample well. RT and real-time PCR reagents may be obtained from Life Technologies (Carlsbad, CA). RT real-time-PCR reactions are carried out by methods well known to those skilled in the art.

Gene (or RNA) target quantities obtained by real time PCR are normalized using either the expression level of a gene whose expression is constant, such as cyclophilin A, or by quantifying total RNA using RIBOGREEN (Life Technologies, Inc. Carlsbad, CA). Cyclophilin A expression is quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RIBOGREEN RNA quantification reagent (Invetrogen, Inc. Eugene, OR). Methods of RNA quantification by RIBOGREEN are taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR 4000 instrument (PE Applied Biosystems) is used to measure RIBOGREEN fluorescence.

Probes and primers are designed to hybridize to a PKK nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS Software (Applied Biosystems, Foster City, CA).

Analysis of Protein Levels

Antisense inhibition of PKK nucleic acids can be assessed by measuring PKK protein levels. Protein levels of PKK can be evaluated or quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA), quantitative protein assays, protein activity assays (for example, caspase activity assays), immunohistochemistry, immunocytochemistry or fluorescence-activated cell sorting (FACS). Antibodies directed to a target can be identified and obtained from a variety of sources, such as the MSRS catalog of

antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art.

In vivo testing of antisense compounds

Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of PKK and produce phenotypic changes.

In certain embodiments, such phenotypic changes include those associated with an inflammatory disease, such as, reduced inflammation, edema/swelling, vascular permeability, and vascular leakage. In certain embodiments, inflammation is measured by measuring the increase or decrease of edema, temperature, pain, color of tissue, and abdominal function in the animal.

In certain embodiments, such phenotypic changes include those associated with a thromboembolic disease, such as, prolonged aPTT, prolonged aPTT time in conjunction with a normal PT, decreased quantity of Platelet Factor 4 (PF-4), and reduced formation of thrombus or increased time for thrombus formation.

Testing may be performed in normal animals, or in experimental disease models. For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as phosphate-buffered saline. Administration includes parenteral routes of administration, such as intraperitoneal, intravenous, and subcutaneous. Calculation of antisense oligonucleotide dosage and dosing frequency is within the abilities of those skilled in the art, and depends upon factors such as route of administration and animal body weight. Following a period of treatment with antisense oligonucleotides, RNA is isolated from liver tissue and changes in PKK nucleic acid expression are measured.

Certain Indications

In certain embodiments, the invention provides methods of treating an individual comprising administering one or more pharmaceutical compositions as described herein.

In certain embodiments, the individual has an inflammatory disease. In certain embodiments, the individual is at risk for developing an inflammatory condition, including, but not limited to hereditary angioedema (HAE), edema, angioedema, swelling, angioedema of the lids, ocular edema, macular edema, and cerebral edema. This includes individuals with an acquired problem, disease, or disorder that leads to a risk of inflammation, for example, genetic predisposition to an inflammatory condition, environmental factors, and exposure to certain medications, including, for example, ACE inhibitors and ARBs. In certain embodiments, the individual has been identified as in need of anti-inflammation therapy. Examples of such individuals include, but are not limited to those having a mutation in the genetic code for complement 1 esterase inhibitor (i.e., C1-INH) or Factor 12. In certain embodiments, an abnormal code can lead to a

deficiency in C1-INH (i.e., type I HAE), an inability of existing C1-INH to function properly (type II HAE), or hyperfunctional Factor 12 (i.e., type III HAE).

In certain embodiments, the individual has a thromboembolic disease. In certain embodiments, the individual is at risk for a blood clotting disorder, including, but not limited to, infarct, thrombosis, embolism, thromboembolism such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. This includes individuals with an acquired problem, disease, or disorder that leads to a risk of thrombosis, for example, surgery, cancer, immobility, sepsis, atherosclerosis atrial fibrillation, as well as genetic predisposition, for example, antiphospholipid syndrome and the autosomal dominant condition, Factor V Leiden. In certain embodiments, the individual has been identified as in need of anticoagulation therapy. Examples of such individuals include, but are not limited to, those undergoing major orthopedic surgery (e.g., hip/knee replacement or hip fracture surgery) and patients in need of chronic treatment, such as those suffering from arterial fibrillation to prevent stroke.

In certain embodiments the invention provides methods for prophylactically reducing PKK expression in an individual. Certain embodiments include treating an individual in need thereof by administering to an individual a therapeutically effective amount of an antisense compound targeted to a PKK nucleic acid.

In one embodiment, administration of a therapeutically effective amount of an antisense compound targeted to a PKK nucleic acid is accompanied by monitoring of PKK levels in the serum of an individual, to determine an individual's response to administration of the antisense compound. An individual's response to administration of the antisense compound is used by a physician to determine the amount and duration of therapeutic intervention.

In certain embodiments, administration of an antisense compound targeted to a PKK nucleic acid results in reduction of PKK expression by at least 15, 20, 25, 30, 35, 40, 45, 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, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%, or a range defined by any two of these values. In certain embodiments, pharmaceutical compositions comprising an antisense compound targeted to PKK are used for the preparation of a medicament for treating a patient suffering or susceptible to an inflammatory disease or thromboembolic disease.

Certain Compositions

1. ISIS 546254

In certain embodiments, ISIS 546254 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') TGCAAGTCTCTTGGCAAACA (incorporated herein as SEQ ID NO: 570), wherein each

internucleoside linkage is a phosphorothioate linkage, each cytosine is a 5'-methylcytosine, each of nucleosides 1-5 and 16-20 are 2'-O-methoxyethyl modified nucleosides, and each of nucleosides 6-15 are 2'-deoxynucleosides.

In certain embodiments, ISIS 546254 is described by the following chemical notation: Tes Ges mCes Aes Aes Gds Tds mCds Tds mCds Tds Tds Gds Gds mCds Aes Aes Aes mCes Ae; wherein,

A = an adenine,

mC = a 5'-methylcytosine

G = a guanine,

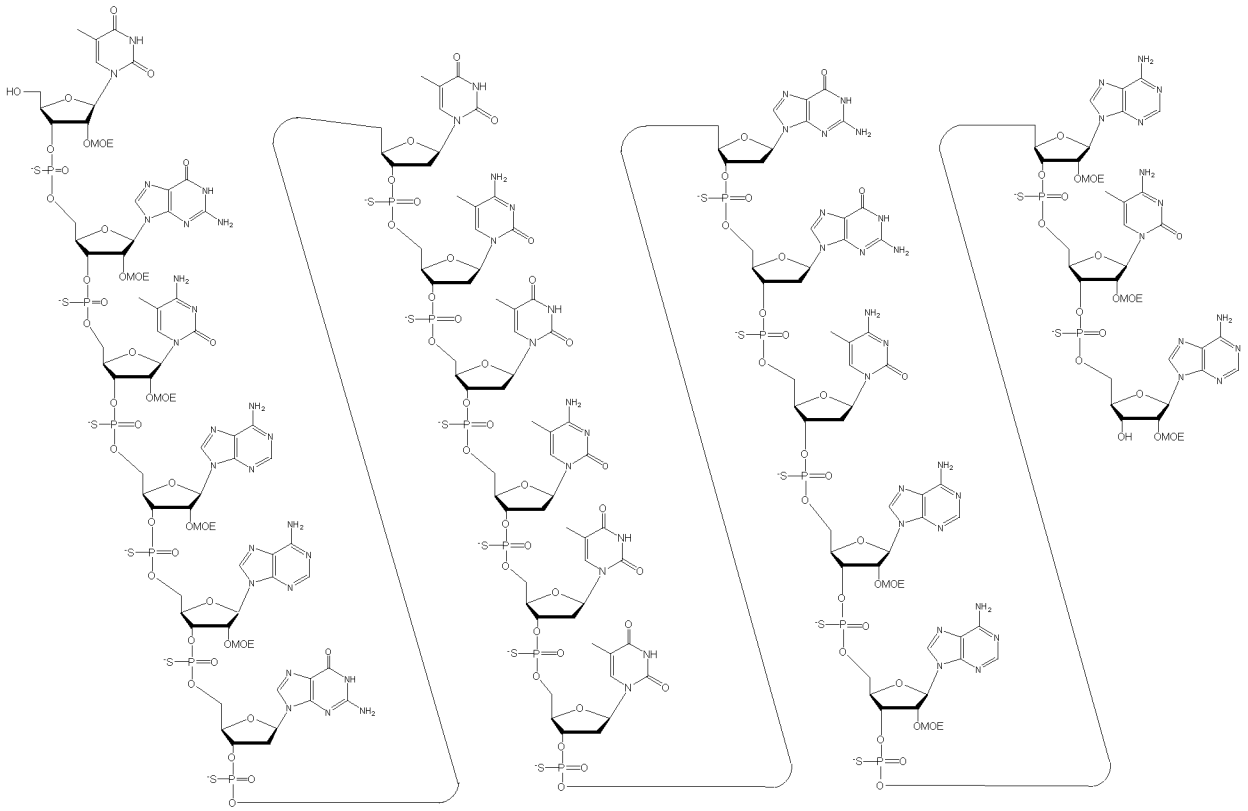
T = a thymine,

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

d = a 2'-deoxynucleoside, and

s = a phosphorothioate internucleoside linkage.

In certain embodiments, ISIS 546254 is described by the following chemical structure:



Structure 1. ISIS 546254

In certain embodiments, as provided in Example 2 (hereinbelow), ISIS 546254 achieved 95% inhibition of human PKK mRNA in cultured HepaRG™ cells (density of 20,000 cells per well) when transfected using electroporation with 5,000 nM antisense oligonucleotide after a treatment period of 24

hours and measured by quantitative real-time PCR using human primer probe set RTS3454 and adjusted according to total RNA content, as measured by RIBOGREEN®.

In certain embodiments, as provided in Example 5 (see Tables 34 and 41 hereinbelow), ISIS 546254 achieved an IC_{50} of 0.2μM and 0.3μM in a 4 point dose response curve (0.19 μM, 0.56 μM, 1.67 μM, and 5.0 μM) in cultured HepaRG™ cells (density of 20,000 cells per well) when transfected using electroporation after a treatment period of 16 and measured by quantitative real-time PCR using human primer probe set RTS3454 and adjusted according to total RNA content, as measured by RIBOGREEN®.

In certain embodiments, as provided in Example 7 (hereinbelow), ISIS 546254 achieved 31%, 55%, 84%, and 83% human PKK mRNA inhibition and 0%, 36%, 51%, and 76% human PKK protein inhibition in transgenic mice harboring the human PKK gene sequence when injected subcutaneously twice a week for 3 weeks with 2.5 mg/kg/week, 5.0 mg/kg/week, 10 mg/kg/week or 20 mg/kg/week with ISIS 546254.

In certain embodiments, as provided in Example 8 (hereinbelow), ISISI 546254 is effective for inhibiting PKK mRNA and protein expression and is tolerable in primates.

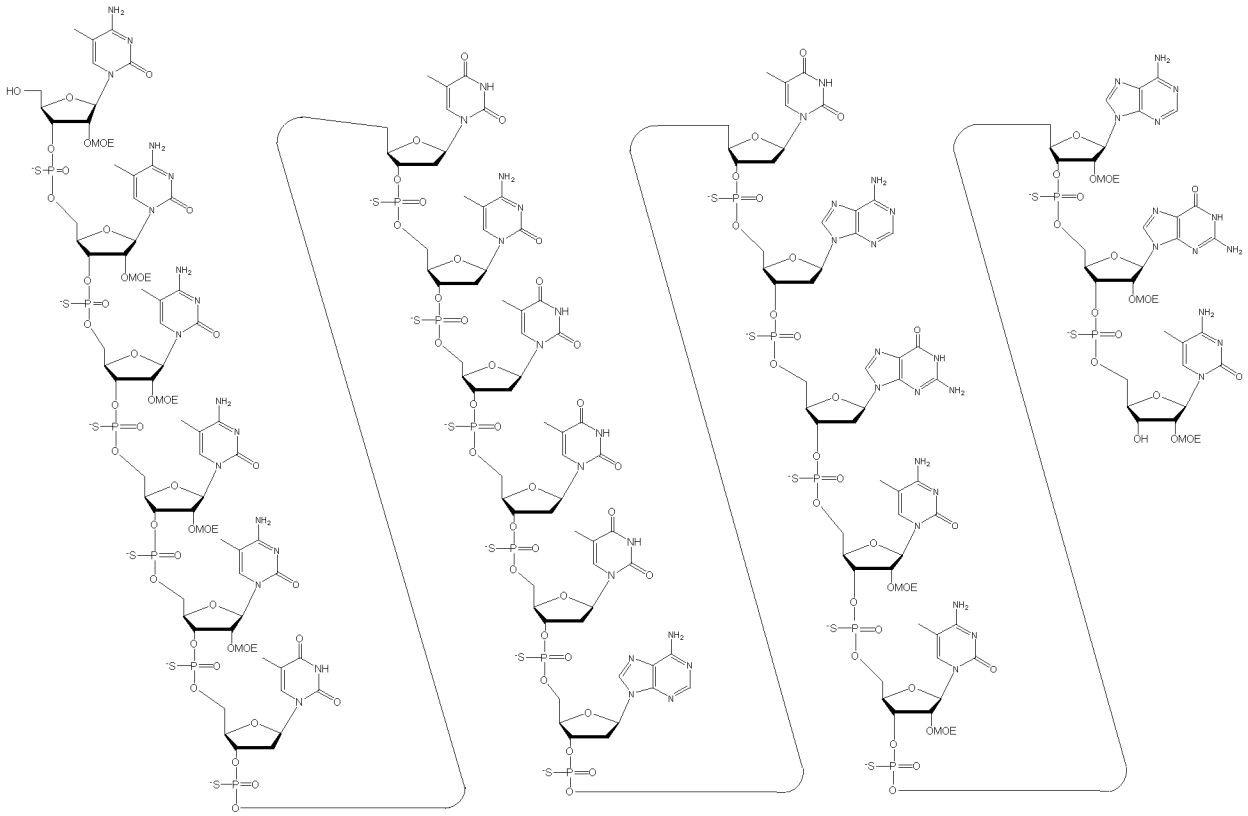
2. ISIS 546343

In certain embodiments, ISIS 546343 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') CCCCCTTCTTTATAGCCAGC (incorporated herein as SEQ ID NO: 705), wherein each internucleoside linkage is a phosphorothioate linkage, each cytosine is a 5'-methylcytosine, each of nucleosides 1-5 and 16-20 are 2'-O-methoxyethyl modified nucleosides, and each of nucleosides 6-15 are 2'-deoxynucleosides.

In certain embodiments, ISIS 546343 is described by the following chemical notation: mCes mCes mCes mCes mCes Tds Tds mCds Tds Tds Tds Ads Tds Ads Gds mCes mCes Aes Ges mCe; 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, ISIS 546343 is described by the following chemical structure:



Structure 2. ISIS 546343

In certain embodiments, as provided in Example 2 (see Tables 9 and 10 hereinbelow), ISIS 546343 achieved 97% and 91% human PKK mRNA inhibition in cultured HepaRG™ cells (density of 20,000 cells per well) when transfected using electroporation with 5,000 nM antisense oligonucleotide after a treatment period of 24 hours and measured by quantitative real-time PCR using human primer probe set RTS3454 and adjusted according to total RNA content, as measured by RIBOGREEN®.

In certain embodiments, as provided twice in Example 5 (see Tables 34 and 41 hereinbelow), ISIS 546343 achieved an IC_{50} of 0.4μM in a 4 point dose response curve (0.19 μM, 0.56 μM, 1.67 μM, and 5.0 μM) in cultured HepaRG™ cells (density of 20,000 cells per well) when transfected using electroporation after a treatment period of 16 and measured by quantitative real-time PCR using human primer probe set RTS3454 and adjusted according to total RNA content, as measured by RIBOGREEN®.

In certain embodiments, as provided in Example 7 (hereinbelow), ISIS 546343 achieved 46%, 66%, and 86% human PKK mRNA inhibition and 0%, 38%, and 79% human PKK protein inhibition in transgenic

mice harboring the human PKK gene sequence when injected subcutaneously twice a week for 3 weeks with 2.5 mg/kg/week, 5.0 mg/kg/week, 10 mg/kg/week or 20 mg/kg/week with ISIS 546343.

In certain embodiments, as provided in Example 8 (hereinbelow), ISISI 546343 is effective for inhibiting PKK mRNA and protein expression and is tolerable in primates.

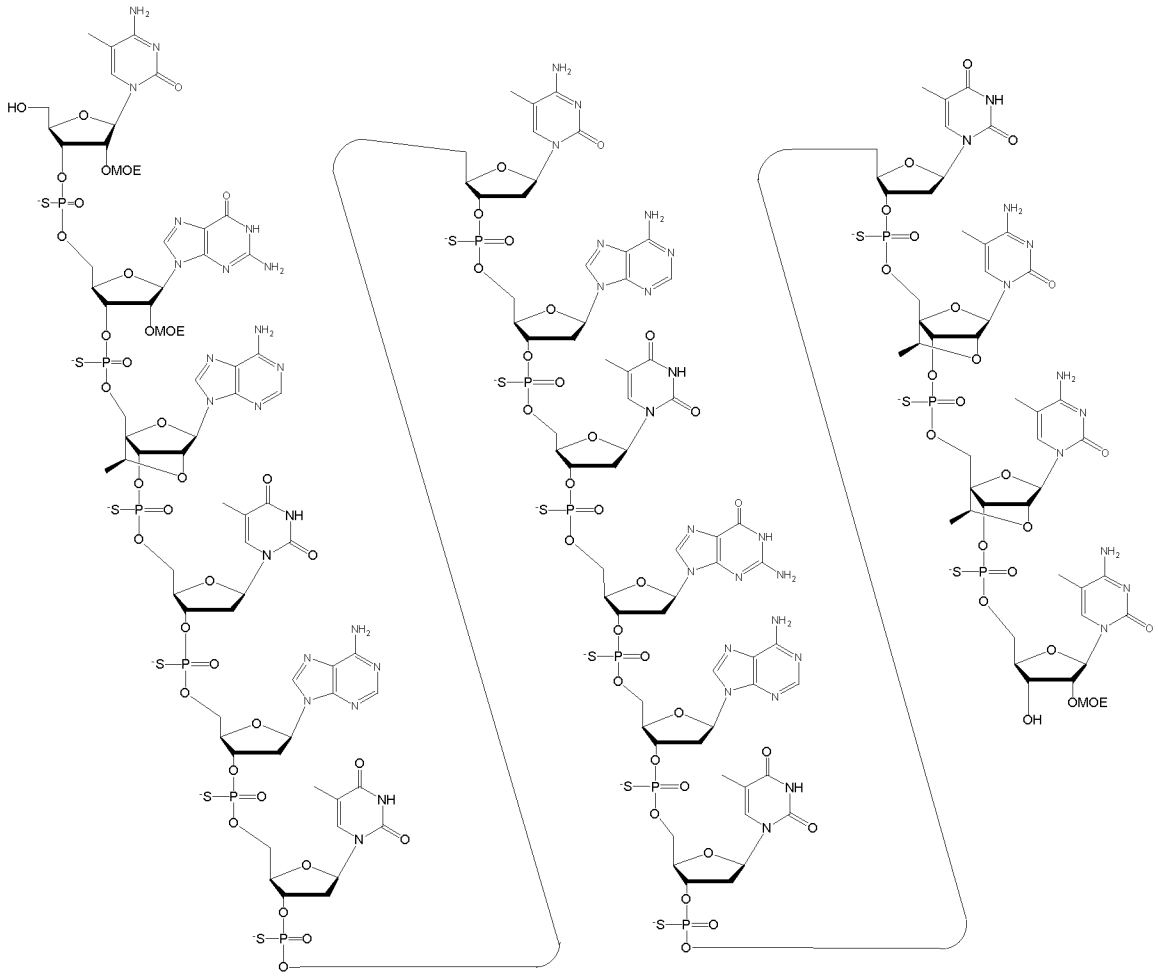
3. ISIS 548048

In certain embodiments, ISIS 548048 is characterized as a modified antisense oligonucleotide having the nucleobase sequence (from 5' to 3') CGATATCATGATTCCC (incorporated herein as SEQ ID NO: 1666), consisting of a combination of sixteen 2'-deoxynucleosides, 2'-O-methoxyethyl modified nucleosides, and cEt modified nucleosides, wherein each of nucleosides 1, 2, and 16 are 2'-O-methoxyethyl modified nucleosides, wherein each of nucleosides 3, 14, and 15 are cEt modified nucleosides, wherein each of nucleosides 4-13 are 2'-deoxynucleosides, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage, and wherein each cytosine is a 5'-methylcytosine.

In certain embodiments, ISIS 548048 is described by the following chemical notation: mCes Ges Aks Tds Ads Tds mCds Ads Tds Gds Ads Tds Tds mCks mCks mCe; wherein,

A = an adenine,
mC = a 5'-methylcytosine;
G = a guanine,
T = a thymine,
e = a 2'-O-methoxyethyl modified nucleoside,
k = a cEt modified nucleoside,
d = a 2'-deoxynucleoside, and
s = a phosphorothioate internucleoside linkage.

In certain embodiments, ISIS 548048 is described by the following chemical structure:



Structure 3. ISIS 548048

In certain embodiments, as provided in Example 3 (hereinbelow), ISIS 548048 achieved 84% mRNA inhibition in cultured HepaRG™ cells (density of 20,000 cells per well) when transfected using electroporation with 1,000 nM antisense oligonucleotide after a treatment period of 24 hours and measured by quantitative real-time PCR using human primer probe set RTS3454 and adjusted according to total RNA content, as measured by RIBOGREEN®.

In certain embodiments, as provided in Example 6 (hereinbelow), ISIS 548048 achieved an IC_{50} of 0.1μM in a 4 point dose response curve (0.11 μM, 0.33 μM, 1.00 μM, and 3.00 μM) in cultured HepaRG™ cells (density of 20,000 cells per well) when transfected using electroporation after a treatment period of 16 and measured by quantitative real-time PCR using human primer probe set RTS3454 and adjusted according to total RNA content, as measured by RIBOGREEN®.

In certain embodiments, as provided in Example 7 (hereinbelow), ISIS 548048 achieved 7%, 77%, 72% and 80% human PKK mRNA inhibition and 23%, 70%, 89%, and 98% human PKK protein inhibition

in transgenic mice harboring the human PKK gene sequence when injected subcutaneously twice a week for 3 weeks with 2.5 mg/kg/week, 5.0 mg/kg/week, 10 mg/kg/week or 20 mg/kg/week with ISIS 548048.

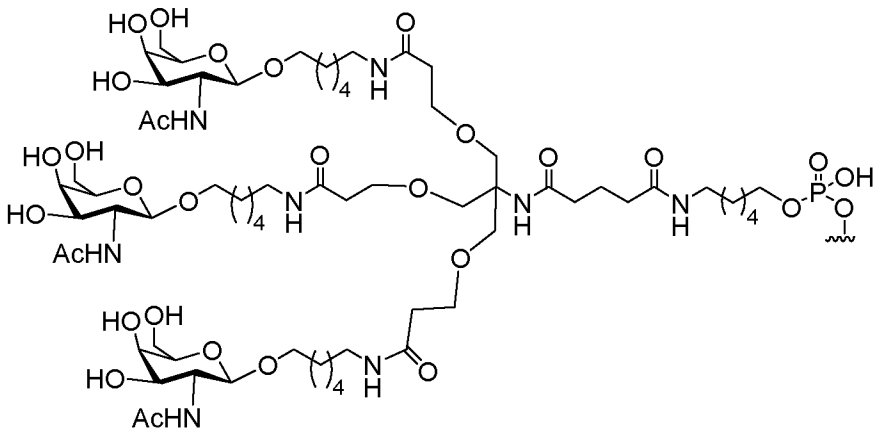
In certain embodiments, as provided in Example 8 (hereinbelow), ISISI 548048 is effective for inhibiting PKK mRNA and protein expression and is tolerable in primates.

4. ISIS 721744

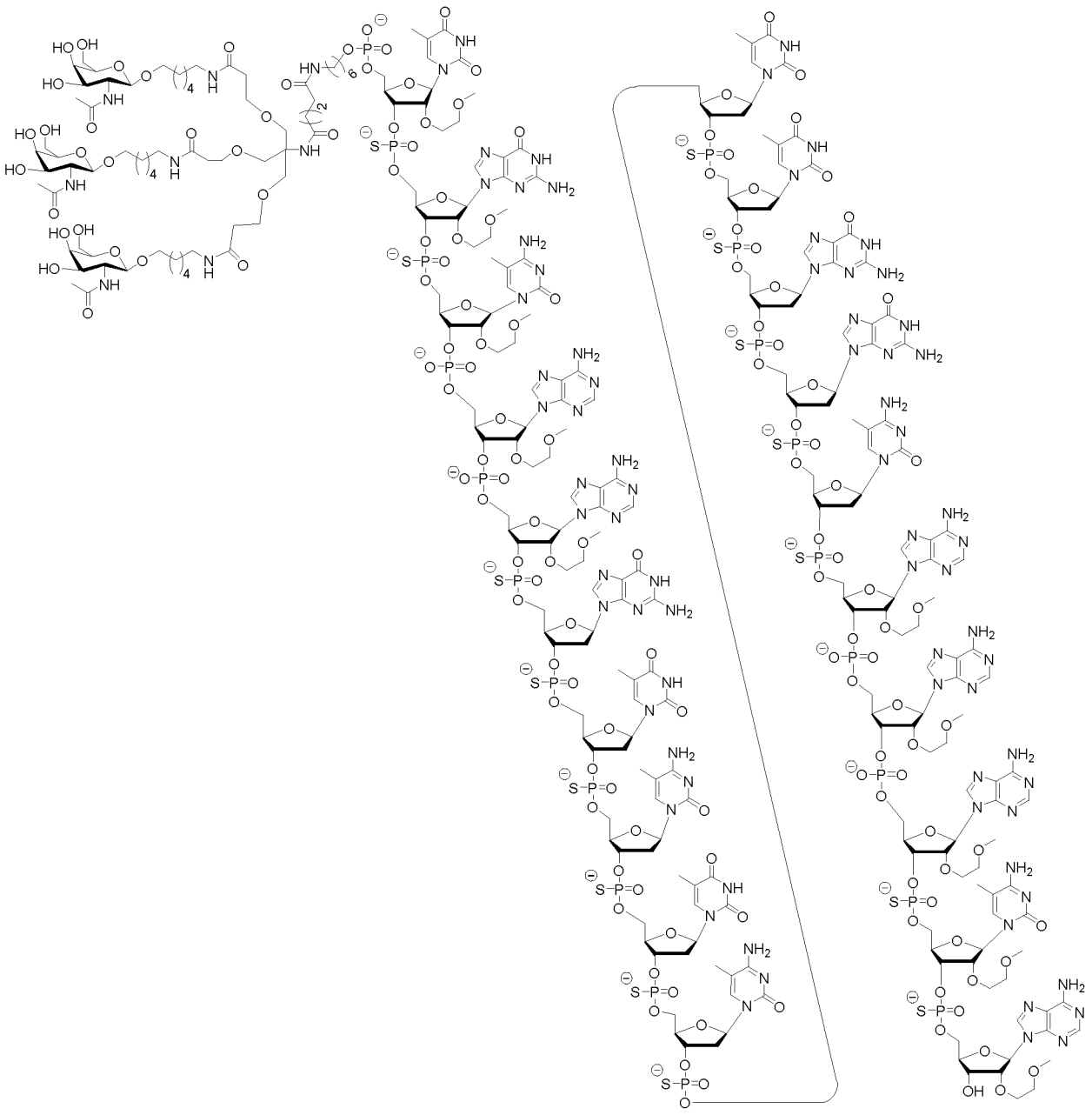
In certain embodiments, ISIS 721744 is characterized as a 5-10-5 MOE gapmer, having a sequence of (from 5' to 3') TGCAAGTCTCTTGGCAAACA (incorporated herein as SEQ ID NO: 570), wherein the internucleoside linkages between nucleosides 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester linkages and the internucleoside linkages between nucleosides 1 to 2, 2 to 3, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate linkages, each cytosine is a 5'-methylcytosine, each of nucleosides 1-5 and 16-20 are 2'-O-methoxyethyl modified nucleosides, and each of nucleosides 6-15 are 2'-deoxynucleosides.

In certain embodiments, ISIS 721744 is described by the following chemical notation: GalNAc3-$7_{a-o'}$Tes Ges mCeo Aeo Aes Gds Tds mCds Tds mCds Tds Tds Gds Gds mCds Aeo Aeo Aes 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,
o= a phosphodiester internucleoside linkage,
s = a phosphorothioate internucleoside linkage, and
GalNAc3-$7_{a-o'}$ =



In certain embodiments, ISIS 721744 is described by the following chemical structure:



Certain Hotspot Regions

1. Nucleobases 27427-27466 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 27427-27466 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 27427-27466 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 27427-27466 of SEQ ID NO: 10 are targeted by antisense

oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense olignonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 27427-27466 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 530993, 530994, 530995, 546251, 546252, 546253, 546254, 546255, 546256, 547410, 547411, 547978, 547979, 547980, and 547981.

In certain embodiments, nucleobases nucleobases 27427-27466 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 94, 95, 96, 566, 567, 568, 569, 570, 571, 572, 573, 1597, 1598, 1599, and 1600.

In certain embodiments, antisense oligonucleotides targeting nucleobases 27427-27466 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

2. Nucleobases 33183-33242 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 33183-33242 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 33183-33242 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 33183-33242 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the

nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 33183-33242 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 531052, 531053, 531054, 531055, 531056, 531057, 531158, 546343, 546345, 547480, 547481, 547482, and 547483.

In certain embodiments, nucleobases nucleobases 33183-33242 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 155, 156, 157, 158, 159, 160, 261, 702, 703, 704, 705, 706, and 707.

In certain embodiments, antisense oligonucleotides targeting nucleobases 33183-33242 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK mRNA and/or protein levels in vitro and/or in vivo.

3. Nucleobases 30570-30610 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 30570-30610 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 30570-30610 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 30570-30610 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 30570-30610 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 531026, 546309, 546310, 546311, 546313, 547453, 547454, 547455, 547456, 547457, 547458, 548046, 548047, 548048, 548049, and 548050.

In certain embodiments, nucleobases nucleobases 30570-30610 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 129, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 1664, 1665, 1666, 1667, and 1668.

In certain embodiments, antisense oligonucleotides targeting nucleobases 30570-30610 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK mRNA and/or protein levels in vitro and/or in vivo.

4. Nucleobases 27427-27520 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 27427-27520 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 27427-27520 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 27427-27520 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense olignonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 27427-27520 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 530993-530999, 546251-546256, 546258-546260, 546263, 546265-546268, 547410-547417, and 547978-547992.

In certain embodiments, nucleobases nucleobases 27427-27520 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 94-100, 566-587, and 1597-1611.

In certain embodiments, antisense oligonucleotides targeting nucleobases 27427-27520 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%,

at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

5. Nucleobases 33085-33247 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 33085-33247 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 33085-33247 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 33085-33247 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 33085-33247 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 531041-531158, 546336, 546339, 546340, 546343, 546345, 547474-547483, 547778, 548077-548082, and 548677-548678.

In certain embodiments, nucleobases nucleobases 33085-33247 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 144-160, 261, 693-707, 1256, 1320-1325, 2214, and 2215.

In certain embodiments, antisense oligonucleotides targeting nucleobases 33085-33247 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at lest 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

6. Nucleobases 30475-30639 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 30475-30639 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 30475-30639 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 30475-30639 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense olignonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 30475-30639 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 531021-531029, 531146, 546297, 546299-546304, 546306-546311, 546313, 546316-546319, 547444-547462, 548031, 548032, and 548034-548056.

In certain embodiments, nucleobases nucleobases 30475-30639 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 124-132, 249, 633-669, and 1650-1674.

In certain embodiments, antisense oligonucleotides targeting nucleobases 30475-30639 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

7. Nucleobases 27362-27524 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 27362-27524

of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 27362-27524 correspond to exon 9 of PKK (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 27362-27524 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 27362-27524 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense olignonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 27361-27524 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 530985-530999, 546244, 546247-546256, 546258-546260, 546263, 546265-546268, 547403-547417, 547723, 547968-547970, and 547972-547992.

In certain embodiments, nucleobases nucleobases 27361-27524 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 86-100, 554-587, 1217, and 1588-1611.

In certain embodiments, antisense oligonucleotides targeting nucleobases 27362-27524 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

8. Nucleobases 33101-33240 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 33101-33240 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 33101-33240 correspond to exon 14 of PKK (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 33101-33240 of SEQ ID NO: 10 are a hotspot region. In certain embodiments,

nucleobases 33101-33240 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense olignonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 33101-33240 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 531041-531158, 546336, 546339, 546340, 546343, 546345, 547474-547483, 548077-548082, and 548678-548678.

In certain embodiments, nucleobases nucleobases 33101-33240 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 144-160, 261, 693-707, 1320-1325, and 2215.

In certain embodiments, antisense oligonucleotides targeting nucleobases 33101-33240 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

9. Nucleobases 30463-30638 of SEQ ID NO: 10

In certain embodiments, antisense oligonucletoides are designed to target nucleobases 30463-30638 of SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 30463-30638 correspond to exon 12 of PKK (GENBANK Accession No. NT_016354.19 truncated from nucleobases 111693001 to 111730000). In certain embodiments, nucleobases 30463-30638 of SEQ ID NO: 10 are a hotspot region. In certain embodiments, nucleobases 30463-30638 of SEQ ID NO: 10 are targeted by antisense oligonucleotides. In certain embodiments, the antisense oligonucleotides are 15, 16, 17, 18, 19, or 20 nucleobases in length. In certain embodiments, the antisense oligonucleotides are gapmers. In certain embodiments, the gapmers are 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or

3-10-3 MOE gapmers. In certain embodiments, the gapmers are 5-10-5 MOE and cEt gapmers, 4-9-4 MOE and cEt gapmers, 4-10-4 MOE and cEt gapmers, 4-10-3 MOE and cEt gapmers, 3-10-4 MOE and cEt gapmers, or 3-10-3 MOE and cEt gapmers. In certain embodiments, the nucleosides of the antisense oligonucleotides are linked by phosphorothioate internucleoside linkages.

In certain embodiments, nucleobases 30463-30638 of SEQ ID NO: 10 are targeted by the following ISIS numbers: 531021-531029, 531146, 546297, 546299-546304, 546306-546311, 546313, 546316-546319, 547444-547462, 548031, 548032, and 548034-548056.

In certain embodiments, nucleobases nucleobases 30463-30638 of SEQ ID NO: 10 are targeted by the following SEQ ID NOs: 124-132, 249, 633-669, and 1650-1674.

In certain embodiments, antisense oligonucleotides targeting nucleobases 30463-30638 of SEQ ID NO: 10 achieve at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, 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%, or at least 99% reduction of PKK and/or protein levels in vitro and/or in vivo.

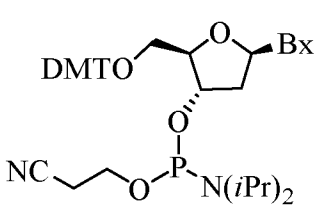
EXAMPLES

Non-limiting disclosure and incorporation by reference

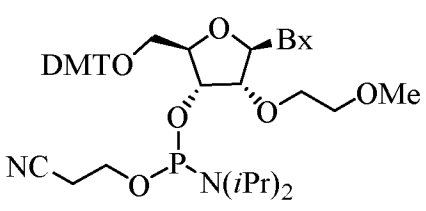
While certain compounds, compositions and methods described herein have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the compounds described herein and are not intended to limit the same. Each of the references recited in the present application is incorporated herein by reference in its entirety.

The following examples illustrate certain embodiments of the present disclosure and are not limiting. Moreover, where specific embodiments are provided, the inventors have contemplated generic application of those specific embodiments. For example, disclosure of an oligonucleotide having a particular motif provides reasonable support for additional oligonucleotides having the same or similar motif. And, for example, where a particular high-affinity modification appears at a particular position, other high-affinity modifications at the same position are considered suitable, unless otherwise indicated.

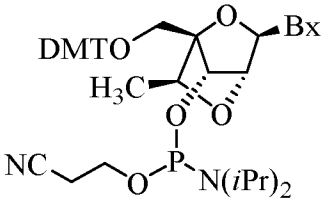
Example 1: General Method for the Preparation of Phosphoramidites, Compounds 1, 1a and 2



1



1a

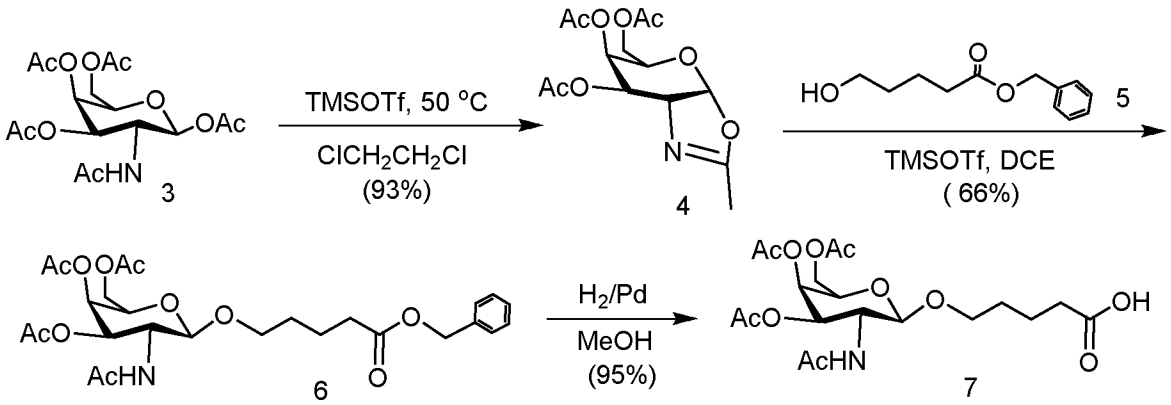


2

Bx is a heterocyclic base;

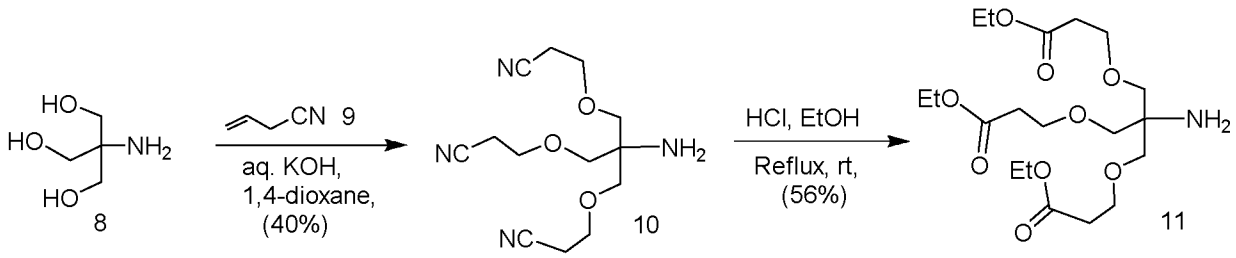
Compounds 1, 1a and 2 were prepared as per the procedures well known in the art as described in the specification herein (see Seth et al., Bioorg. Med. Chem., 2011, 21(4), 1122-1125, J. Org. Chem., 2010, 75(5), 1569-1581, Nucleic Acids Symposium Series, 2008, 52(1), 553-554); and also see published PCT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

Example 2: Preparation of Compound 7



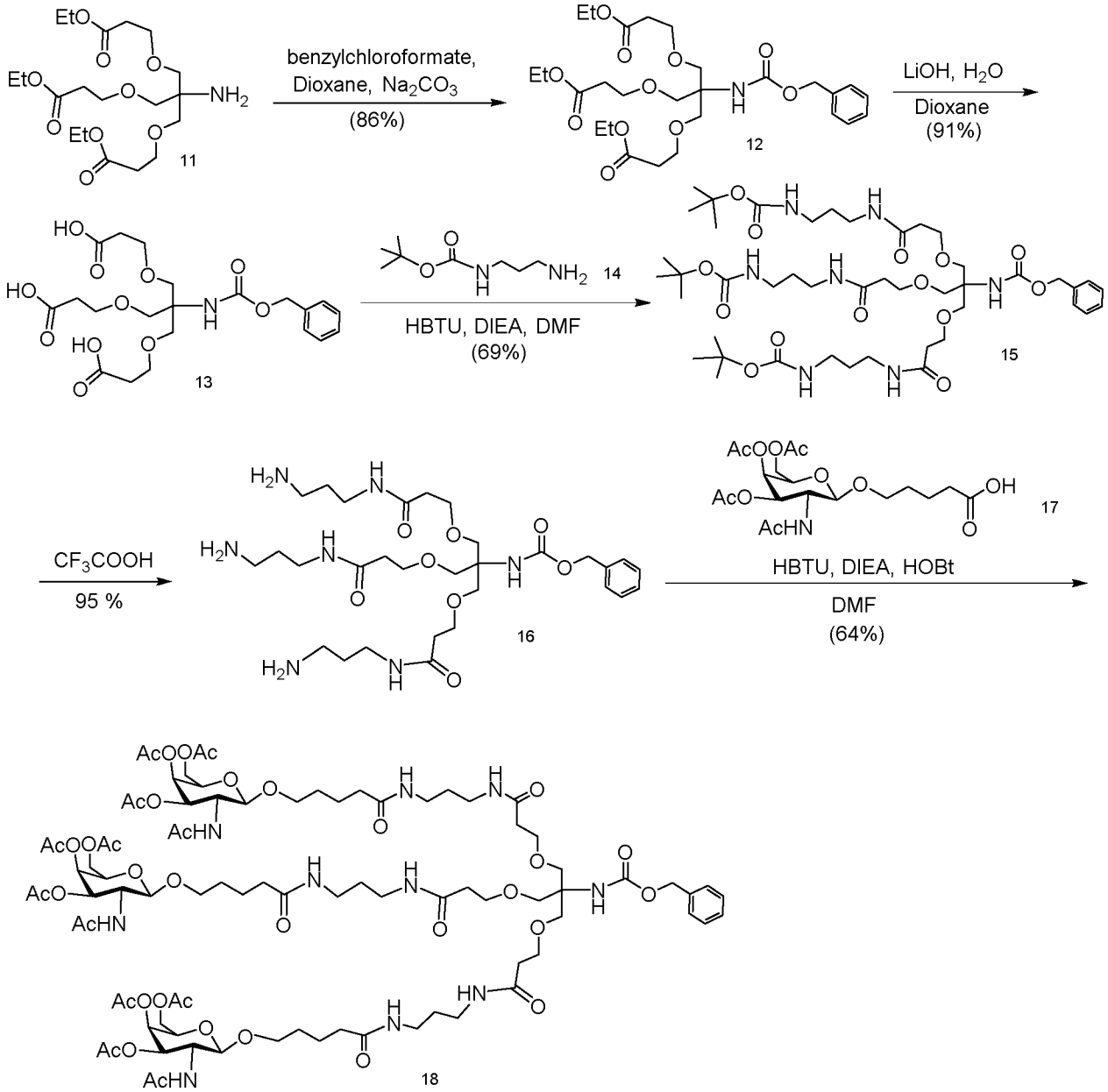
Compounds 3 (2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-Dgalactopyranose or galactosamine pentaacetate) is commercially available. Compound 5 was prepared according to published procedures (Weber *et al., J. Med. Chem.*, 1991, *34*, 2692).

Example 3: Preparation of Compound 11



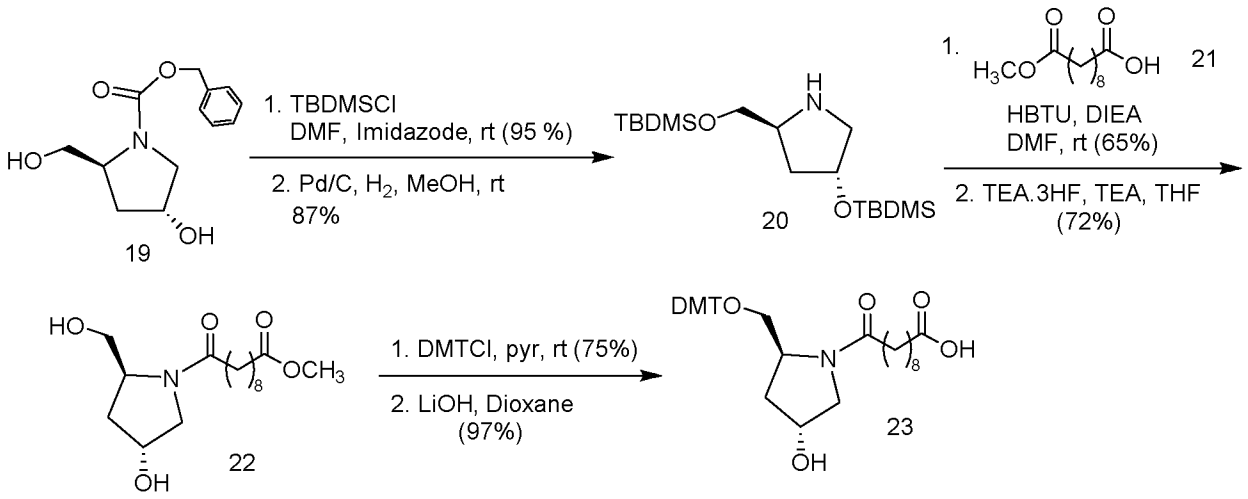
Compounds 8 and 9 are commercially available.

Example 4: Preparation of Compound 18



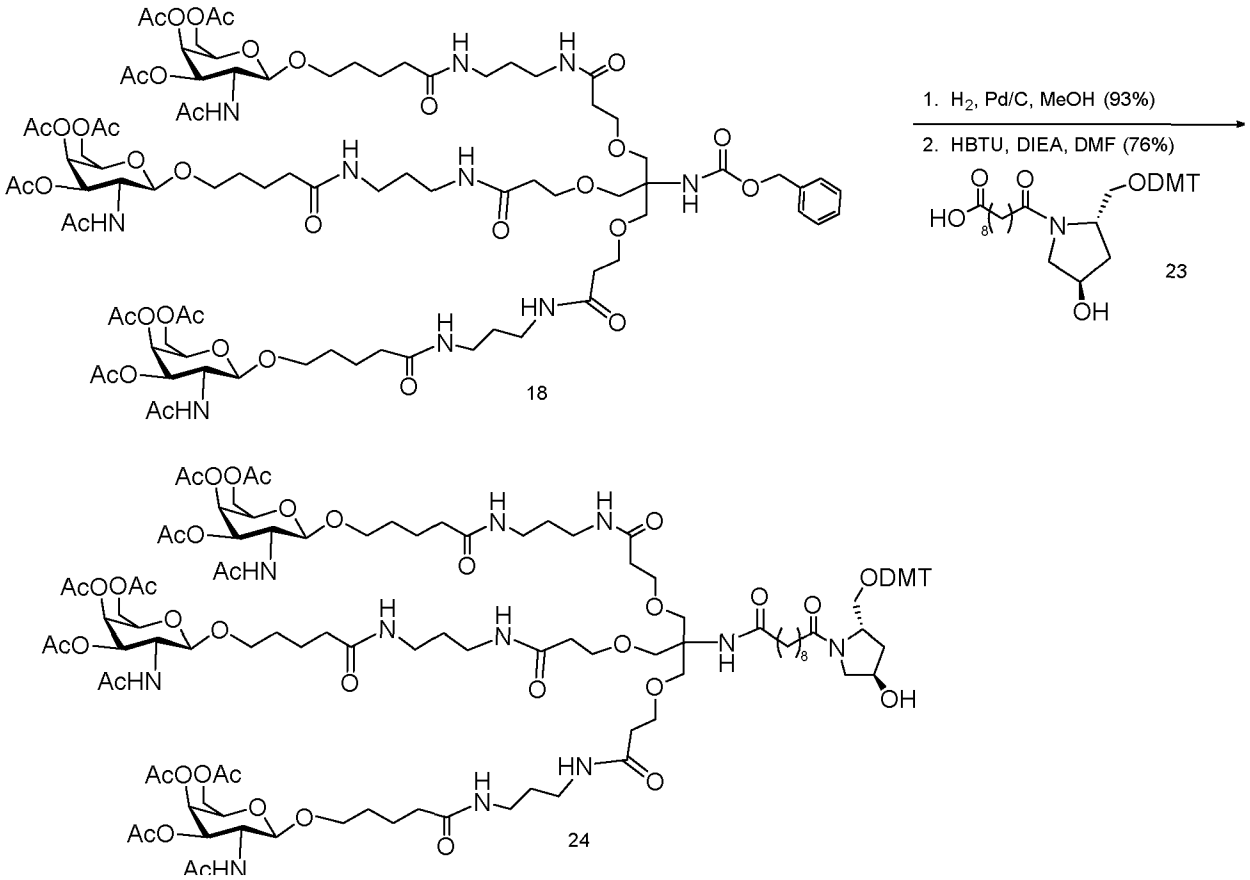
Compound 11 was prepared as per the procedures illustrated in Example 3. Compound 14 is commercially available. Compound 17 was prepared using similar procedures reported by Rensen *et al., J. Med. Chem.*, 2004, *47,* 5798-5808.

Example 5: Preparation of Compound 23



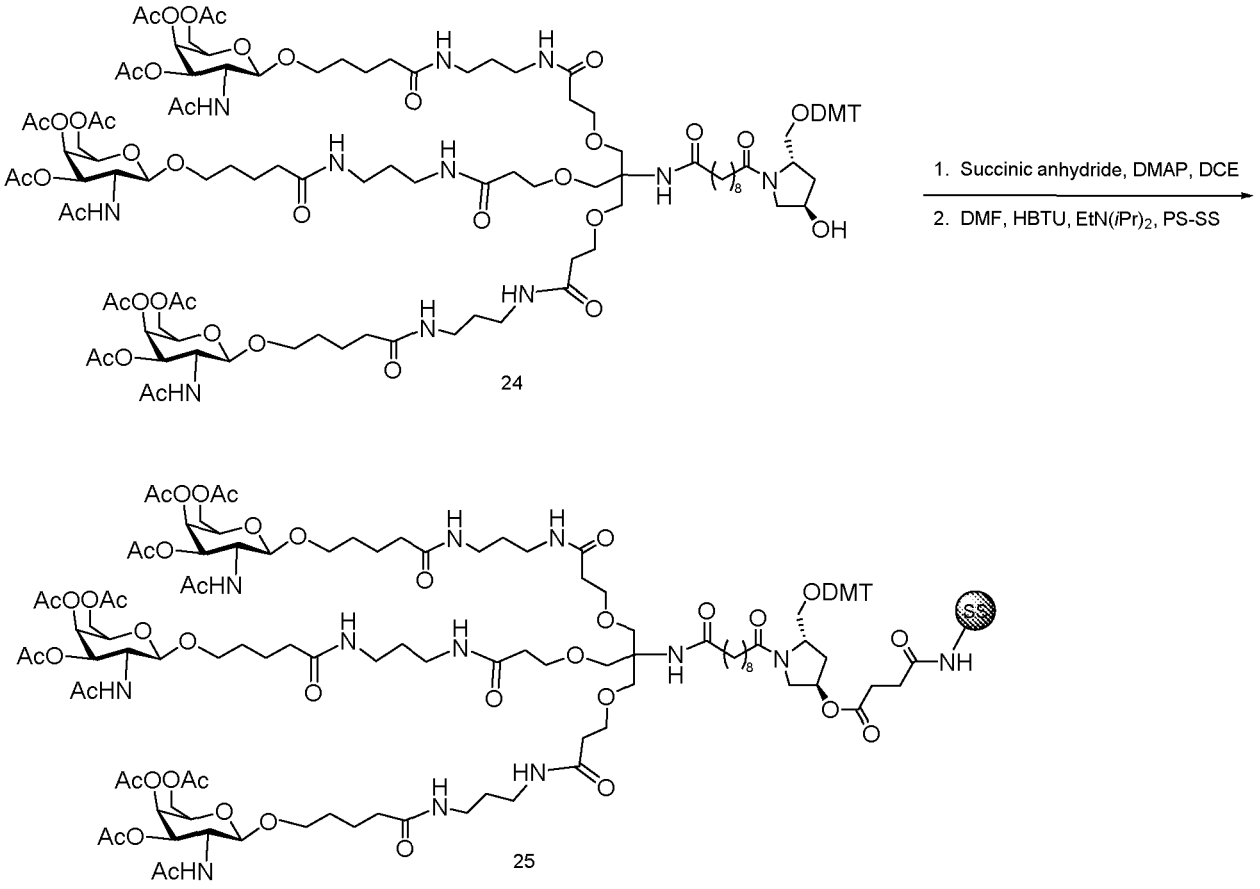
Compounds 19 and 21 are commercially available.

Example 6: Preparation of Compound 24



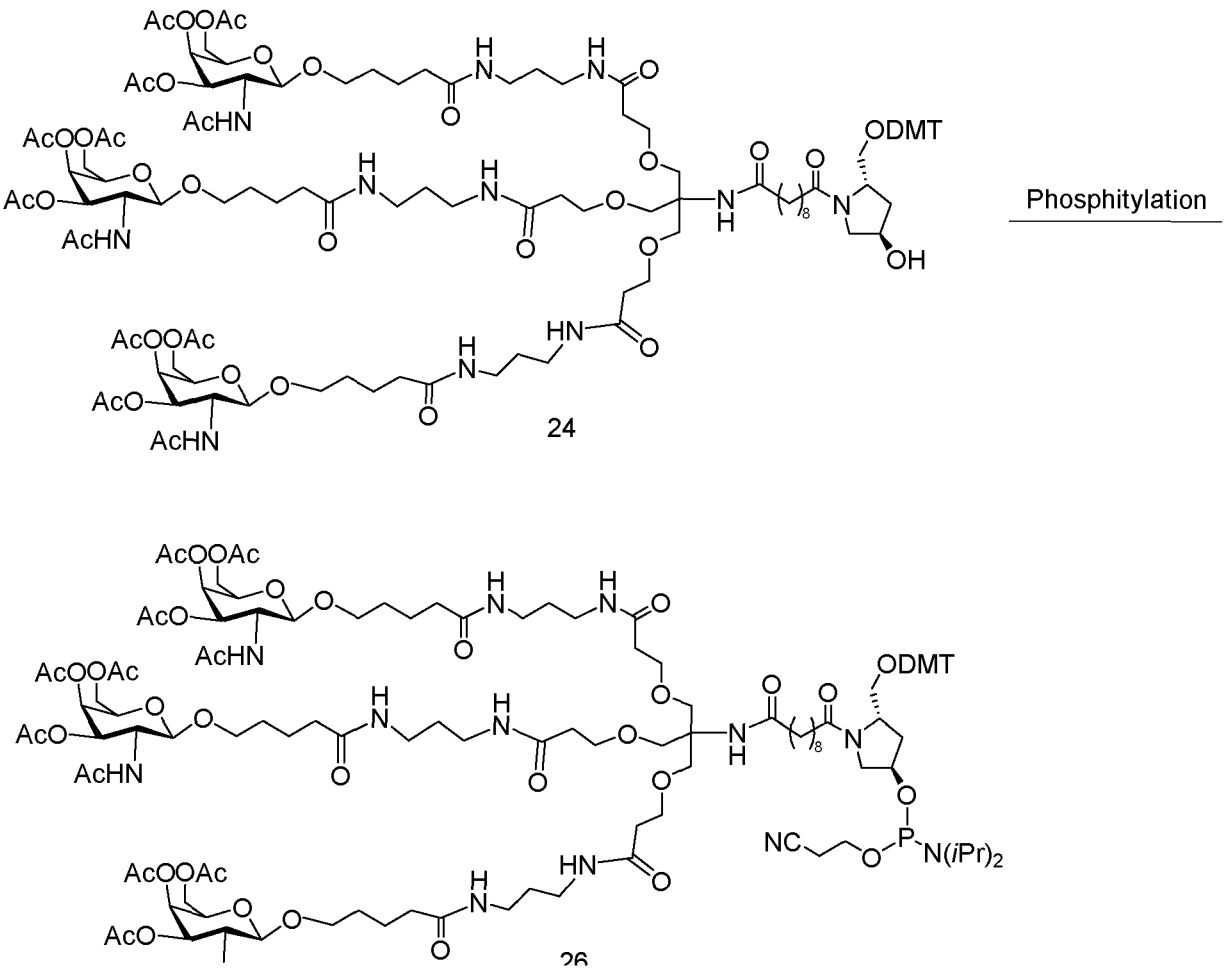
Compounds 18 and 23 were prepared as per the procedures illustrated in Examples 4 and 5.

Example 7: Preparation of Compound 25



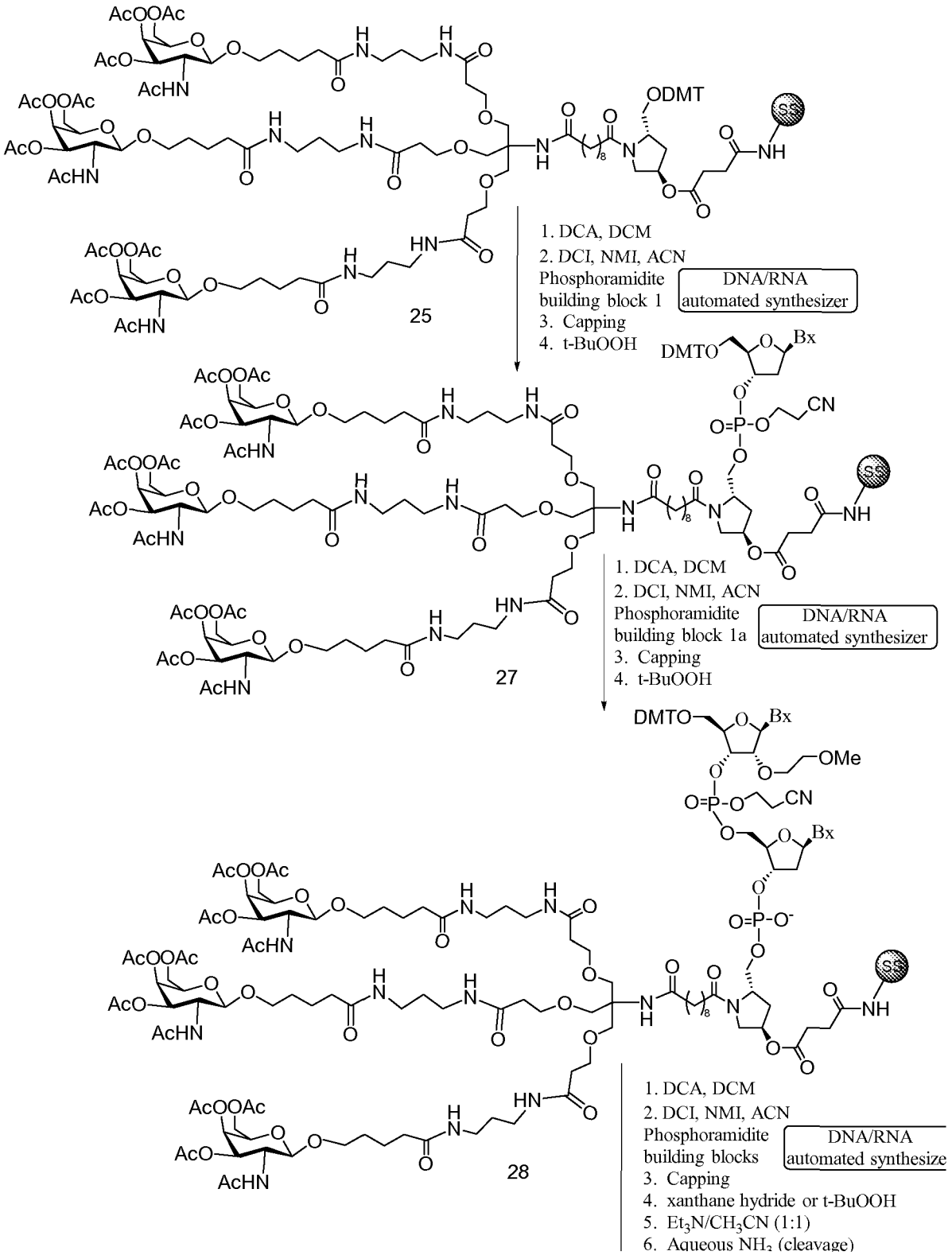
Compound 24 was prepared as per the procedures illustrated in Example 6.

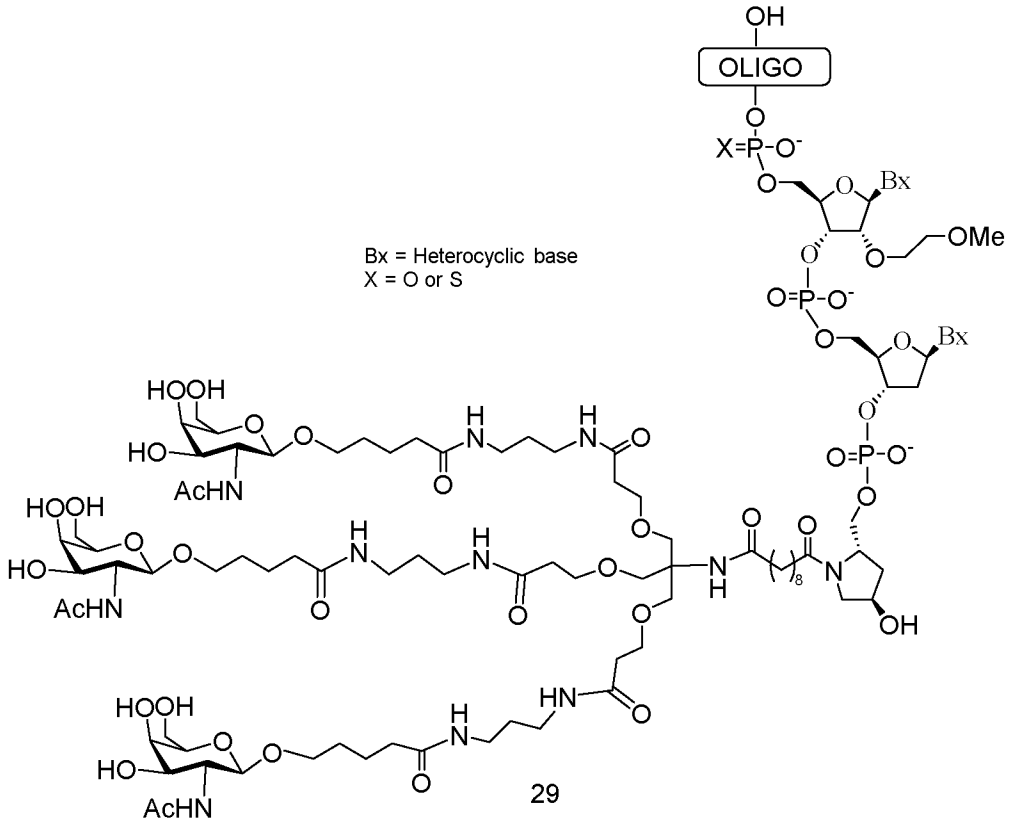
Example 8: Preparation of Compound 26



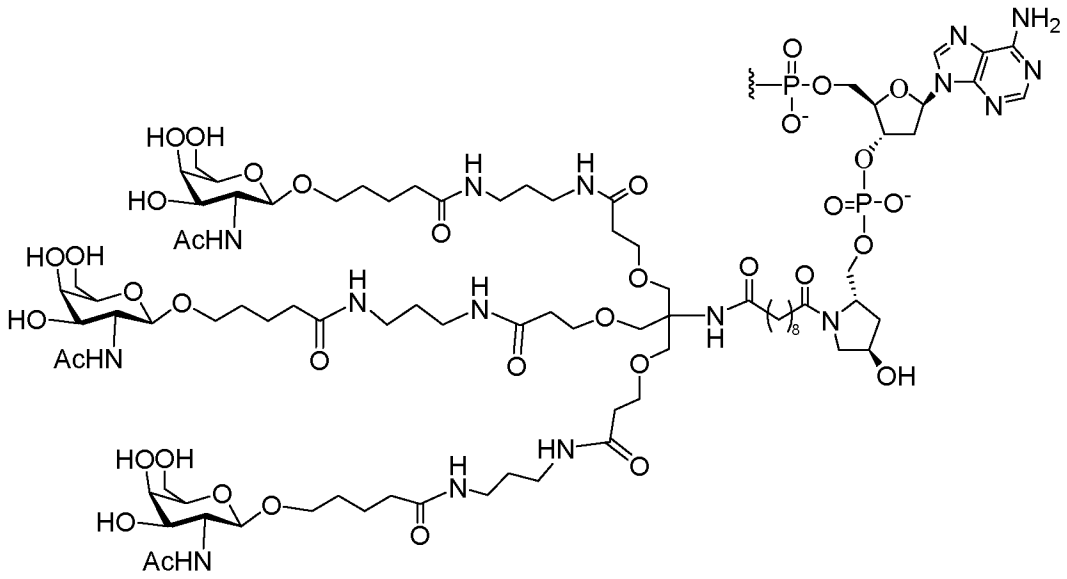
Compound 24 is prepared as per the procedures illustrated in Example 6.

Example 9: General preparation of conjugated ASOs comprising $GalNAc_3$-1 at the 3' terminus, Compound 29

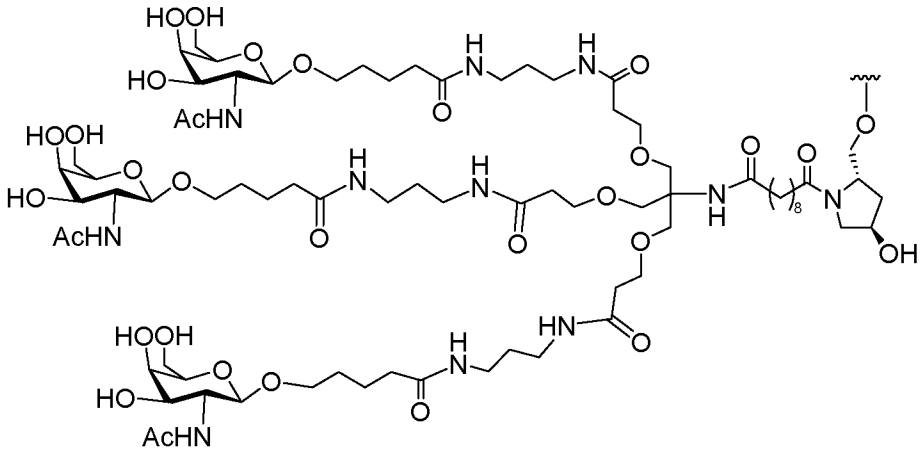




Wherein the protected **GalNAc$_3$-1** has the structure:

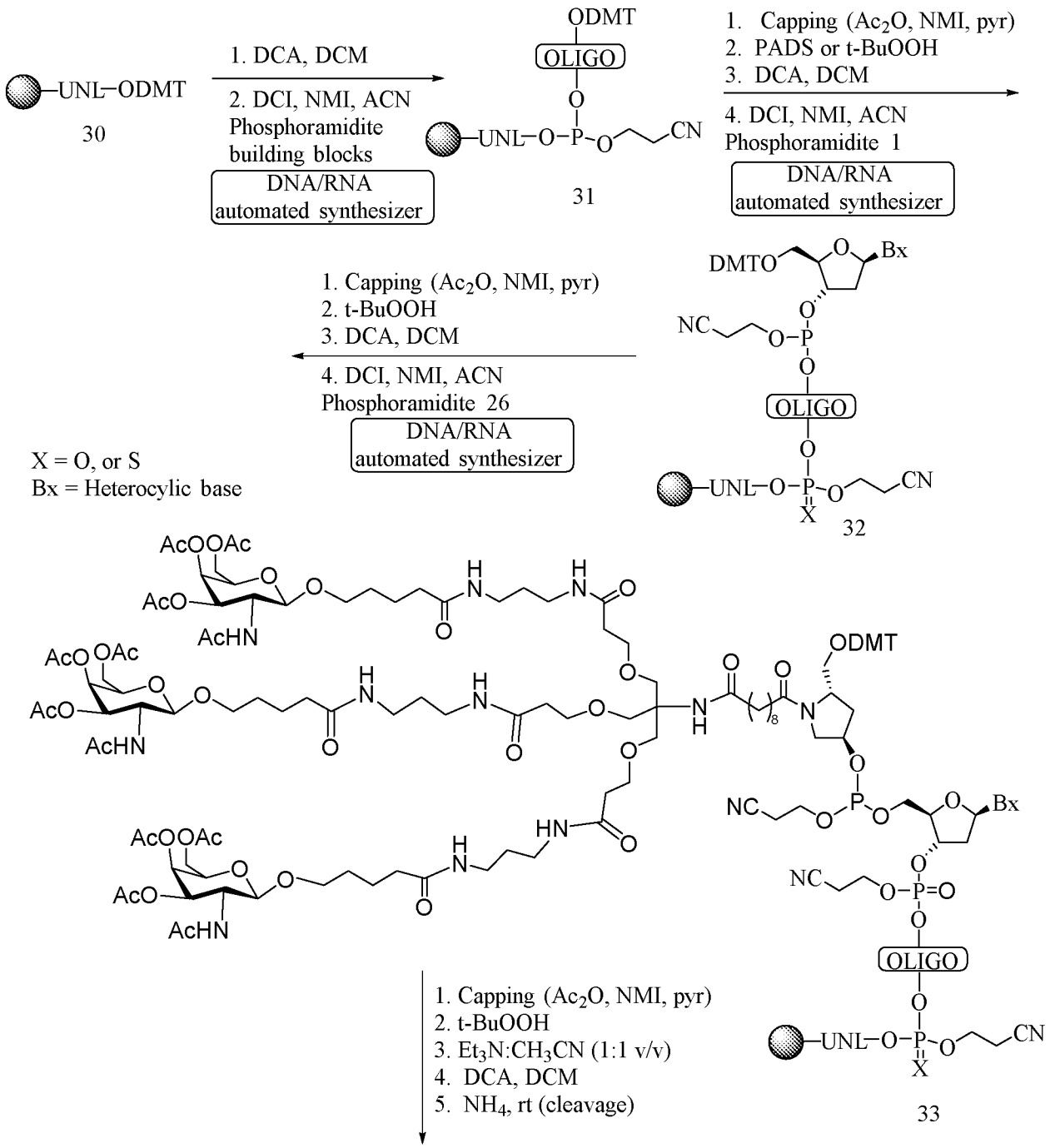


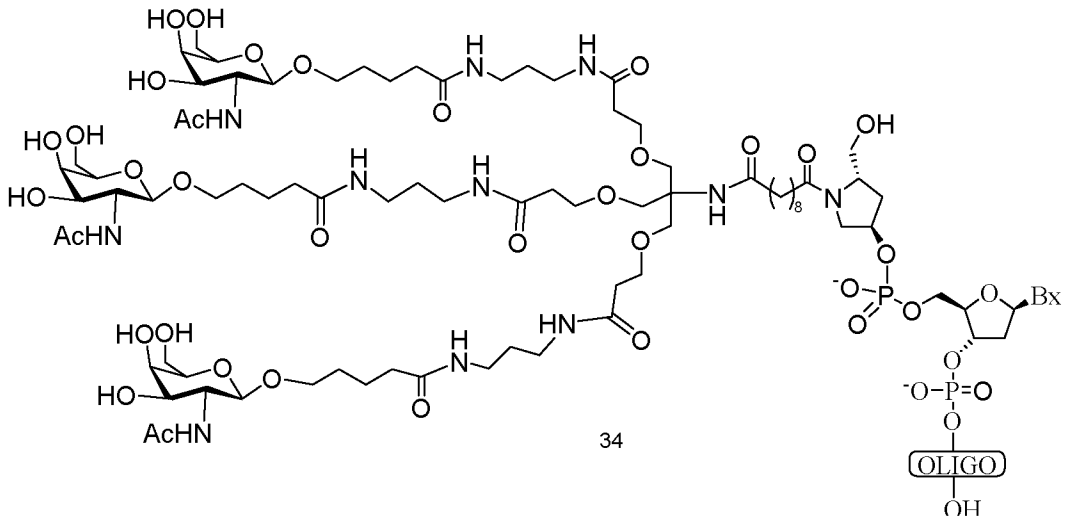
The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-1 (GalNAc$_3$-1$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-1$_a$ has the formula:



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

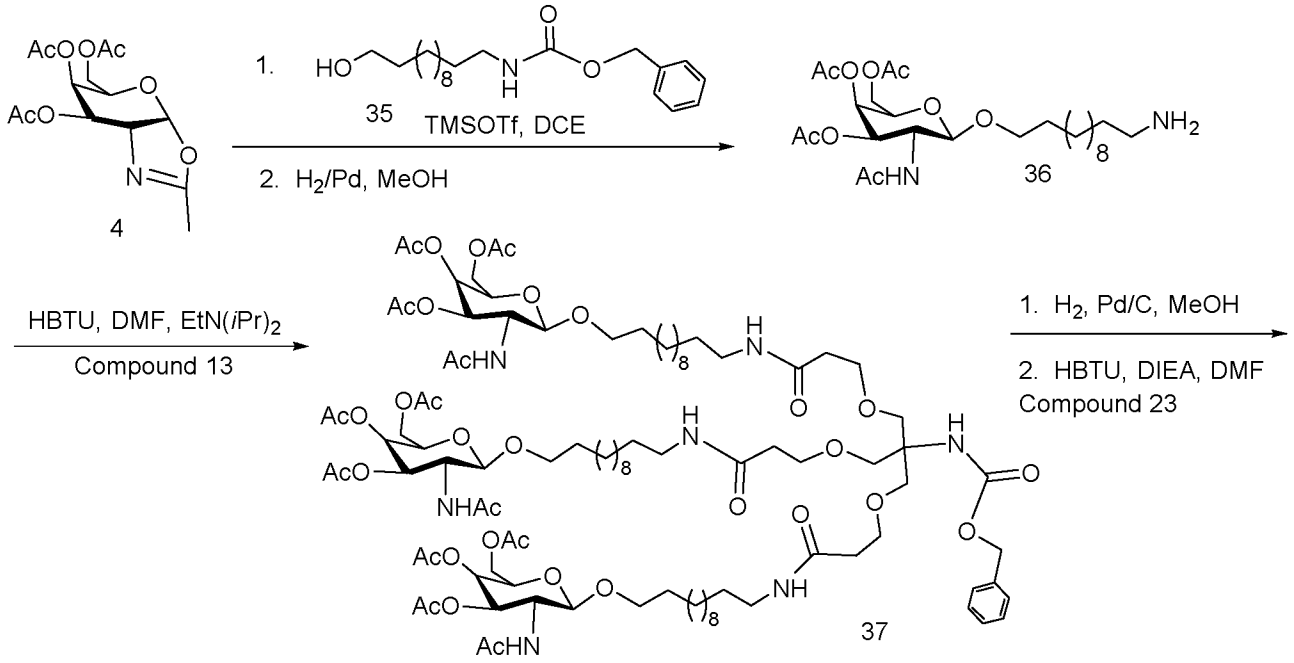


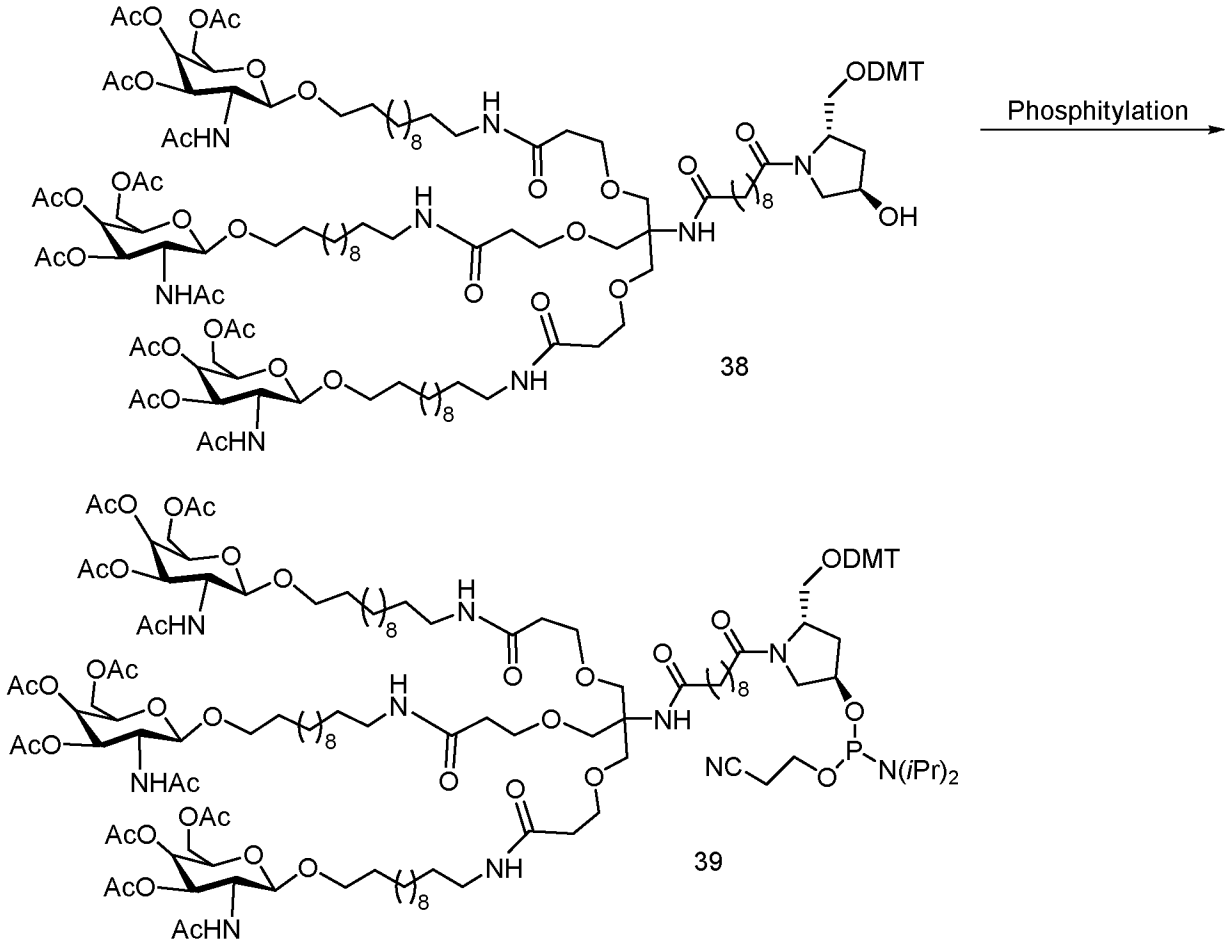


34

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.

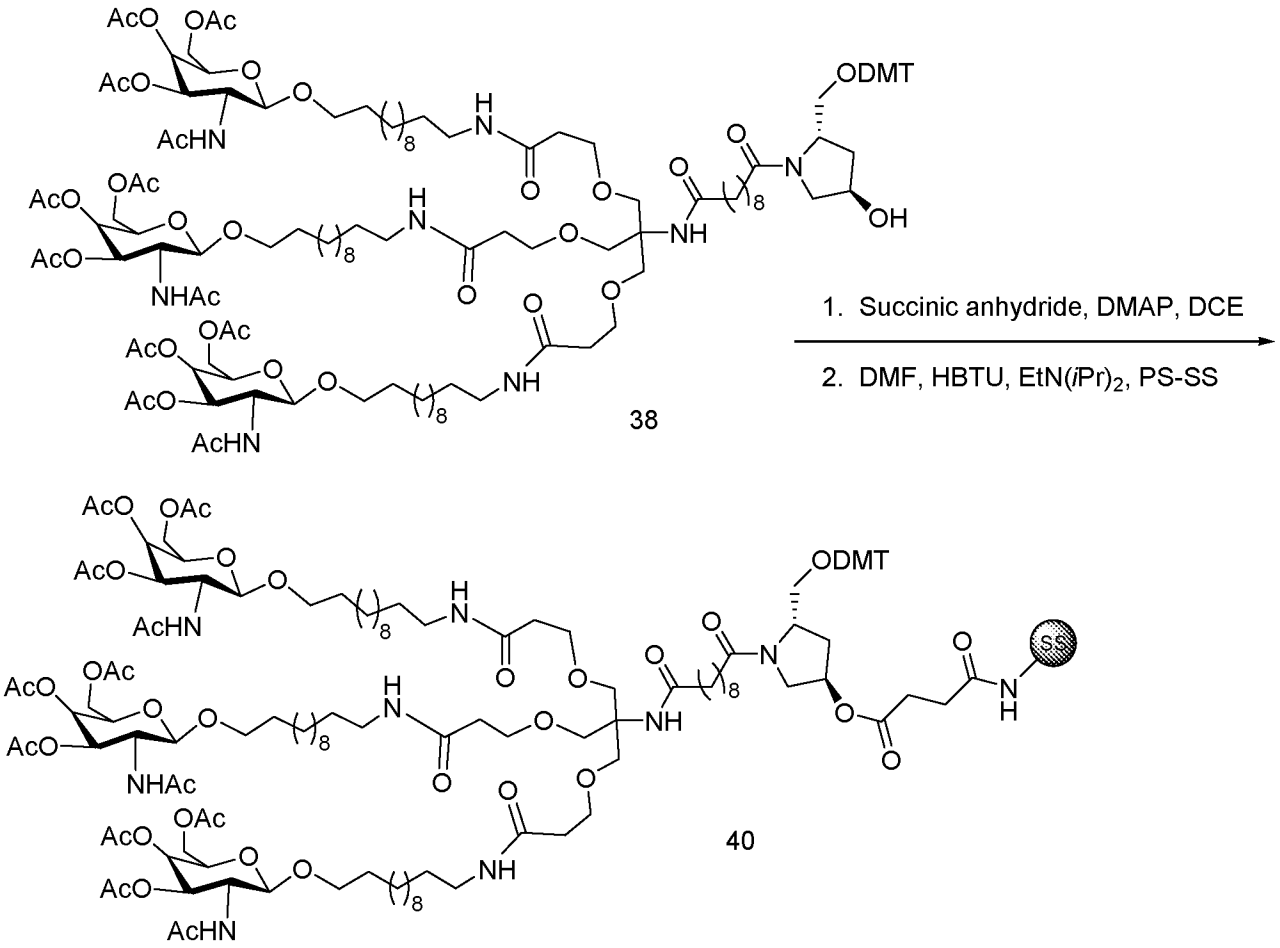
Example 11: Preparation of Compound 39





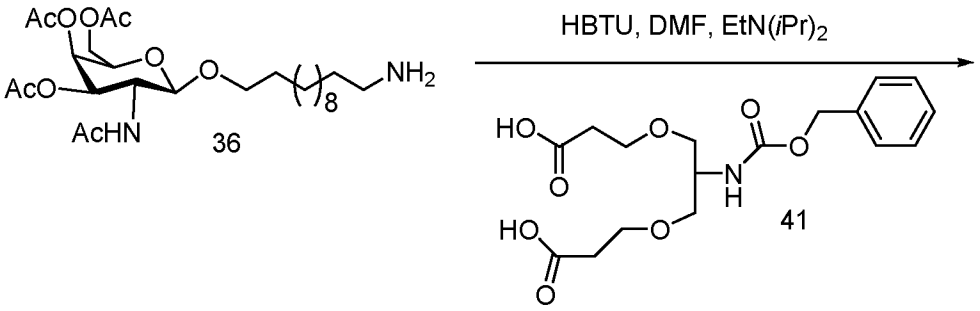
Compounds 4, 13 and 23 were prepared as per the procedures illustrated in Examples 2, 4, and 5. Compound 35 is prepared using similar procedures published in Rouchaud *et al., Eur. J. Org. Chem.,* 2011, *12*, 2346-2353.

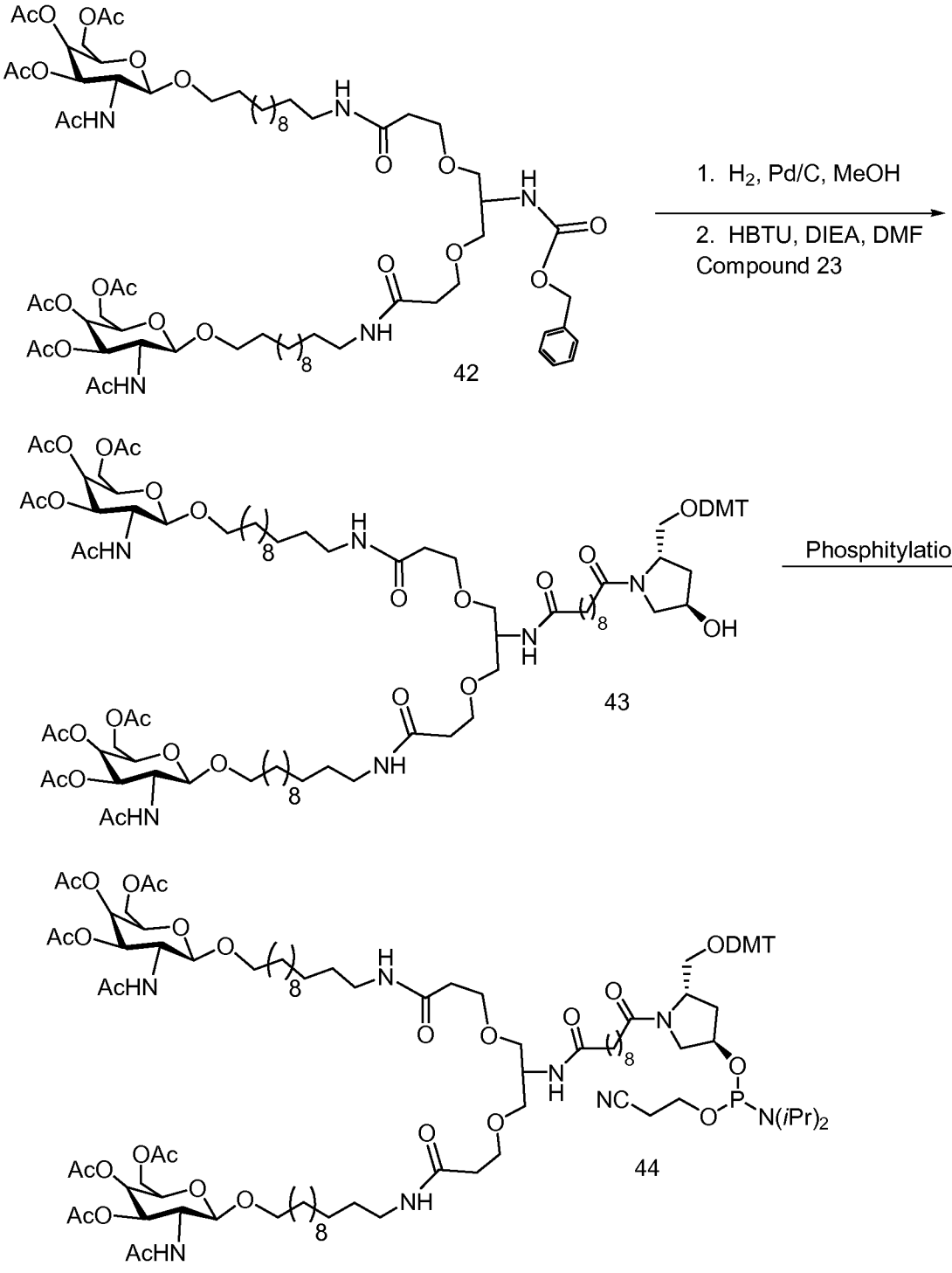
Example 12: Preparation of Compound 40



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

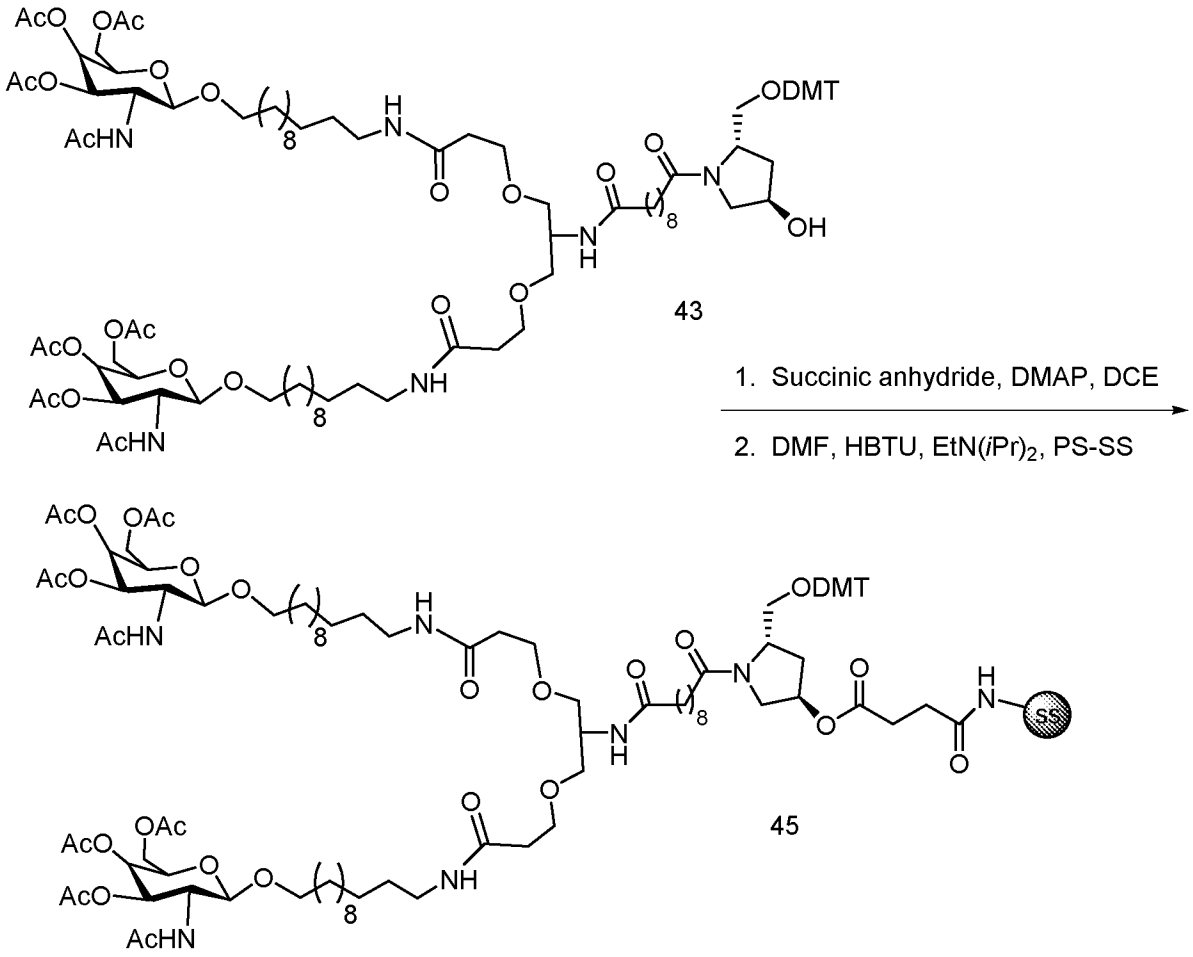
Example 13: Preparation of Compound 44





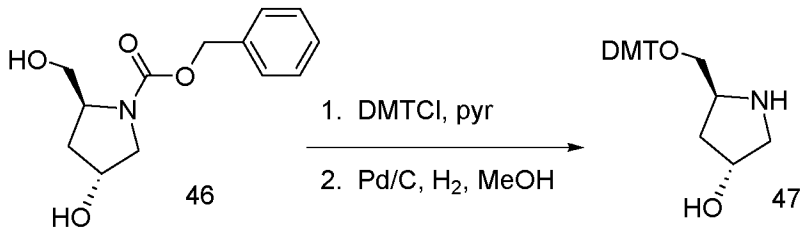
Compounds 23 and 36 are prepared as per the procedures illustrated in Examples 5 and 11. Compound 41 is prepared using similar procedures published in WO 2009082607.

Example 14: Preparation of Compound 45



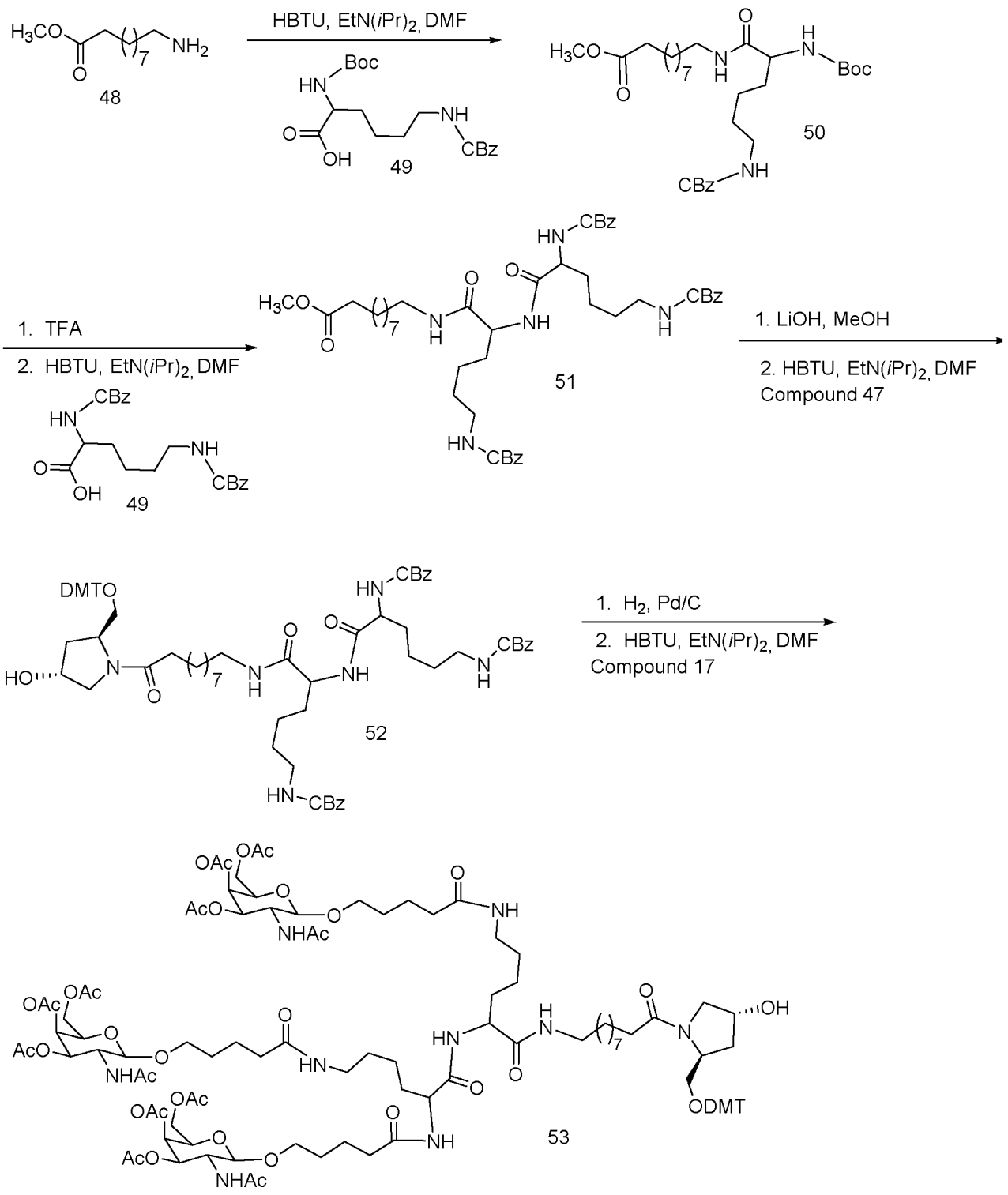
Compound 43 is prepared as per the procedures illustrated in Example 13.

Example 15: Preparation of Compound 47



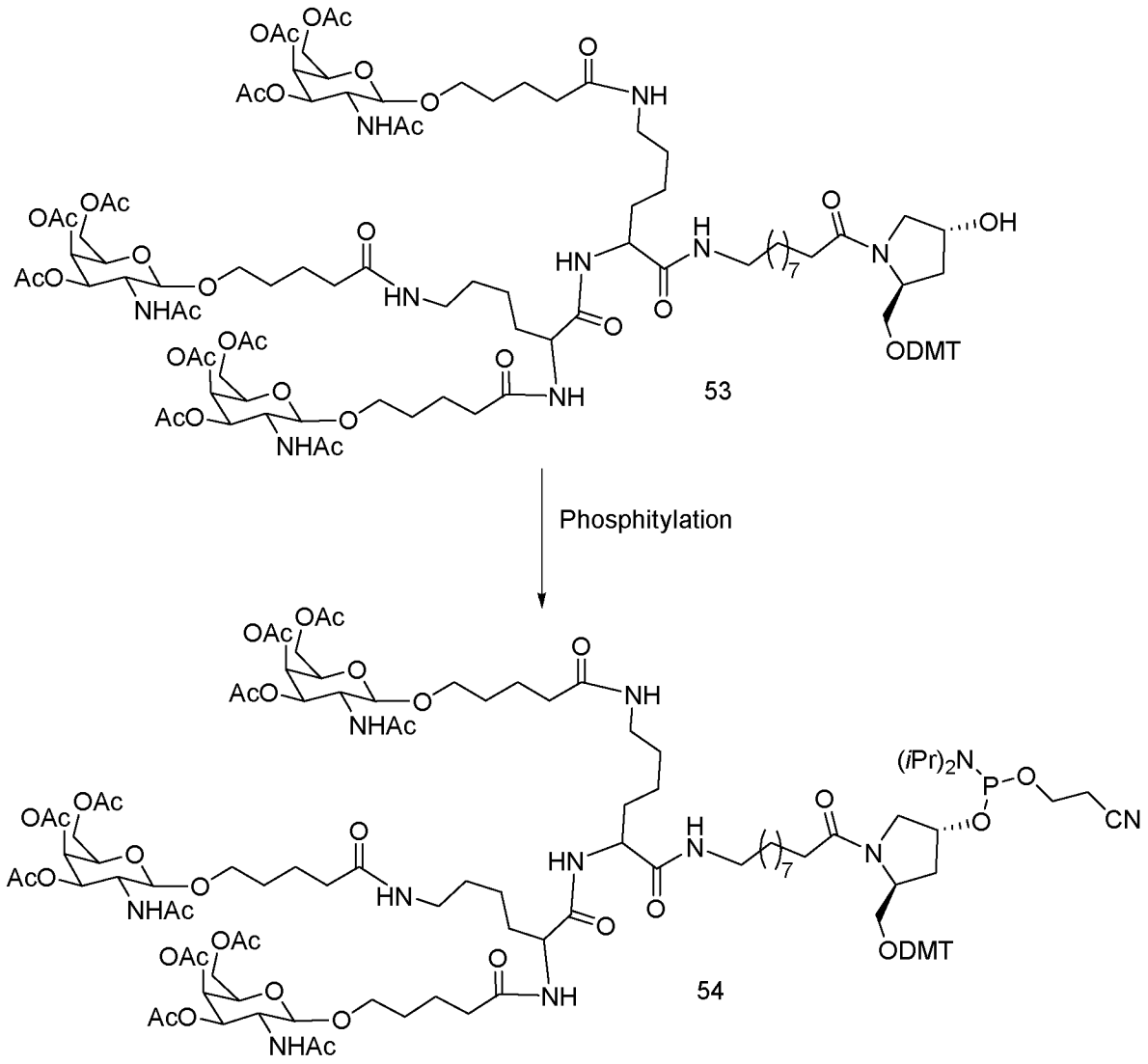
Compound 46 is commercially available.

Example 16: Preparation of Compound 53



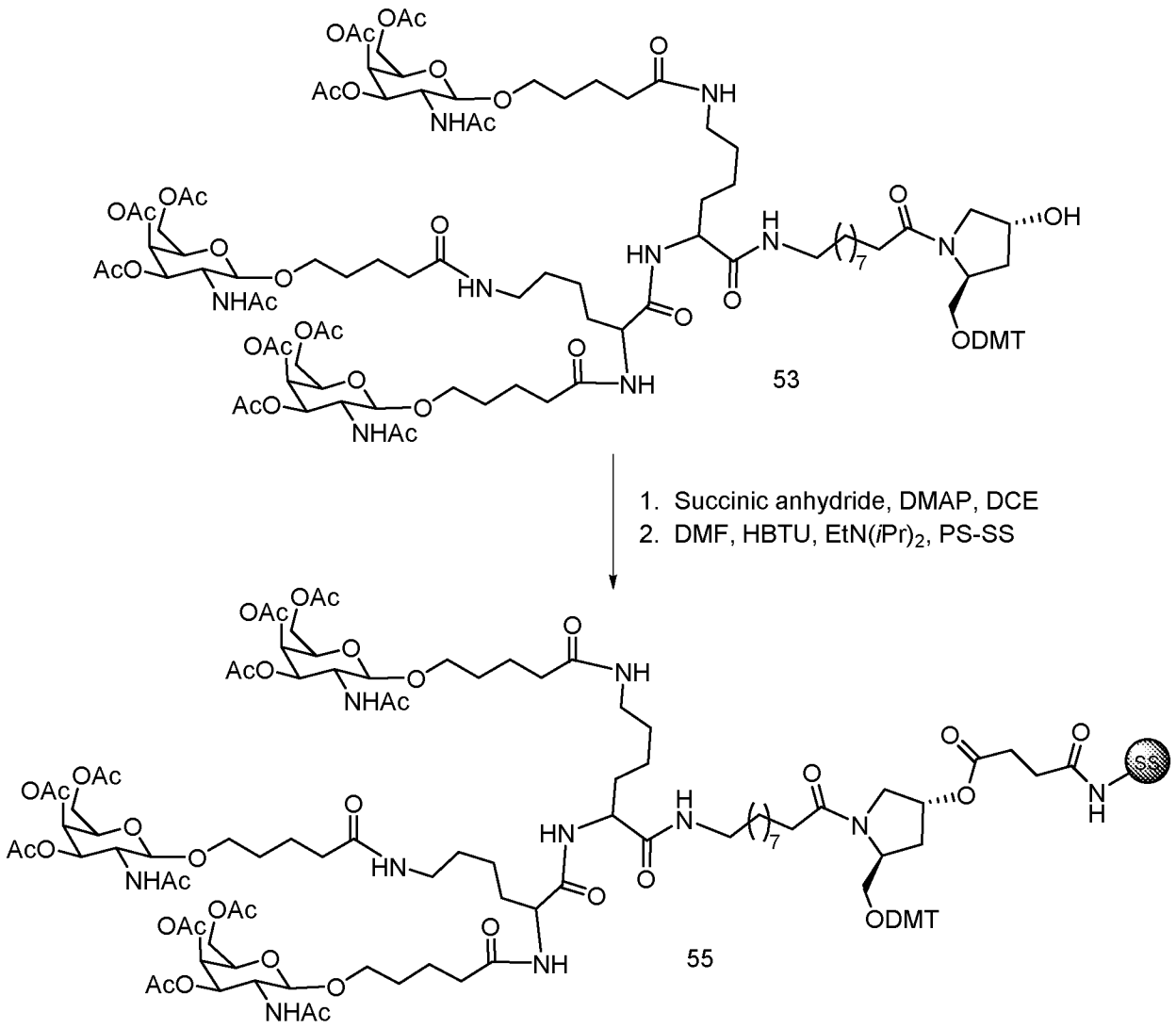
Compounds 48 and 49 are commercially available. Compounds 17 and 47 are prepared as per the procedures illustrated in Examples 4 and 15.

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	2248
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	2249

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	2249
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	2250
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	2251

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	2248
	0.75	42				
	2.25	32				
	6.75	19				
ISIS 647535	0.08	50	0.074	**$GalNAc_3$-1**	PS/20	2249
	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	2248
	0.75	51				
	2.25	23				
	6.75	13				
ISIS 647535	0.08	72	0.19	**$GalNAc_3$-1**	PS/20	2249
	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	2248
	0.75	46				
	2.25	21				
	6.75	12				
ISIS 647535	0.08	65	0.13	**$GalNAc_3$-1**	PS/20	2249
	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	2248
	0.75	164			
	2.25	110			
	6.75	82			
ISIS 647535	0.08	230	**GalNAc$_3$-1**	PS/20	2249
	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	2248
	0.75	27	12			
	2.25	50	4			
	6.75	45	2			
ISIS 647535	0.08	21	21	**GalNAc$_3$-1**	PS/20	2249
	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	2248
	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	2249
	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 cleabable 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.

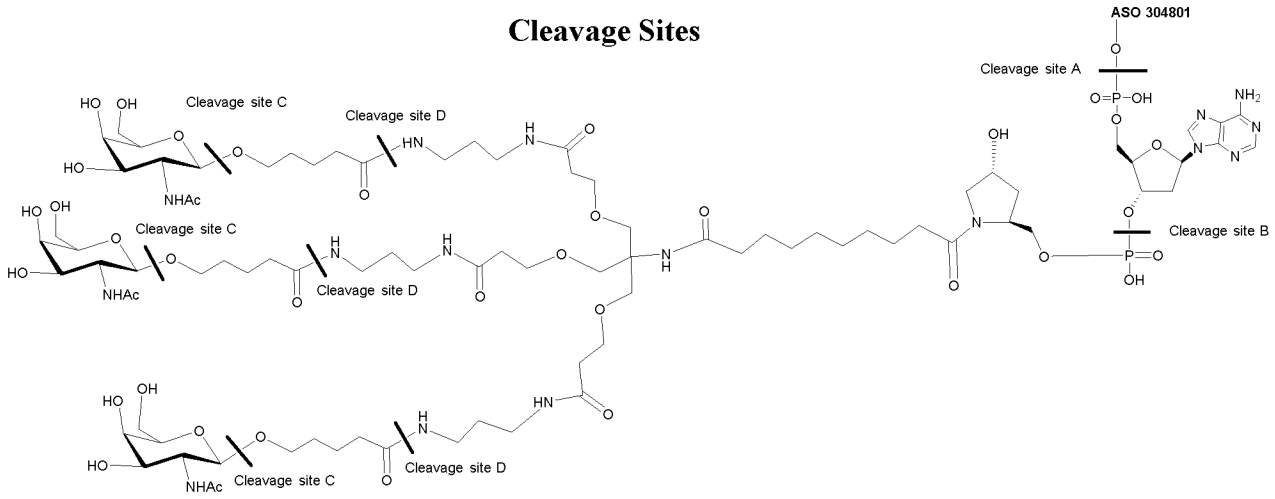
Table 23a

Observed full length metabolites of ISIS 647535

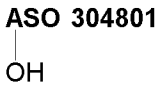
Metabolite	ASO	Cleavage site	Relative %
1	ISIS 304801	A	36.1
2	ISIS 304801 + dA	B	10.5
3	ISIS 647535 minus [3 GalNAc]	C	16.1
4	ISIS 647535 minus [3 GalNAc + 1 5-hydroxy-pentanoic acid tether]	D	17.6
5	ISIS 647535 minus [2 GalNAc + 2 5-hydroxy-pentanoic acid tether]	D	9.9
6	ISIS 647535 minus [3 GalNAc + 3 5-hydroxy-pentanoic acid tether]	D	9.8

5

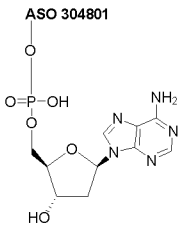
Cleavage Sites

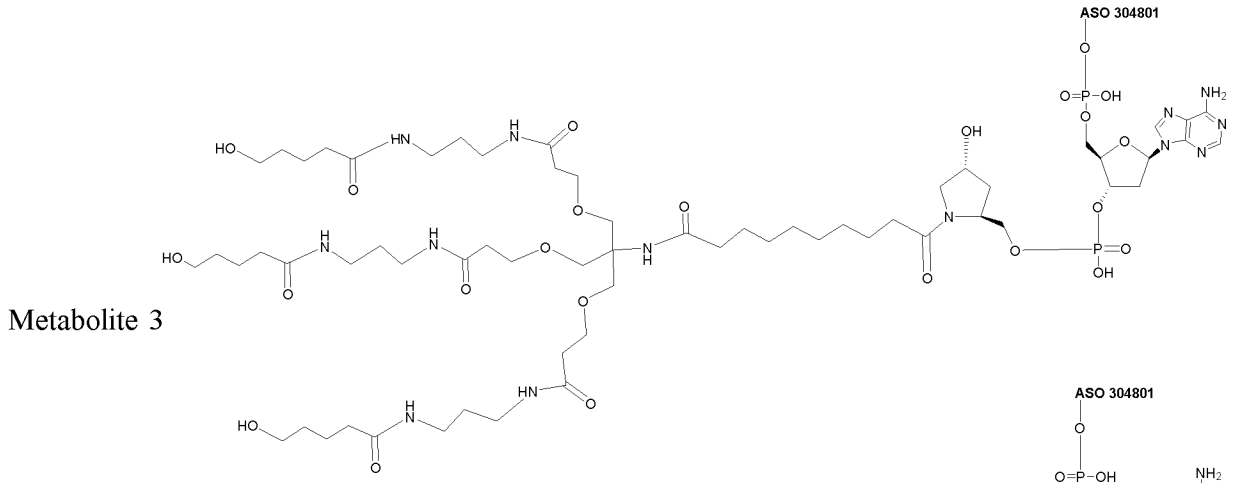


Metabolite 1

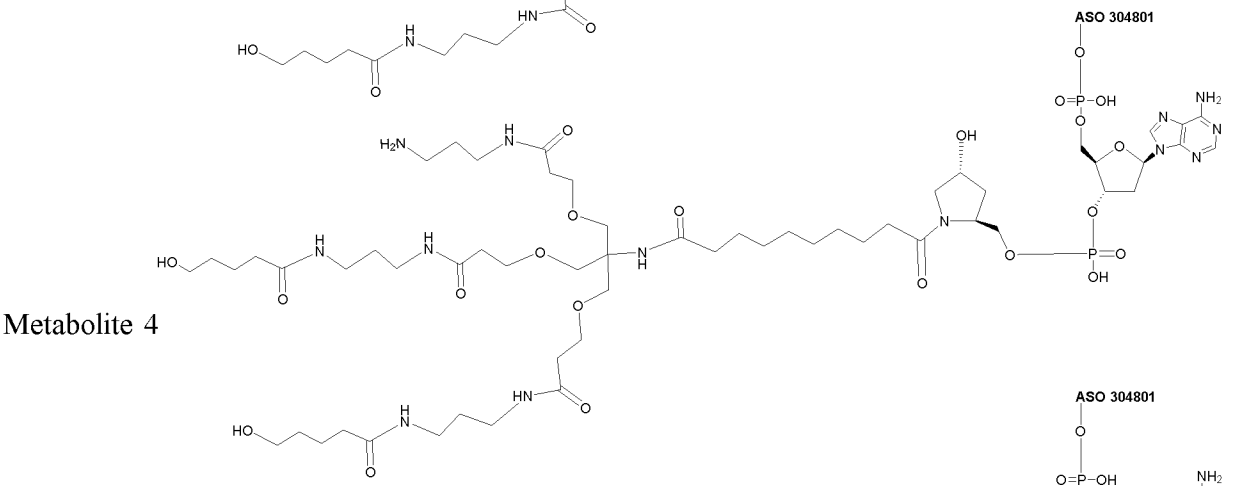


Metabolite 2

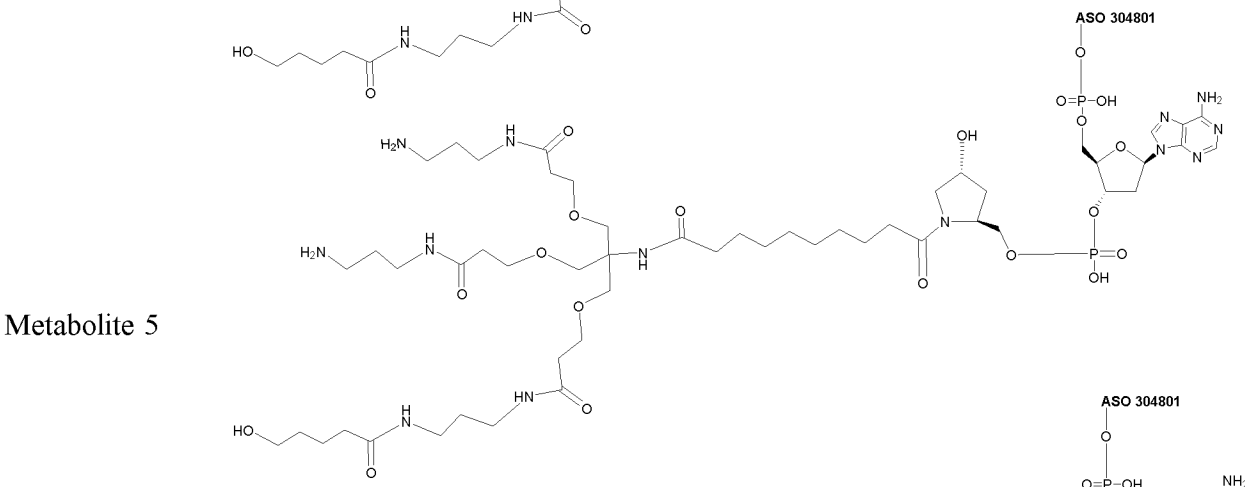




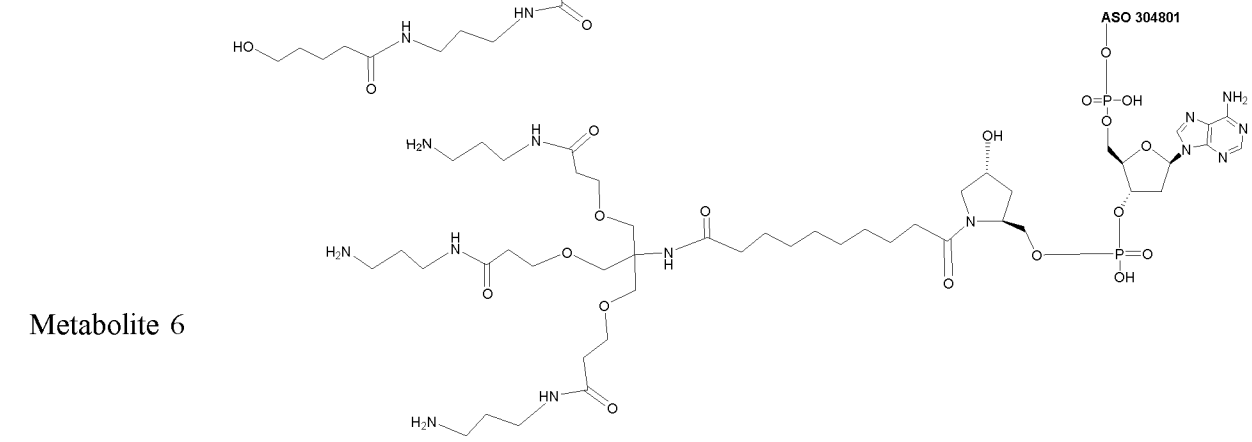
Metabolite 3



Metabolite 4



Metabolite 5



Metabolite 6

Example 21: Antisense inhibition of human ApoC III in human ApoC III transgenic mice in single administration study

ISIS 304801, 647535 and 647536 each targeting human ApoC III and described in Table 17, were further evaluated in a single administration study for their ability to inhibit human ApoC III in human ApoC III transgenic mice.

Treatment

Human ApoCIII transgenic mice were maintained on a 12-hour light/dark cycle and fed *ad libitum* Teklad lab chow. Animals were acclimated for at least 7 days in the research facility before initiation of the experiment. ASOs were prepared in PBS and sterilized by filtering through a 0.2 micron filter. ASOs were dissolved in 0.9% PBS for injection.

Human ApoC III transgenic mice were injected intraperitoneally once at the dosage shown below with ISIS 304801, 647535 or 647536 (described above) or with PBS treated control. The treatment group consisted of 3 animals and the control group consisted of 4 animals. Prior to the treatment as well as after the last dose, blood was drawn from each mouse and plasma samples were analyzed. The mice were sacrificed 72 hours following the last administration .

Samples were collected and analyzed to determine the ApoC III mRNA and protein levels in the liver; plasma triglycerides; and cholesterol, including HDL and LDL fractions were assessed as described above (Example 20). Data from those analyses are presented in Tables 24-28, below. Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. The ALT and AST levels showed that the antisense compounds were well tolerated at all administered doses.

These results show improvement in potency for antisense compounds comprising a **GalNAc$_3$-1** conjugate at the 3' terminus (ISIS 647535 and 647536) compared to the antisense compound lacking a **GalNAc$_3$-1** conjugate (ISIS 304801). Further, ISIS 647536, which comprises a **GalNAc$_3$-1** conjugate and some phosphodiester linkages was as potent as ISIS 647535, which comprises the same conjugate and all internucleoside linkages within the ASO are phosphorothioate.

Table 24

Effect of ASO treatment on ApoC III mRNA levels in human ApoC III transgenic mice

ASO	Dose (mg/kg)	% PBS	ED_{50} (mg/kg)	3' Conjugate	Internucleoside linkage/Length	SEQ ID No.
PBS	0	99	--	-	--	
ISIS 304801	1	104	13.2	None	PS/20	2248
	3	92				
	10	71				
	30	40				

ISIS 647535	0.3	98	1.9	**GalNAc$_3$-1**	PS/20	2249
	1	70				
	3	33				
	10	20				
ISIS 647536	0.3	103	1.7	**GalNAc$_3$-1**	PS/PO/20	2249
	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	2248
	3	92				
	10	71				
	30	40				
ISIS 647535	0.3	98	2.1	**GalNAc$_3$-1**	PS/20	2249
	1	70				
	3	33				
	10	20				
ISIS 647536	0.3	103	1.8	**GalNAc$_3$-1**	PS/PO/20	2249
	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	2248
	3	92				
	10	70				
	30	47				
ISIS 647535	0.3	100	2.2	**GalNAc$_3$-1**	PS/20	2249
	1	70				
	3	34				
	10	23				

ISIS 647536	0.3	95	1.9	**GalNAc$_3$-1**	PS/PO/20	2249
	1	66				
	3	31				
	10	23				

Table 27

Effect of ASO treatment on total cholesterol levels in transgenic mice

ASO	Dose (mg/kg)	% PBS	3' Conjugate	Internucleoside Linkage/Length	SEQ ID No.
PBS	0	96	--	--	
ISIS 304801	1	104	None	PS/20	2248
	3	96			
	10	86			
	30	72			
ISIS 647535	0.3	93	**GalNAc$_3$-1**	PS/20	2249
	1	85			
	3	61			
	10	53			
ISIS 647536	0.3	115	**GalNAc$_3$-1**	PS/PO/20	2249
	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	2248
	3	186	79			
	10	226	63			
	30	240	46			
ISIS 647535	0.3	98	86	**GalNAc$_3$-1**	PS/20	2249
	1	214	67			
	3	212	39			
	10	218	35			
ISIS 647536	0.3	143	89	**GalNAc$_3$-1**	PS/PO/20	2249
	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	2250
	2	55					
	7	12					
	20	3					
ISIS 651900	0.07	98	0.3	**$GalNAc_3$-1**		PS/14	2251
	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	2252
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	2253
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	2248
ISIS 647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	ApoC III	2249
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	2248

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. "$\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$" 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	2253
ISIS 304801	0.07	106.55	1,522	None	PS/20	2248
ISIS 647535	0.12	138	1,150	**GalNAc$_3$-1**	PS/20	2249
ISIS 616468	0.32	71.52	224	None	PS/PO/20	2248

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	2248
ISIS 647535	0.31	**$GalNAc_3$-1**	PS/20	2249

In this experiment, the large potency benefits of **$GalNAc_3$-1** conjugation that are observed *in vivo* were not observed *in vitro*. Subsequent free uptake experiments in primary hepatocytes *in vitro* did show increased potency of oligonucleotides comprising various GalNAc conjugates relative to oligonucleotides that lacking the GalNAc conjugate.(see Examples 60, 82, and 92)

Example 26: Effect of PO/PS linkages on ApoC III ASO Activity

Human ApoC III transgenic mice were injected intraperitoneally once at 25 mg/kg of ISIS 304801, or ISIS 616468 (both described above) or with PBS treated control once per week for two weeks. The treatment group consisted of 3 animals and the control group consisted of 4 animals. Prior to the treatment as well as after the last dose, blood was drawn from each mouse and plasma samples were analyzed. The mice were sacrificed 72 hours following the last administration.

Samples were collected and analyzed to determine the ApoC III protein levels in the liver as described above (Example 20). Data from those analyses are presented in Table 33, below.

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

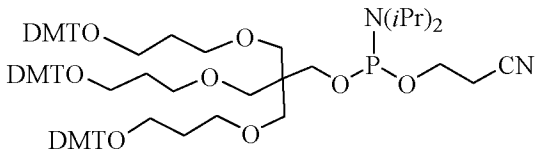
Table 33

Effect of ASO treatment on ApoC III protein levels in human ApoC III transgenic mice

ASO	Dose (mg/kg)	% PBS	3' Conjugate	Internucleoside linkage/Length	SEQ ID No.
PBS	0	99	-	--	

ISIS 304801	25 mg/kg/wk for 2 wks	24	None	Full PS	2248
ISIS 616468	25 mg/kg/wk for 2 wks	40	None	14 PS/6 PO	2248

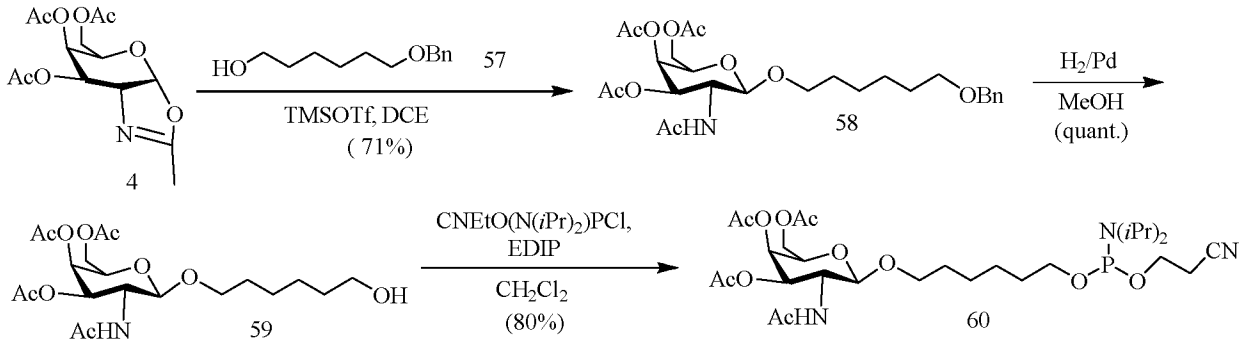
Example 27: Compound 56



56

Compound 56 is commercially available from Glen Research or may be prepared according to published procedures reported by Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

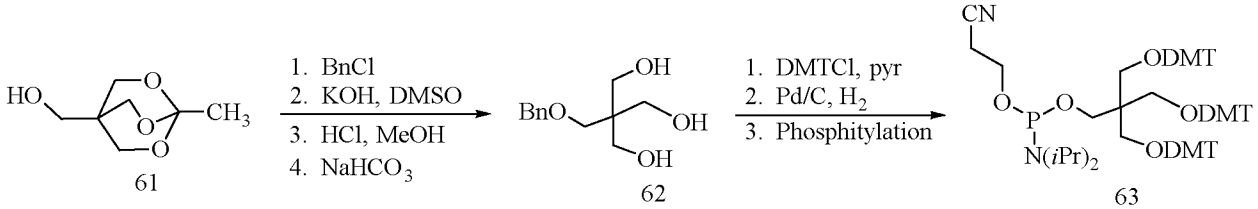
Example 28: Preparation of Compound 60



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

Compound 57 is meant to be representative and not intended to be limiting as other monoprotected substituted or unsubstituted alkyl diols including but not limited to those presented in the specification herein can be used to prepare phosphoramidites having a predetermined composition.

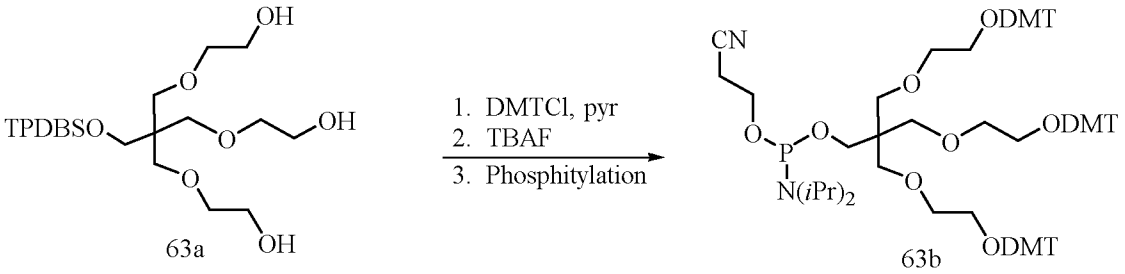
Example 29: Preparation of Compound 63



Compounds 61 and 62 are prepared using procedures similar to those reported by Tober *et al., Eur. J. Org. Chem.*, 2013, *3*, 566-577; and Jiang *et al., Tetrahedron*, 2007, *63(19)*, 3982-3988.

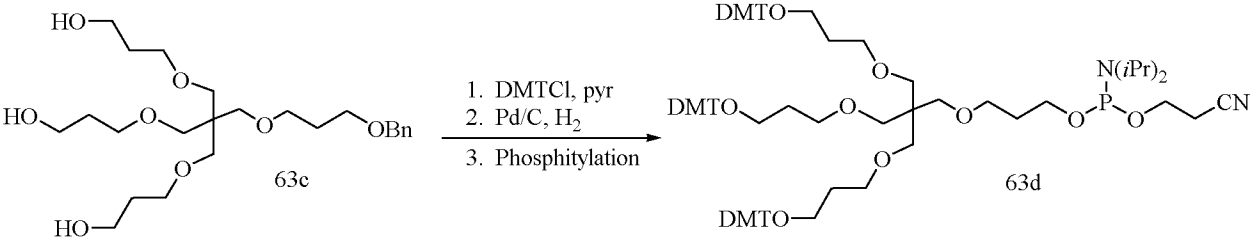
Alternatively, Compound 63 is prepared using procedures similar to those reported in scientific and patent literature by Kim *et al., Synlett*, 2003, *12*, 1838-1840; and Kim *et al.*, published PCT International Application, WO 2004063208.

Example 30: Preparation of Compound 63b



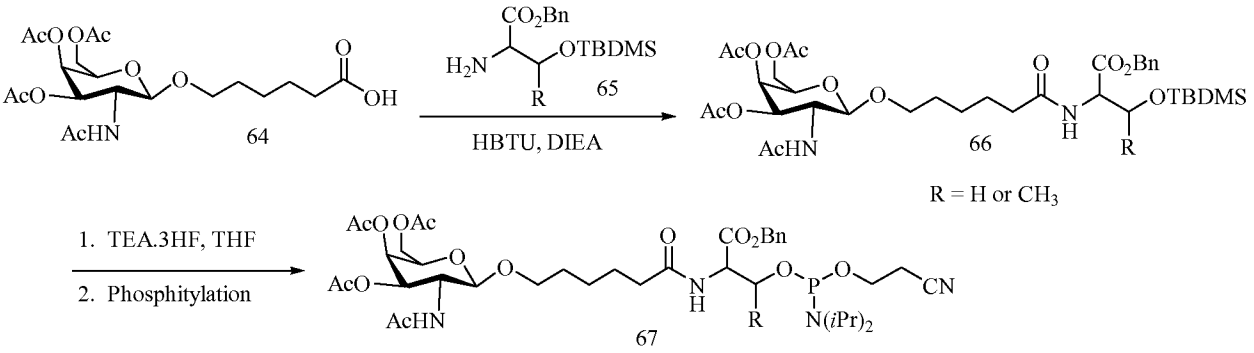
Compound 63a is prepared using procedures similar to those reported by Hanessian *et al., Canadian Journal of Chemistry*, 1996, *74(9)*, 1731-1737.

Example 31: Preparation of Compound 63d



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

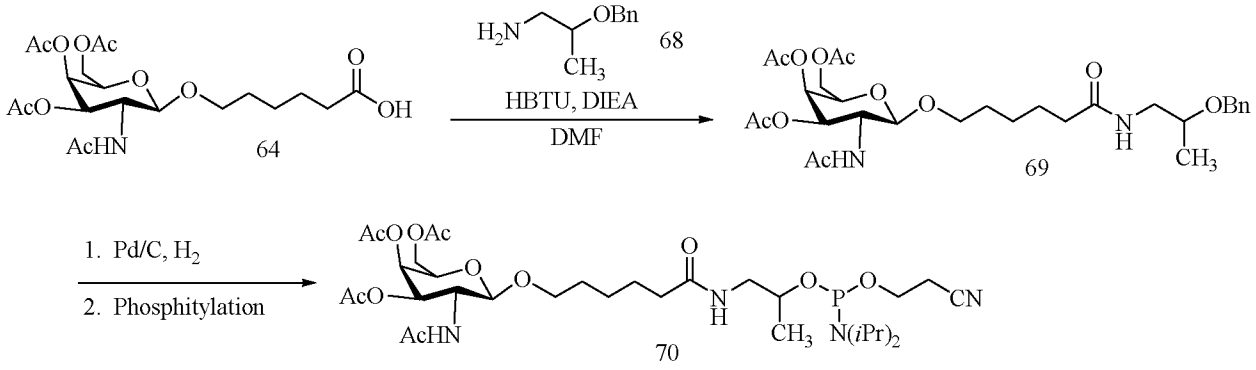
Example 32: Preparation of Compound 67



Compound 64 was prepared as per the procedures illustrated in Example 2. Compound 65 is prepared using procedures similar to those reported by Or *et al.*, published PCT International Application, WO 2009003009. The protecting groups used for Compound 65 are meant to be representative and not

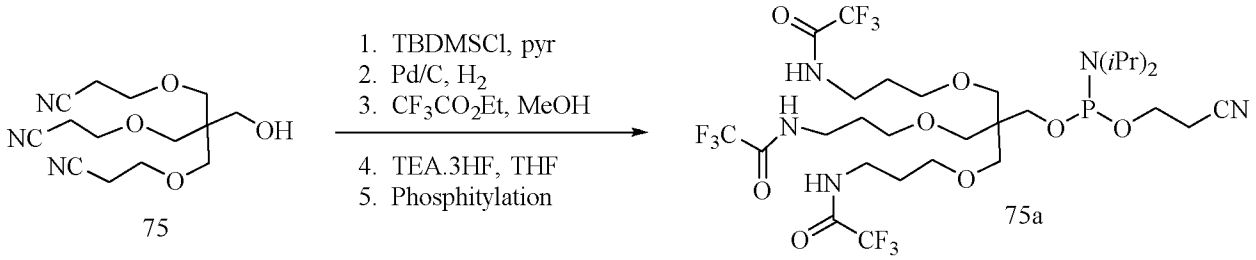
intended to be limiting as other protecting groups including but not limited to those presented in the specification herein can be used.

Example 33: Preparation of Compound 70



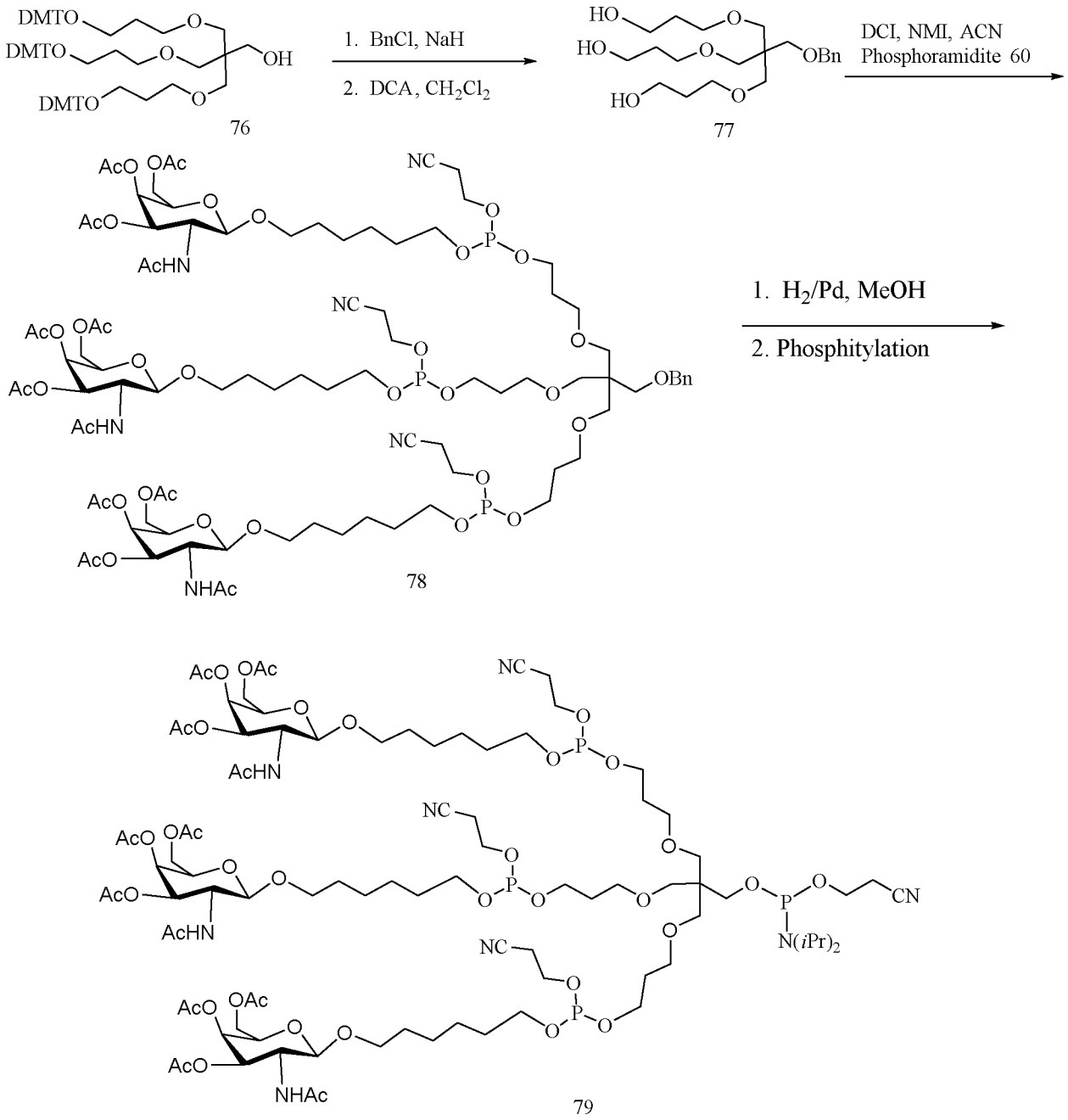
Compound 64 was prepared as per the procedures illustrated in Example 2. Compound 68 is commercially available. The protecting group used for Compound 68 is meant to be representative and not intended to be limiting as other protecting groups including but not limited to those presented in the specification herein can be used.

Example 34: Preparation of Compound 75a



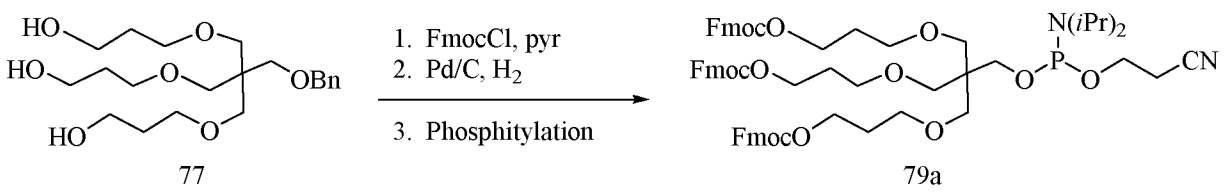
Compound 75 is prepared according to published procedures reported by Shchepinov *et al., Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

Example 35: Preparation of Compound 79



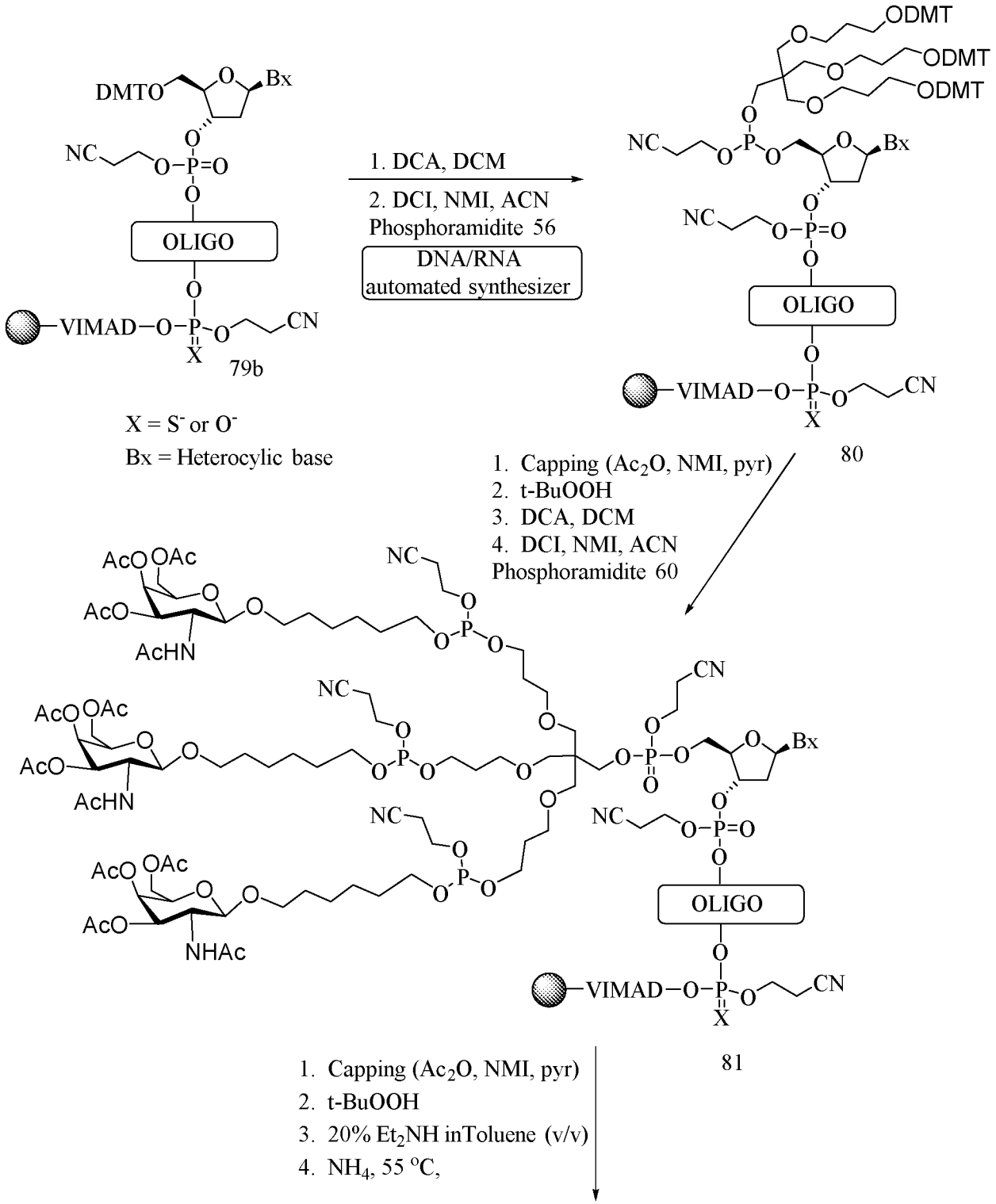
Compound 76 was prepared according to published procedures reported by Shchepinov *et al.*, *Nucleic Acids Research,* 1997, *25(22)*, 4447-4454.

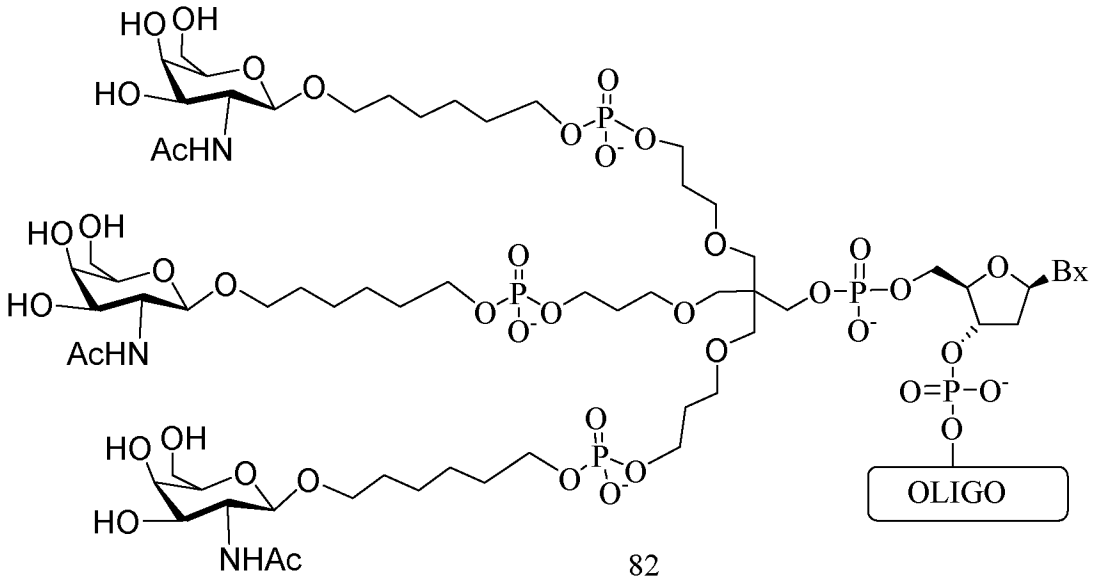
Example 36: Preparation of Compound 79a



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

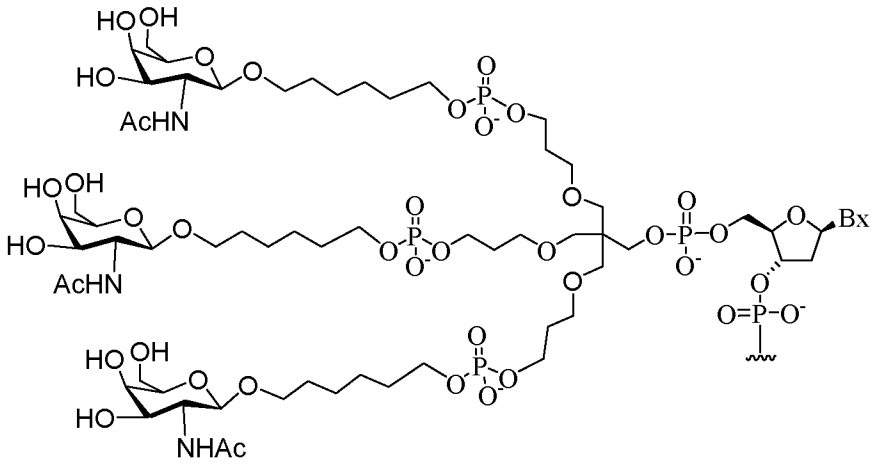
Example 37: General method for the preparation of conjugated oligomeric compound 82 comprising a phosphodiester linked GalNAc$_3$-2 conjugate at 5' terminus *via* solid support (Method I)



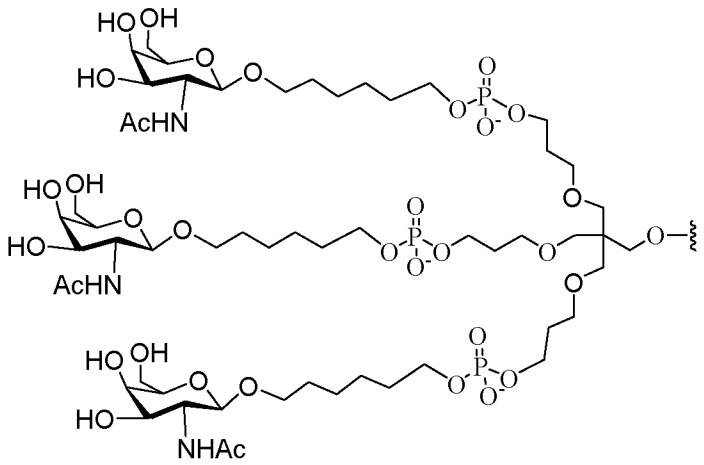


82

wherein GalNAc$_3$-2 has the structure:

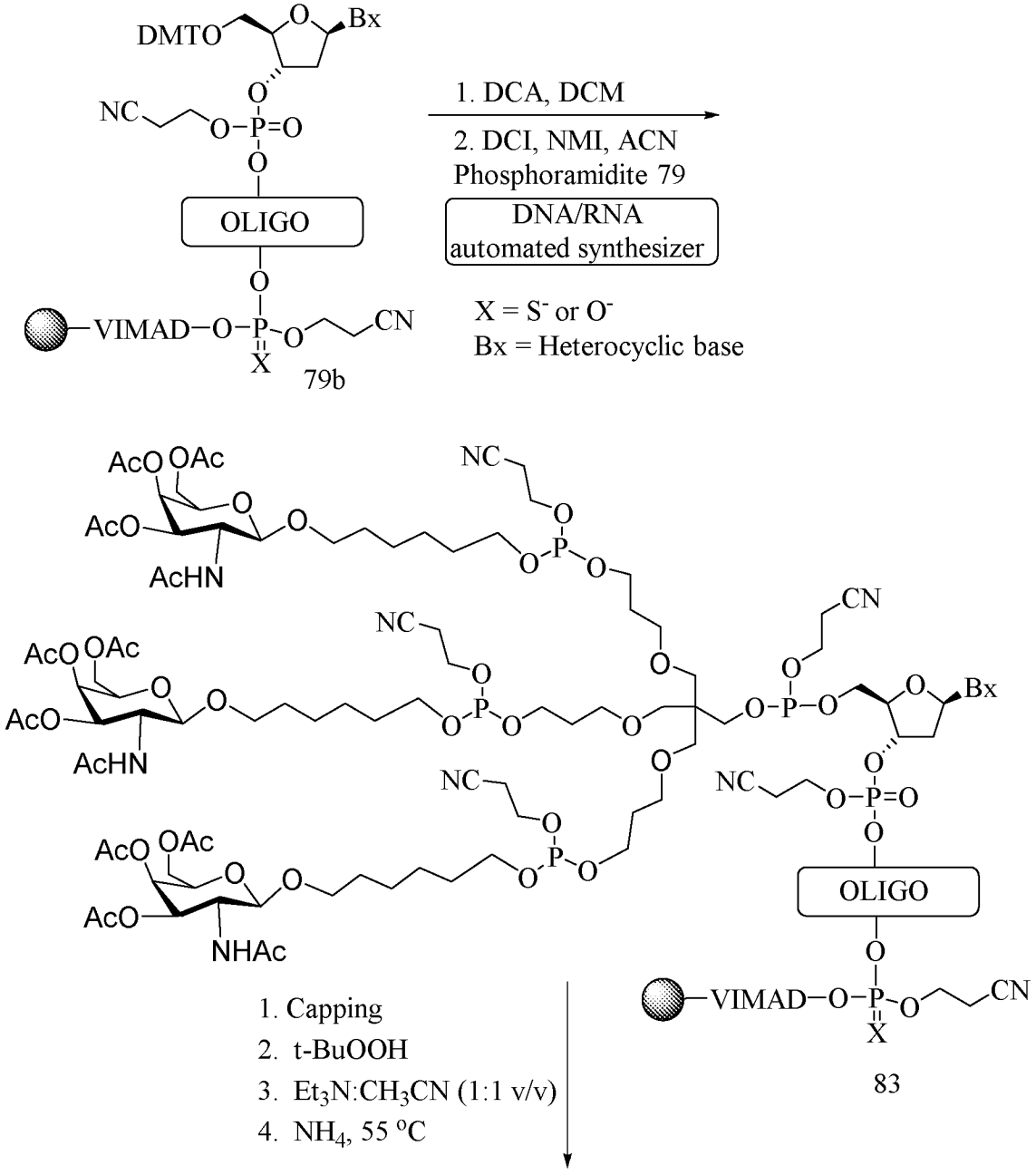


The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-2 (GalNAc$_3$-2$_a$) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein GalNAc$_3$-2$_a$ has the formula:



The VIMAD-bound oligomeric compound 79b was prepared using standard procedures for automated DNA/RNA synthesis (see Dupouy *et al., Angew. Chem. Int. Ed.,* 2006, *45,* 3623-3627). The phosphoramidite Compounds 56 and 60 were prepared as per the procedures illustrated in Examples 27 and 28, respectively. The phosphoramidites illustrated are meant to be representative and not intended to be limiting as other phosphoramidite building blocks including but not limited those presented in the specification herein can be used to prepare an oligomeric compound having a phosphodiester linked conjugate group at the 5' terminus. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare the oligomeric compounds as described herein having any predetermined sequence and composition.

Example 38: Alternative method for the preparation of oligomeric compound 82 comprising a phosphodiester linked GalNAc$_3$-2 conjugate at 5' terminus (Method II)

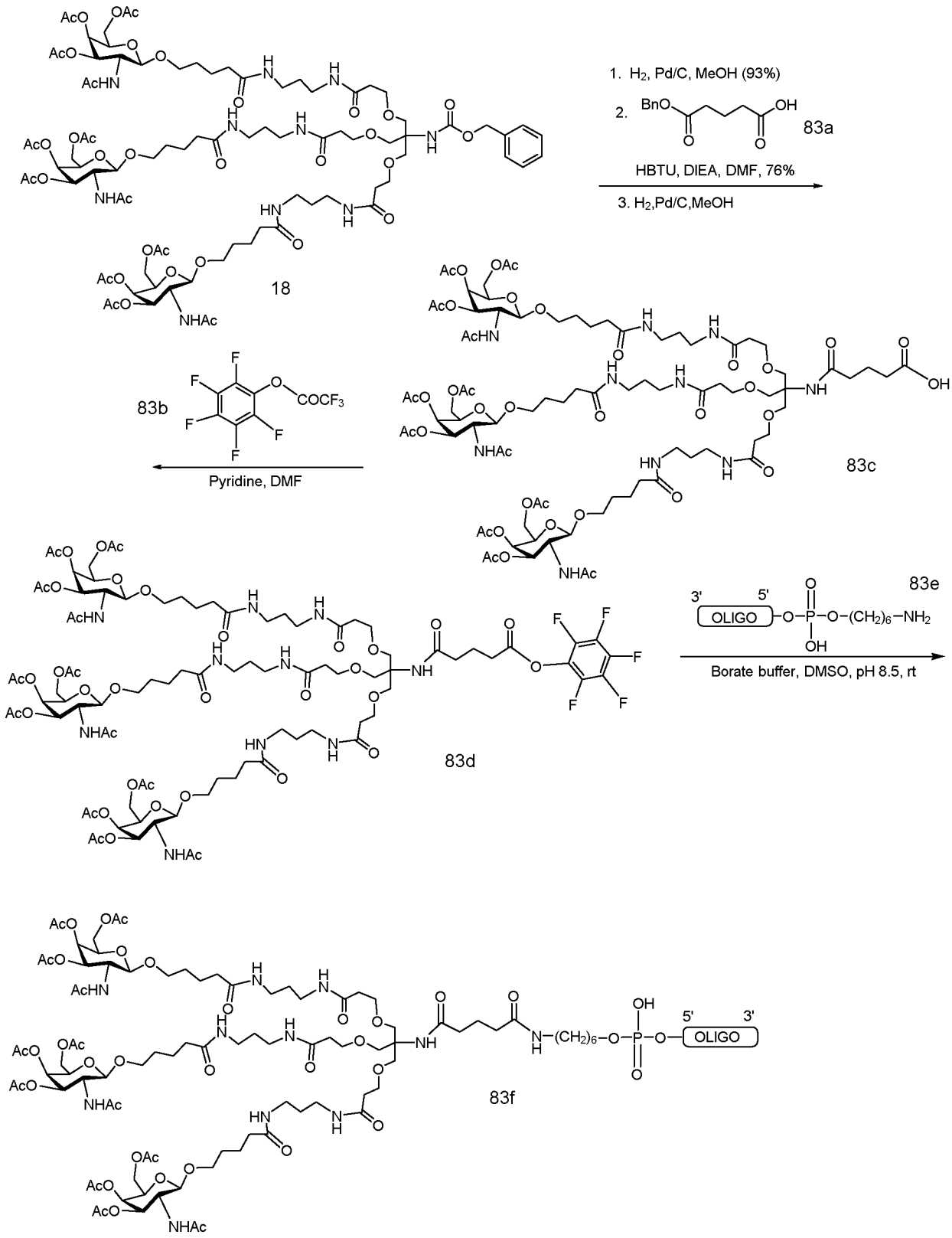


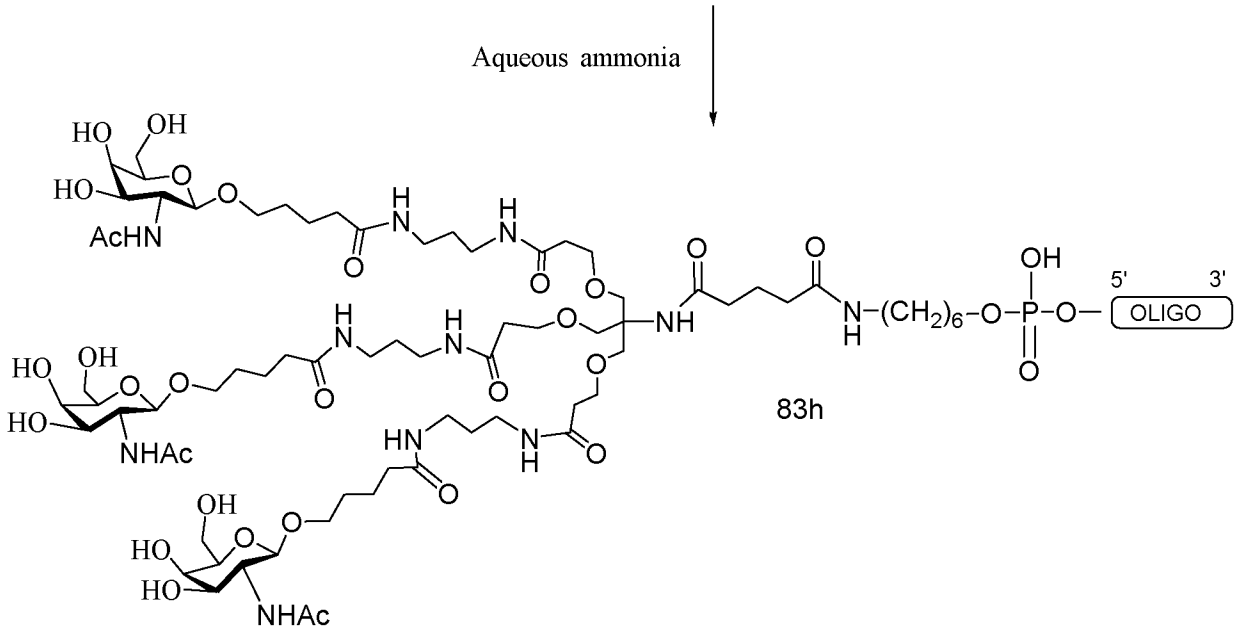
Oligomeric Compound 82

The VIMAD-bound oligomeric compound 79b was prepared using standard procedures for automated DNA/RNA synthesis (see Dupouy *et al., Angew. Chem. Int. Ed.,* 2006, *45,* 3623-3627). The GalNAc$_3$-2 cluster phosphoramidite, Compound 79 was prepared as per the procedures illustrated in Example 35. This alternative method allows a one-step installation of the phosphodiester linked GalNAc$_3$-2 conjugate to the oligomeric compound at the final step of the synthesis. The phosphoramidites illustrated are meant to

be representative and not intended to be limiting, as other phosphoramidite building blocks including but not limited to those presented in the specification herein can be used to prepare oligomeric compounds having a phosphodiester conjugate at the 5' terminus. The order and quantity of phosphoramidites added to the solid support can be adjusted to prepare the oligomeric compounds as described herein having any predetermined sequence and composition.

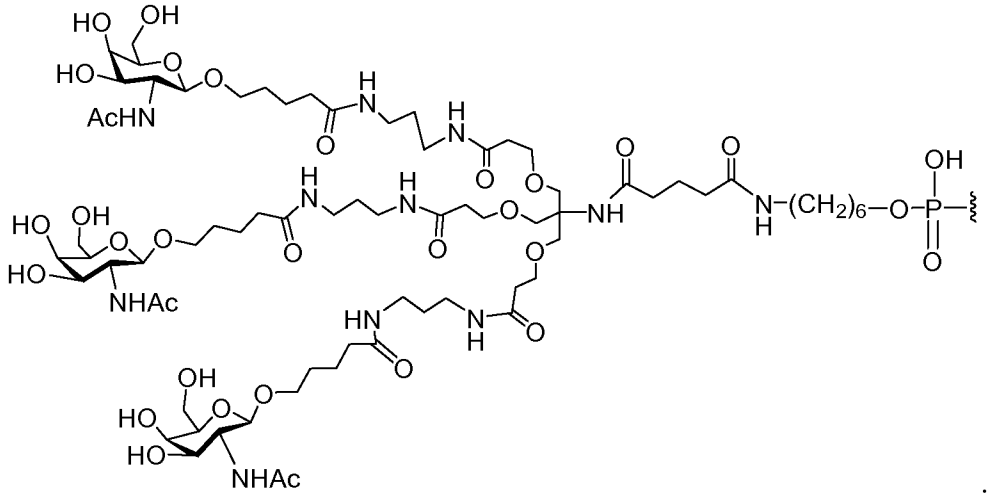
Example 39: General method for the preparation of oligomeric compound 83h comprising a GalNAc$_3$-3 Conjugate at the 5' Terminus (GalNAc$_3$-1 modified for 5' end attachment) *via* Solid Support



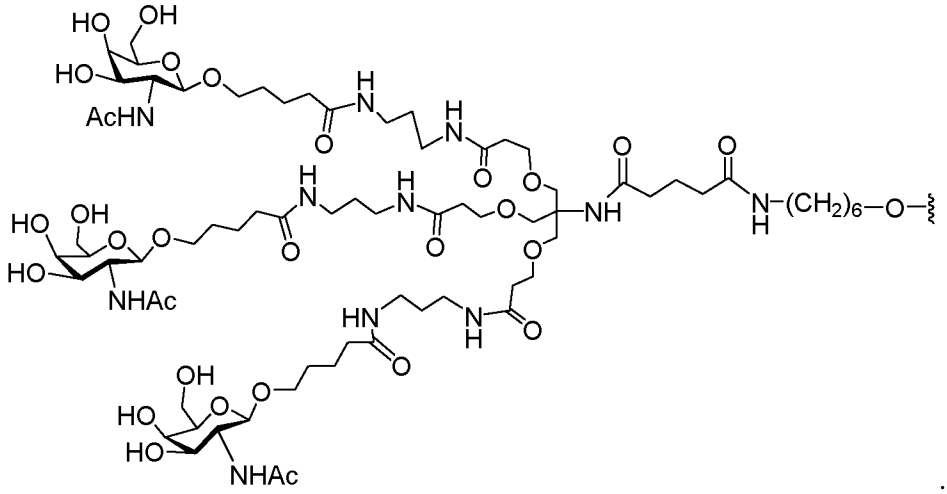


Compound 18 was prepared as per the procedures illustrated in Example 4. Compounds 83a and 83b are commercially available. Oligomeric Compound 83e comprising a phosphodiester linked hexylamine was prepared using standard oligonucleotide synthesis procedures. Treatment of the protected oligomeric compound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

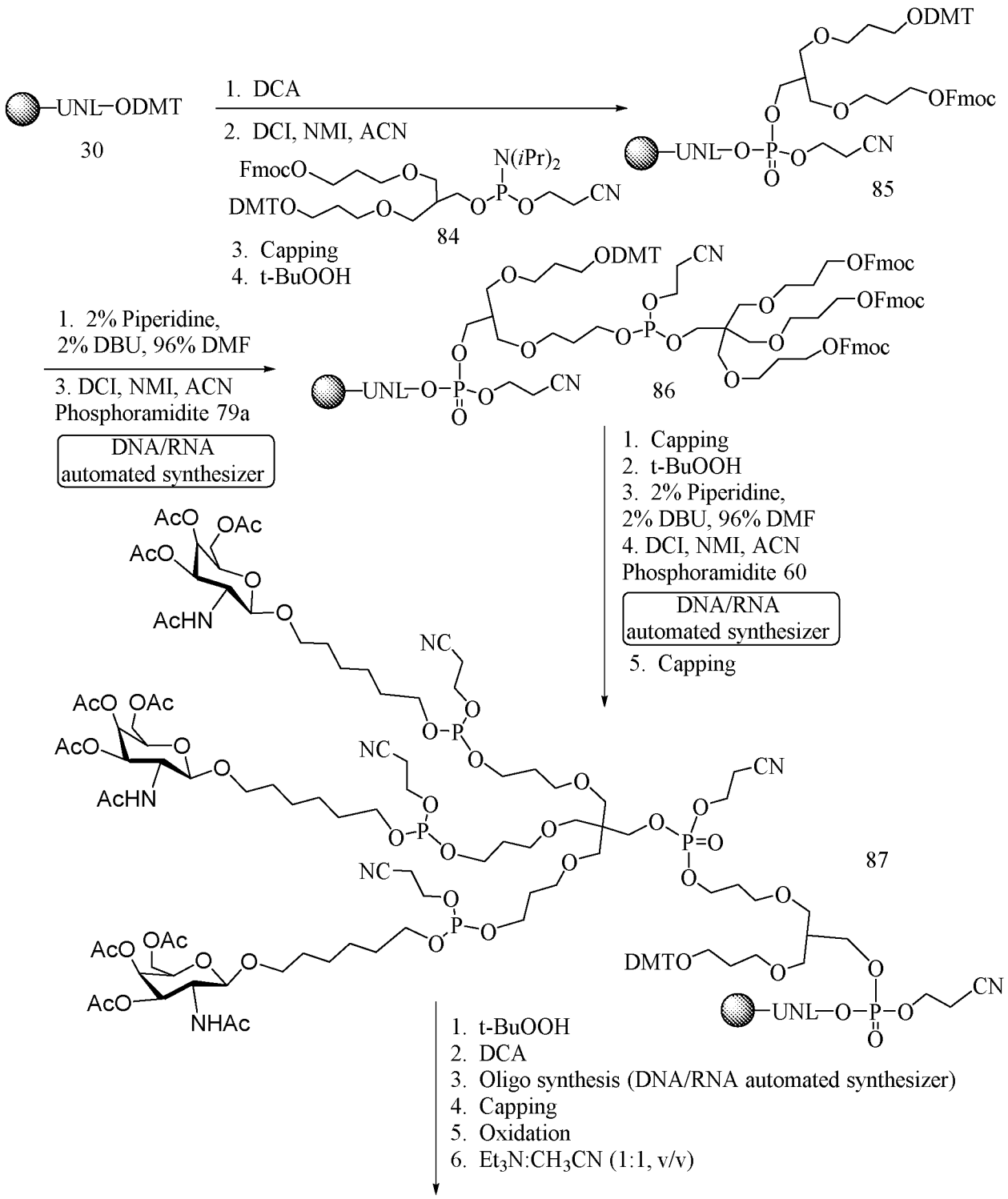
Wherein GalNAc$_3$-3 has the structure:

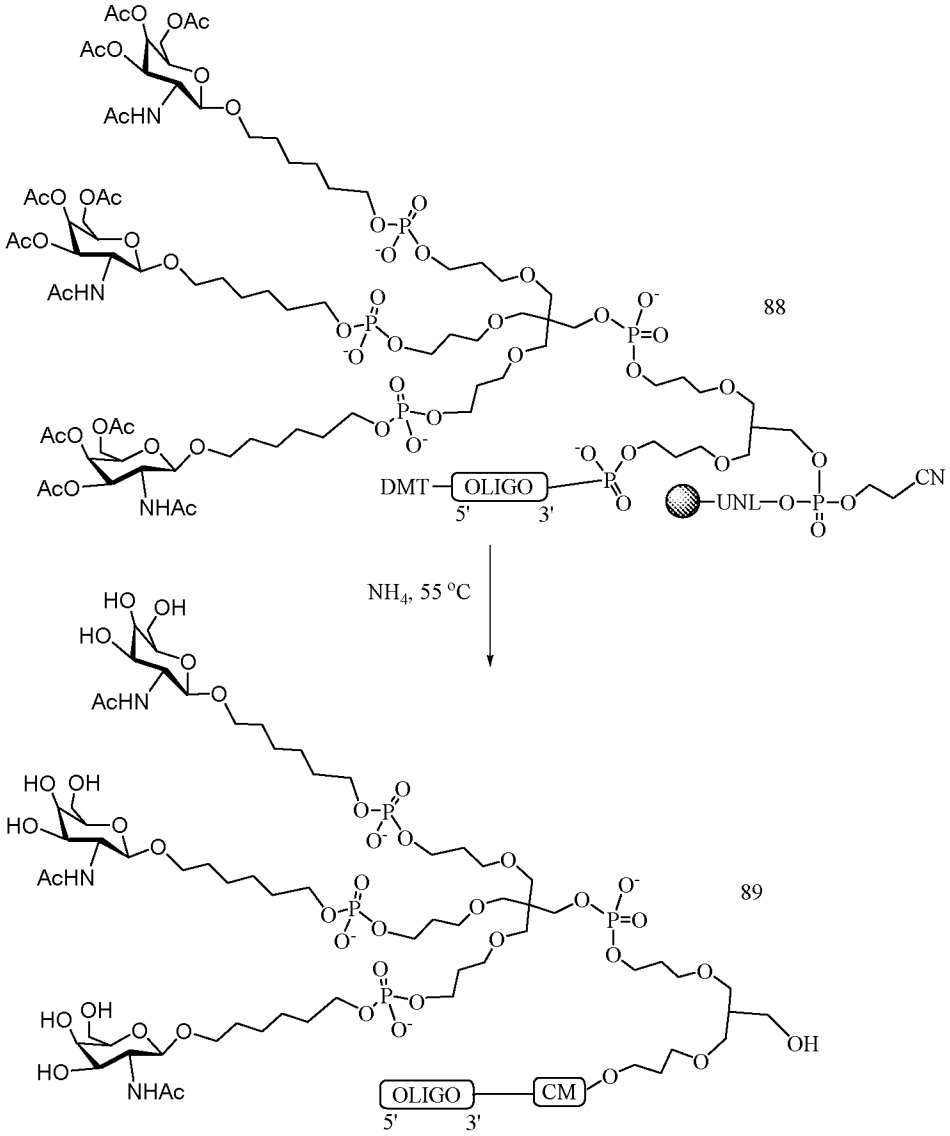


The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-3 ($GalNAc_3$-3_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. Wherein $GalNAc_3$-3_a has the formula:

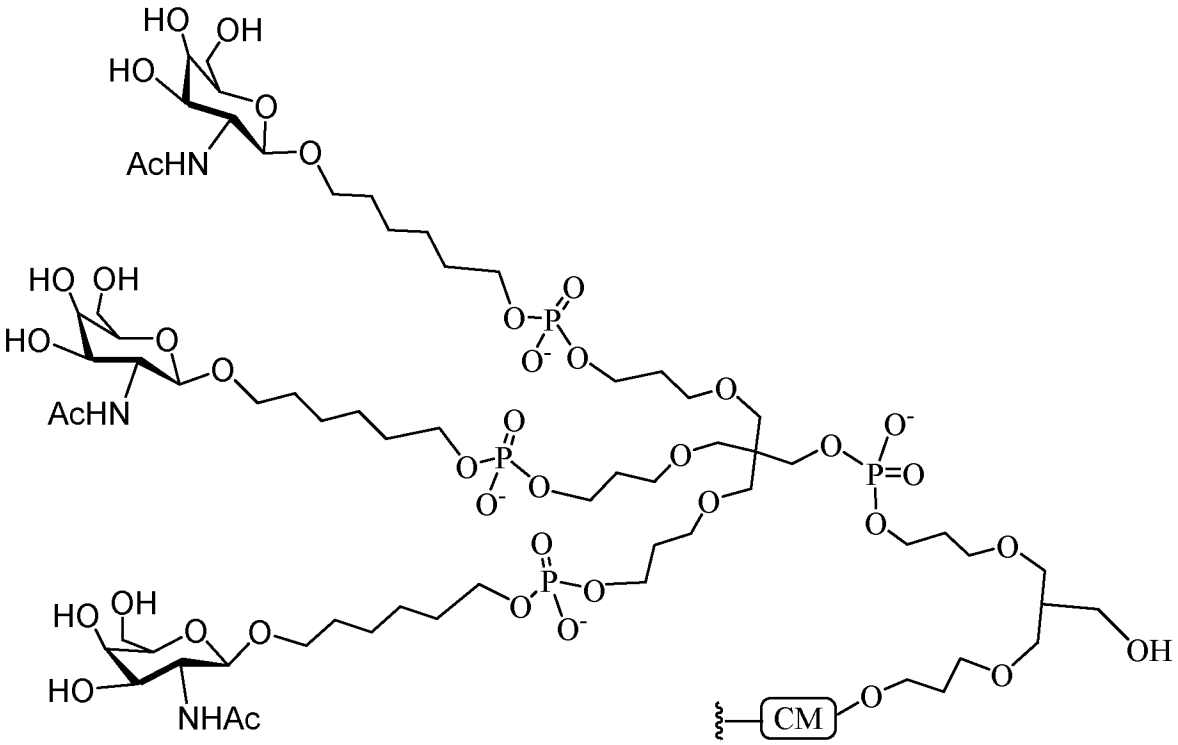


Example 40: General method for the preparation of oligomeric compound 89 comprising a phosphodiester linked GalNAc$_3$-4 conjugate at the 3' terminus *via* solid support

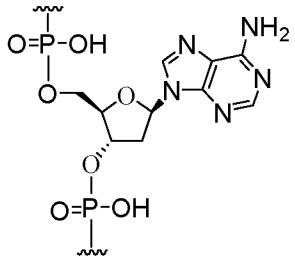



AcO
OAc
AcO
AcHN
O
O-P=O
O
O

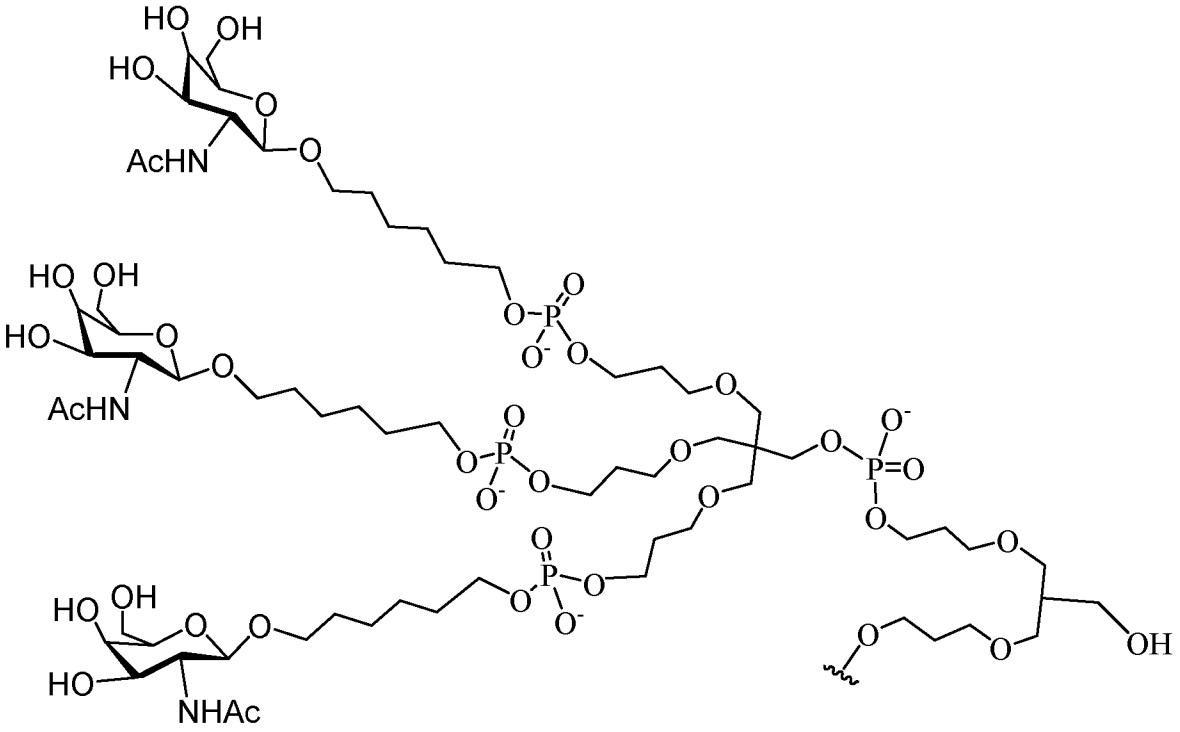
Wherein $GalNAc_3$-4 has the structure:



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	2254

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'-**$GalNAc_3$-$3_{a\text{-}o}$**-$^{m}C_{es}G_{es}G_{es}T_{es}G_{es}$ $^{m}C_{ds}A_{ds}A_{ds}G_{ds}G_{ds}$ $^{m}C_{ds}T_{ds}T_{ds}A_{ds}G_{ds}$ $G_{es}A_{es}A_{es}T_{es}T_{e}$	**5'-$GalNAc_3$-3**	8992.16	8990.51	2255

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	2250
	0.7	91			
	2	69			
	7	22			
	20	5			
651900	0.07	95	0.26	**3' $GalNAc_3$-1**	2251
	0.2	77			
	0.7	28			
	2	11			
	7	8			
661134	0.07	107	0.25	**5' $GalNAc_3$-2**	2254
	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	2256
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	2257
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	2257

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	2256
	10	52.40			
	30	24.95			
655861	0.5	81.22	2.2	Full PS with $GalNAc_3$-1 conjugate	2257
	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	2257
	1.5	45.78			
	5	19.70			
	15	12.90			

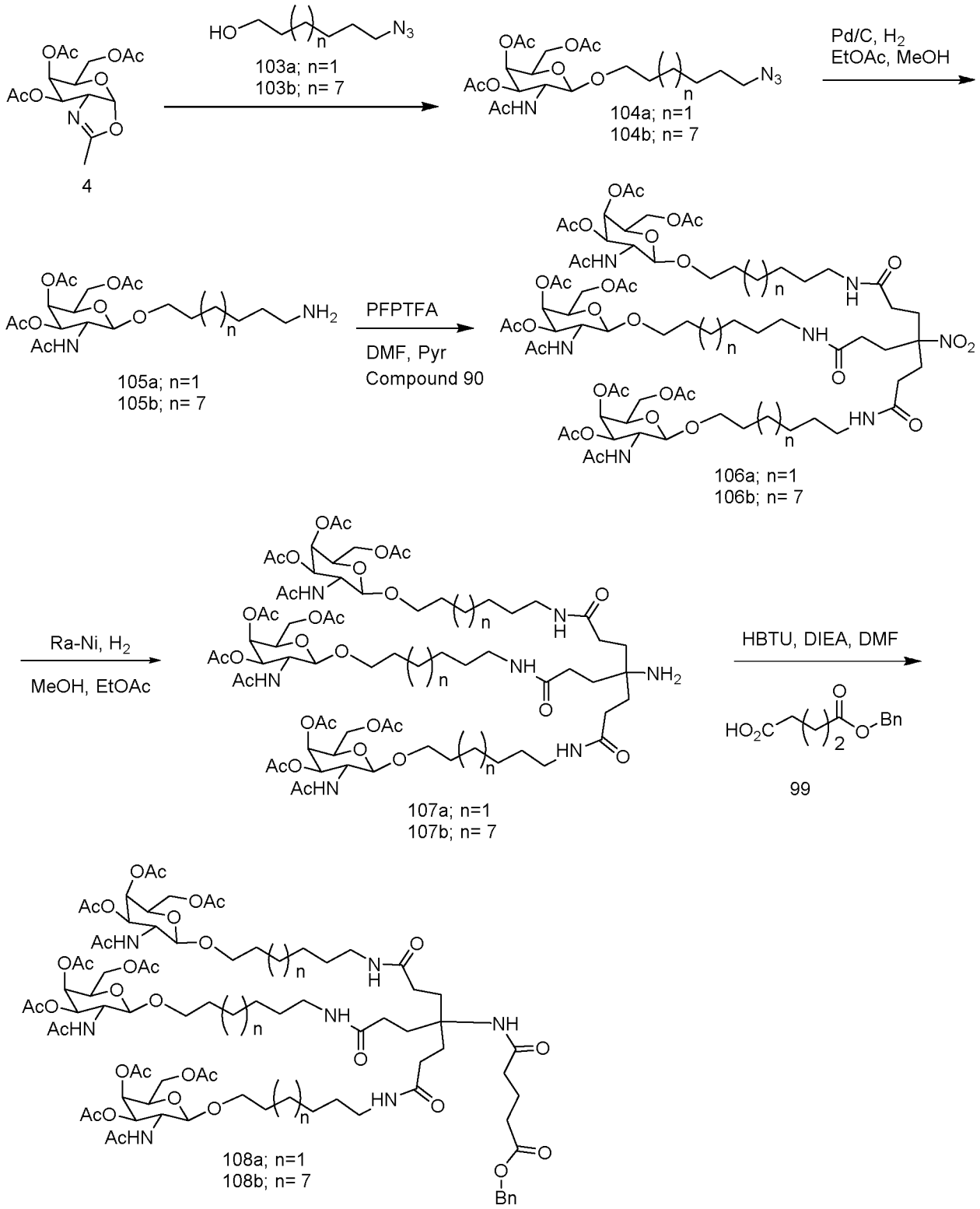
Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Organ weights were also evaluated. The results demonstrated that no elevation in transaminase levels (Table 38) or organ weights (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).

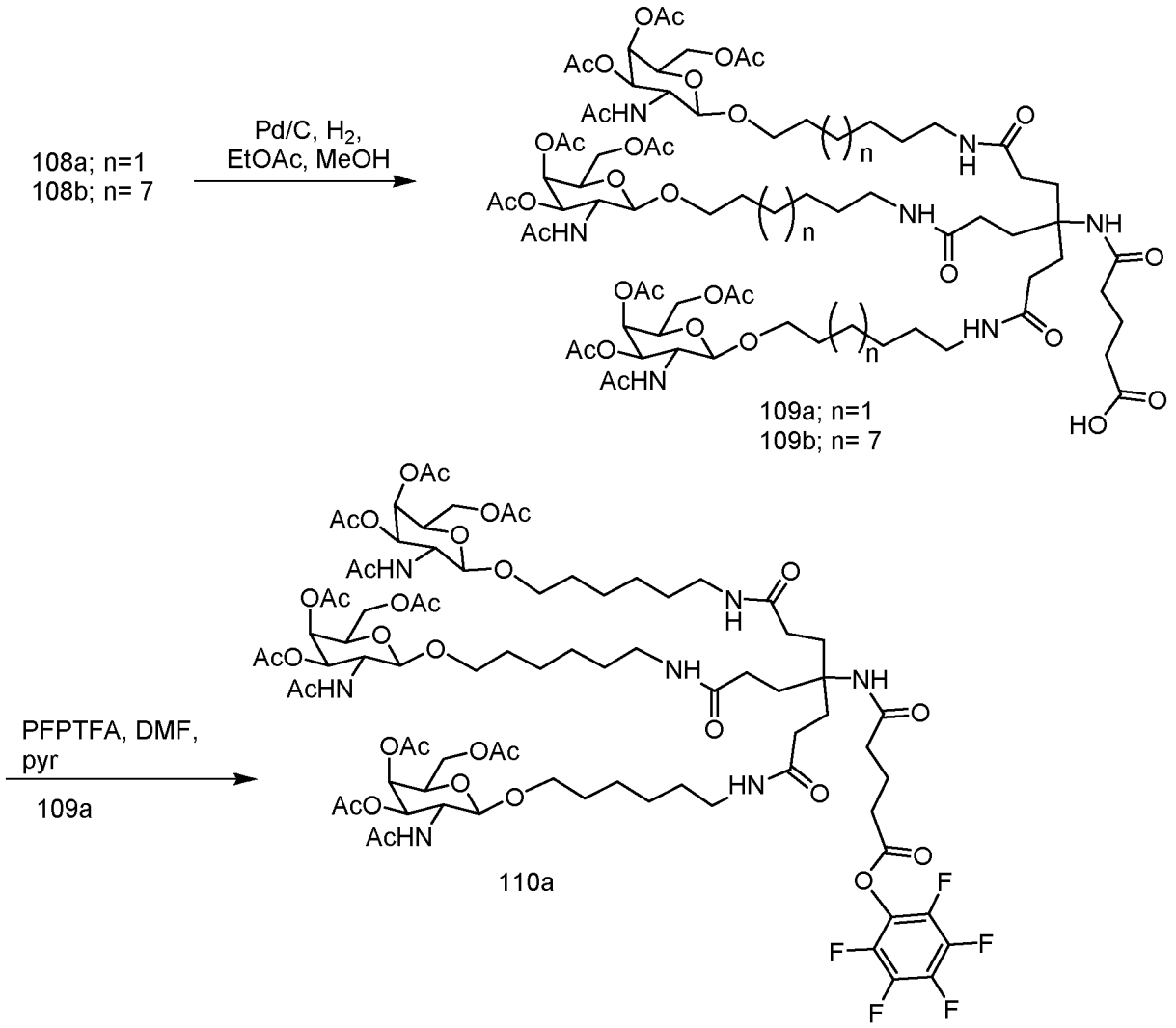
Table 38
Effect of PO/PS linkages on transaminase levels of ASOs comprising $GalNAc_3$-1 conjugate at 3' terminus targeting SRB-1

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	2256
	10	27.5	79.3		
	30	27.3	97		

655861	0.5	28	55.7	Full PS with **$GalNAc_3$-1**	2257
	1.5	30	78		
	5	29	63.5		
	15	28.8	67.8		
655862	0.5	50	75.5	Mixed PS/PO with **$GalNAc_3$-1**	2257
	1.5	21.7	58.5		
	5	29.3	69		
	15	22	61		

Example 45: Preparation of PFP Ester, Compound 110a





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

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

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

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

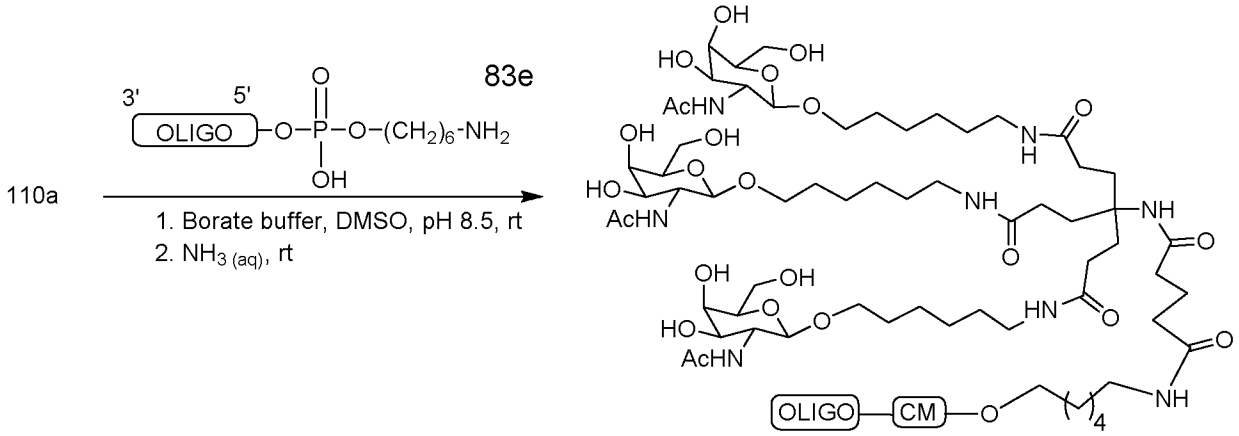
Compounds 107a and 107b were treated to the same conditions as for compounds 97a-d (Example 47), to give compounds 108a and 108b in 40-60% yield. LCMS and proton NMR was consistent with the structure.

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

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

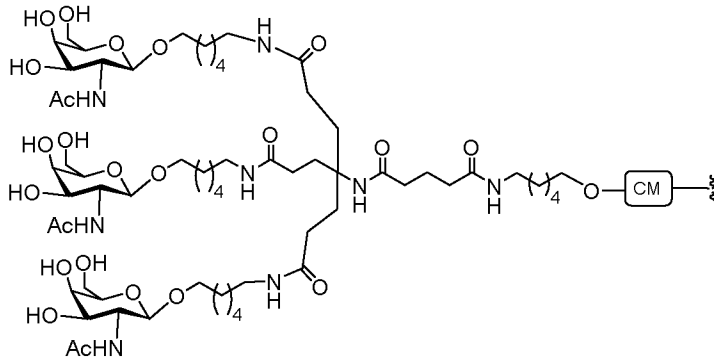
Example 46: General Procedure for Conjugation with PFP Esters (Oligonucleotide 111); Preparation of ISIS 666881 ($GalNAc_3$-10)

A 5'-hexylamino modified oligonucleotide was synthesized and purified using standard solid-phase oligonucleotide procedures. The 5'-hexylamino modified oligonucleotide was dissolved in 0.1 M sodium tetraborate, pH 8.5 (200 μL) and 3 equivalents of a selected PFP esterified $GalNAc_3$ cluster dissolved in DMSO (50 μL) was added. If the PFP ester precipitated upon addition to the ASO solution DMSO was added until all PFP ester was in solution. The reaction was complete after about 16 h of mixing at room temperature. The resulting solution was diluted with water to 12 mL and then spun down at 3000 rpm in a spin filter with a mass cut off of 3000 Da. This process was repeated twice to remove small molecule impurities. The solution was then lyophilized to dryness and redissolved in concentrated aqueous ammonia and mixed at room temperature for 2.5 h followed by concentration *in vacuo* to remove most of the ammonia. The conjugated oligonucleotide was purified and desalted by RP-HPLC and lyophilized to provide the $GalNAc_3$ conjugated oligonucleotide.



111

Oligonucleotide 111 is conjugated with $GalNAc_3$-10. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-10 ($GalNAc_3$-10_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)- as shown in the oligonucleotide (ISIS 666881) synthesized with $GalNAc_3$-10 below. The structure of $GalNAc_3$-10 ($GalNAc_3$-10_a-CM-) is shown below:



Following this general procedure ISIS 666881 was prepared. 5'-hexylamino modified oligonucleotide, ISIS 660254, was synthesized and purified using standard solid-phase oligonucleotide procedures. ISIS 660254 (40 mg, 5.2 μmol) was dissolved in 0.1 M sodium tetraborate, pH 8.5 (200 μL) and 3 equivalents PFP ester (Compound 110a) dissolved in DMSO (50 μL) was added. The PFP ester precipitated upon addition to the ASO solution requiring additional DMSO (600 μL) to fully dissolve the PFP ester. The reaction was complete after 16 h of mixing at room temperature. The solution was diluted with water to 12 mL total volume and spun down at 3000 rpm in a spin filter with a mass cut off of 3000 Da. This process was repeated twice to remove small molecule impurities. The solution was lyophilized to dryness and redissolved in concentrated aqueous ammonia with mixing at room temperature for 2.5 h followed by

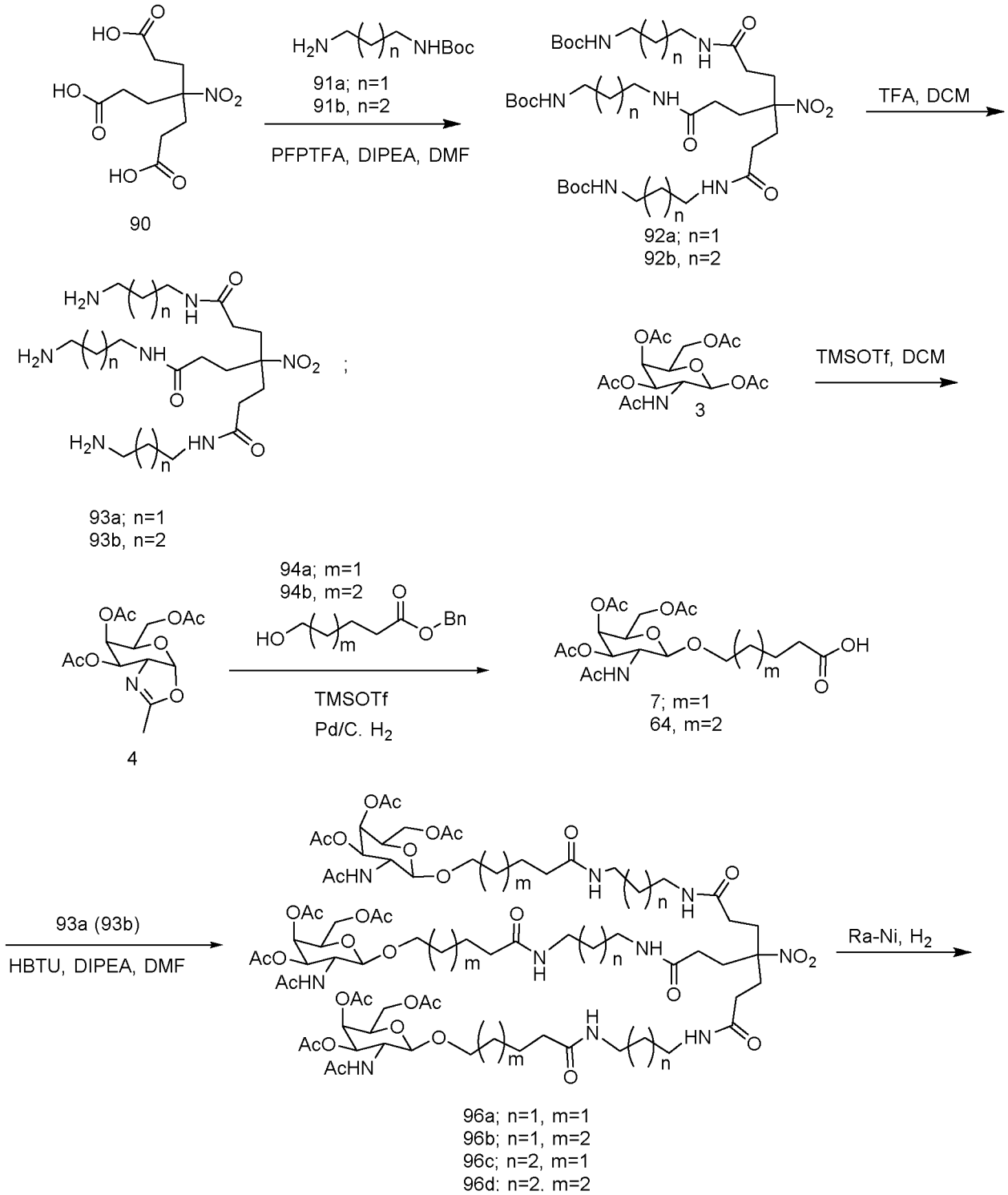
concentration *in vacuo* to remove most of the ammonia. The conjugated oligonucleotide was purified and desalted by RP-HPLC and lyophilized to give ISIS 666881 in 90% yield by weight (42 mg, 4.7 μmol).

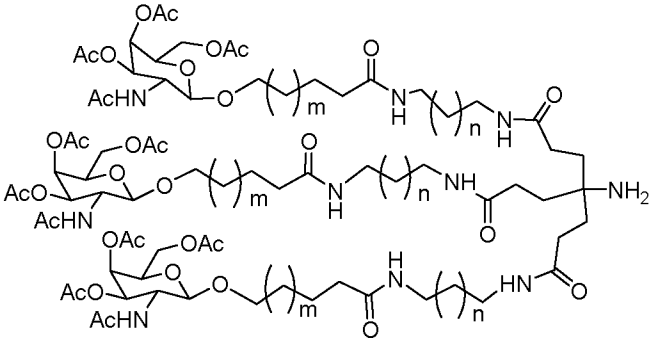
$GalNAc_3$-10 conjugated oligonucleotide

ASO	Sequence (5' to 3')	5' group	SEQ ID No.
ISIS 660254	$NH_2(CH_2)_{6\text{-}o}A_{do}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ ${}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	Hexylamine	2258
ISIS 666881	**$GalNAc_3\text{-}10_{a\text{-}o'}A_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ ${}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	**$GalNAc_3$-10**	2258

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

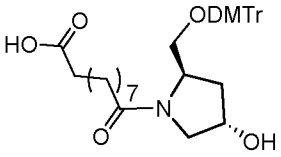
Example 47: Preparation of Oligonucleotide 102 Comprising GalNAc$_3$-8



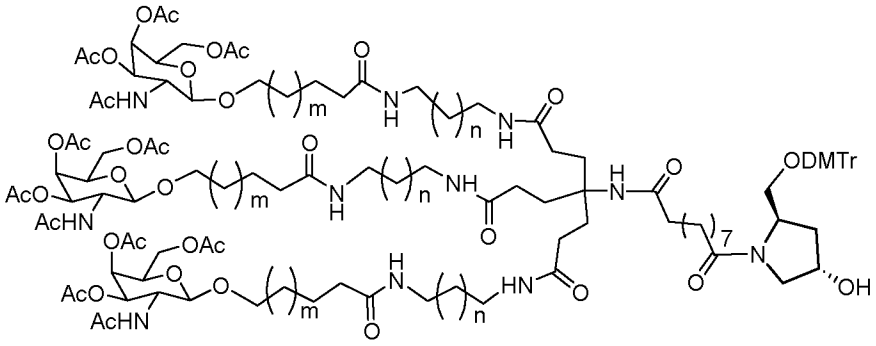


97a; n=1, m=1
97b; n=1, m=2
97c; n=2, m=1
97d; n=2, m=2

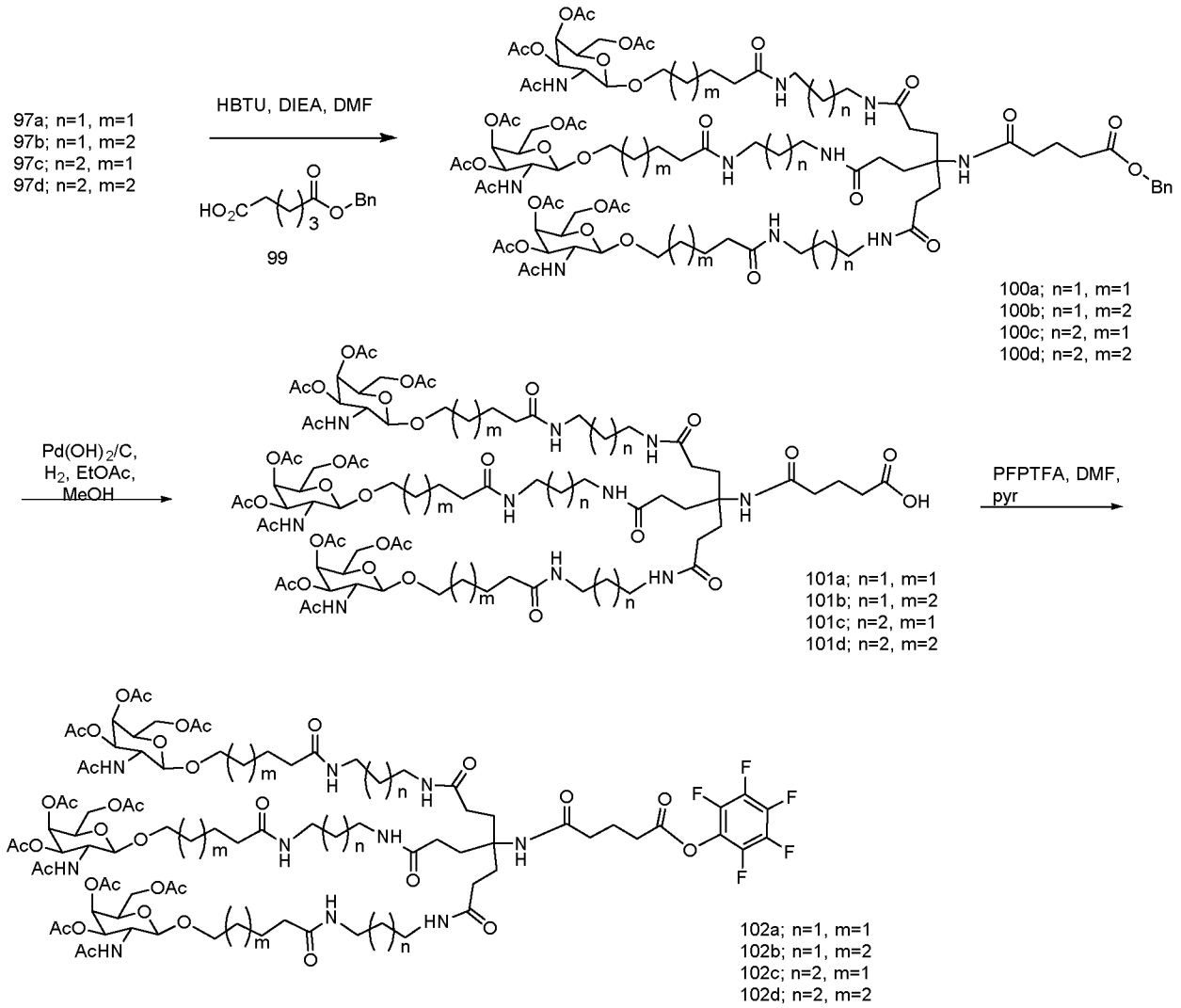
HBTU, DIEA, DMF



23



98a; n=1, m=1
98b; n=1, m=2
98c; n=2, m=1
98d; n=2, m=2



The triacid 90 (4 g, 14.43 mmol) was dissolved in DMF (120 mL) and *N*,*N*-Diisopropylethylamine (12.35 mL, 72 mmoles). Pentafluorophenyl trifluoroacetate (8.9 mL, 52 mmoles) was added dropwise, under argon, and the reaction was allowed to stir at room temperature for 30 minutes. Boc-diamine 91a or 91b (68.87 mmol) was added, along with *N*,*N*-Diisopropylethylamine (12.35 mL, 72 mmoles), and the reaction was allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->10% methanol/dichloromethane) to give compounds 92a and 92b in an approximate 80% yield. LCMS and proton NMR were consistent with the structure.

Compound 92a or 92b (6.7 mmoles) was treated with 20 mL of dichloromethane and 20 mL of trifluoroacetic acid at room temperature for 16 hours. The resultant solution was evaporated and then

dissolved in methanol and treated with DOWEX-OH resin for 30 minutes. The resultant solution was filtered and reduced to an oil under reduced pressure to give 85-90% yield of compounds 93a and 93b.

Compounds 7 or 64 (9.6 mmoles) were treated with HBTU (3.7g, 9.6 mmoles) and *N,N*-Diisopropylethylamine (5 mL) in DMF (20 mL) for 15 minutes. To this was added either compounds 93a or 93b (3 mmoles), and allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (5%-->20% methanol/dichloromethane) to give compounds 96a-d in 20-40% yield. LCMS and proton NMR was consistent with the structure.

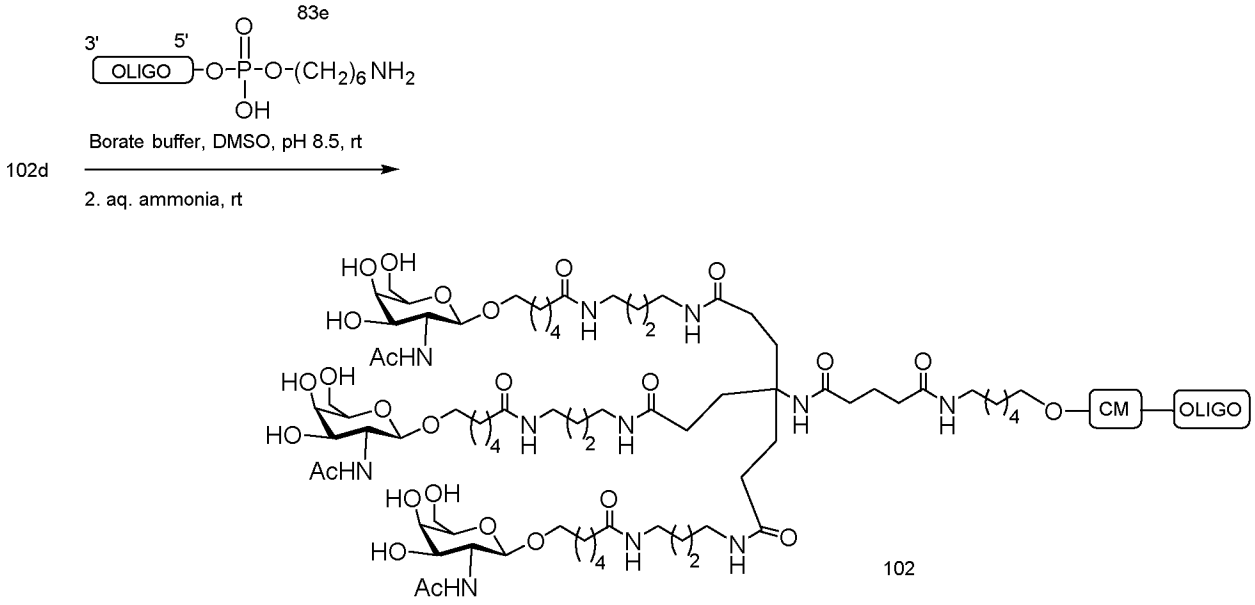
Compounds 96a-d (0.75 mmoles), individually, were hydrogenated over Raney Nickel for 3 hours in Ethanol (75 mL). At that time, the catalyst was removed by filtration thru celite, and the ethanol removed under reduced pressure to give compounds 97a-d in 80-90% yield. LCMS and proton NMR were consistent with the structure.

Compound 23 (0.32g, 0.53 mmoles) was treated with HBTU (0.2g, 0.53 mmoles) and *N,N*-Diisopropylethylamine (0.19 mL, 1.14 mmoles) in DMF (30mL) for 15 minutes. To this was added compounds 97a-d (0.38 mmoles), individually, and allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->20% methanol/dichloromethane) to give compounds 98a-d in 30-40% yield. LCMS and proton NMR was consistent with the structure.

Compound 99 (0.17g, 0.76 mmoles) was treated with HBTU (0.29 g, 0.76 mmoles) and *N,N*-Diisopropylethylamine (0.35 mL, 2.0 mmoles) in DMF (50mL) for 15 minutes. To this was added compounds 97a-d (0.51 mmoles), individually, and allowed to stir at room temperature for 16 hours. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (5%-->20% methanol/ dichloromethane) to give compounds 100a-d in 40-60% yield. LCMS and proton NMR was consistent with the structure.

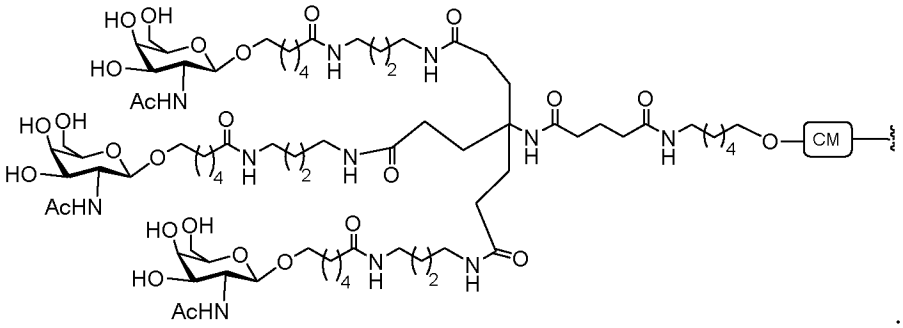
Compounds 100a-d (0.16 mmoles), individually, were hydrogenated over 10% $Pd(OH)_2/C$ for 3 hours in methanol/ethyl acetate (1:1, 50 mL). At that time, the catalyst was removed by filtration thru celite, and the organics removed under reduced pressure to give compounds 101a-d in 80-90% yield. LCMS and proton NMR was consistent with the structure.

Compounds 101a-d (0.15 mmoles), individually, were dissolved in DMF (15 mL) and pyridine (0.016 mL, 0.2 mmoles). Pentafluorophenyl trifluoroacetate (0.034 mL, 0.2 mmoles) was added dropwise, under argon, and the reaction was allowed to stir at room temperature for 30 minutes. At that time, the DMF was reduced by >75% under reduced pressure, and then the mixture was dissolved in dichloromethane. The organic layer was washed with sodium bicarbonate, water and brine. The organic layer was then separated and dried over sodium sulfate, filtered and reduced to an oil under reduced pressure. The resultant oil was purified by silica gel chromatography (2%-->5% methanol/dichloromethane) to give compounds 102a-d in an approximate 80% yield. LCMS and proton NMR were consistent with the structure.

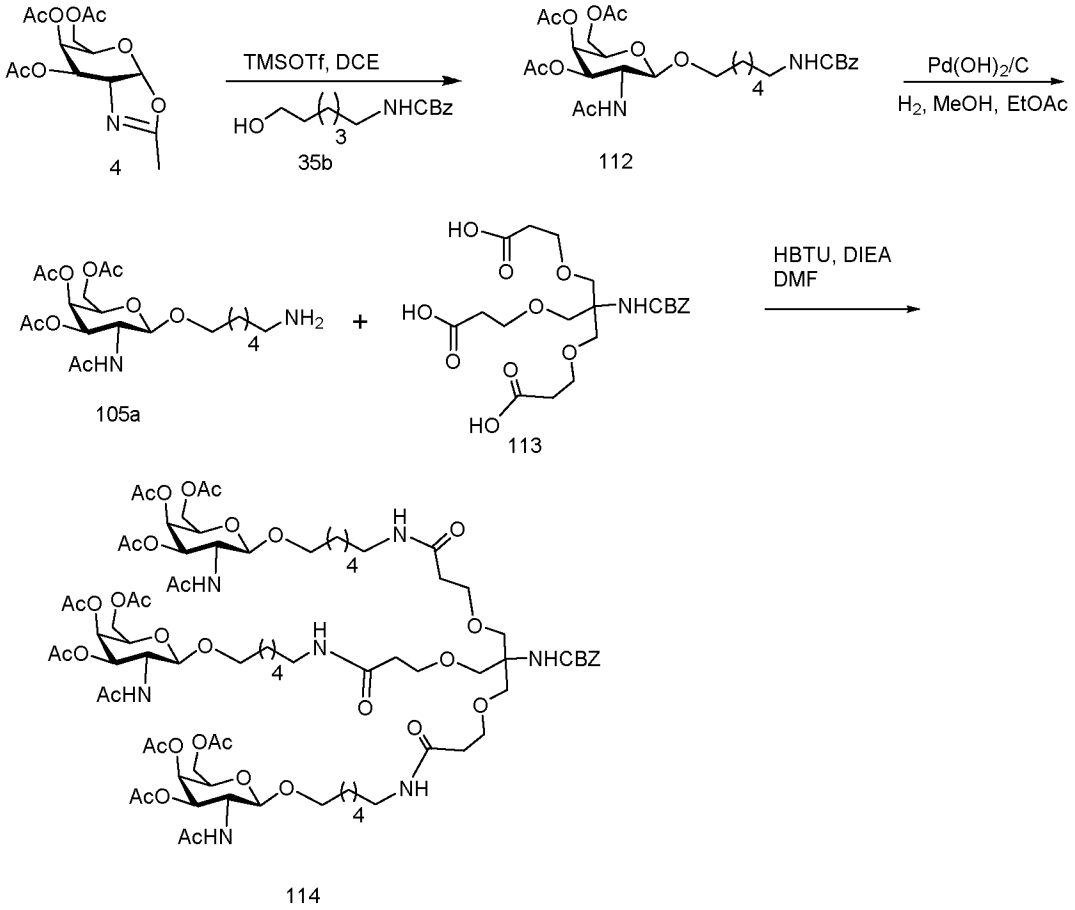


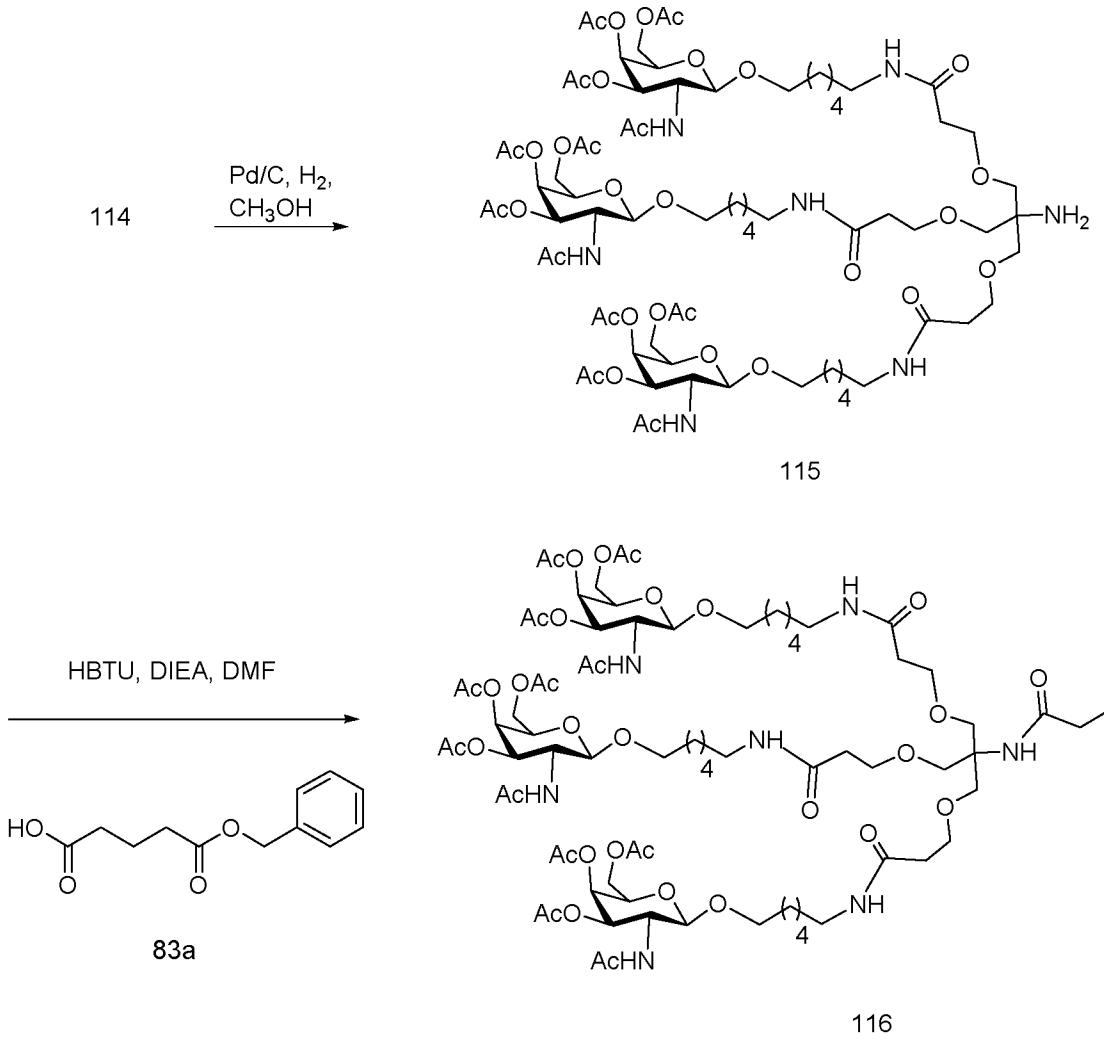
Oligomeric Compound 102, comprising a $GalNAc_3$-8 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-8 ($GalNAc_3$-8_a) can be combined with any cleavable moiety to provide a variety of conjugate groups.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

The structure of $GalNAc_3$-8 ($GalNAc_3$-8_a-CM-) is shown below:



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





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

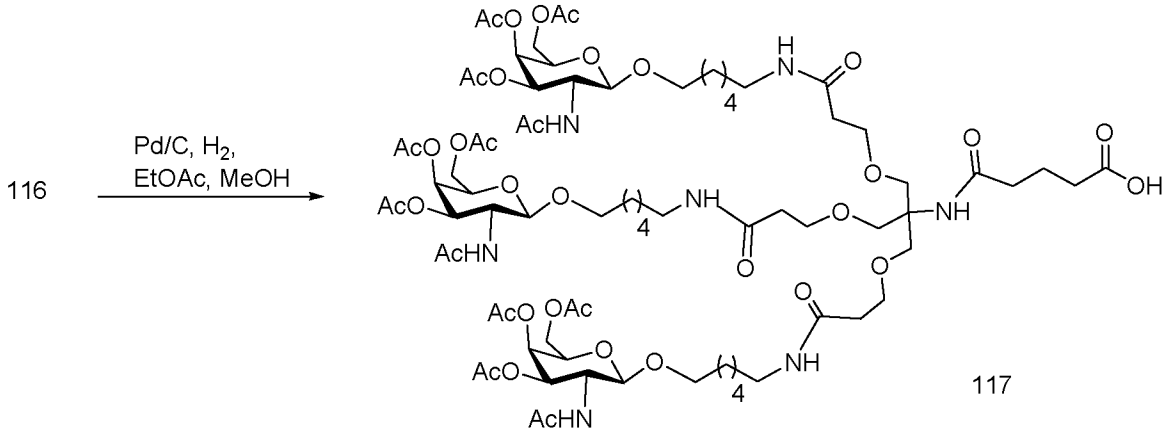
Compound 112 (5 g, 8.6 mmol) was dissolved in 1:1 methanol/ethyl acetate (22 mL/22 mL). Palladium hydroxide on carbon (0.5 g) was added. The reaction mixture was stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite and washed the pad with 1:1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

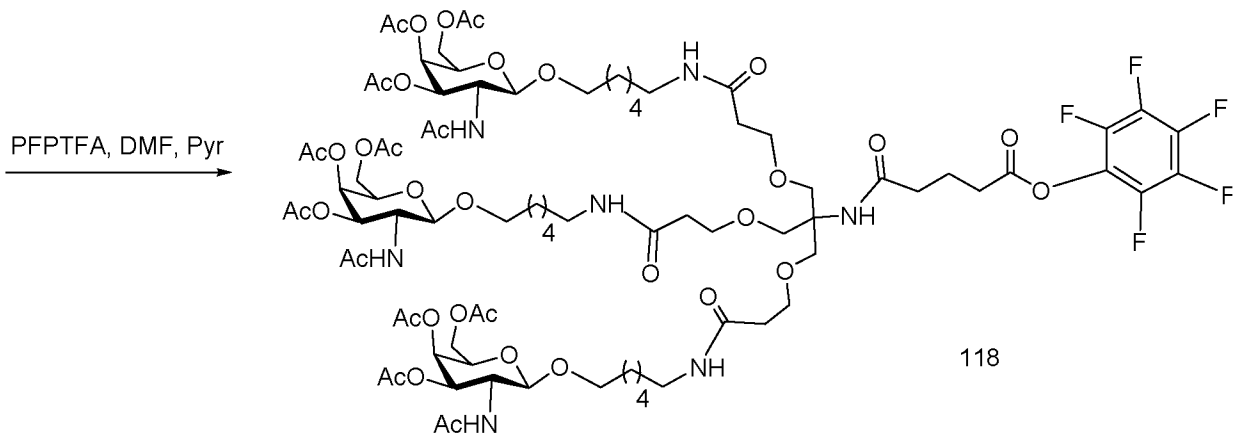
Compound 113 (1.25 g, 2.7 mmol), HBTU (3.2 g, 8.4 mmol) and DIEA (2.8 mL, 16.2 mmol) were dissolved in anhydrous DMF (17 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 105a (3.77 g, 8.4 mmol) in anhydrous DMF (20 mL) was added. The reaction was stirred at room temperature for 6 h. Solvent was removed under reduced pressure to get an oil. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with aqueous saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated. The residue

was purified by silica gel column chromatography and eluted with 10 to 20 % MeOH in dichloromethane to yield Compound 114 (1.45 g, 30%). The structure was confirmed by LCMS and ^{1}H NMR analysis.

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

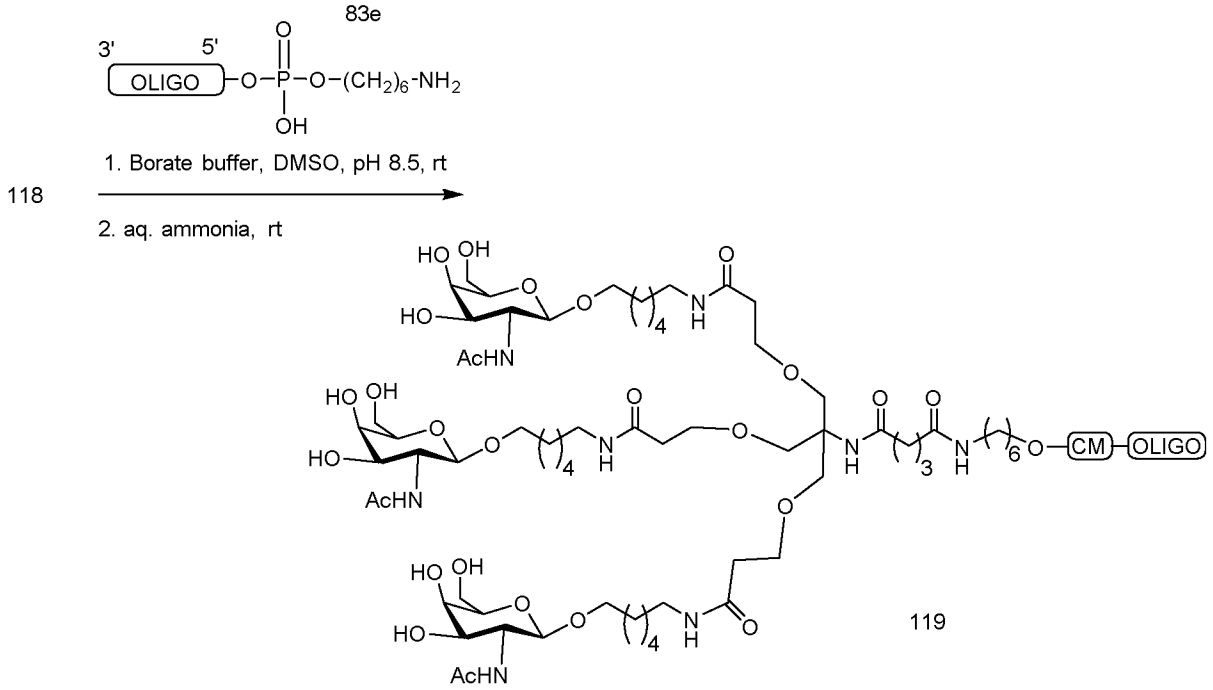
Compound 83a (0.17 g, 0.75 mmol), HBTU (0.31 g, 0.83 mmol) and DIEA (0.26 mL, 1.5 mmol) were dissolved in anhydrous DMF (5 mL) and the reaction mixture was stirred at room temperature for 5 min. To this a solution of Compound 115 (1.22 g, 0.75 mmol) in anhydrous DMF was added and the reaction was stirred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





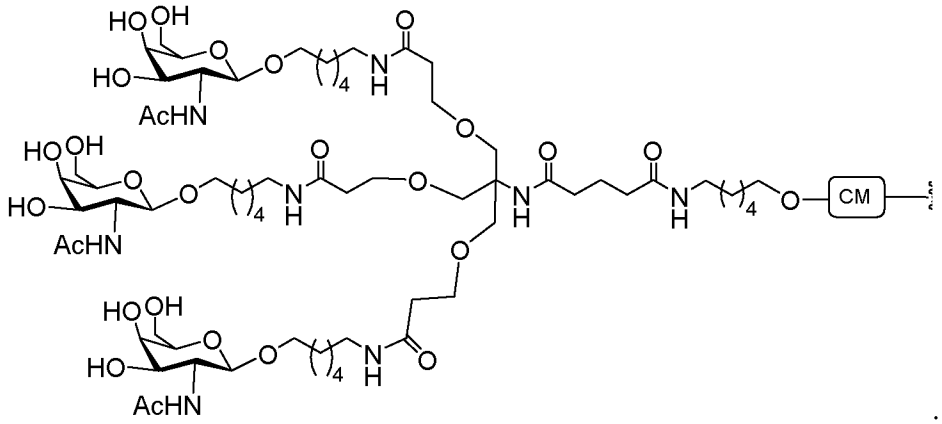
Compound 116 (0.74 g, 0.4 mmol) was dissolved in 1:1 methanol/ethyl acetate (5 mL/5 mL). Palladium on carbon (wet, 0.074 g) was added. The reaction mixture was flushed with hydrogen and stirred at room temperature under hydrogen for 12 h. The reaction mixture was filtered through a pad of celite. The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

Compound 117 (0.63 g, 0.36 mmol) was dissolved in anhydrous DMF (3 mL). To this solution *N*,*N*-Diisopropylethylamine (70 µL, 0.4 mmol) and pentafluorophenyl trifluoroacetate (72 µL, 0.42 mmol) were added. The reaction mixture was stirred at room temperature for 12 h and poured into a aqueous saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane, washed with brine and dried over anhydrous Na_2SO_4. The dichloromethane solution was concentrated to dryness and purified with silica gel column chromatography and eluted with 5 to 10 % MeOH in dichloromethane to yield compound 118 (0.51 g, 79%). The structure was confirmed by LCMS and ^{1}H and ^{1}H and ^{19}F NMR.

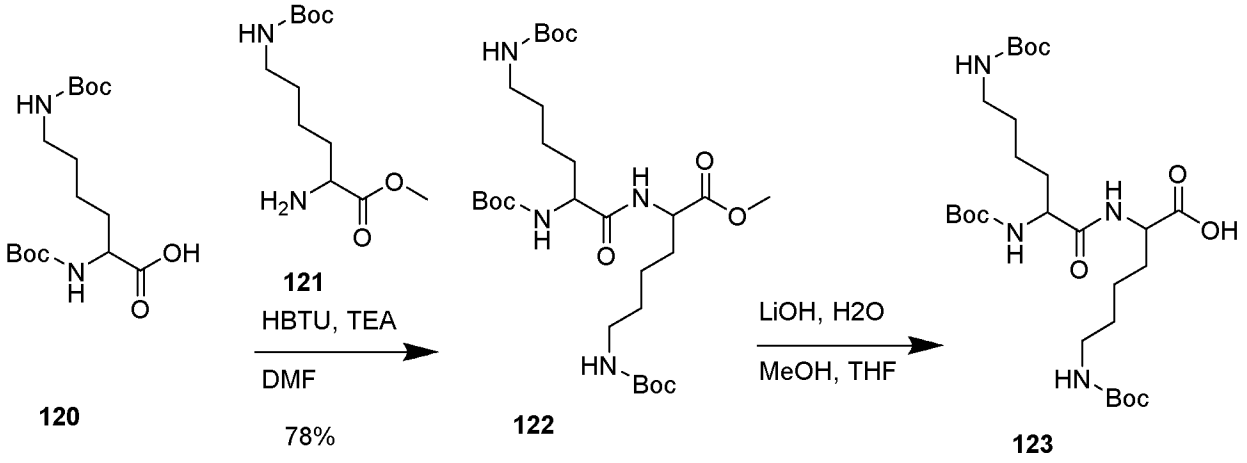


Oligomeric Compound 119, comprising a $GalNAc_3$-7 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-7 ($GalNAc_3$-7_a) can be combined with any cleavable moiety to provide a variety of conjugate groups.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

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



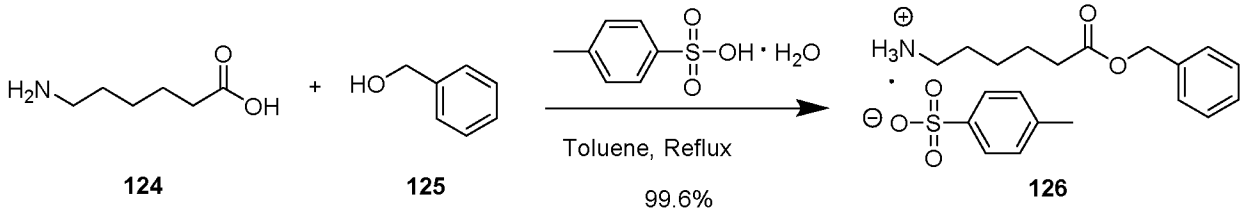
Example 49: Preparation of Oligonucleotide 132 Comprising GalNAc$_3$-5



Compound 120 (14.01 g, 40 mmol) and HBTU (14.06 g, 37 mmol) were dissolved in anhydrous DMF (80 mL). Triethylamine (11.2 mL, 80.35 mmol) was added and stirred for 5 min. The reaction mixture was cooled in an ice bath and a solution of compound 121 (10 g, mmol) in anhydrous DMF (20 mL) was added. Additional triethylamine (4.5 mL, 32.28 mmol) was added and the reaction mixture was stirred for 18 h under an argon atmosphere. The reaction was monitored by TLC (ethyl acetate:hexane; 1:1; Rf = 0.47). The solvent was removed under reduced pressure. The residue was taken up in EtOAc (300 mL) and washed with 1M $NaHSO_4$ (3 x 150 mL), aqueous saturated $NaHCO_3$ solution (3 x 150 mL) and brine (2 x 100 mL). Organic layer was dried with Na_2SO_4. Drying agent was removed by filtration and organic layer was concentrated by rotary evaporation. Crude mixture was purified by silica gel column chromatography and eluted by using 35 – 50% EtOAc in hexane to yield a compound 122 (15.50 g, 78.13%). The structure was confirmed by LCMS and ^{1}H NMR analysis. Mass *m/z* 589.3 $[M + H]^+$.

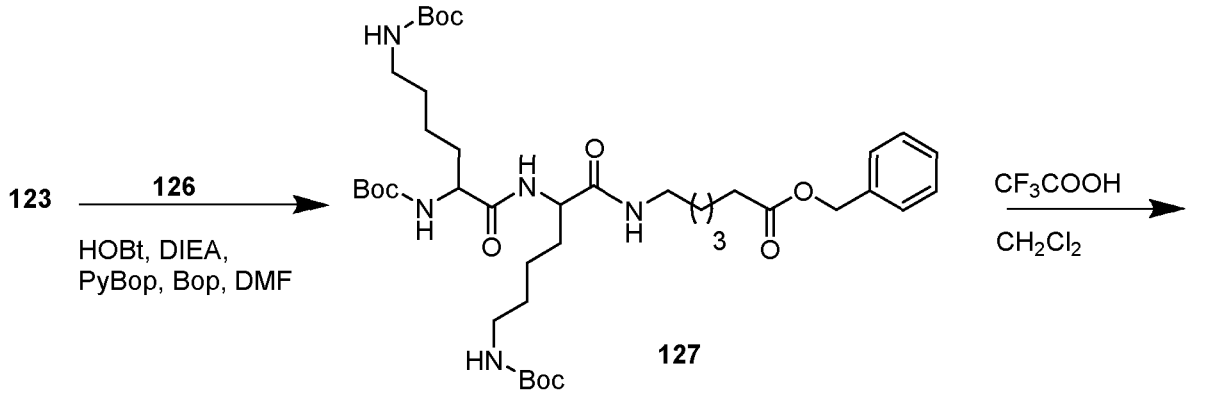
A solution of LiOH (92.15 mmol) in water (20 mL) and THF (10 mL) was added to a cooled solution of Compound 122 (7.75 g,13.16 mmol) dissolved in methanol (15 mL). The reaction mixture was stirred at

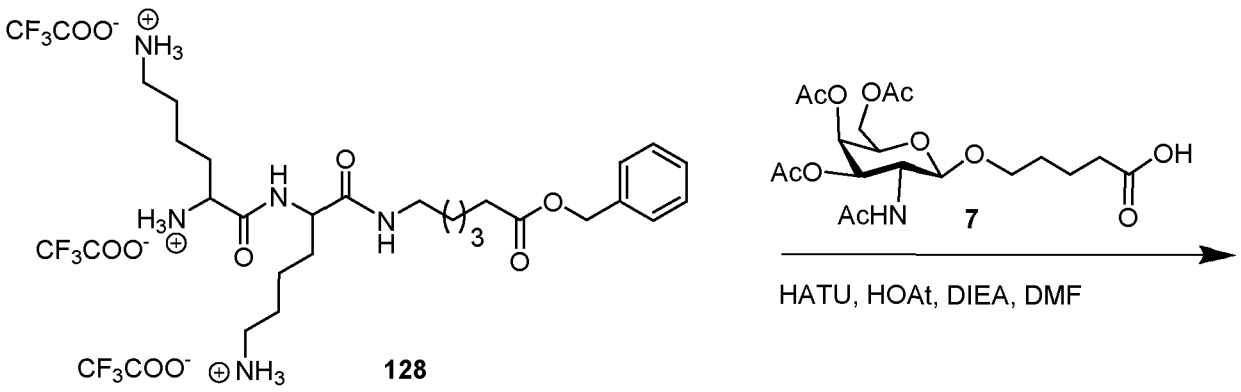
room temperature for 45 min. and monitored by TLC (EtOAc:hexane; 1:1). The reaction mixture was concentrated to half the volume under reduced pressure. The remaining solution was cooled an ice bath and neutralized by adding concentrated HCl. The reaction mixture was diluted, extracted with EtOAc (120 mL) and washed with brine (100 mL). An emulsion formed and cleared upon standing overnight. The organic layer was separated dried (Na_2SO_4), filtered and evaporated to yield Compound 123 (8.42 g). Residual salt is the likely cause of excess mass. LCMS is consistent with structure. Product was used without any further purification. M.W.cal:574.36; M.W.fd:575.3 $[M + H]^+$.

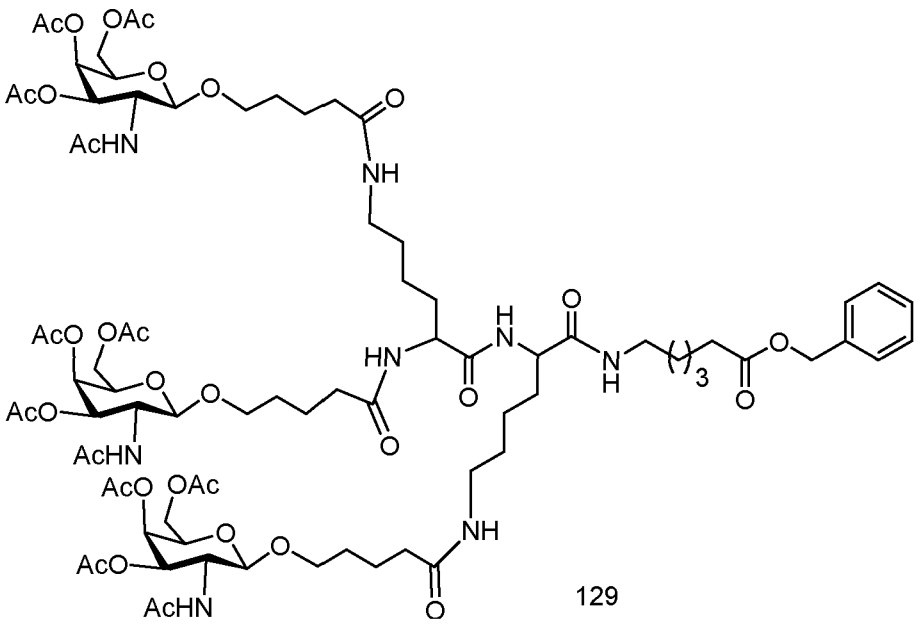


124 **125** **126**

Compound 126 was synthesized following the procedure described in the literature (*J. Am. Chem. Soc.* 2011, *133*, 958-963).


123
126
HOBt, DIEA,
PyBop, Bop, DMF
Boc
HN
Boc
N
H
O
H
N
O
N
H
3
O
O
HN
Boc
127
CF3COOH
CH2Cl2


CF3COO-
NH3
H3N
CF3COO-
CF3COO-
NH3
128
AcO
OAc
AcO
AcHN
7
OH
O
HATU, HOAt, DIEA, DMF


AcO
OAc
AcO
AcHN
O
O
NH
HN
O
O
N
H
3
O
O
AcO
OAc
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AcHN
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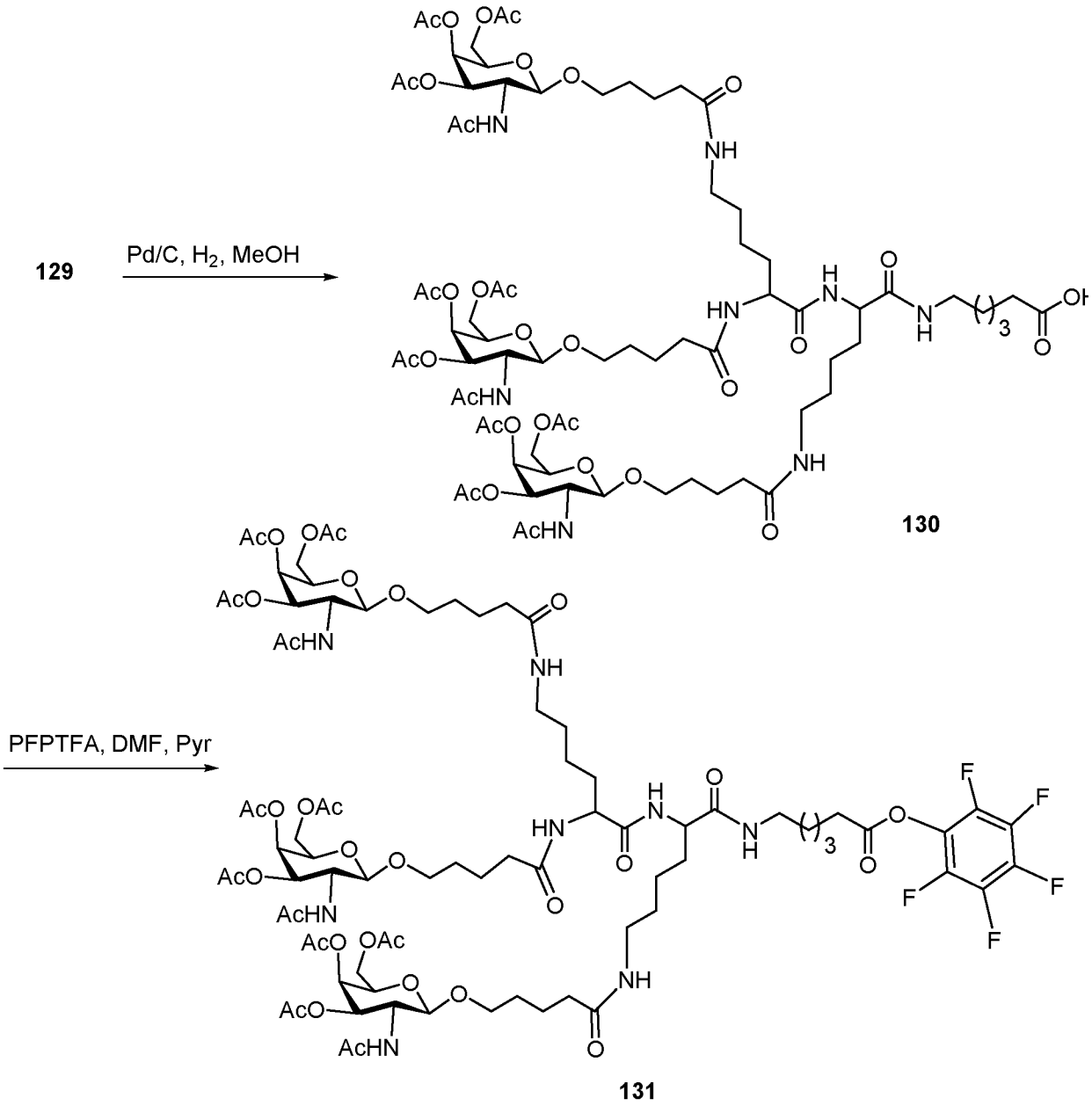
AcHN
NH
O
129



Compound 123 (7.419 g, 12.91 mmol), HOBt (3.49 g, 25.82 mmol) and compound 126 (6.33 g, 16.14 mmol) were dissolved in and DMF (40 mL) and the resulting reaction mixture was cooled in an ice bath. To this *N*,*N*-Diisopropylethylamine (4.42 mL, 25.82 mmol), PyBop (8.7 g, 16.7 mmol) followed by Bop coupling reagent (1.17 g, 2.66 mmol) were added under an argon atmosphere. The ice bath was removed and the solution was allowed to warm to room temperature. The reaction was completed after 1 h as determined by TLC (DCM:MeOH:AA; 89:10:1). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with 1 M $NaHSO_4$ (3x100 mL), aqueous saturated $NaHCO_3$ (3x100 mL) and brine (2x100 mL). The organic phase separated dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography with a gradient of 50% hexanes/EtOAC to 100% EtOAc to yield Compound 127 (9.4 g) as a white foam. LCMS and ^1H NMR

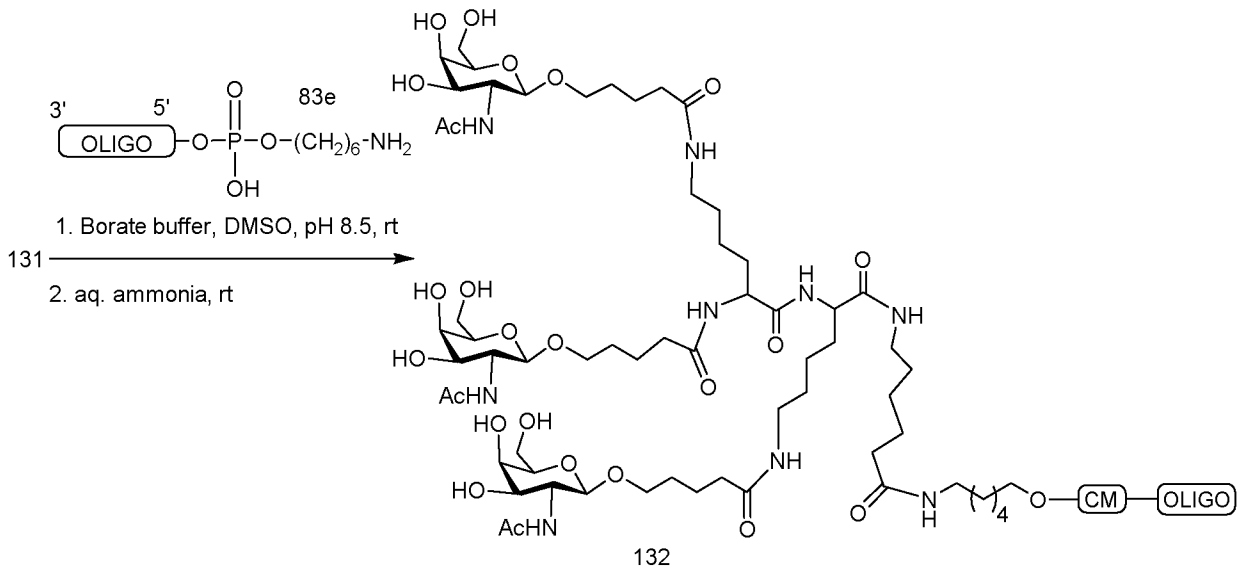
were consistent with structure. Mass *m/z* 778.4 $[M + H]^+$.

Trifluoroacetic acid (12 mL) was added to a solution of compound 127 (1.57 g, 2.02 mmol) in dichloromethane (12 mL) and stirred at room temperature for 1 h. The reaction mixture was co-evaporated with toluene (30 mL) under reduced pressure to dryness. The residue obtained was co-evaporated twice with acetonitrile (30 mL) and toluene (40 mL) to yield Compound 128 (1.67 g) as trifluoro acetate salt and used for next step without further purification. LCMS and ^{1}H NMR were consistent with structure. Mass *m/z* 478.2 $[M + H]^+$.

Compound 7 (0.43 g, 0.963 mmol), HATU (0.35 g, 0.91 mmol), and HOAt (0.035 g, 0.26 mmol) were combined together and dried for 4 h over P_2O_5 under reduced pressure in a round bottom flask and then dissolved in anhydrous DMF (1 mL) and stirred for 5 min. To this a solution of compound 128 (0.20 g, 0.26 mmol) in anhydrous DMF (0.2 mL) and *N*,*N*-Diisopropylethylamine (0.2 mL) was added. The reaction mixture was stirred at room temperature under an argon atmosphere. The reaction was complete after 30 min as determined by LCMS and TLC (7% MeOH/DCM). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (30 mL) and washed with 1 M $NaHSO_4$ (3x20 mL), aqueous saturated $NaHCO_3$ (3 x 20 mL) and brine (3x20 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 5-15% MeOH in dichloromethane to yield Compound 129 (96.6 mg). LC MS and ^{1}H NMR are consistent with structure. Mass *m/z* 883.4 $[M + 2H]^+$.

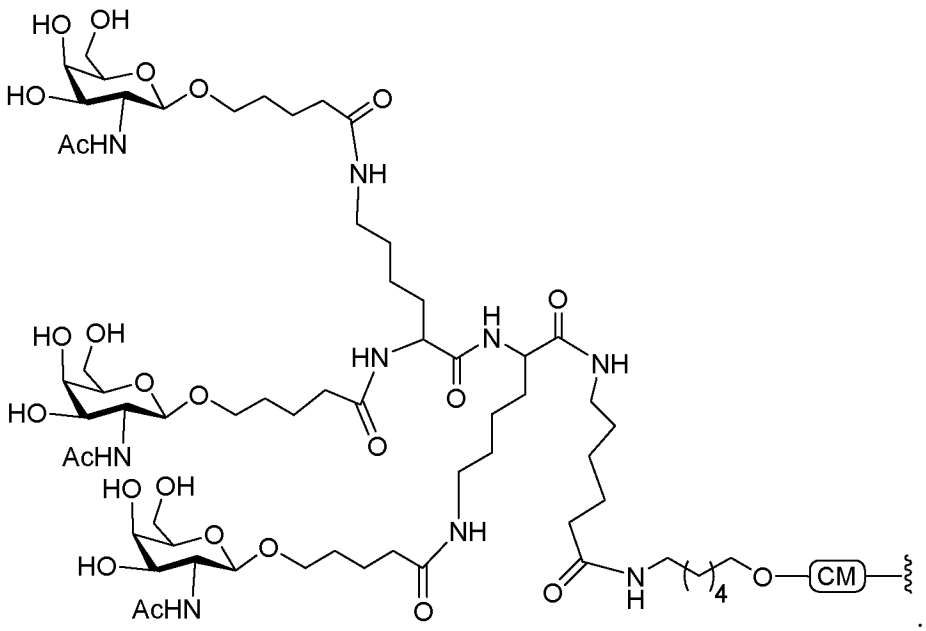
Compound 129 (0.09 g, 0.051 mmol) was dissolved in methanol (5 mL) in 20 mL scintillation vial. To this was added a small amount of 10% Pd/C (0.015 mg) and the reaction vessel was flushed with H_2 gas. The reaction mixture was stirred at room temperature under H_2 atmosphere for 18 h. The reaction mixture was filtered through a pad of Celite and the Celite pad was washed with methanol. The filtrate washings were pooled together and concentrated under reduced pressure to yield Compound 130 (0.08 g). LCMS and ^{1}H NMR were consistent with structure. The product was used without further purification. Mass *m/z* 838.3 $[M + 2H]^+$.

To a 10 mL pointed round bottom flask were added compound 130 (75.8 mg, 0.046 mmol), 0.37 M pyridine/DMF (200 µL) and a stir bar. To this solution was added 0.7 M pentafluorophenyl trifluoroacetate/DMF (100 µL) drop wise with stirring. The reaction was completed after 1 h as determined by LC MS. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (~ 10 mL). The organic layer was partitioned against $NaHSO_4$ (1 M, 10 mL) , aqueous saturated $NaHCO_3$ (10 mL) and brine (10 mL) three times each. The organic phase separated and dried over Na_2SO_4, filtered and concentrated to yield Compound 131 (77.7 mg). LCMS is consistent with structure. Used without further purification. Mass *m/z* 921.3 $[M + 2H]^+$.

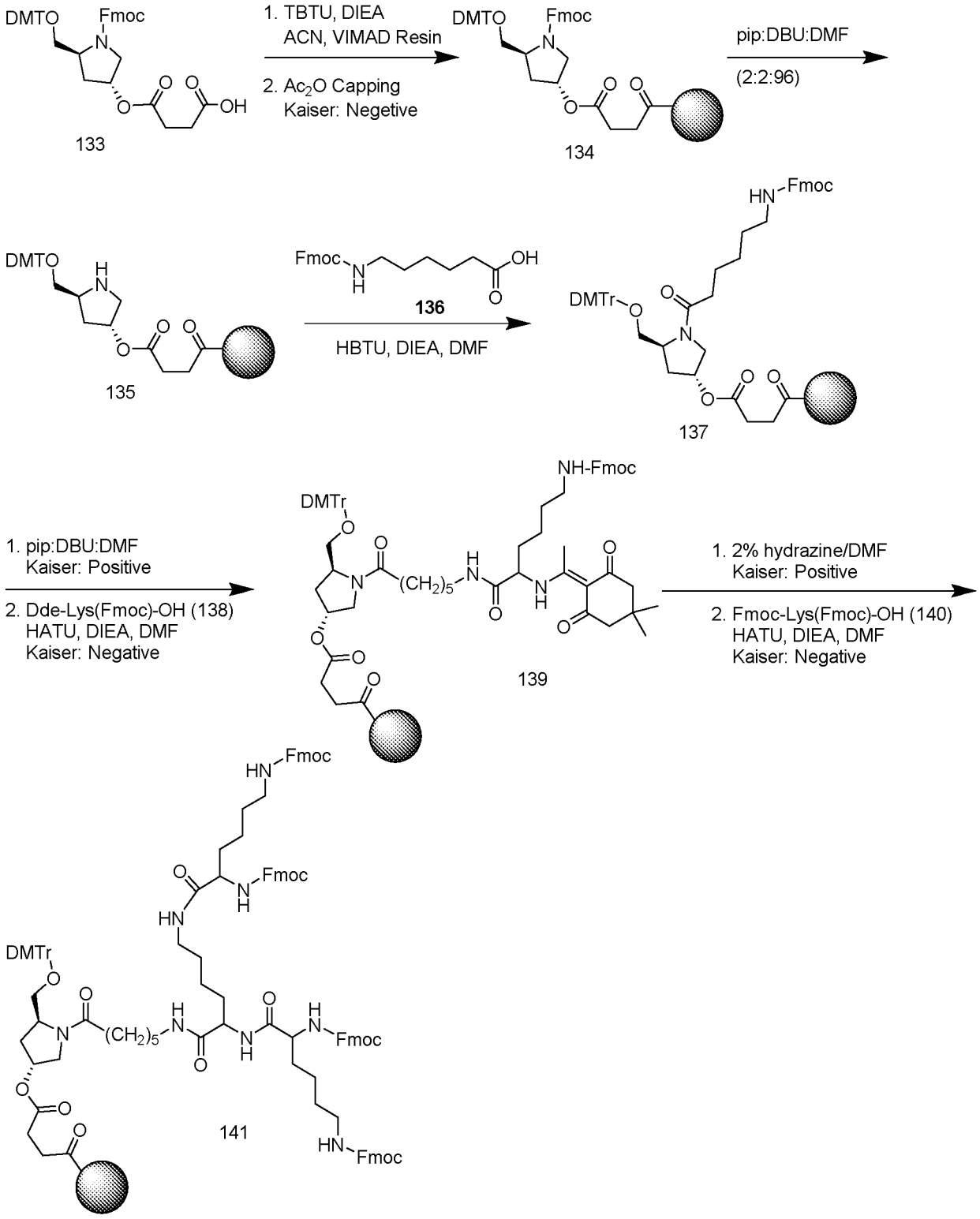


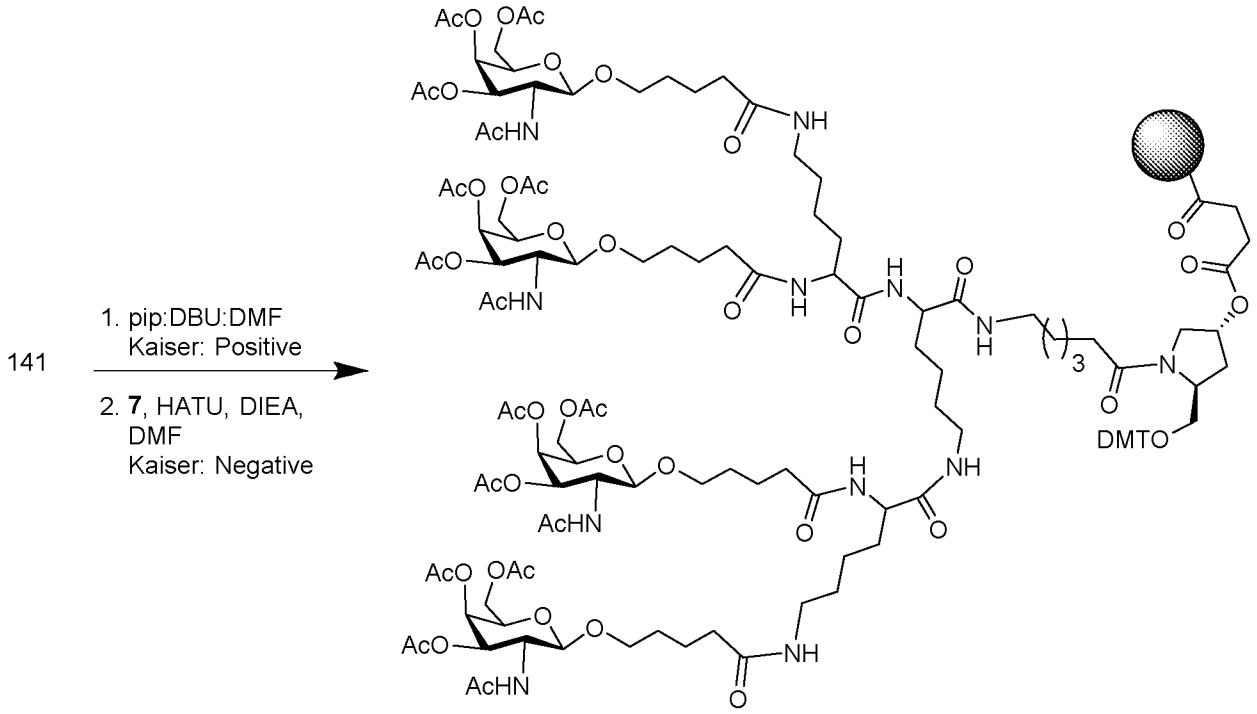
Oligomeric Compound 132, comprising a $GalNAc_3$-5 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-5 ($GalNAc_3$-5_a) can be combined with any cleavable moiety to provide a variety of conjugate groups.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

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



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



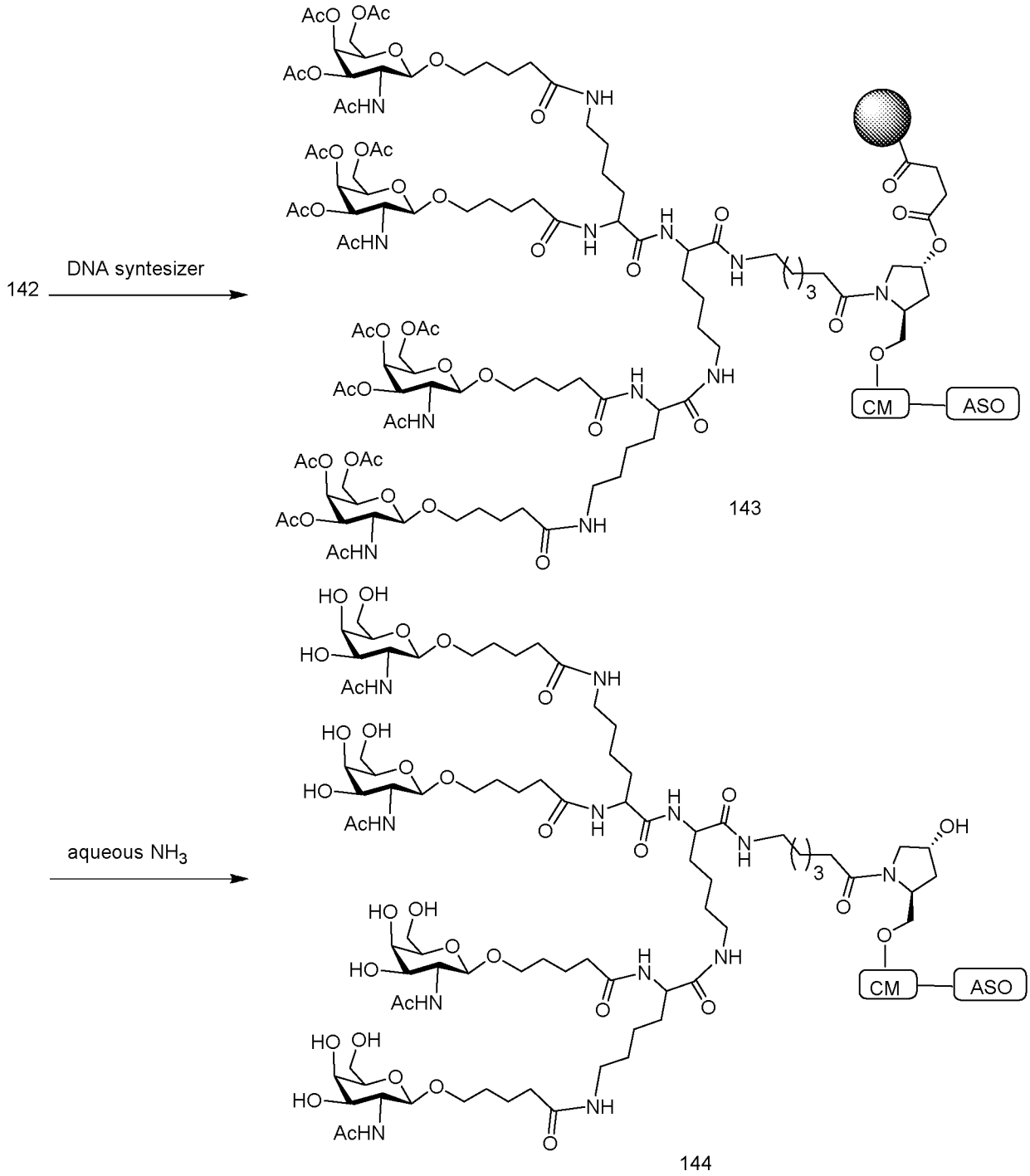


142

Synthesis of Compound 134. To a Merrifield flask was added aminomethyl VIMAD resin (2.5 g, 450 μmol/g) that was washed with acetonitrile, dimethylformamide, dichloromethane and acetonitrile. The resin was swelled in acetonitrile (4 mL). Compound 133 was pre-activated in a 100 mL round bottom flask by adding 20 (1.0 mmol, 0.747 g), TBTU (1.0 mmol, 0.321 g), acetonitrile (5 mL) and DIEA (3.0 mmol, 0.5 mL). This solution was allowed to stir for 5 min and was then added to the Merrifield flask with shaking. The suspension was allowed to shake for 3 h. The reaction mixture was drained and the resin was washed with acetonitrile, DMF and DCM. New resin loading was quantitated by measuring the absorbance of the DMT cation at 500 nm (extinction coefficient = 76000) in DCM and determined to be 238 μmol/g. The resin was capped by suspending in an acetic anhydride solution for ten minutes three times.

The solid support bound compound 141 was synthesized using iterative Fmoc-based solid phase peptide synthesis methods. A small amount of solid support was withdrawn and suspended in aqueous ammonia (28-30 wt%) for 6 h. The cleaved compound was analyzed by LC-MS and the observed mass was consistent with structure. Mass *m/z* 1063.8 $[M + 2H]^+$.

The solid support bound compound 142 was synthesized using solid phase peptide synthesis methods.



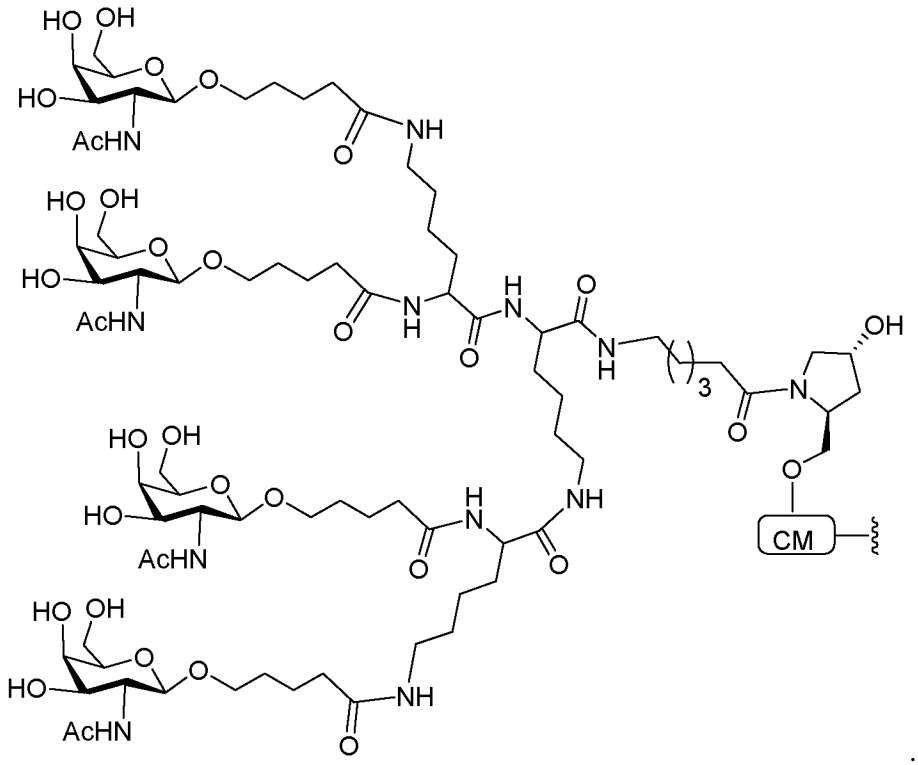
The solid support bound compound 143 was synthesized using standard solid phase synthesis on a DNA synthesizer.

The solid support bound compound 143 was suspended in aqueous ammonia (28-30 wt%) and heated at 55 °C for 16 h. The solution was cooled and the solid support was filtered. The filtrate was concentrated and the residue dissolved in water and purified by HPLC on a strong anion exchange column. The fractions containing full length compound 144 were pooled together and desalted. The resulting $GalNAc_4$-11

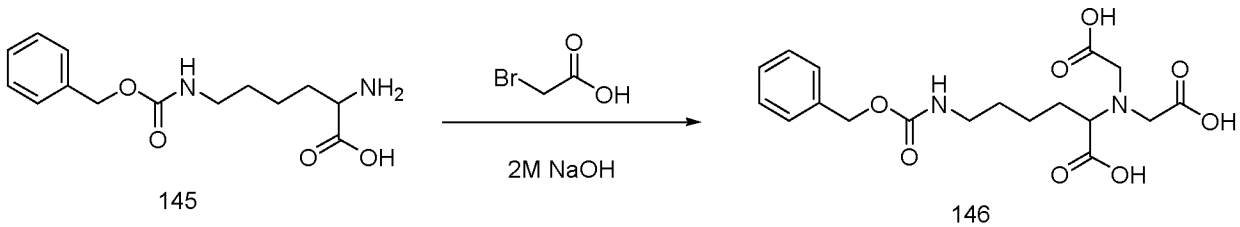
conjugated oligomeric compound was analyzed by LC-MS and the observed mass was consistent with structure.

The $GalNAc_4$ cluster portion of the conjugate group $GalNAc_4$-11 ($GalNAc_4$-11_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-.

The structure of $GalNAc_4$-11 ($GalNAc_4$-11_a-CM) is shown below:

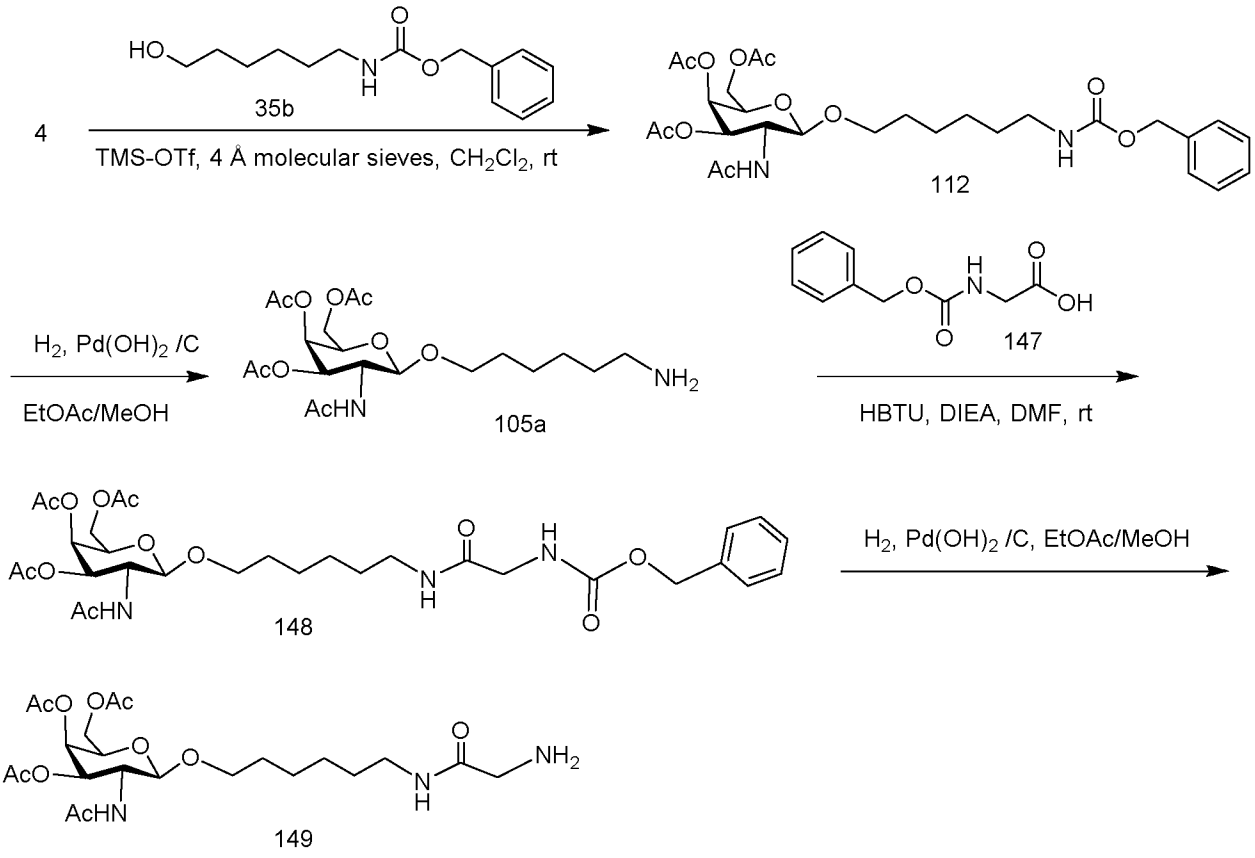


Example 51: Preparation of Oligonucleotide 155 Comprising $GalNAc_3$-6



145 146

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

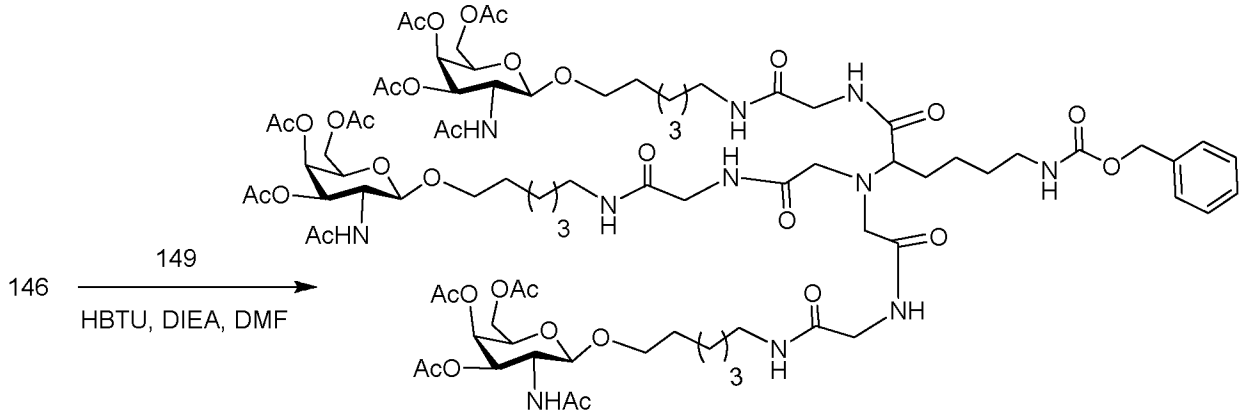


Compound 4 (15 g, 45.55 mmol) and compound 35b (14.3 grams, 57 mmol) were dissolved in CH_2Cl_2 (200 ml). Activated molecular sieves (4 Å. 2 g, powdered) were added, and the reaction was allowed to stir for 30 minutes under nitrogen atmosphere. TMS-OTf was added (4.1 ml, 22.77 mmol) and the reaction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

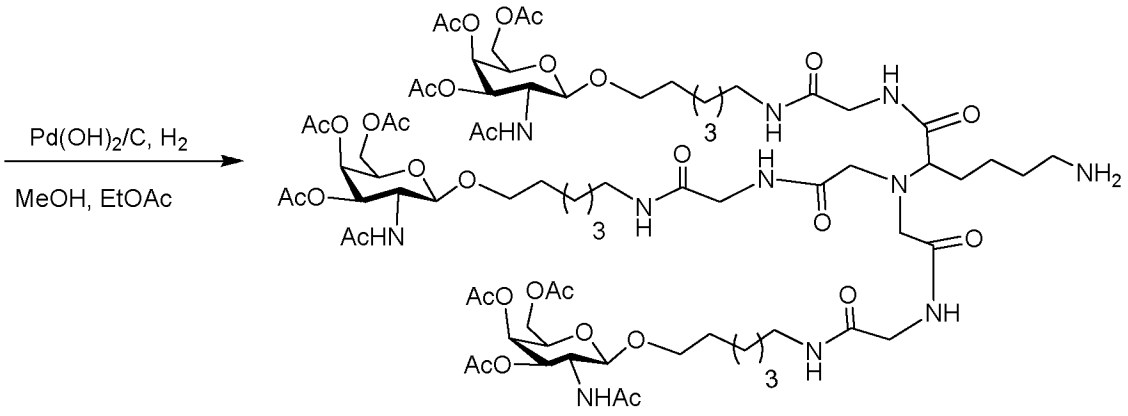
Compound 112 (4.27 g, 7.35 mmol) was dissolved in 1:1 MeOH/EtOAc (40 ml). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon, 400 mg) was added, and hydrogen gas was bubbled through the solution for 30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



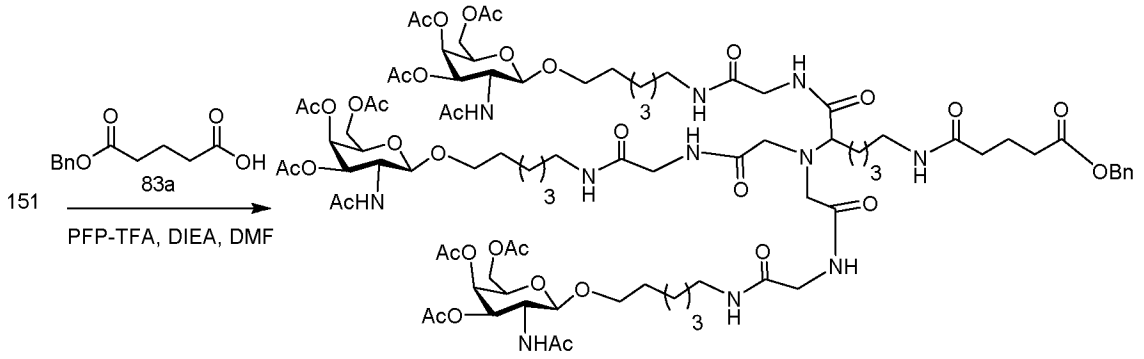
150



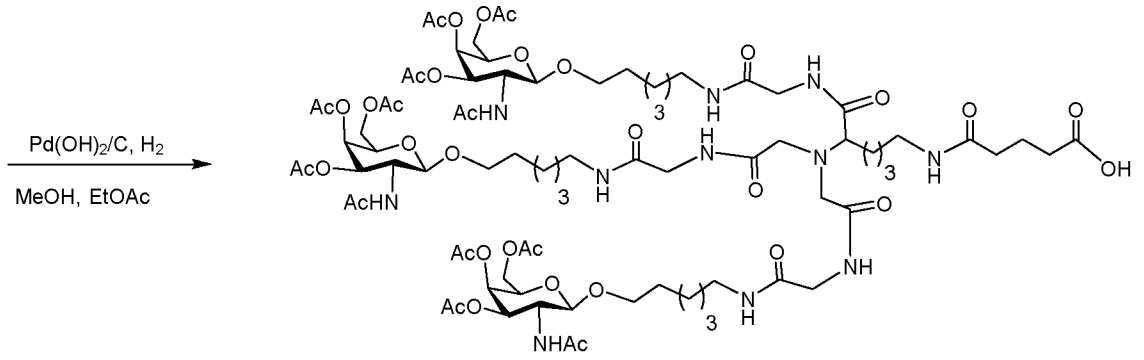
151

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.

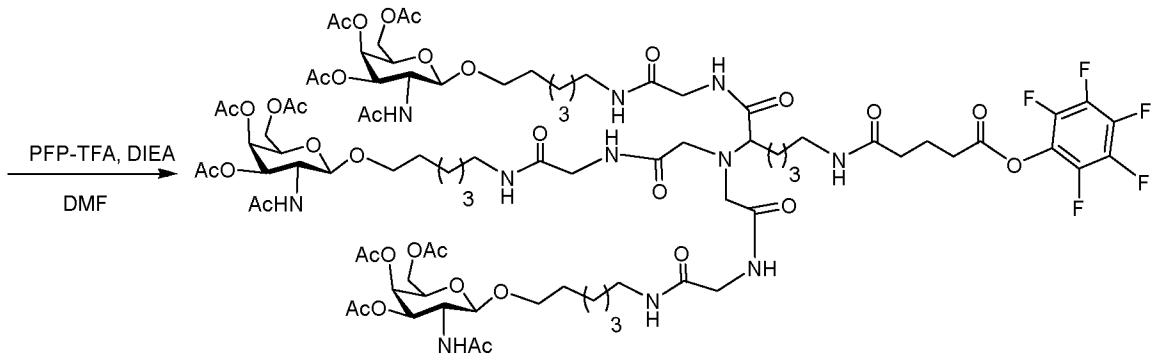
Compound 150 (0.62 g) was dissolved in 1:1 MeOH/ EtOAc (5 L). The reaction mixture was purged by bubbling a stream of argon through the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (60 mg). Hydrogen gas was bubbled through the solution for 30 minutes. Upon completion (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.



152



153



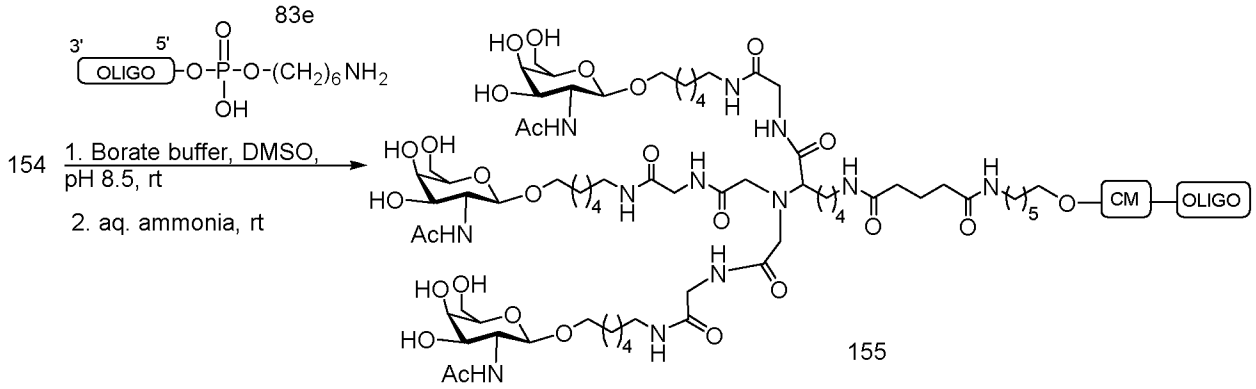
154

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

silica gel column chromatography (2-10 % MeOH in CH_2Cl_2) to yield Compound 152 (0.35 g, 55 %). LCMS and ^{1}H NMR were consistent with the desired product.

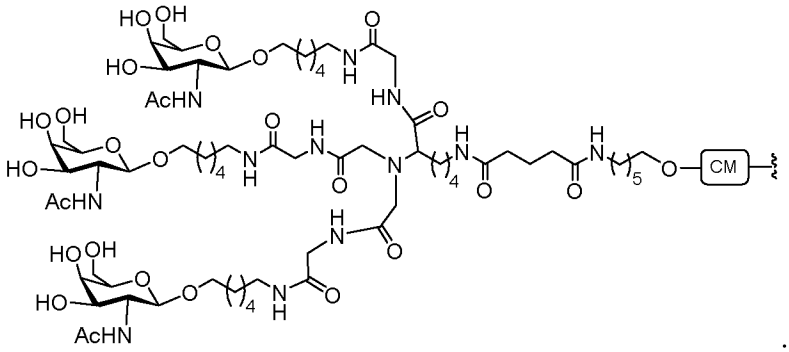
Compound 152 (0.35 g, 0.182 mmol) was dissolved in 1:1 MeOH/EtOAc (10 mL). The reaction mixture was purged by bubbling a stream of argon thru the solution for 15 minutes. Pearlman's catalyst (palladium hydroxide on carbon) was added (35 mg). Hydrogen gas was bubbled thru the solution for 30 minutes.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

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

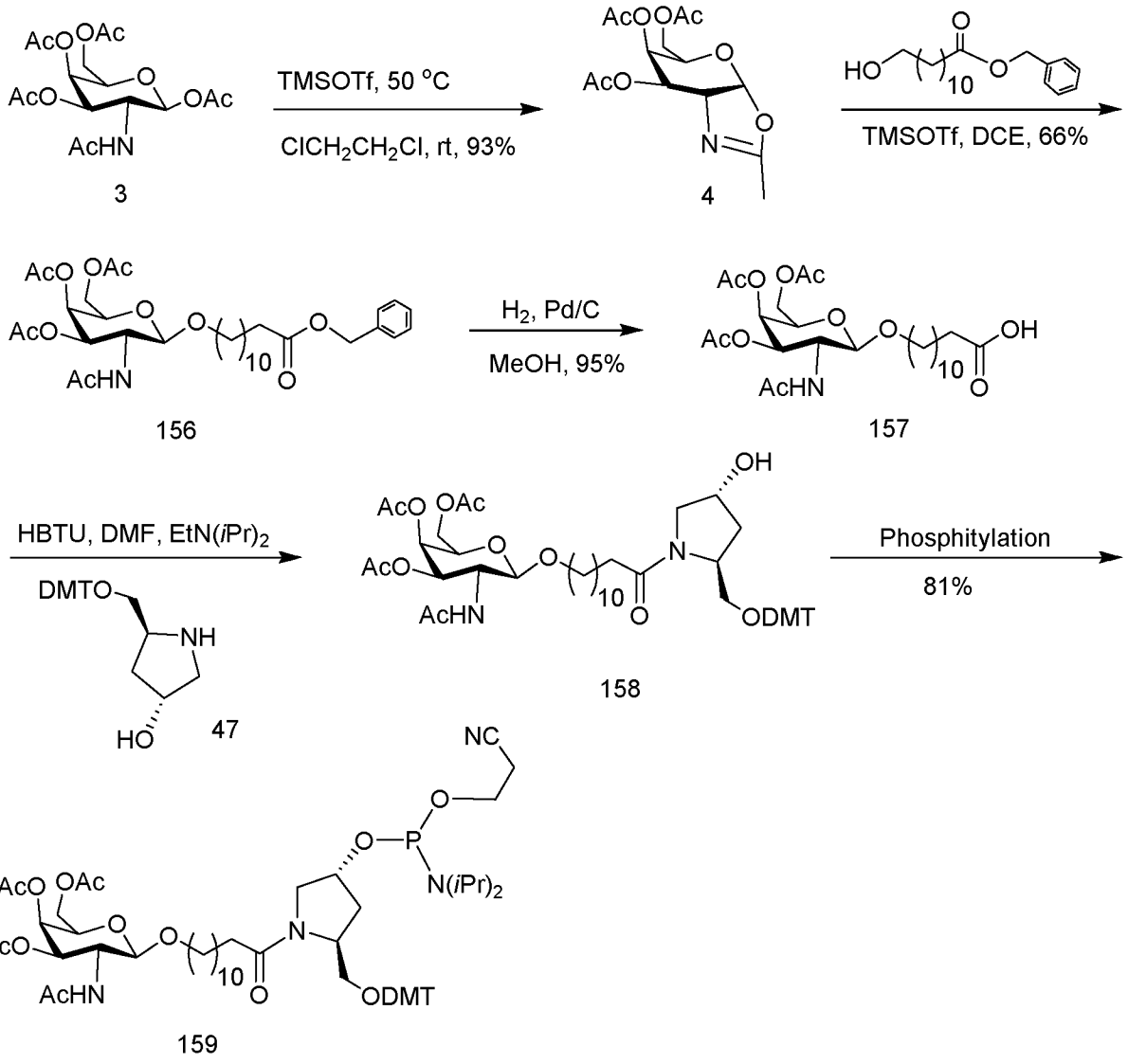


Oligomeric Compound 155, comprising a $GalNAc_3$-6 conjugate group, was prepared using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-6 ($GalNAc_3$-6_a) can be combined with any cleavable moiety to provide a variety of conjugate groups.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

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



Example 52: Preparation of Oligonucleotide 160 Comprising GalNAc$_3$-9



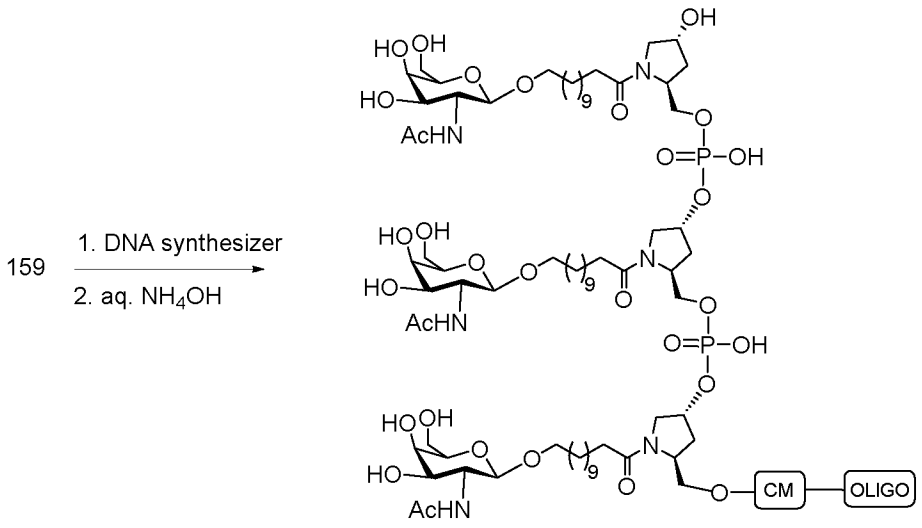
Compound 156 was synthesized following the procedure described in the literature (*J. Med. Chem.* 2004, *47*, 5798-5808).

Compound 156, (18.60 g, 29.28 mmol) was dissolved in methanol (200 mL). Palladium on carbon (6.15 g, 10 wt%, loading (dry basis), matrix carbon powder, wet) was added. The reaction mixture was

stirred at room temperature under hydrogen for 18 h. The reaction mixture was filtered through a pad of celite and the celite pad was washed thoroughly with methanol. The combined filtrate was washed and concentrated to dryness. The residue was purified by silica gel column chromatography and eluted with 5-10 % methanol in dichloromethane to yield Compound 157 (14.26 g, 89%). Mass *m/z* 544.1 $[M-H]^-$.

Compound 157 (5 g, 9.17 mmol) was dissolved in anhydrous DMF (30 mL). HBTU (3.65 g, 9.61 mmol) and *N*,*N*-Diisopropylethylamine (13.73 mL, 78.81 mmol) were added and the reaction mixture was stirred at room temperature for 5 minutes. To this a solution of compound 47 (2.96 g, 7.04 mmol) was added. The reaction was stirred at room temperature for 8 h. The reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution. The mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried (Na_2SO_4), filtered and evaporated. The residue obtained was purified by silica gel column chromatography and eluted with 50% ethyl acetate in hexane to yield compound 158 (8.25g, 73.3%). The structure was confirmed by MS and ^1H NMR analysis.

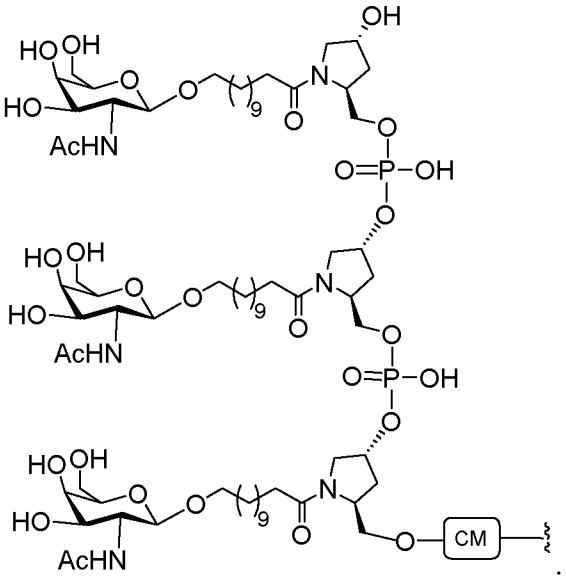
Compound 158 (7.2 g, 7.61 mmol) was dried over P_2O_5 under reduced pressure. The dried compound was dissolved in anhydrous DMF (50 mL). To this 1H-tetrazole (0.43 g, 6.09 mmol) and *N*-methylimidazole (0.3 mL, 3.81 mmol) and 2-cyanoethyl-*N*,*N*,*N*',*N*'-tetraisopropyl phosphorodiamidite (3.65 mL, 11.50 mmol) were added. The reaction mixture was stirred t under an argon atmosphere for 4 h. The reaction mixture was diluted with ethyl acetate (200 mL). The reaction mixture was washed with saturated $NaHCO_3$ and brine. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography and eluted with 50-90 % ethyl acetate in hexane to yield Compound 159 (7.82 g, 80.5%). The structure was confirmed by LCMS and ^{31}P NMR analysis.



160

Oligomeric Compound 160, comprising a $GalNAc_3$-9 conjugate group, was prepared using standard oligonucleotide synthesis procedures. Three units of compound 159 were coupled to the solid support, followed by nucleotide phosphoramidites. Treatment of the protected oligomeric compound with aqueous

ammonia yielded compound 160. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-9 ($GalNAc_3$-9_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-9 ($GalNAc_3$-9_a-CM) is shown below:



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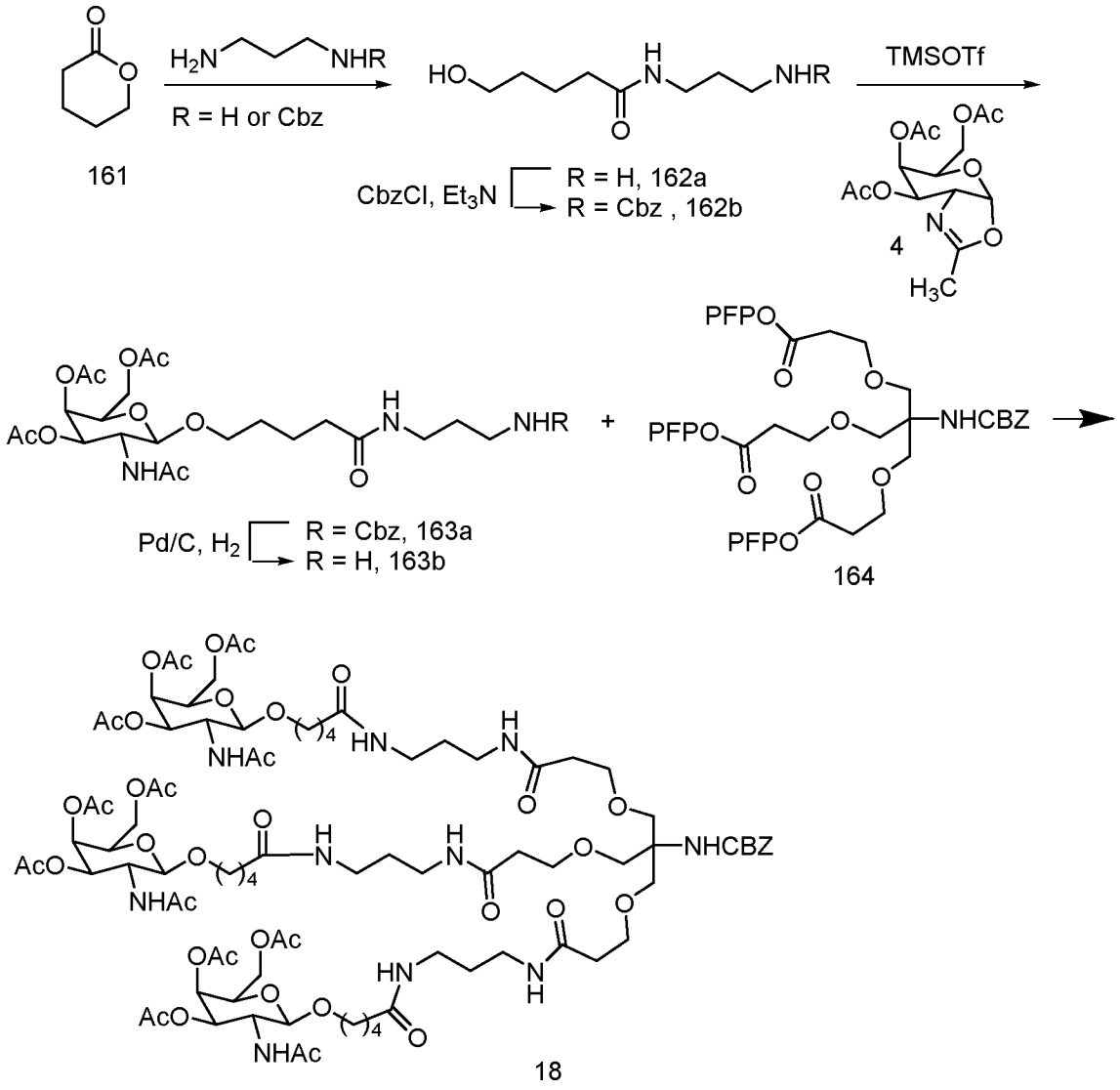
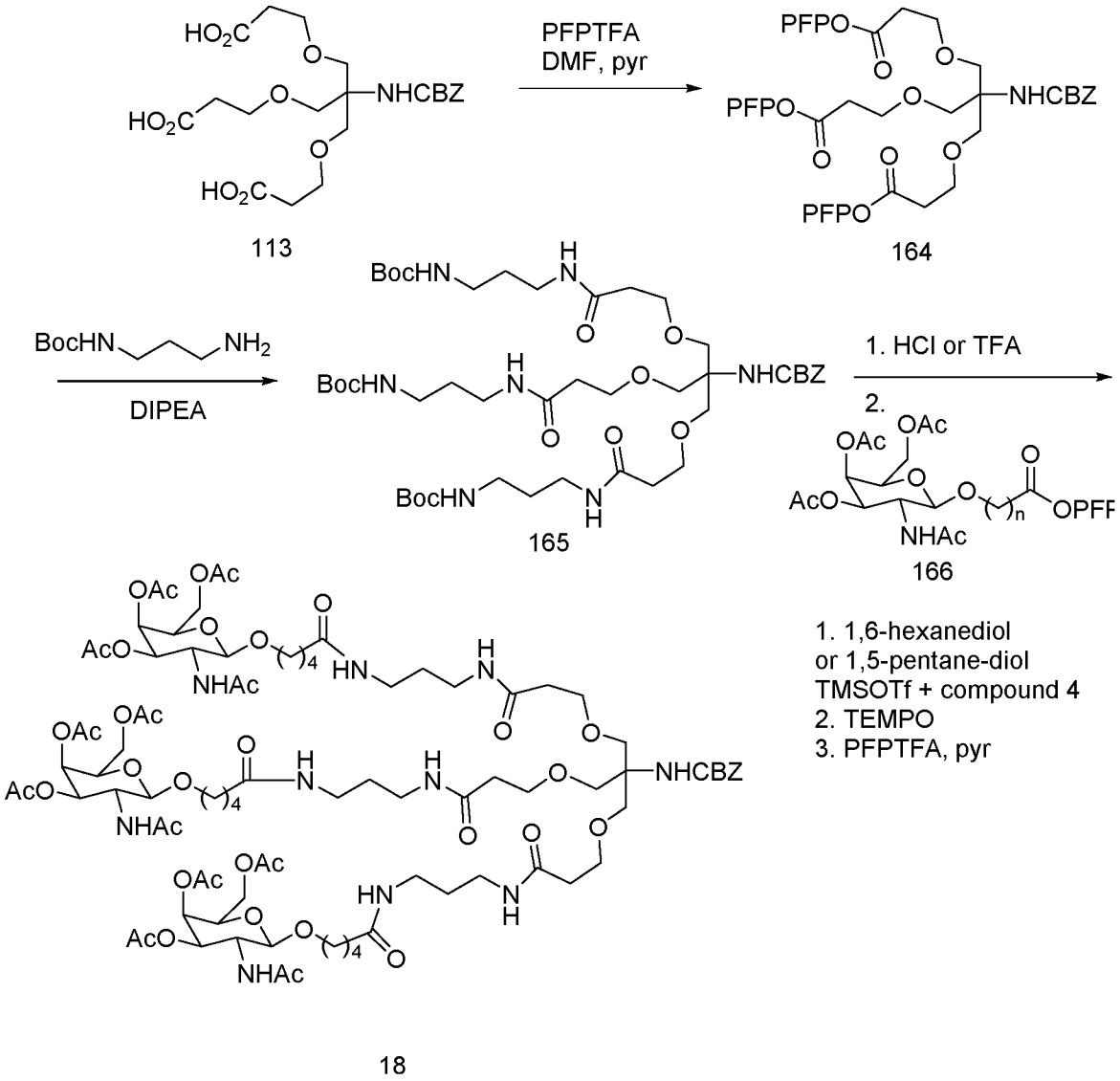
Example 53: Alternate procedure for preparation of Compound 18 ($GalNAc_3$-1a and $GalNAc_3$-3a)



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	2256
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**	2257
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**	2257
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**	2258
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**	2258

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	2256
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**	2257
ISIS 664507	**GalNAc$_3$-2$_{a\text{-}o'}$$A_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-2**	2258
ISIS 661161	**GalNAc$_3$-3$_{a\text{-}o'}$$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**	2258

ISIS 666224	**$GalNAc_3$-5_{a-o}-A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-5**	2258
ISIS 666961	**$GalNAc_3$-6_{a-o}-A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-6**	2258
ISIS 666981	**$GalNAc_3$-7_{a-o}-A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-7**	2258
ISIS 666881	**$GalNAc_3$-10_{a-o}-A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}$ $^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**$GalNAc_3$-10**	2258

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	2248
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	2249
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	2249

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	2250
		2	59.66	
		6	23.50	
ISIS 651900	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	0.2	62.75	2251
		0.6	29.14	
		2	8.61	
		6	5.62	
ISIS 663748	$T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ks}{}^{m}C_{ko}\mathbf{A_{do'}\text{-}GalNAc_4\text{-}11_a}$	0.2	63.99	2251
		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	2259
ISIS 656172	$T_{es}G_{es}G_{es}T_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{es}G_{es}A_{es}G_{es}G_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-1_a$**	PS	2260
ISIS 656173	$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-1_a$**	PO/PS	2260

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	2256
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**	2257
ISIS 655862	$G_{es}{}^{m}C_{eo}T_{eo}T_{eo}{}^{m}C_{eo}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{eo}{}^{m}C_{eo}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do'}$-GalNAc$_3-1_a$**	5/10/5	**GalNAc$_3$-1**	2257
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**	2258
ISIS 665001	**GalNAc$_3$-8$_{a\text{-}o}$,A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	5/10/5	**GalNAc$_3$-8**	2258
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**	2257
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**	2258
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**	2258

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**	2258
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**	2258
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**	2258

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.

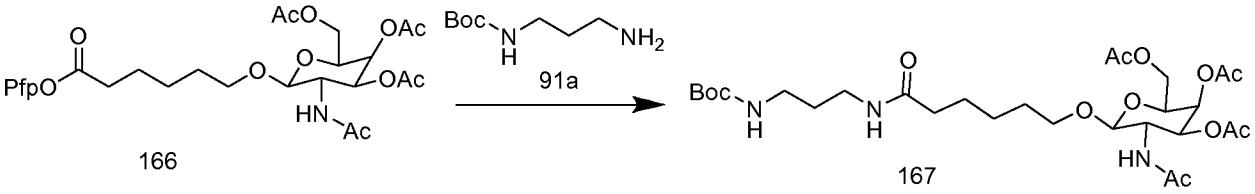
Table 53

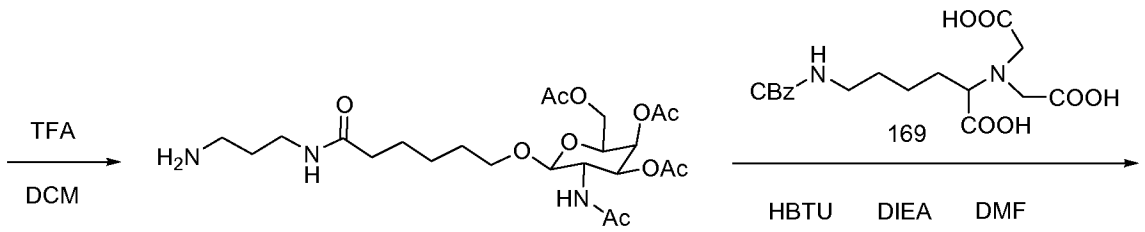
ASO	IC_{50} (nM)	Internucleoside linkages	Conjugate	SEQ ID No.
ISIS 353382	190[a]	PS	none	2256
ISIS 655861	11[a]	PS	**$GalNAc_3$-1**	2257
ISIS 655862	3	PO/PS	**$GalNAc_3$-1**	2257
ISIS 661161	15[a]	PS	**$GalNAc_3$-3**	2258

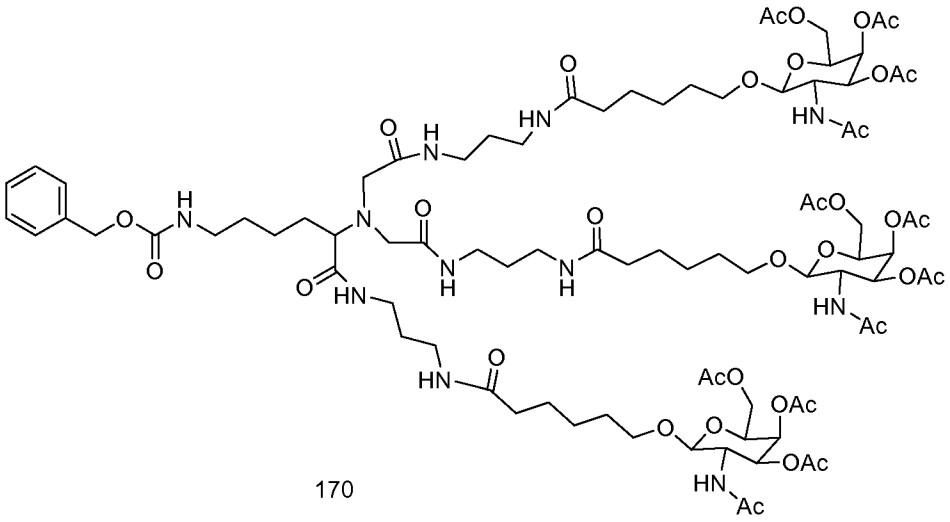
ISIS 665001	20	PS	**GalNAc$_3$-8**	2258
ISIS 664078	55	PS	**GalNAc$_3$-9**	2257
ISIS 666961	22[a]	PS	**GalNAc$_3$-6**	2258
ISIS 664507	30	PS	**GalNAc$_3$-2**	2258
ISIS 666881	30	PS	**GalNAc$_3$-10**	2258
ISIS 666224	30[a]	PS	**GalNAc$_3$-5**	2258
ISIS 666981	40	PS	**GalNAc$_3$-7**	2258

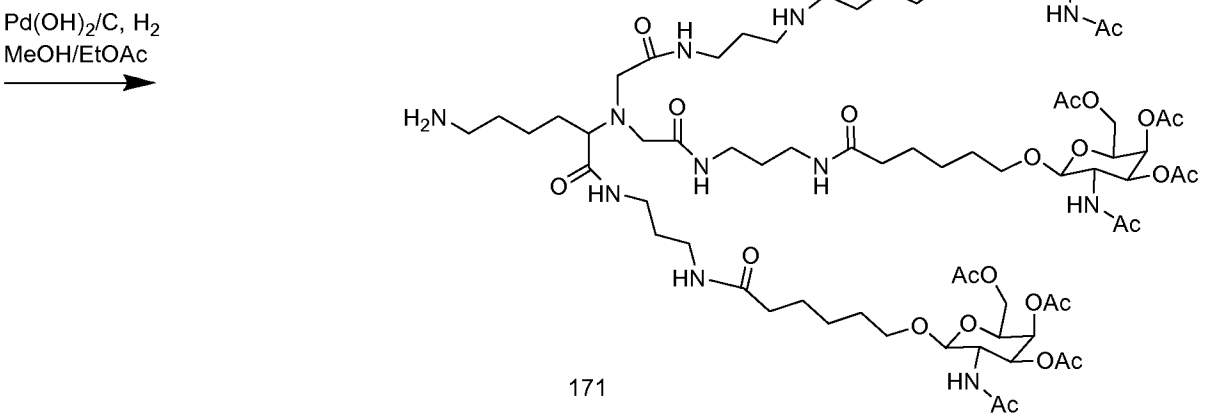
[a]Average of multiple runs.

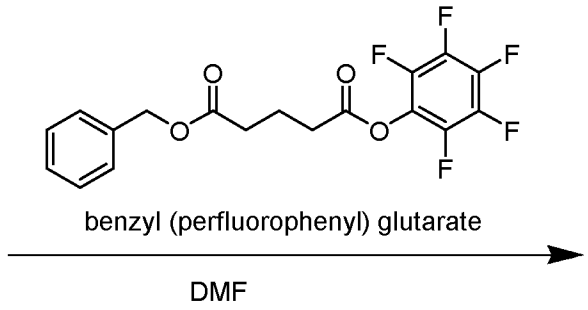
Example 61: Preparation of oligomeric compound 175 comprising GalNAc$_3$-12

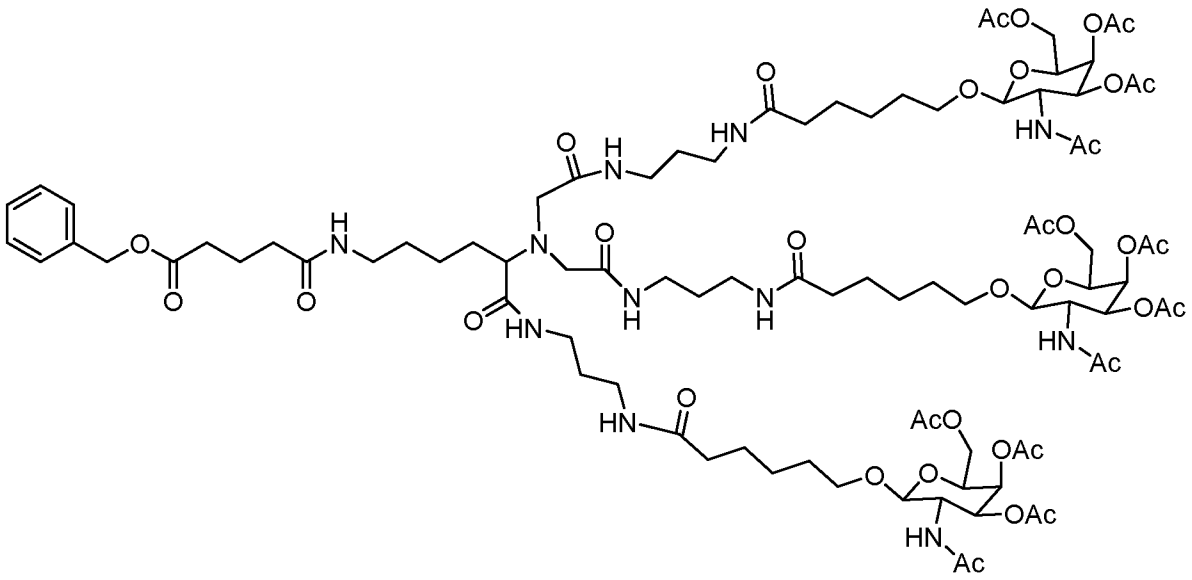

AcO
OAc
Boc
NH2
PfpO
O
OAc
HN
Ac
91a
166
167


HOOC
CBz
COOH
COOH
169
TFA
DCM
H2N
HBTU
DIEA
DMF
168

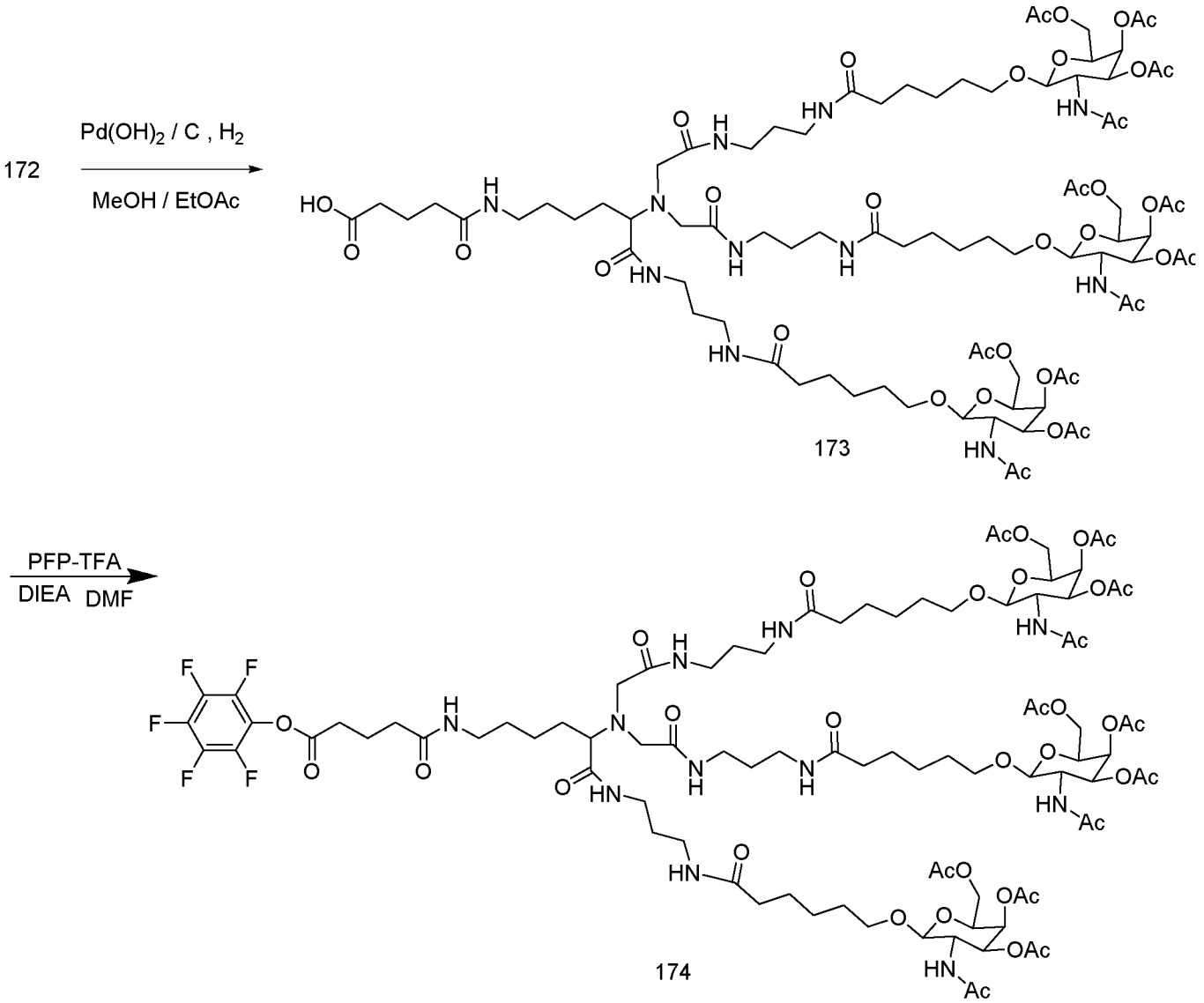

AcO
OAc
HN
Ac
170

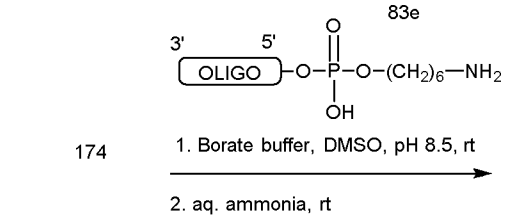

Pd(OH)2/C, H2
MeOH/EtOAc
H2N
AcO
OAc
HN
Ac
171

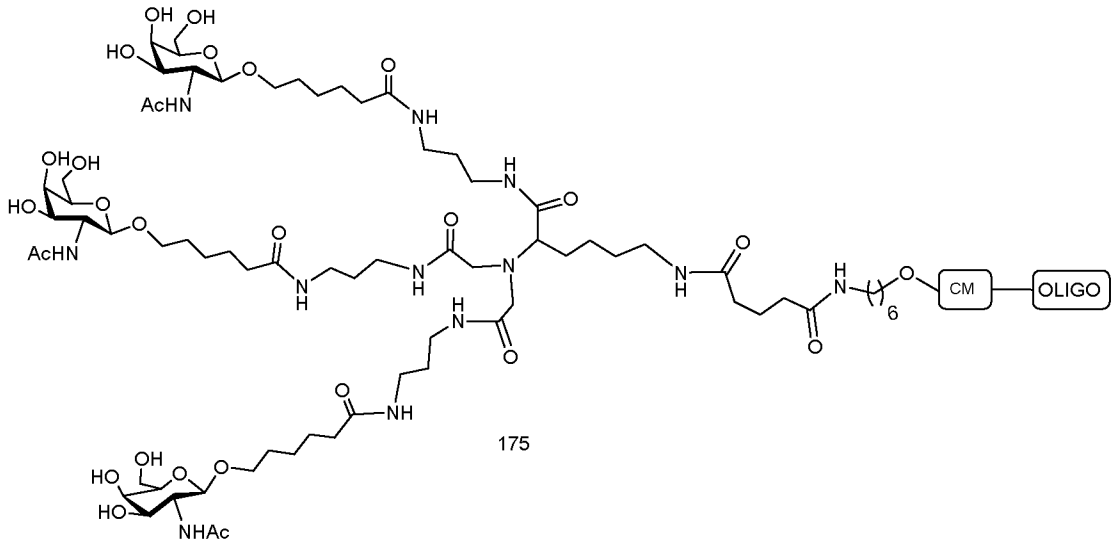




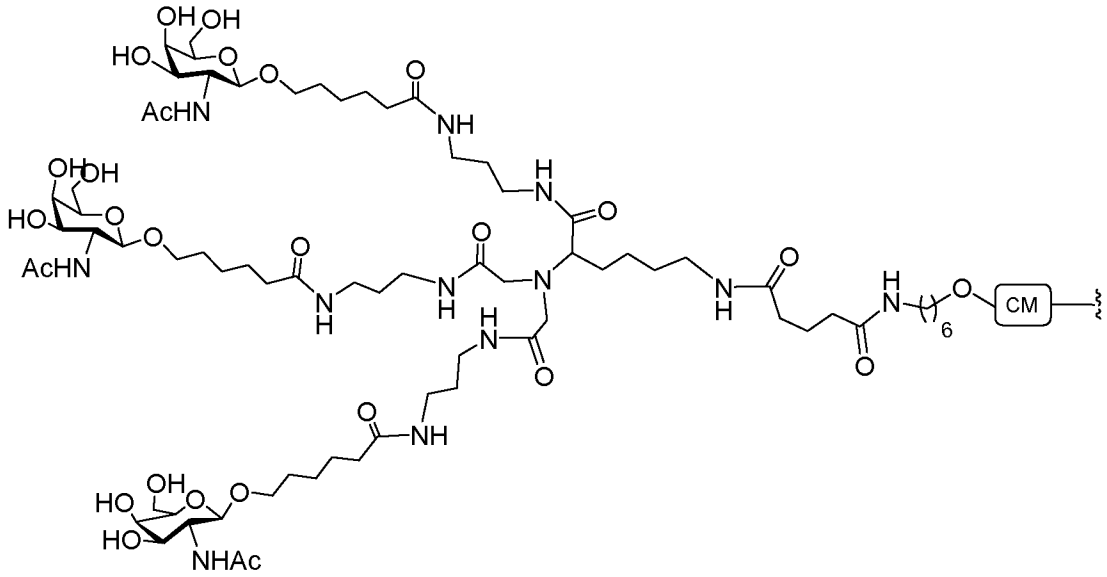
172


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

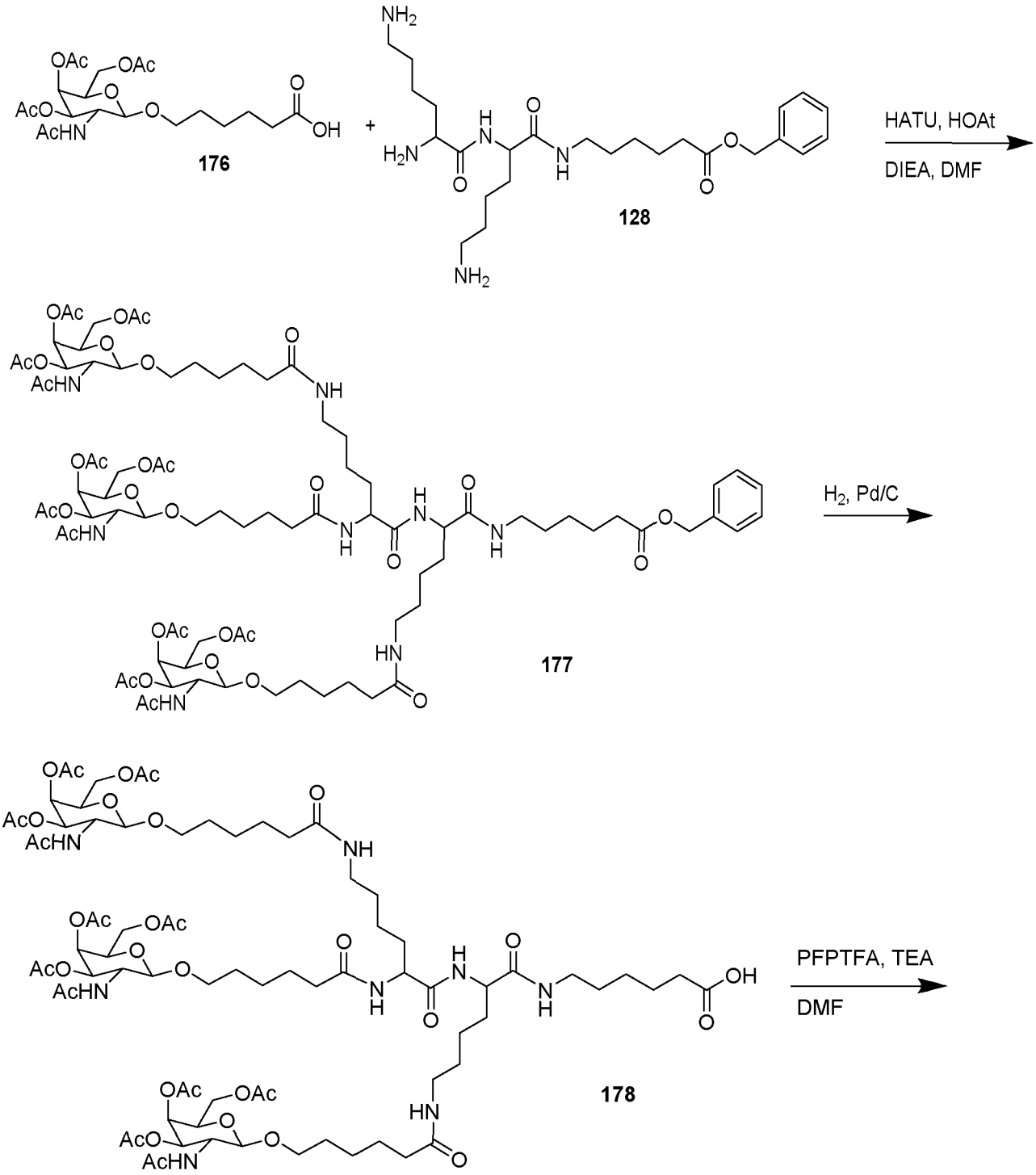


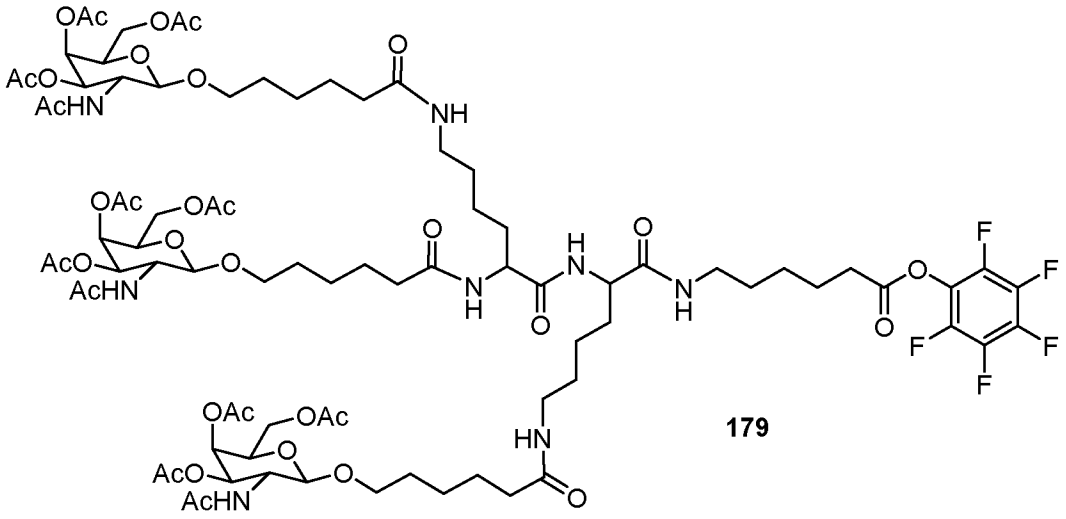


Compound 169 is commercially available. Compound 172 was prepared by addition of benzyl (perfluorophenyl) glutarate to compound 171. The benzyl (perfluorophenyl) glutarate was prepared by adding PFP-TFA and DIEA to 5-(benzyloxy)-5-oxopentanoic acid in DMF. Oligomeric compound 175, comprising a $GalNAc_3$-12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

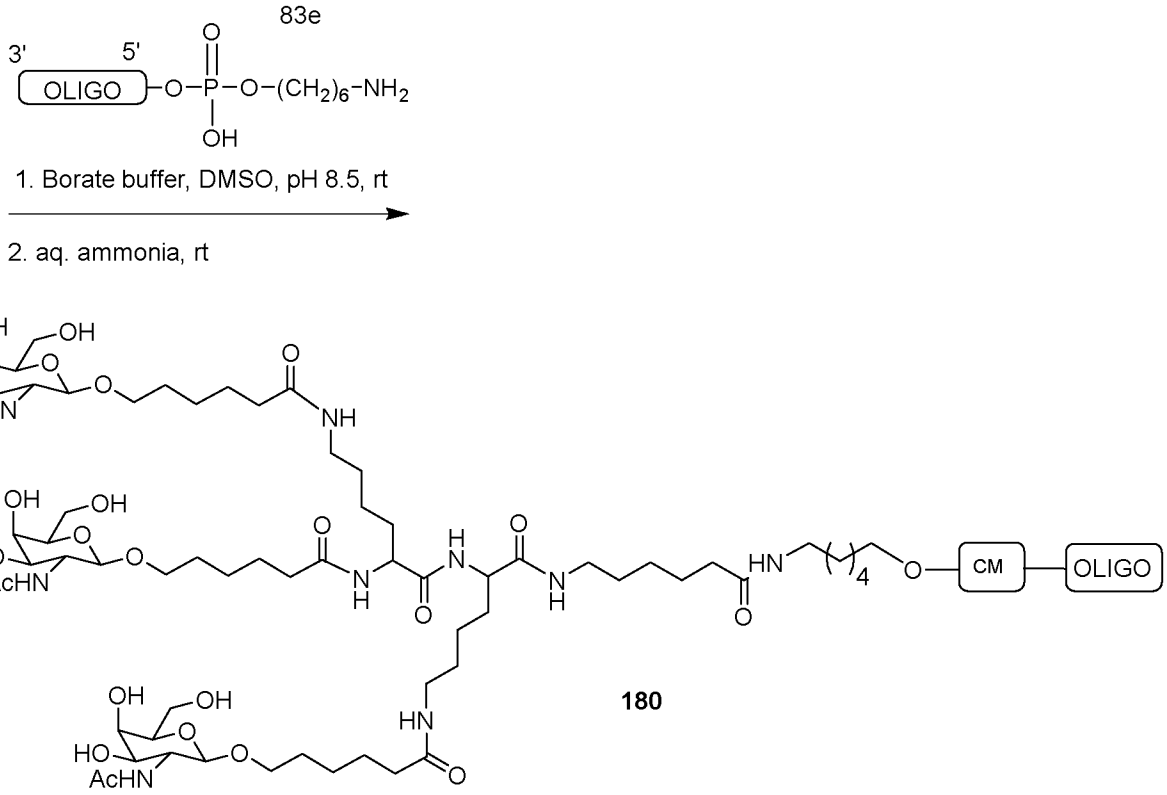


Example 62: Preparation of oligomeric compound 180 comprising GalNAc$_3$-13


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



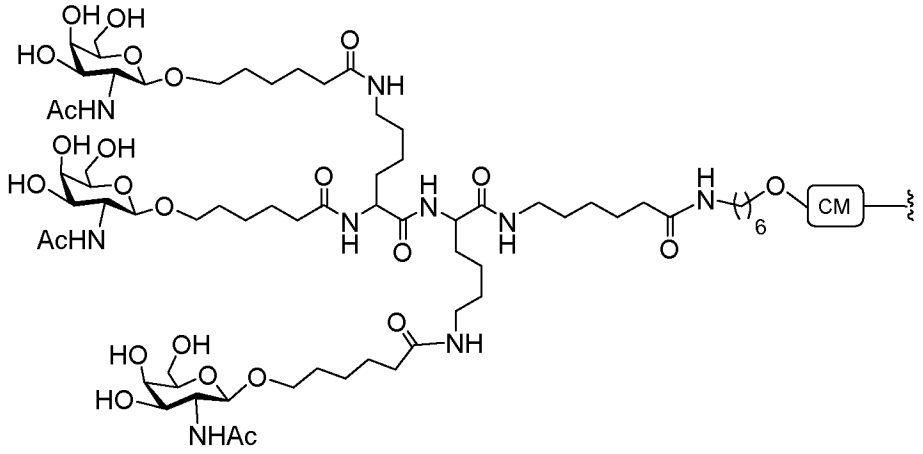
179



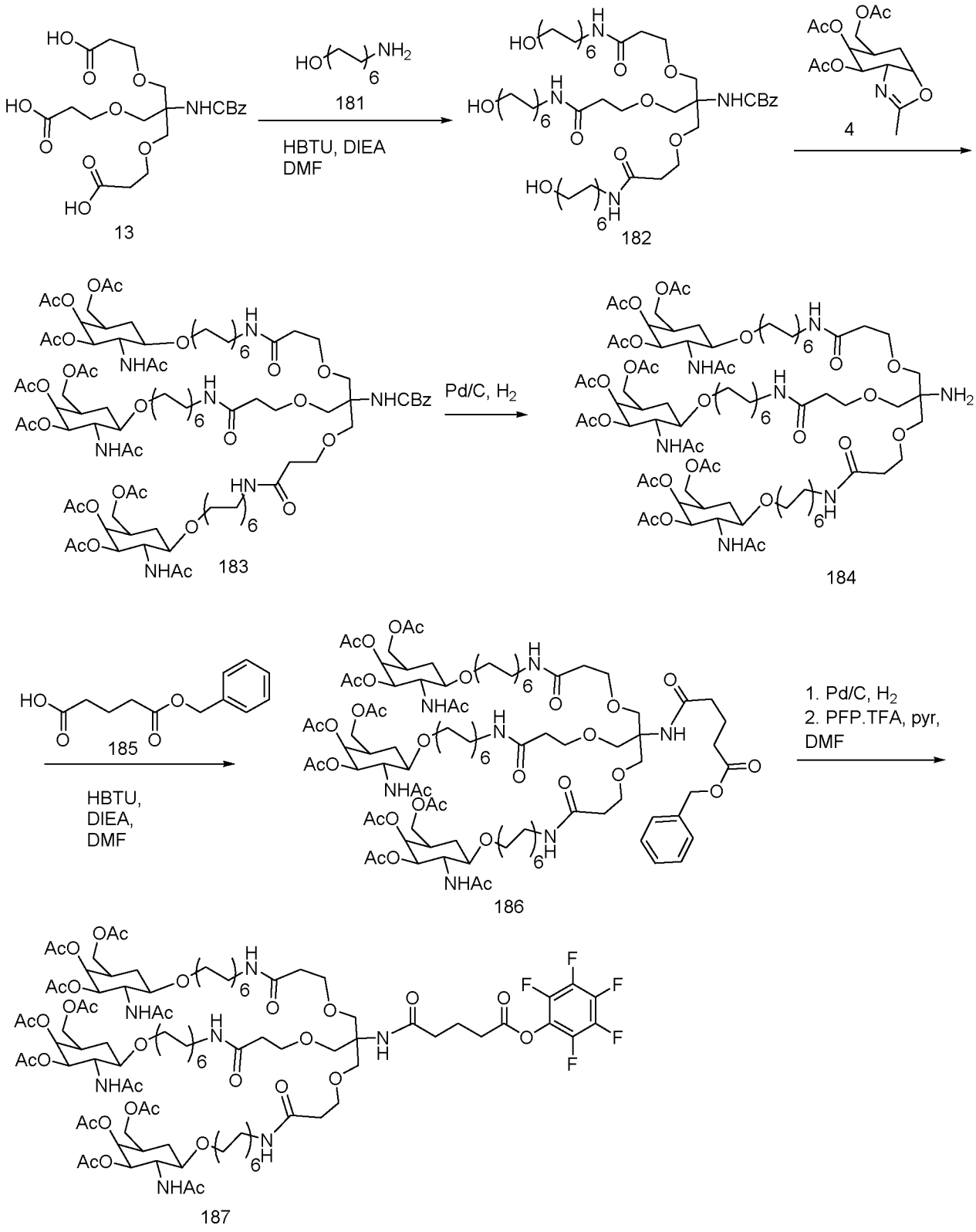
180

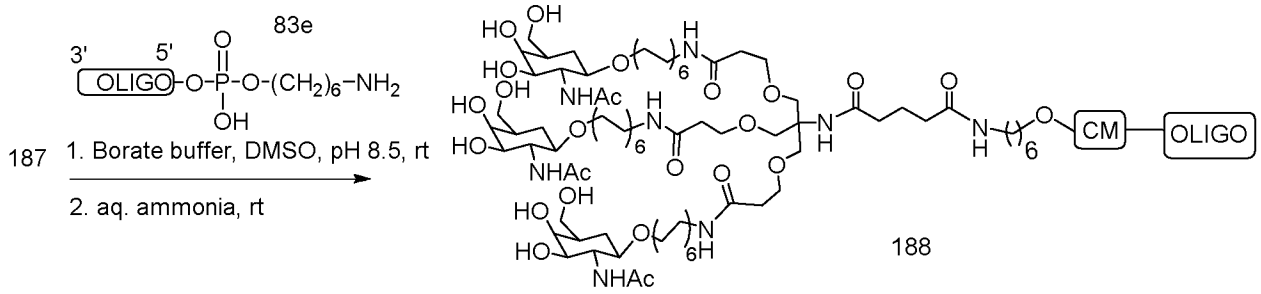
Compound 176 was prepared using the general procedure shown in Example 2. Oligomeric compound 180, comprising a $GalNAc_3$-13 conjugate group, was prepared from compound 177 using the general procedures illustrated in Example 49. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-13 ($GalNAc_3$-13_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In a

certainembodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-13 ($GalNAc_3$-13_a-CM-) is shown below:

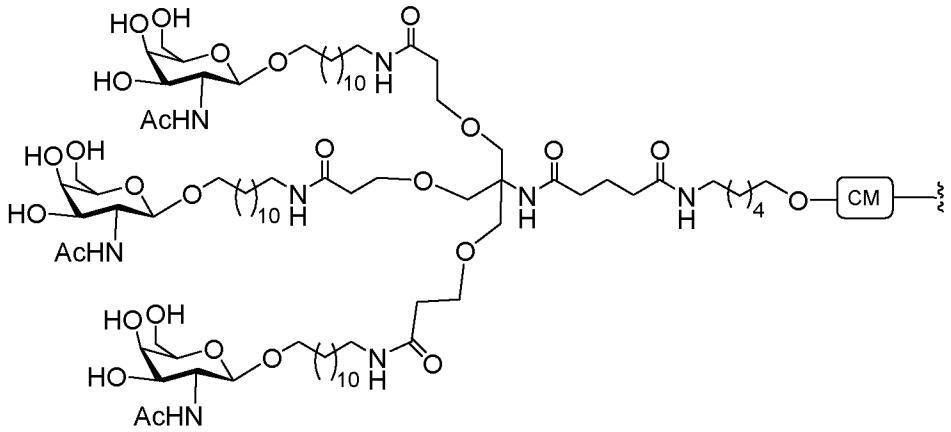


Example 63: Preparation of oligomeric compound 188 comprising $GalNAc_3$-14

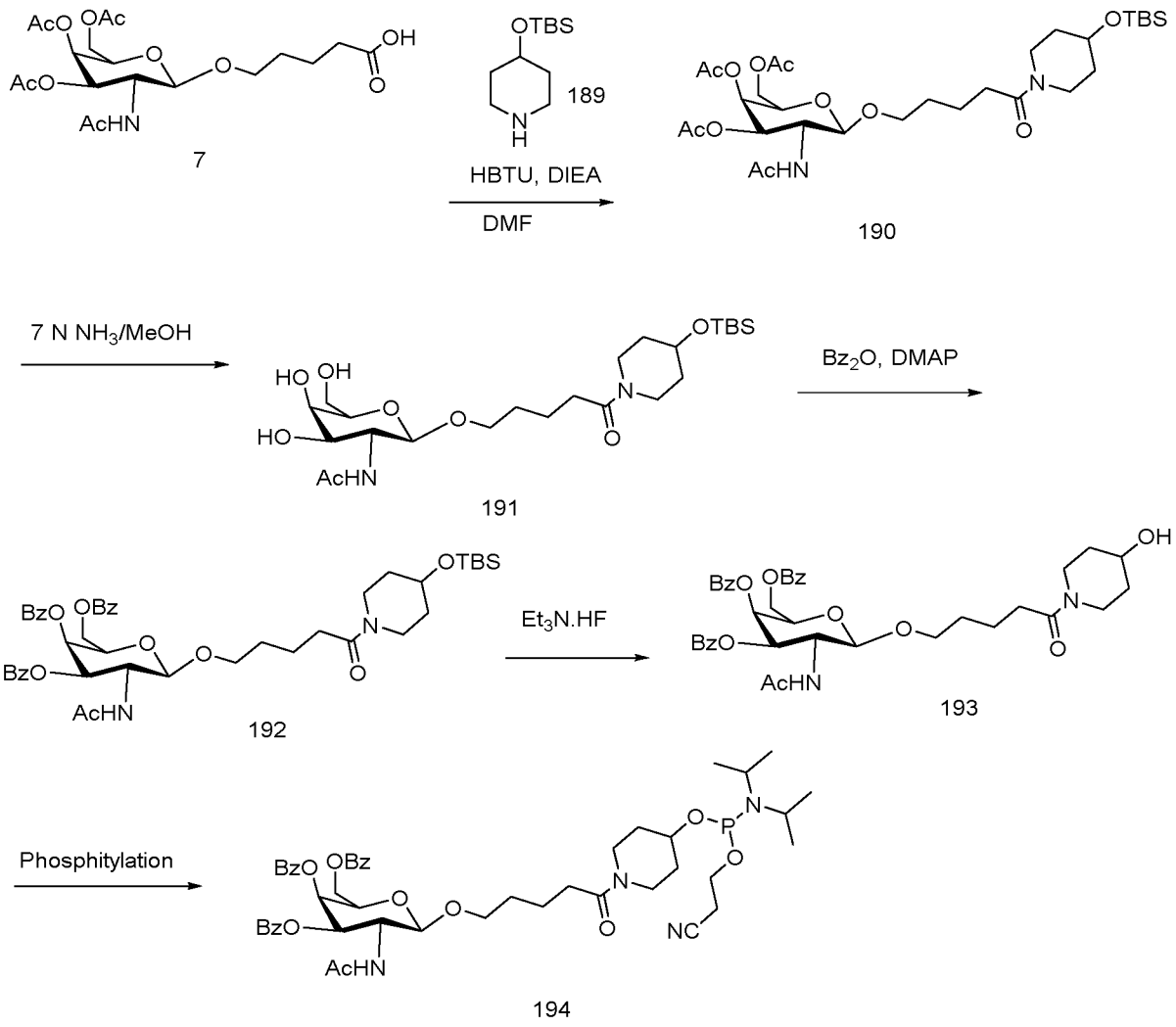

13
181
HBTU, DIEA
DMF
182
4
Pd/C, H2
183
184
185
HBTU,
DIEA,
DMF
186
1. Pd/C, H2
2. PFP.TFA, pyr,
DMF
187

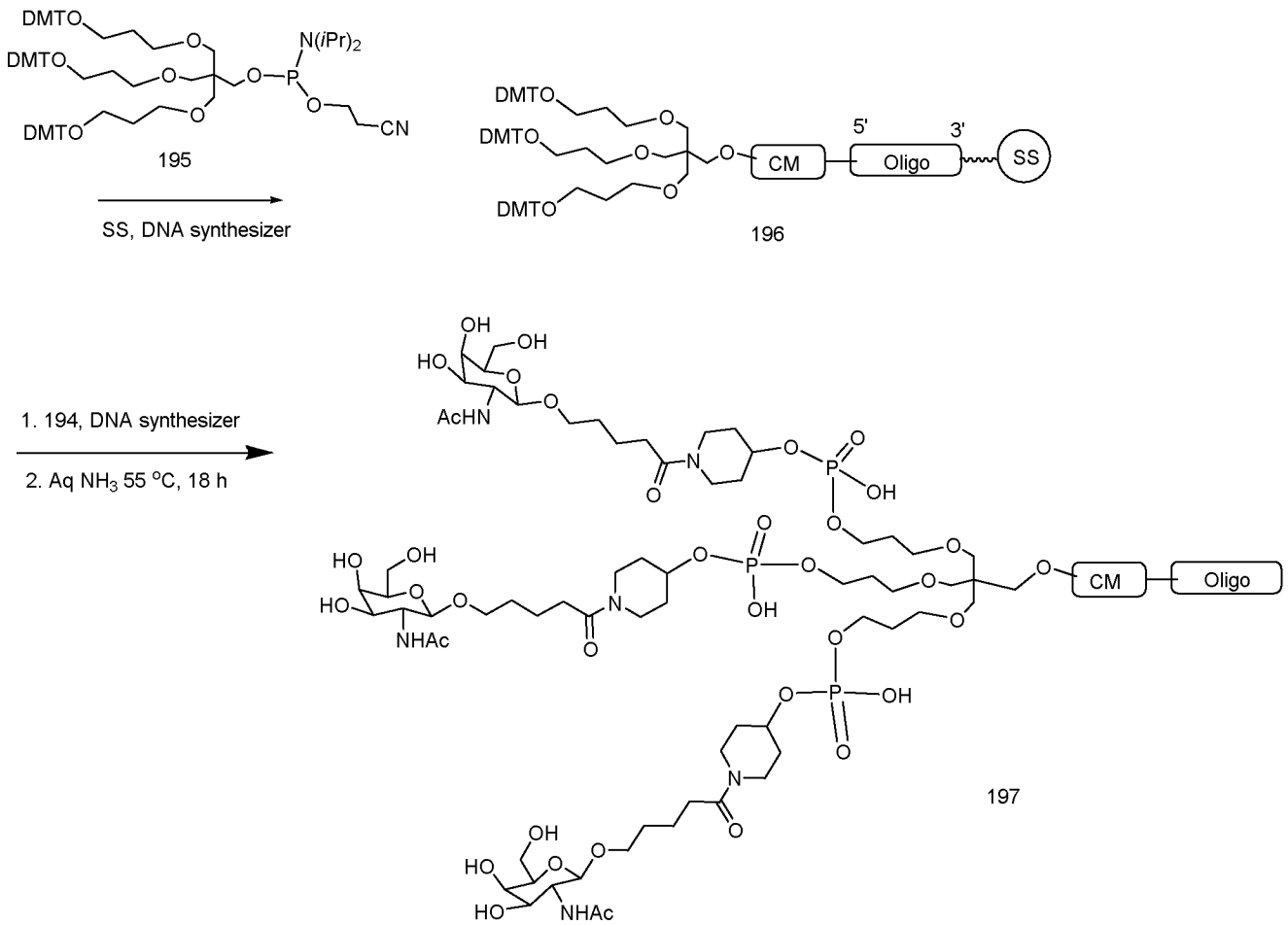


Compounds 181 and 185 are commercially available. Oligomeric compound 188, comprising a $GalNAc_3$-14 conjugate group, was prepared from compound 187 using the general procedures illustrated in Example 46. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-14 ($GalNAc_3$-14_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-14 ($GalNAc_3$-14_a-CM-) is shown below:

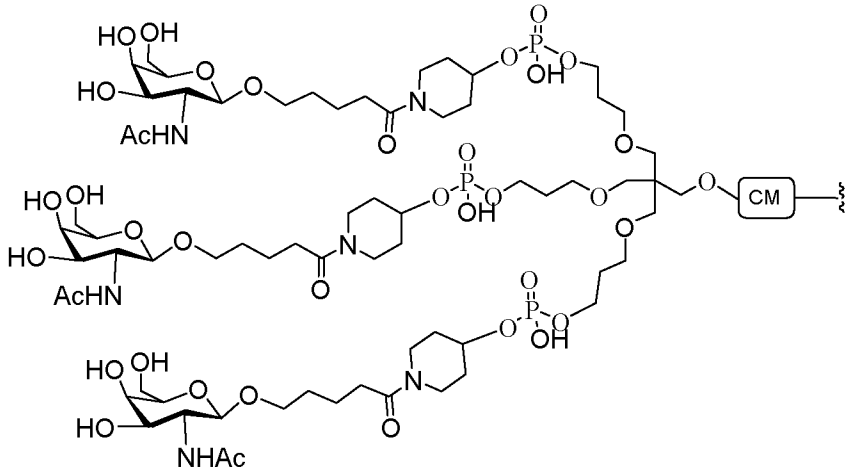


Example 64: Preparation of oligomeric compound 197 comprising $GalNAc_3$-15


AcO
OAc
AcO
AcHN
OH
O
7
OTBS
189
N
H
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	2256
661161	**GalNAc$_3$-3$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-3	2258
671144	**GalNAc$_3$-12$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-12	2258
670061	**GalNAc$_3$-13$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-13	2258
671261	**GalNAc$_3$-14$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-14	2258
671262	**GalNAc$_3$-15$_a$-$_o$,A$_{do}$**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	GalNAc$_3$-15	2258

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	2258
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	2261
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	2258
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	2261
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	2258

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

The structure of GalNAc$_3$-3$_a$ was shown previously in Example 39. The structure of GalNAc$_3$-13a was shown previously in Example 62.

Treatment

Six to eight week old C57bl6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with ISIS 661161, 670699, 670700, 670701, 671165, or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration to determine the liver SRB-1 mRNA levels using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. The results below are presented as the average percent of SRB-1 mRNA levels for each treatment group, normalized to the saline control.

As illustrated in Table 58, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. The antisense oligonucleotides comprising various cleavable moieties all showed similar potencies.

Table 58

SRB-1 mRNA (% Saline)

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100.0	n/a	n/a
661161	0.5	87.8	$GalNAc_3$-3a	A_d
	1.5	61.3		
	5	33.8		
	15	14.0		
670699	0.5	89.4	$GalNAc_3$-3a	T_d
	1.5	59.4		
	5	31.3		
	15	17.1		
670700	0.5	79.0	$GalNAc_3$-3a	A_e
	1.5	63.3		
	5	32.8		
	15	17.9		
670701	0.5	79.1	$GalNAc_3$-3a	T_e
	1.5	59.2		
	5	35.8		
	15	17.7		
671165	0.5	76.4	$GalNAc_3$-13a	A_d
	1.5	43.2		
	5	22.6		
	15	10.0		

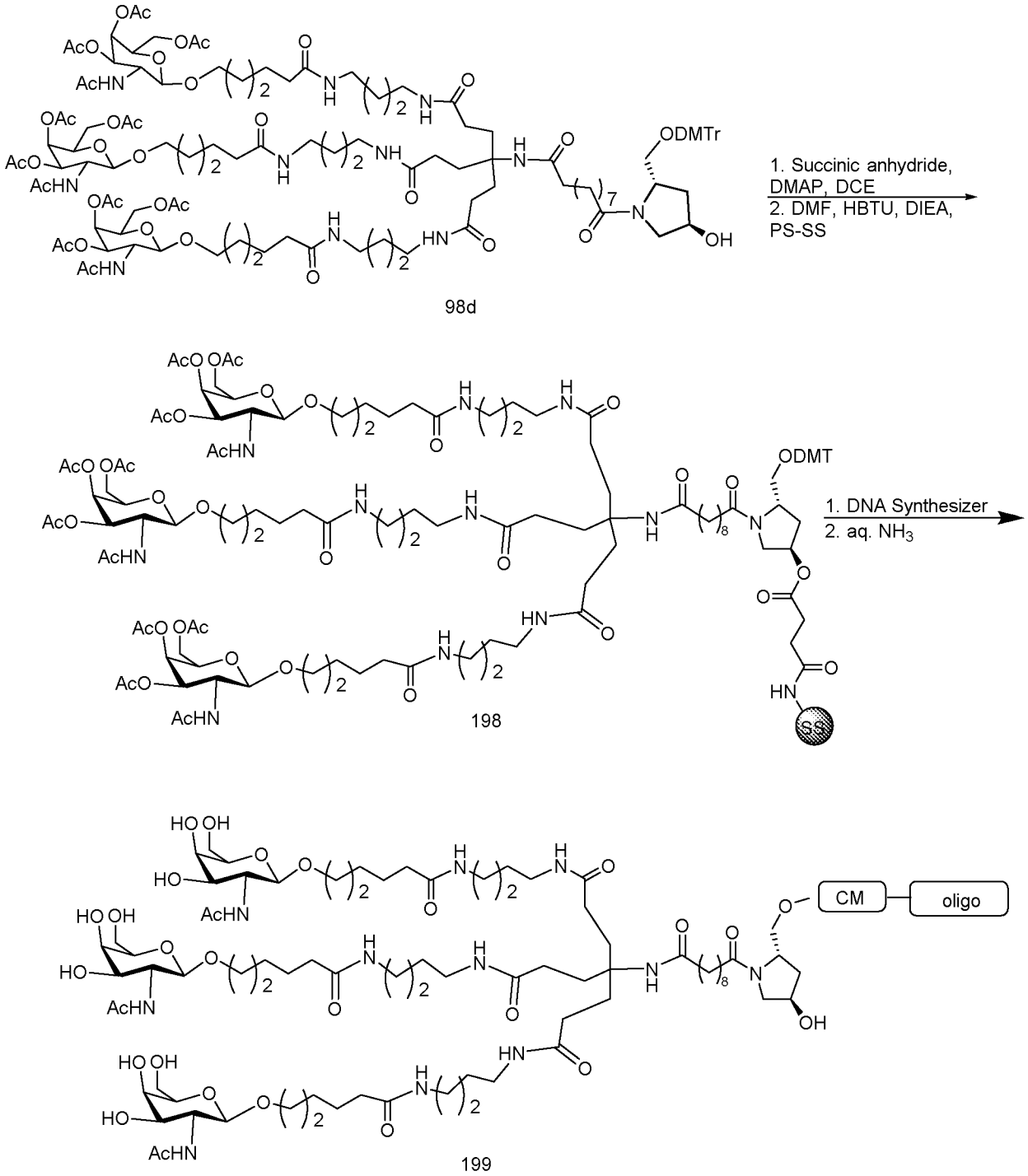
Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Total bilirubin and BUN were also evaluated. The changes in body weights were evaluated with no significant differences from the saline group (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 56 below.

Table 59

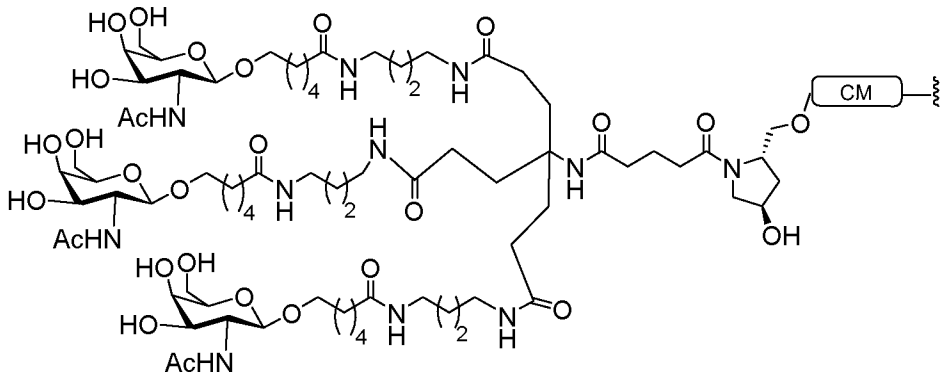
ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	$GalNAc_3$ Cluster	CM
Saline	n/a	24	64	0.2	31	n/a	n/a
661161	0.5	25	64	0.2	31	$GalNAc_3$-3a	A_d
	1.5	24	50	0.2	32		
	5	26	55	0.2	28		
	15	27	52	0.2	31		
670699	0.5	42	83	0.2	31	$GalNAc_3$-3a	T_d
	1.5	33	58	0.2	32		
	5	26	70	0.2	29		

	15	25	67	0.2	29		
670700	0.5	40	74	0.2	27	$GalNAc_3$-3a	A_e
	1.5	23	62	0.2	27		
	5	24	49	0.2	29		
	15	25	87	0.1	25		
670701	0.5	30	77	0.2	27	$GalNAc_3$-3a	T_e
	1.5	22	55	0.2	30		
	5	81	101	0.2	25		
	15	31	82	0.2	24		
671165	0.5	44	84	0.2	26	$GalNAc_3$-13a	A_d
	1.5	47	71	0.1	24		
	5	33	91	0.2	26		
	15	33	56	0.2	29		

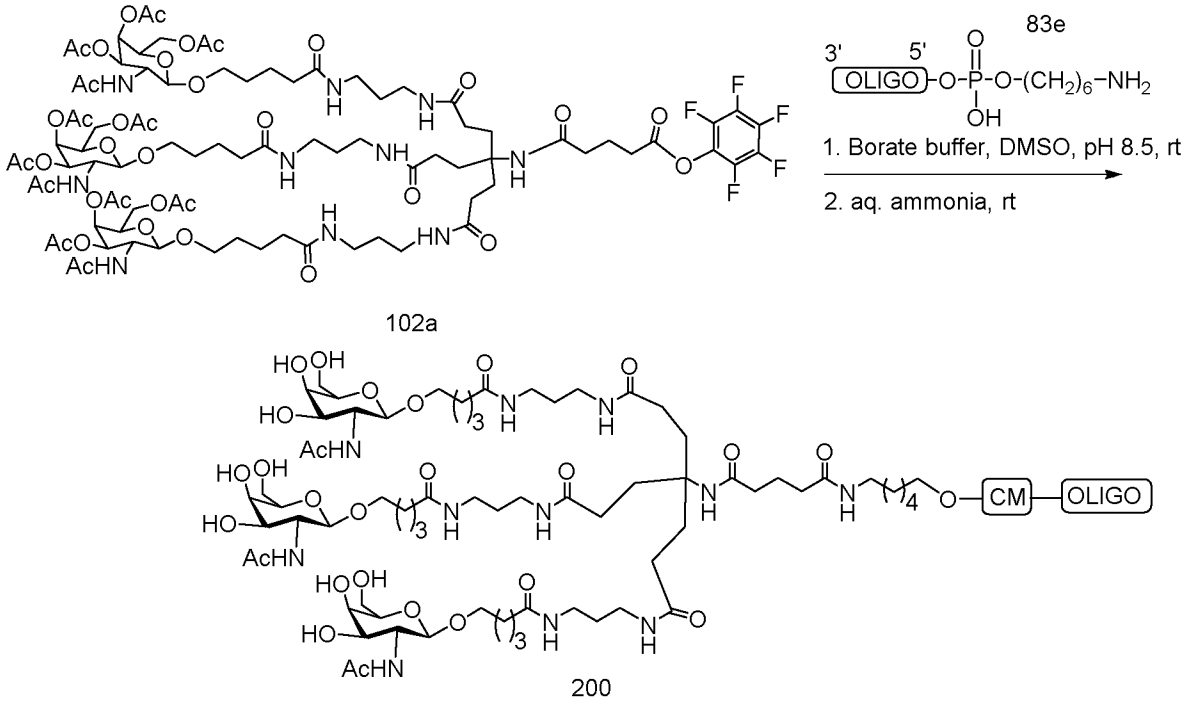
Example 67: Preparation of oligomeric compound 199 comprising GalNAc$_3$-16



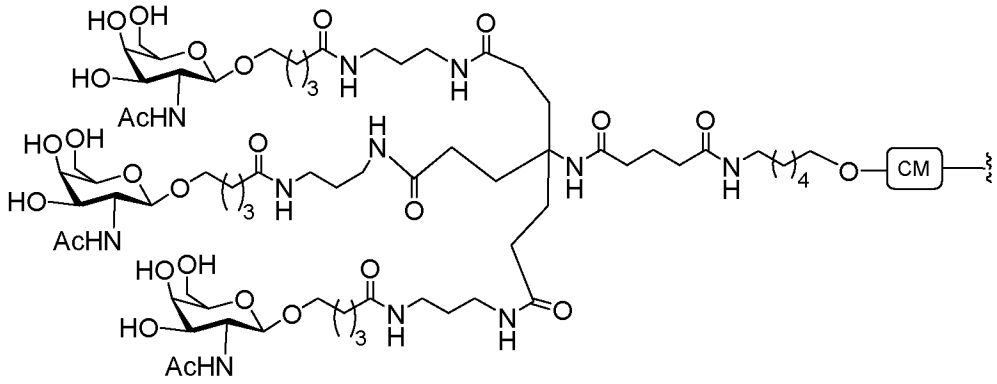
Oligomeric compound 199, comprising a GalNAc$_3$-16 conjugate group, is prepared using the general procedures illustrated in Examples 7 and 9. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-16 (GalNAc$_3$-16$_a$) can be combined with any cleavable moiety to provide a variety of conjugate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



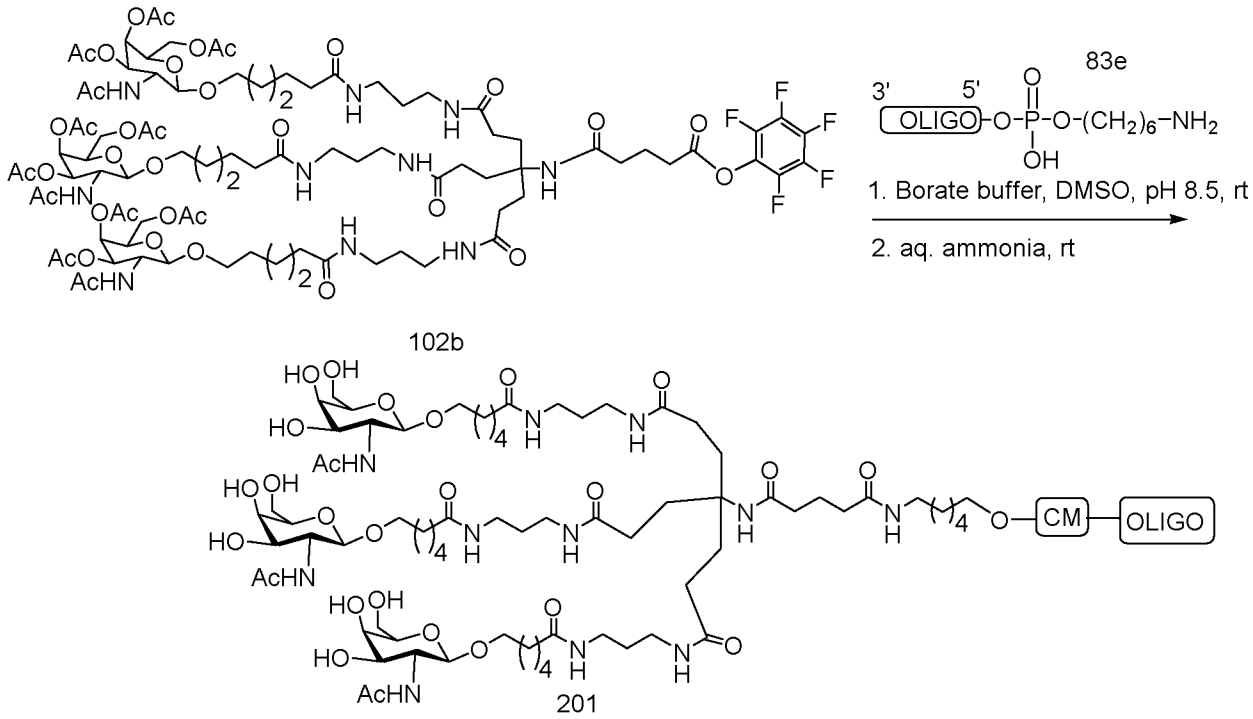
Example 68: Preparation of oligomeric compound 200 comprising GalNAc$_3$-17



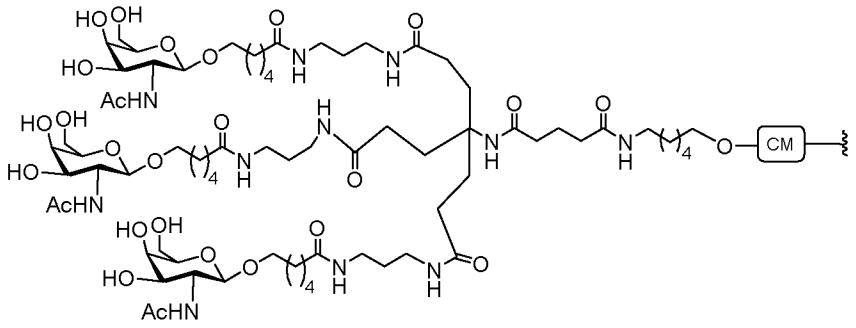
Oligomeric compound 200, comprising a GalNAc$_3$-17 conjugate group, was prepared using the general procedures illustrated in Example 46. The GalNAc$_3$ cluster portion of the conjugate group GalNAc$_3$-17 (GalNAc$_3$-17$_a$) can be combined with any cleavable moiety to provide a variety of conjugate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



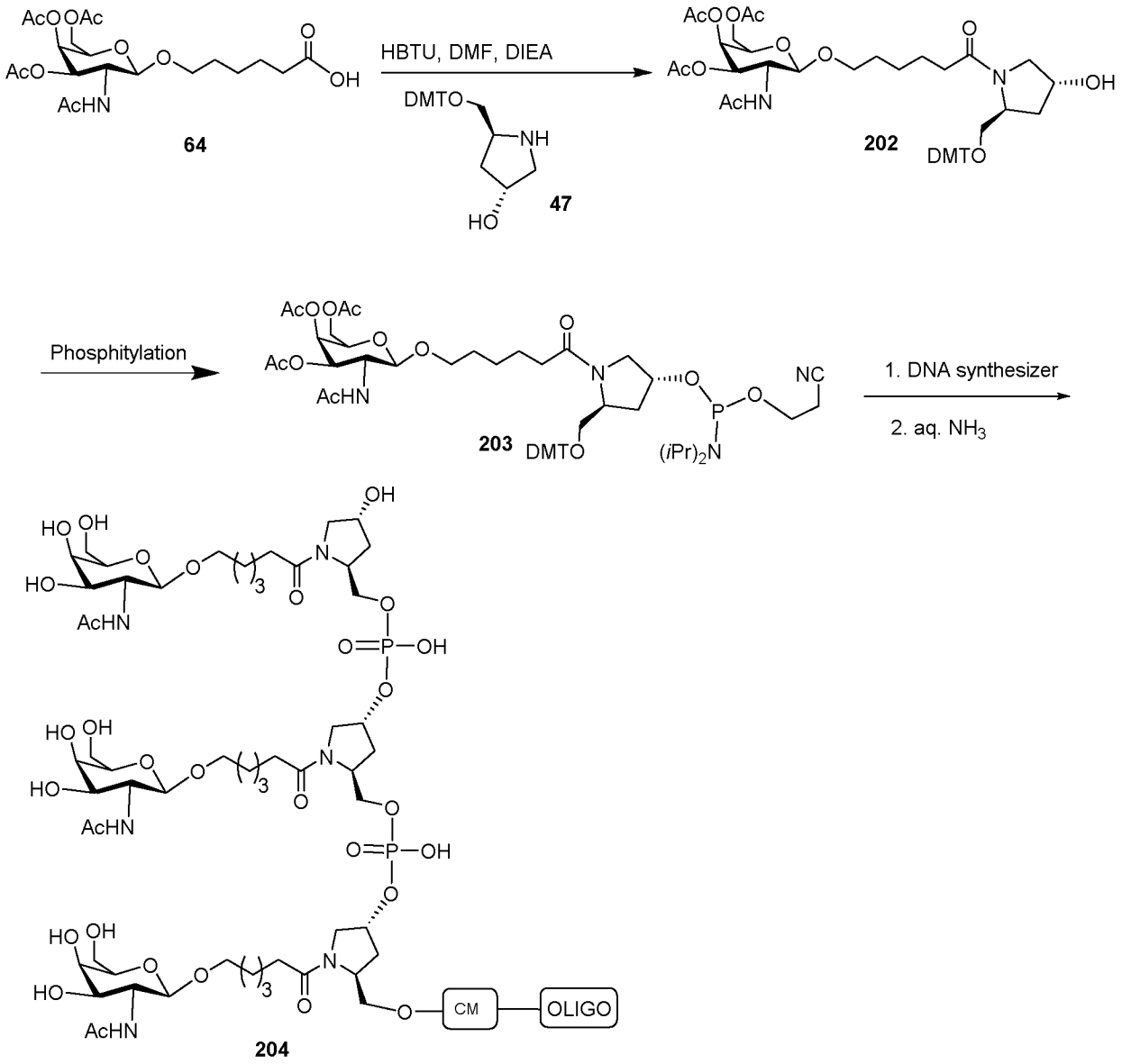
Example 69: Preparation of oligomeric compound 201 comprising GalNAc$_3$-18



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:

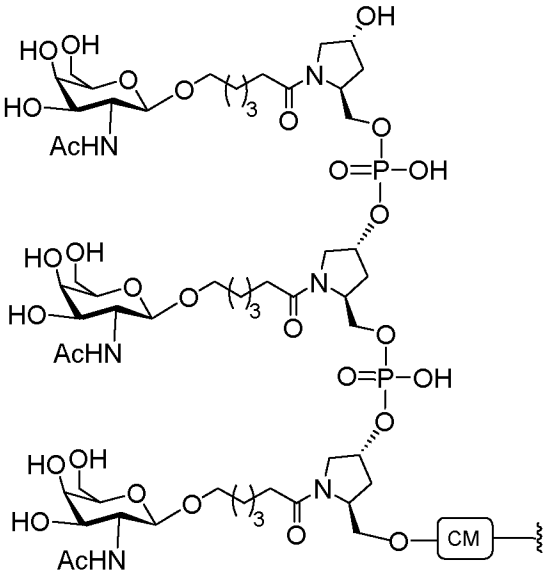


Example 70: Preparation of oligomeric compound 204 comprising GalNAc$_3$-19

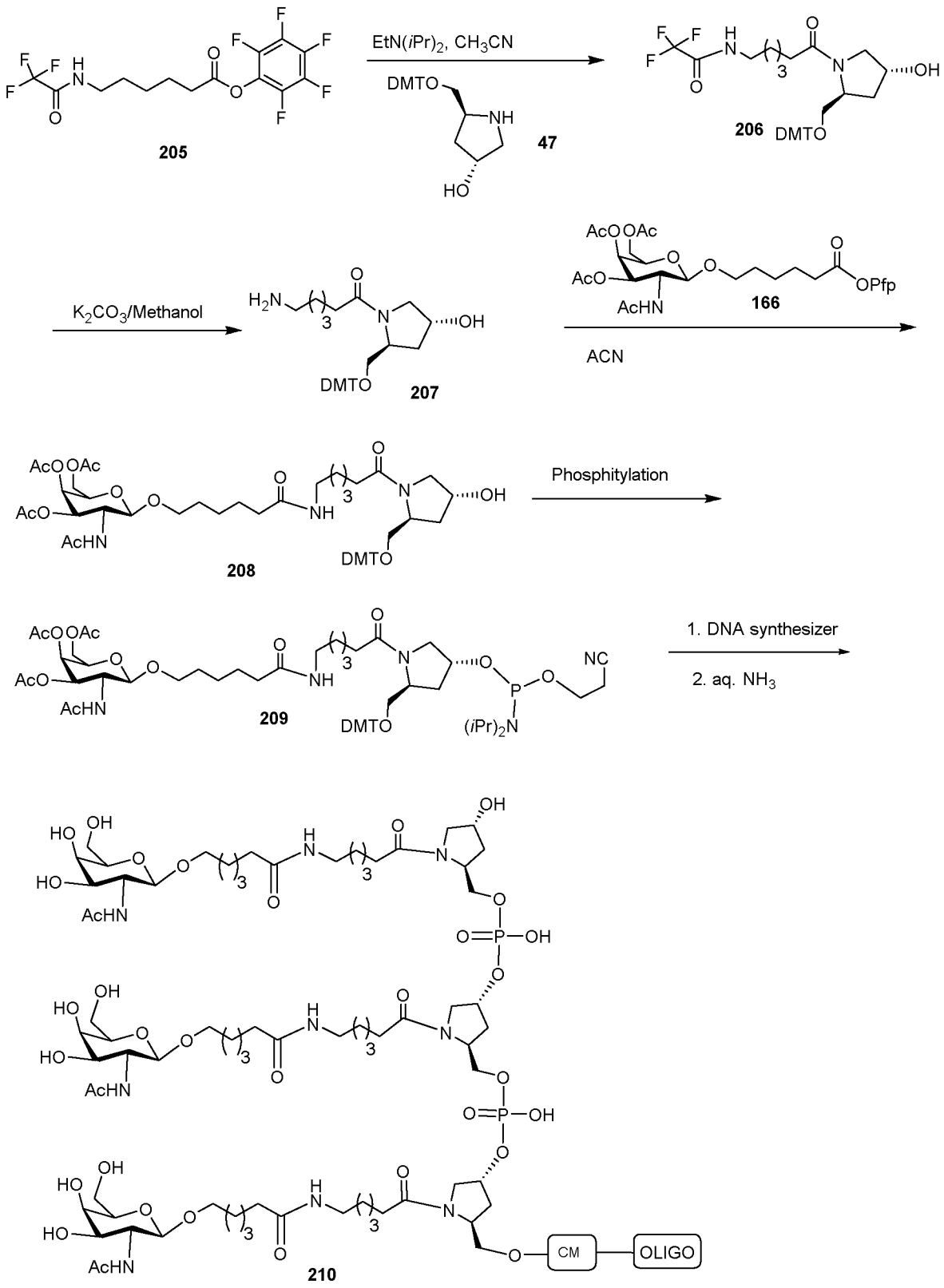


Oligomeric compound 204, comprising a GalNAc$_3$-19 conjugate group, was prepared from compound 64 using the general procedures illustrated in Example 52. The GalNAc$_3$ cluster portion of the conjugate group

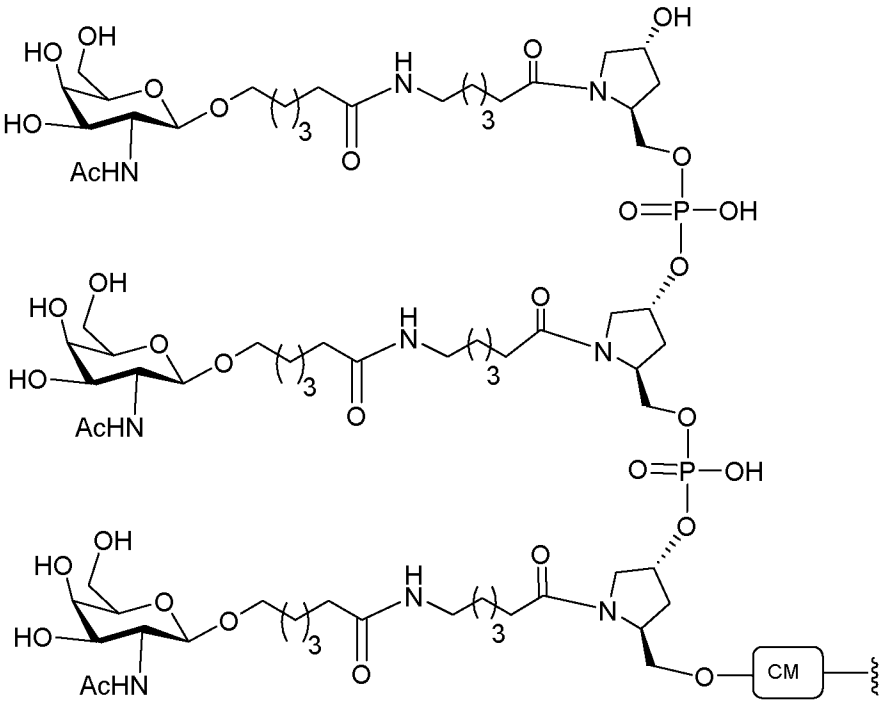
$GalNAc_3$-19 ($GalNAc_3$-19_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. In certain embodiments, the cleavable moiety is -P(=O)(OH)-A_d-P(=O)(OH)-. The structure of $GalNAc_3$-19 ($GalNAc_3$-19_a-CM-) is shown below:



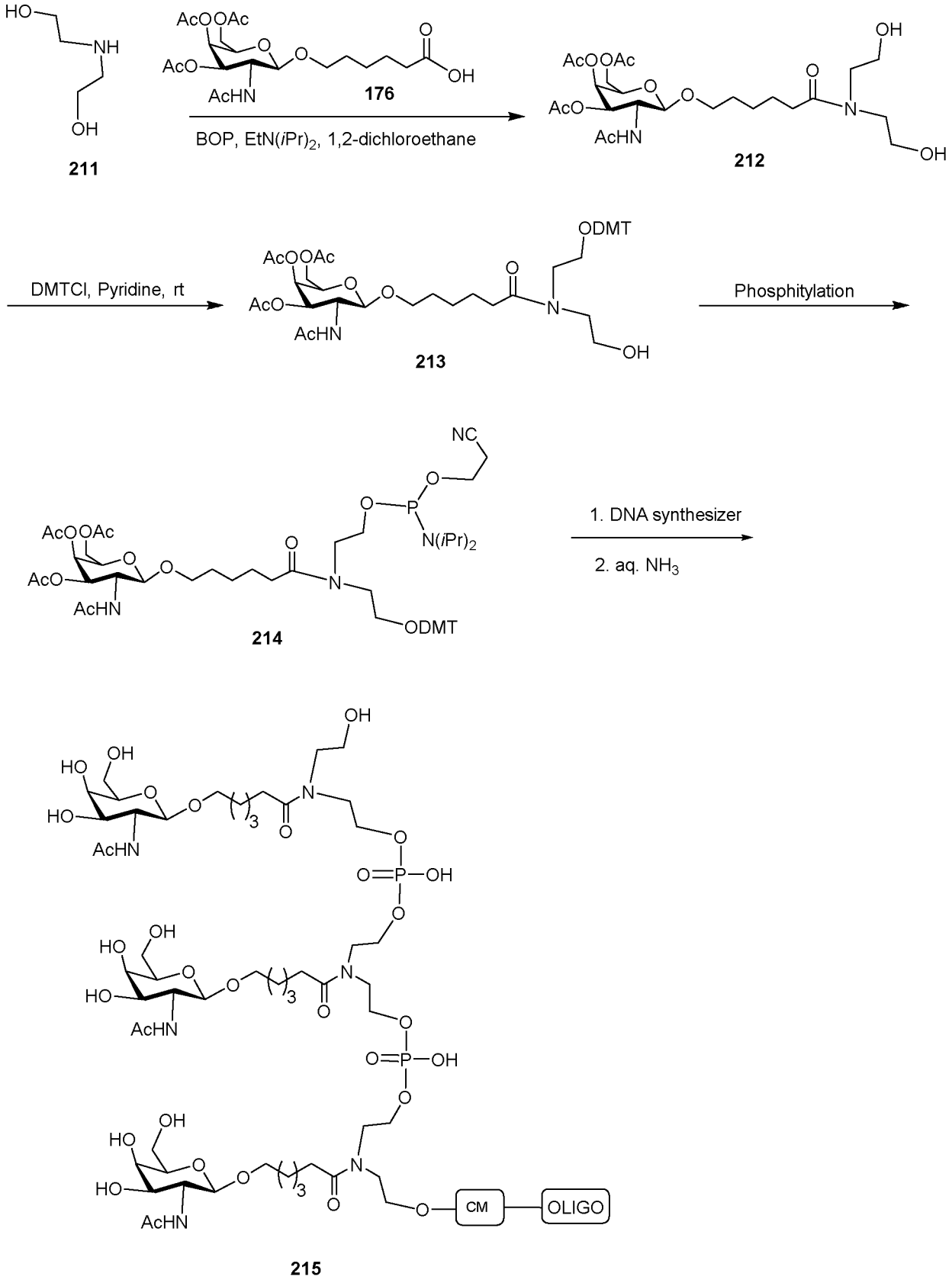
Example 71: Preparation of oligomeric compound 210 comprising $GalNAc_3$-20



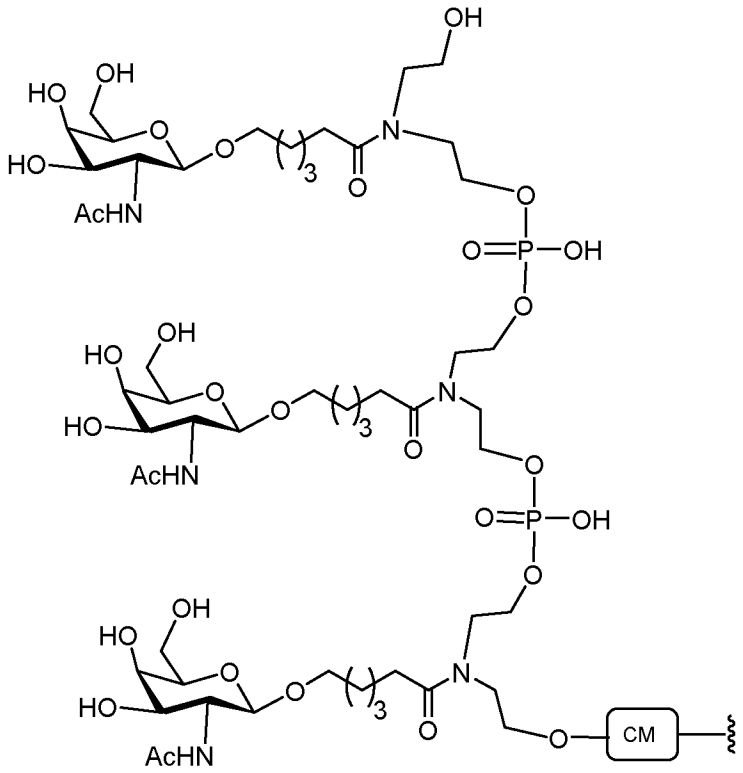
Compound 205 was prepared by adding PFP-TFA and DIEA to 6-(2,2,2-trifluoroacetamido)hexanoic acid in acetonitrile ,which was prepared by adding triflic anhydride to 6-aminohexanoic acid. The reaction mixture was heated to 80 °C, then lowered to rt. Oligomeric compound 210, comprising a $GalNAc_3$-20 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:



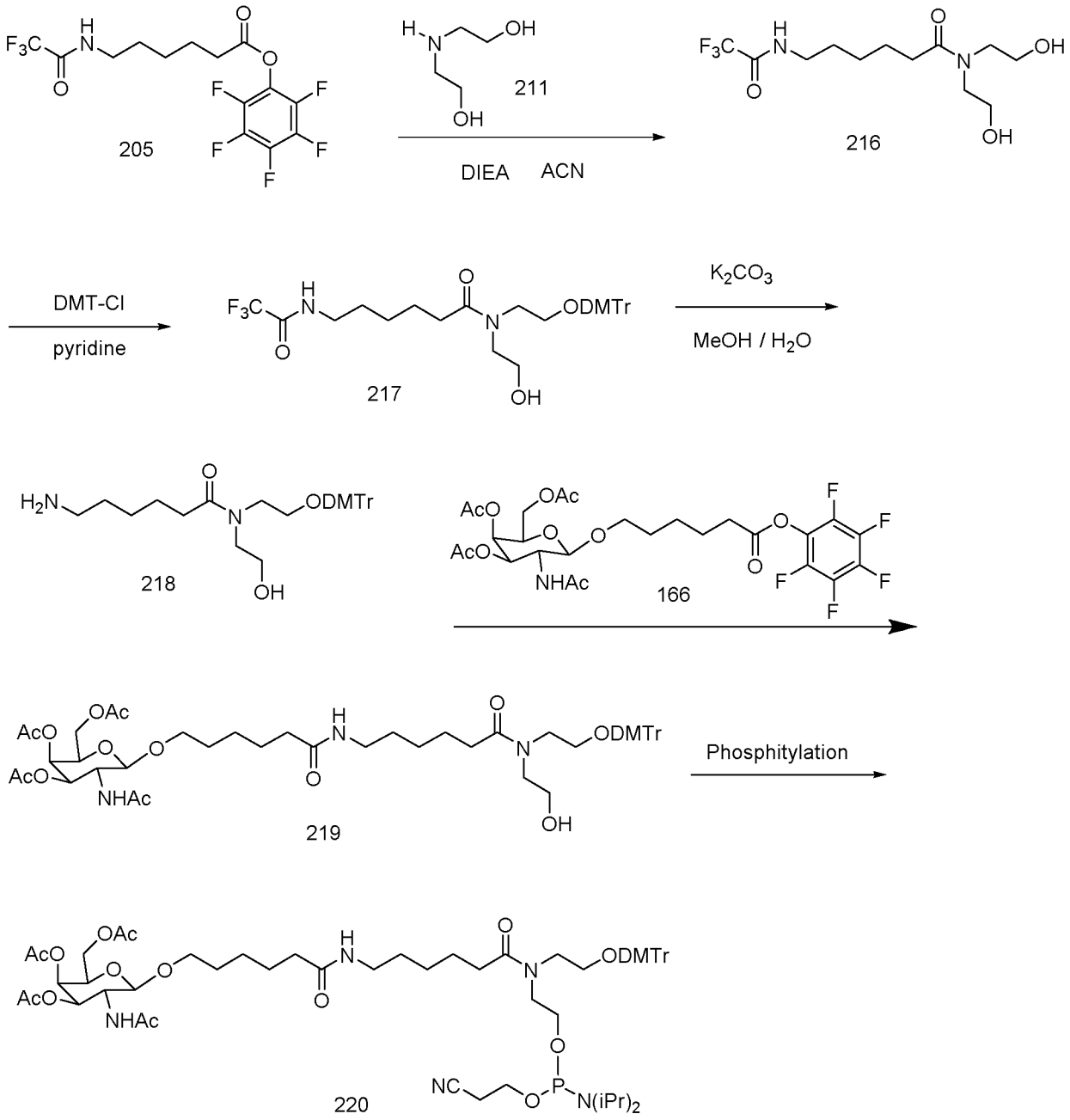
Example 72: Preparation of oligomeric compound 215 comprising GalNAc$_3$-21

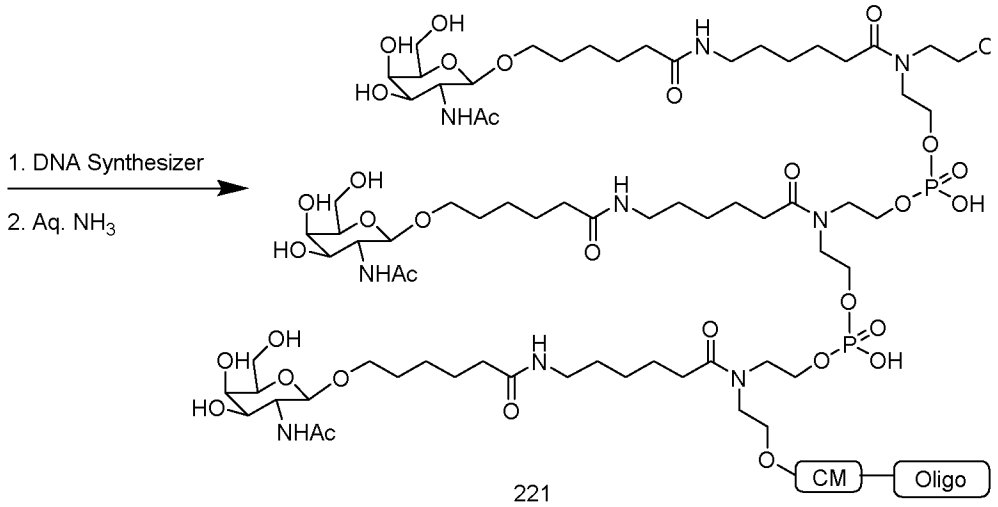


Compound 211 is commercially available. Oligomeric compound 215, comprising a $GalNAc_3$-21 conjugate group, was prepared from compound 213 using the general procedures illustrated in Example 52. The $GalNAc_3$ cluster portion of the conjugate group $GalNAc_3$-21 ($GalNAc_3$-21_a) can be combined with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



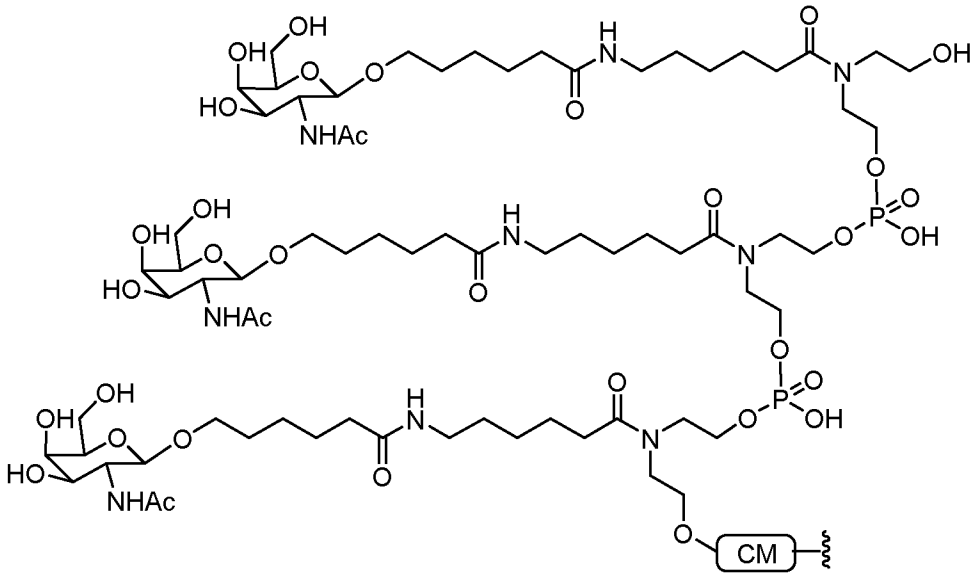
Example 73: Preparation of oligomeric compound 221 comprising GalNAc$_3$-22





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	2256
661161	**$GalNAc_3$-$3_{a\text{-}o}$,A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	A_d	2258
666904	**$GalNAc_3$-$3_{a\text{-}o}$,**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-3a	PO	2256
675441	**$GalNAc_3$-$17_{a\text{-}o}$,A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-17a	A_d	2258
675442	**$GalNAc_3$-$18_{a\text{-}o}$,A_{do}**$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	$GalNAc_3$-18a	A_d	2258

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

The structure of $GalNAc_3$-3_a was shown previously in Example 39. The structure of $GalNAc_3$-17a was shown previously in Example 68, and the structure of $GalNAc_3$-18a was shown in Example 69.

Treatment

Six to eight week old C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with an oligonucleotide listed in Table 60 or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration to determine the SRB-1 mRNA levels using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. The results below are presented as the average percent of SRB-1 mRNA levels for each treatment group, normalized to the saline control.

As illustrated in Table 61, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner. The antisense oligonucleotides comprising a GalNAc conjugate showed similar potencies and were significantly more potent than the parent oligonucleotide lacking a GalNAc conjugate.

Table 61

SRB-1 mRNA (% Saline)

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100.0	n/a	n/a
353382	3	79.38	n/a	n/a
	10	68.67		
	30	40.70		
661161	0.5	79.18	$GalNAc_3$-3a	A_d
	1.5	75.96		
	5	30.53		
	15	12.52		
666904	0.5	91.30	$GalNAc_3$-3a	PO
	1.5	57.88		
	5	21.22		
	15	16.49		
675441	0.5	76.71	$GalNAc_3$-17a	A_d
	1.5	63.63		
	5	29.57		
	15	13.49		
675442	0.5	95.03	$GalNAc_3$-18a	A_d
	1.5	60.06		
	5	31.04		
	15	19.40		

Liver transaminase levels, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in serum were measured relative to saline injected mice using standard protocols. Total bilirubin and BUN were also evaluated. The change in body weights was evaluated with no significant change from the saline group (data not shown). ALTs, ASTs, total bilirubin and BUN values are shown in Table 62 below.

Table 62

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dL)	BUN (mg/dL)	$GalNAc_3$ Cluster	CM
Saline	n/a	26	59	0.16	42	n/a	n/a
353382	3	23	58	0.18	39	n/a	n/a
	10	28	58	0.16	43		
	30	20	48	0.12	34		
661161	0.5	30	47	0.13	35	$GalNAc_3$-3a	A_d
	1.5	23	53	0.14	37		
	5	26	48	0.15	39		
	15	32	57	0.15	42		
666904	0.5	24	73	0.13	36	$GalNAc_3$-3a	PO
	1.5	21	48	0.12	32		
	5	19	49	0.14	33		
	15	20	52	0.15	26		
675441	0.5	42	148	0.21	36	$GalNAc_3$-17a	A_d
	1.5	60	95	0.16	34		
	5	27	75	0.14	37		

	15	24	61	0.14	36		
675442	0.5	26	65	0.15	37	$GalNAc_3$-18a	A_d
	1.5	25	64	0.15	43		
	5	27	69	0.15	37		
	15	30	84	0.14	37		

Example 75: Pharmacokinetic analysis of oligonucleotides comprising a 5'-conjugate group

The PK of the ASOs in Tables 54, 57 and 60 above was evaluated using liver samples that were obtained following the treatment procedures described in Examples 65, 66, and 74. The liver samples were minced and extracted using standard protocols and analyzed by IP-HPLC-MS alongside an internal standard. The combined tissue level (μg/g) of all metabolites was measured by integrating the appropriate UV peaks, and the tissue level of the full-length ASO missing the conjugate ("parent," which is Isis No. 353382 in this case) was measured using the appropriate extracted ion chromatograms (EIC).

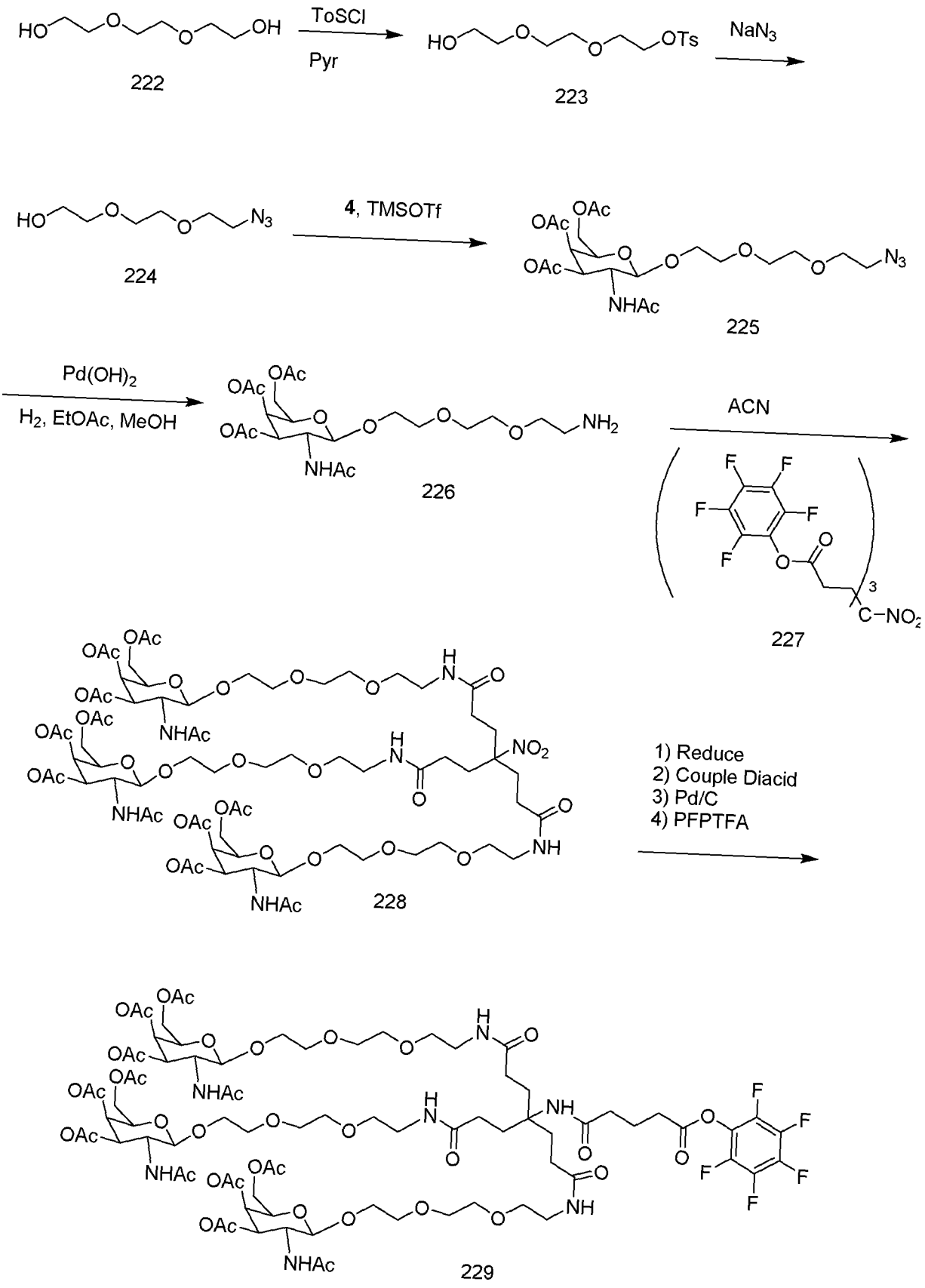
Table 63

PK Analysis in Liver

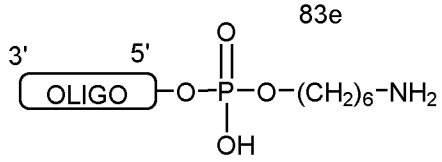
ISIS No.	Dosage (mg/kg)	Total Tissue Level by UV (μg/g)	Parent ASO Tissue Level by EIC (μg/g)	$GalNAc_3$ Cluster	CM
353382	3	8.9	8.6	n/a	n/a
	10	22.4	21.0		
	30	54.2	44.2		
661161	5	32.4	20.7	$GalNAc_3$-3a	A_d
	15	63.2	44.1		
671144	5	20.5	19.2	$GalNAc_3$-12a	A_d
	15	48.6	41.5		
670061	5	31.6	28.0	$GalNAc_3$-13a	A_d
	15	67.6	55.5		
671261	5	19.8	16.8	$GalNAc_3$-14a	A_d
	15	64.7	49.1		
671262	5	18.5	7.4	$GalNAc_3$-15a	A_d
	15	52.3	24.2		
670699	5	16.4	10.4	$GalNAc_3$-3a	T_d
	15	31.5	22.5		
670700	5	19.3	10.9	$GalNAc_3$-3a	A_e
	15	38.1	20.0		
670701	5	21.8	8.8	$GalNAc_3$-3a	T_e
	15	35.2	16.1		
671165	5	27.1	26.5	$GalNAc_3$-13a	A_d
	15	48.3	44.3		
666904	5	30.8	24.0	$GalNAc_3$-3a	PO
	15	52.6	37.6		
675441	5	25.4	19.0	$GalNAc_3$-17a	A_d
	15	54.2	42.1		
675442	5	22.2	20.7	$GalNAc_3$-18a	A_d
	15	39.6	29.0		

The results in Table 63 above show that there were greater liver tissue levels of the oligonucleotides comprising a $GalNAc_3$ conjugate group than of the parent oligonucleotide that does not comprise a $GalNAc_3$ conjugate group (ISIS 353382) 72 hours following oligonucleotide administration, particularly when taking into consideration the differences in dosing between the oligonucleotides with and without a $GalNAc_3$ conjugate group. Furthermore, by 72 hours, 40-98% of each oligonucleotide comprising a $GalNAc_3$ conjugate group was metabolized to the parent compound, indicating that the $GalNAc_3$ conjugate groups were cleaved from the oligonucleotides.

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

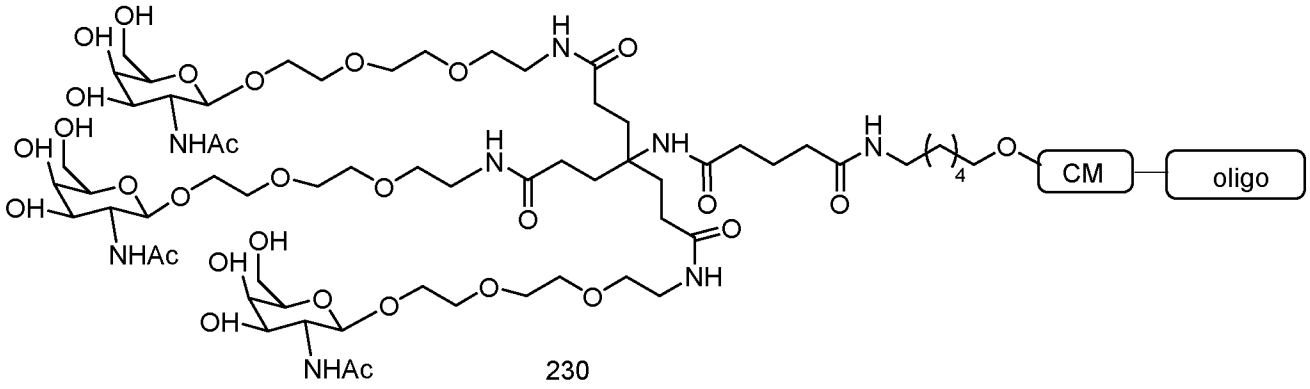


222 223 224 225 226 227 228 229



1. Borate buffer, DMSO, pH 8.5, rt

2. aq. ammonia, rt



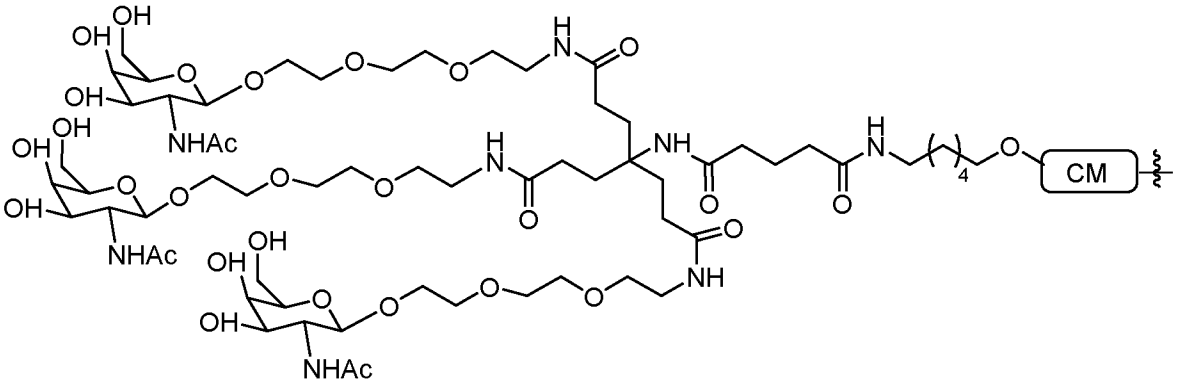
230

Compound 222 is commercially available. 44.48 ml (0.33 mol) of compound 222 was treated with tosyl chloride (25.39 g, 0.13 mol) in pyridine (500mL) for 16 hours. The reaction was then evaporated to an oil, dissolved in EtOAc and washed with water, sat. $NaHCO_3$, brine, and dried over Na_2SO_4. The ethyl acetate was concentrated to dryness and purified by column chromatography, eluted with EtOAc/hexanes (1:1) followed by 10% methanol in CH_2Cl_2 to give compound 223 as a colorless oil. LCMS and NMR were consistent with the structure. 10 g (32.86 mmol) of 1-Tosyltriethylene glycol (compound 223) was treated with sodium azide (10.68 g, 164.28 mmol) in DMSO (100mL) at room temperature for 17 hours. The reaction mixture was then poured onto water, and extracted with EtOAc. The organic layer was washed with water three times and dried over Na_2SO_4. The organic layer was concentrated to dryness to give 5.3g of compound 224 (92%). LCMS and NMR were consistent with the structure. 1-Azidotriethylene glycol (compound 224, 5.53 g, 23.69 mmol) and compound 4 (6 g, 18.22 mmol) were treated with 4A molecular sieves (5g), and TMSOTf (1.65 ml, 9.11 mmol) in dichloromethane (100mL) under an inert atmosphere. After 14 hours, the reaction was filtered to remove the sieves, and the organic layer was washed with sat. $NaHCO_3$, water, brine, and dried over Na_2SO_4. The organic layer was concentrated to dryness and purified by column chromatography, eluted with a gradient of 2 to 4% methanol in dichloromethane to give compound 225. LCMS and NMR were consistent with the structure. Compound 225 (11.9 g, 23.59 mmol) was hydrogenated in EtOAc/Methanol (4:1, 250mL) over Pearlman's catalyst. After 8 hours, the catalyst was

removed by filtration and the solvents removed to dryness to give compound 226. LCMS and NMR were consistent with the structure.

In order to generate compound 227, a solution of nitromethanetrispropionic acid (4.17 g, 15.04 mmol) and Hunig's base (10.3 ml, 60.17 mmol) in DMF (100mL) were treated dropwise with pentaflourotrifluoro acetate (9.05 ml, 52.65 mmol). After 30 minutes, the reaction was poured onto ice water and extracted with EtOAc. The organic layer was washed with water, brine, and dried over Na_2SO_4. The organic layer was concentrated to dryness and then recrystallized from heptane to give compound 227 as a white solid. LCMS and NMR were consistent with the structure. Compound 227 (1.5 g, 1.93 mmol) and compound 226 (3.7 g, 7.74 mmol) were stirred at room temperature in acetonitrile (15 mL) for 2 hours. The reaction was then evaporated to dryness and purified by column chromatography, eluting with a gradient of 2 to10% methanol in dichloromethane to give compound 228. LCMS and NMR were consistent with the structure. Compound 228 (1.7 g, 1.02 mmol) was treated with Raney Nickel (about 2g wet) in ethanol (100mL) in an atmosphere of hydrogen. After 12 hours, the catalyst was removed by filtration and the organic layer was evaporated to a solid that was used directly in the next step. LCMS and NMR were consistent with the structure. This solid (0.87 g, 0.53 mmol) was treated with benzylglutaric acid (0.18 g, 0.8 mmol), HBTU (0.3 g, 0.8 mmol) and DIEA (273.7 µl, 1.6 mmol) in DMF (5mL). After 16 hours, the DMF was removed under reduced pressure at 65°C to an oil, and the oil was dissolved in dichloromethane. The organic layer was washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. After evaporation of the organic layer, the compound was purified by column chromatography and eluted with a gradient of 2 to 20% methanol in dichloromethane to give the coupled product. LCMS and NMR were consistent with the structure. The benzyl ester was deprotected with Pearlman's catalyst under a hydrogen atmosphere for 1 hour. The catalyst was them removed by filtration and the solvents removed to dryness to give the acid. LCMS and NMR were consistent with the structure. The acid (486 mg, 0.27 mmol) was dissolved in dry DMF (3 mL). Pyridine (53.61 µl, 0.66 mmol) was added and the reaction was purged with argon. Pentaflourotriflouro acetate (46.39 µl, 0.4 mmol) was slowly added to the reaction mixture. The color of the reaction changed from pale yellow to burgundy, and gave off a light smoke which was blown away with a stream of argon. The reaction was allowed to stir at room temperature for one hour (completion of reaction was confirmed by LCMS). The solvent was removed under reduced pressure (rotovap) at 70 °C. The residue was diluted with DCM and washed with 1N $NaHSO_4$, brine, saturated sodium bicarbonate and brine again. The organics were dried over Na_2SO_4, filtered, and were concentrated to dryness to give 225 mg of compound 229 as a brittle yellow foam. LCMS and NMR were consistent with the structure.

Oligomeric compound 230, comprising a $GalNAc_3$-23 conjugate group, was prepared from compound 229 using the general procedure illustrated in Example 46. The $GalNAc_3$ cluster portion of the $GalNAc_3$-23 conjugate group ($GalNAc_3$-23_a) can be combined with any cleavable moiety to provide a variety of conjugate groups. The structure of $GalNAc_3$-23 ($GalNAc_3$-23_a-CM) is shown below:



Example 77: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a GalNAc$_3$ conjugate

The oligonucleotides listed below were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Table 64

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	GalNAc$_3$ Cluster	CM	SEQ ID No.
661161	**GalNAc$_3$-3$_a$-$_o$,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$_d$	2258
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	2256
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$_d$	2258
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$_d$	2258
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$_d$	2258
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$_d$	2257
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$_d$	2257
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$_d$	2257

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	2262
669509	$^{m}C_{es}A_{es}{}^{m}C_{es}T_{es}G_{es}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{ds}{}^{m}C_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{es}G_{es}G_{es}A_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	$GalNAc_3$-1_a	A_d	2263

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	2248
647535	$A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}$ $T_{es}A_{es}T_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	$GalNAc_3$-1a	A_d	2249
663083	$\mathbf{GalNAc_3\text{-}3_{a\text{-}o'}A_{do}}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-3a	A_d	2264
674449	$\mathbf{GalNAc_3\text{-}7_{a\text{-}o'}A_{do}}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-7a	A_d	2264
674450	$\mathbf{GalNAc_3\text{-}10_{a\text{-}o'}A_{do}}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-10a	A_d	2264
674451	$\mathbf{GalNAc_3\text{-}13_{a\text{-}o'}A_{do}}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $^{m}C_{ds}A_{ds}G_{ds}{}^{m}C_{ds}T_{es}T_{es}T_{es}A_{es}T_{e}$	$GalNAc_3$-13a	A_d	2264

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	2265
656326	$A_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{es}A_{es}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{ds}G_{ds}A_{ds}A_{ds}G_{ds}G_{ds}A_{es}A_{es}G_{es}G_{es}A_{eo}\mathbf{A_{do}}$-**$GalNAc_3-1_a$**	$GalNAc_3$-1a	A_d	2266
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	2267
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	2267
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	2267
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	2267

The structure of $GalNAc_3$-1_a was shown previously in Example 9, $GalNAc_3$-3_a was shown in Example 39, $GalNAc_3$-7_a was shown in Example 48, $GalNAc_3$-10_a was shown in Example 46, and $GalNAc_3$-13_a was shown in Example 62.

Treatment

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

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

Table 73

A1AT liver mRNA and plasma protein levels

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

Liver transaminase and BUN levels in plasma were measured at time of sacrifice using standard protocols. Body weights and organ weights were also measured. The results are shown in Table 74 below. Body weight is shown as % relative to baseline. Organ weights are shown as % of body weight relative to the PBS control group.

Table 74

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

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

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

Treatment

Six week old, male C57BL/6 mice were each injected subcutaneously once with an oligonucleotide listed in Table 72 or with PBS. Each treatment group consisted of 4 animals. Blood was drawn the day before dosing to determine baseline and at 5, 12, 19, and 25 days following the dose. Plasma A1AT protein levels were measured via ELISA (see Example 80). The results below are presented as the average percent of

plasma A1AT protein levels for each treatment group, normalized to baseline levels. The results show that the oligonucleotides comprising a GalNAc conjugate were more potent and had longer duration of action than the parent lacking a GalNAc conjugate (ISIS 476366). Furthermore, the oligonucleotides comprising a 5'-GalNAc conjugate (ISIS 678381, 678382, 678383, and 678384) were generally even more potent with even longer duration of action than the oligonucleotide comprising a 3'-GalNAc conjugate (ISIS 656326).

Table 75

Plasma A1AT protein levels in mice

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

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

Primary mouse liver hepatocytes were seeded in 96 well plates at 15,000 cells/well 2 hours prior to treatment. The oligonucleotides listed in Table 76 were added at 2, 10, 50, or 250 nM in Williams E medium and cells were incubated overnight at 37 °C in 5% CO_2. Cells were lysed 16 hours following oligonucleotide

addition, and total RNA was purified using RNease 3000 BioRobot (Qiagen). SRB-1 mRNA levels were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. IC_{50} values were determined using Prism 4 software (GraphPad). The results show that oligonucleotides comprising a variety of different GalNAc conjugate groups and a variety of different cleavable moieties are significantly more potent in an *in vitro* free uptake experiment than the parent oligonucleotides lacking a GalNAc conjugate group (ISIS 353382 and 666841).

Table 76

Inhibition of SRB-1 expression *in vitro*

ISIS No.	Sequence (5' to 3')	Linkages	GalNAc cluster	CM	IC_{50} (nM)	SEQ ID No.
353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	PS	n/a	n/a	250	2256
655861	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do}$-GalNAc$_3-1_a$**	PS	GalNAc$_3$-1$_a$	A_d	40	2257
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	2258
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	2258
664078	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{eo}$**$A_{do}$-GalNAc$_3-9_a$**	PS	GalNAc$_3$-9$_a$	A_d	20	2257
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	2258
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	2258
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	2256
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	2258
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	2256
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	2261
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	2258
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	2258
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	2258
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	2261
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	2258

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	2261
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	2258
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	2258
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	2258
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	2258
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	2258
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	2258
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	2258
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	2258
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	2257
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	2257
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	2258

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

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

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

Table 77

Modified oligonucleotides targeting Factor XI

ISIS No.	Sequence (5' to 3')	GalNAc cluster	CM	SEQ ID No.
404071	$T_{es}G_{es}G_{es}T_{es}A_{es}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{es}G_{es}$ $A_{es}G_{es}G_{e}$	n/a	n/a	2259
656173	$T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}$ $A_{es}G_{es}G_{eo}\mathbf{A_{do'}\text{-}GalNAc_3\text{-}1_a}$	$GalNAc_3\text{-}1_a$	A_d	2260
663086	$\mathbf{GalNAc_3\text{-}3_a\text{-}_o,A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}3_a$	A_d	2268
678347	$\mathbf{GalNAc_3\text{-}7_a\text{-}_o,A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}T_{ds}$ $T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}7_a$	A_d	2268
678348	$\mathbf{GalNAc_3\text{-}10_a\text{-}_o,A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}10_a$	A_d	2268
678349	$\mathbf{GalNAc_3\text{-}13_a\text{-}_o,A_{do}}T_{es}G_{eo}G_{eo}T_{eo}A_{eo}A_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ds}T_{ds}{}^{m}C_{ds}A_{eo}G_{eo}A_{es}G_{es}G_{e}$	$GalNAc_3\text{-}13_a$	A_d	2268

The structure of $GalNAc_3\text{-}1_a$ was shown previously in Example 9, $GalNAc_3\text{-}3_a$ was shown in Example 39, $GalNAc_3\text{-}7_a$ was shown in Example 48, $GalNAc_3\text{-}10_a$ was shown in Example 46, and $GalNAc_3\text{-}13_a$ was shown in Example 62.

Treatment

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

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

Table 78

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

ISIS No.	Dosage (mg/kg)	Factor XI mRNA (% PBS)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	Bilirubin (mg/dL)	$GalNAc_3$ Cluster	SEQ ID No.
PBS	n/a	100	63	70	21	0.18	n/a	n/a
404071	3	65	41	58	21	0.15	n/a	2259
	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	2260
	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	2268
	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	2268
	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	2268
	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	2268
	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	2259
		10	47			
		17	52			
656173	6	3	1	$GalNAc_3$-1a	A_d	2260
		10	3			
		17	21			
663086	6	3	1	$GalNAc_3$-3a	A_d	2268
		10	2			
		17	9			
678347	6	3	1	$GalNAc_3$-7a	A_d	2268
		10	1			
		17	8			
678348	6	3	1	$GalNAc_3$-10a	A_d	2268
		10	1			
		17	6			
678349	6	3	1	$GalNAc_3$-13a	A_d	2268
		10	1			
		17	5			

Example 85: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising a $GalNAc_3$ Conjugate

Oligonucleotides listed in Table 76 were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Treatment

Six to eight week old C57BL/6 mice were each injected subcutaneously once per week at a dosage shown below, for a total of three doses, with an oligonucleotide listed in Table 76 or with saline. Each treatment group consisted of 4 animals. The mice were sacrificed 48 hours following the final administration to determine the SRB-1 mRNA levels using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) according to standard protocols. The results below are presented as the average percent of liver SRB-1 mRNA levels for each treatment group, normalized to the saline control.

As illustrated in Tables 80 and 81, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner.

Table 80

SRB-1 mRNA in liver

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
Saline	n/a	100	n/a	n/a
655861	0.1	94	$GalNAc_3$-1a	A_d
	0.3	119		
	1	68		
	3	32		
661161	0.1	120	$GalNAc_3$-3a	A_d
	0.3	107		

	1	68		
	3	26		
666881	0.1	107	$GalNAc_3$-10a	A_d
	0.3	107		
	1	69		
	3	27		
666981	0.1	120	$GalNAc_3$-7a	A_d
	0.3	103		
	1	54		
	3	21		
670061	0.1	118	$GalNAc_3$-13a	A_d
	0.3	89		
	1	52		
	3	18		
677842	0.1	119	$GalNAc_3$-20a	A_d
	0.3	96		
	1	65		
	3	23		

Table 81

SRB-1 mRNA in liver

ISIS No.	Dosage (mg/kg)	SRB-1 mRNA (% Saline)	$GalNAc_3$ Cluster	CM
661161	0.1	107	$GalNAc_3$-3a	A_d
	0.3	95		
	1	53		
	3	18		
677841	0.1	110	$GalNAc_3$-19a	A_d
	0.3	88		
	1	52		
	3	25		

Liver transaminase levels, total bilirubin, BUN, and body weights were also measured using standard protocols. Average values for each treatment group are shown in Table 82 below.

Table 82

ISIS No.	Dosage (mg/kg)	ALT (U/L)	AST (U/L)	Bilirubin (mg/dL)	BUN (mg/dL)	Body Weight (% baseline)	$GalNAc_3$ Cluster	CM
Saline	n/a	19	39	0.17	26	118	n/a	n/a
655861	0.1	25	47	0.17	27	114	$GalNAc_3$-1a	A_d
	0.3	29	56	0.15	27	118		
	1	20	32	0.14	24	112		
	3	27	54	0.14	24	115		
661161	0.1	35	83	0.13	24	113	$GalNAc_3$-3a	A_d
	0.3	42	61	0.15	23	117		
	1	34	60	0.18	22	116		
	3	29	52	0.13	25	117		
666881	0.1	30	51	0.15	23	118	$GalNAc_3$-10a	A_d
	0.3	49	82	0.16	25	119		

	1	23	45	0.14	24	117		
	3	20	38	0.15	21	112		
666981	0.1	21	41	0.14	22	113	$GalNAc_3$-7a	A_d
	0.3	29	49	0.16	24	112		
	1	19	34	0.15	22	111		
	3	77	78	0.18	25	115		
670061	0.1	20	63	0.18	24	111	$GalNAc_3$-13a	A_d
	0.3	20	57	0.15	21	115		
	1	20	35	0.14	20	115		
	3	27	42	0.12	20	116		
677842	0.1	20	38	0.17	24	114	$GalNAc_3$-20a	A_d
	0.3	31	46	0.17	21	117		
	1	22	34	0.15	21	119		
	3	41	57	0.14	23	118		

Example 86: Antisense inhibition *in vivo* by oligonucleotides targeting TTR comprising a $GalNAc_3$ cluster

Oligonucleotides listed in Table 83 below were tested in a dose-dependent study for antisense inhibition of human transthyretin (TTR) in transgenic mice that express the human TTR gene.

Treatment

Eight week old TTR transgenic mice were each injected subcutaneously once per week for three weeks, for a total of three doses, with an oligonucleotide and dosage listed in the tables below or with PBS. Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration. Tail bleeds were performed at various time points throughout the experiment, and plasma TTR protein, ALT, and AST levels were measured and reported in Tables 85-87. After the animals were sacrificed, plasma ALT, AST, and human TTR levels were measured, as were body weights, organ weights, and liver human TTR mRNA levels. TTR protein levels were measured using a clinical analyzer (AU480, Beckman Coulter, CA). Real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) were used according to standard protocols to determine liver human TTR mRNA levels. The results presented in Tables 84-87 are the average values for each treatment group. The mRNA levels are the average values relative to the average for the PBS group. Plasma protein levels are the average values relative to the average value for the PBS group at baseline. Body weights are the average percent weight change from baseline until sacrifice for each individual treatment group. Organ weights shown are normalized to the animal's body weight, and the average normalized organ weight for each treatment group is then presented relative to the average normalized organ weight for the PBS group.

In Tables 84-87, "BL" indicates baseline, measurements that were taken just prior to the first dose. As illustrated in Tables 84 and 85, treatment with antisense oligonucleotides lowered TTR expression levels in a dose-dependent manner. The oligonucleotides comprising a GalNAc conjugate were more potent than the parent lacking a GalNAc conjugate (ISIS 420915). Furthermore, the oligonucleotides comprising a GalNAc

conjugate and mixed PS/PO internucleoside linkages were even more potent than the oligonucleotide comprising a GalNAc conjugate and full PS linkages.

Table 83

Oligonucleotides targeting human TTR

Isis No.	Sequence 5' to 3'	Linkages	GalNAc cluster	CM	SEQ ID No.
420915	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}$ $A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS	n/a	n/a	2269
660261	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}$ $A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{eo}\mathbf{A_{do'}}$-**GalNAc$_3-1_a$**	PS	GalNAc$_3$-1a	A_d	2270
682883	**GalNAc$_3$-3$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}$ $T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-3a	PO	2269
682884	**GalNAc$_3$-7$_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}$ $T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	GalNAc$_3$-7a	PO	2269
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	2269
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	2269
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	2270

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	2269
	20	48	65			
	60	18	28			
660261	0.6	113	87	GalNAc$_3$-1a	A_d	2270
	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	2269
	20	43	102	66	61	58			
	60	24	92	43	29	32			
682883	0.6	60	88	73	63	68	$GalNAc_3$-3a	PO	2269
	2	18	75	38	23	23			
	6	10	80	35	11	9			
682884	0.6	56	88	78	63	67	$GalNAc_3$-7a	PO	2269
	2	19	76	44	25	23			
	6	15	82	35	21	24			
682885	0.6	60	92	77	68	76	$GalNAc_3$-10a	PO	2269
	2	22	93	58	32	32			
	6	17	85	37	25	20			
682886	0.6	57	91	70	64	69	$GalNAc_3$-13a	PO	2269
	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	2270
	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	2269
	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	2270
	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	2269
	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	2269
	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	2269
	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	2269
	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	2269
	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	2270
	2	33	32	31	40	54	57	56	87	103	100	112	97	
	6	39	33	35	40	67	52	55	92	98	104	121	108	

Example 87: Duration of action *in vivo* by single doses of oligonucleotides targeting TTR comprising a $GalNAc_3$ cluster

ISIS numbers 420915 and 660261 (see Table 83) were tested in a single dose study for duration of action in mice. ISIS numbers 420915, 682883, and 682885 (see Table 83) were also tested in a single dose study for duration of action in mice.

Treatment

Eight week old, male transgenic mice that express human TTR were each injected subcutaneously once with 100 mg/kg ISIS No. 420915 or 13.5 mg/kg ISIS No. 660261. Each treatment group consisted of 4 animals. Tail bleeds were performed before dosing to determine baseline and at days 3, 7, 10, 17, 24, and 39 following the dose. Plasma TTR protein levels were measured as described in Example 86. The results below are presented as the average percent of plasma TTR levels for each treatment group, normalized to baseline levels.

Table 88

Plasma TTR protein levels

ISIS No.	Dosage (mg/kg)	Time point (days post-dose)	TTR (% baseline)	$GalNAc_3$ Cluster	CM	SEQ ID No.
420915	100	3	30	n/a	n/a	2269
		7	23			
		10	35			
		17	53			
		24	75			
		39	100			
660261	13.5	3	27	$GalNAc_3$-1a	A_d	2270
		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	2269
		7	48			
		10	48			
		17	66			
		31	80			
682883	10.0	3	45	$GalNAc_3$-3a	PO	2269
		7	37			
		10	38			
		17	42			
		31	65			
682885	10.0	3	40	$GalNAc_3$-10a	PO	2269
		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

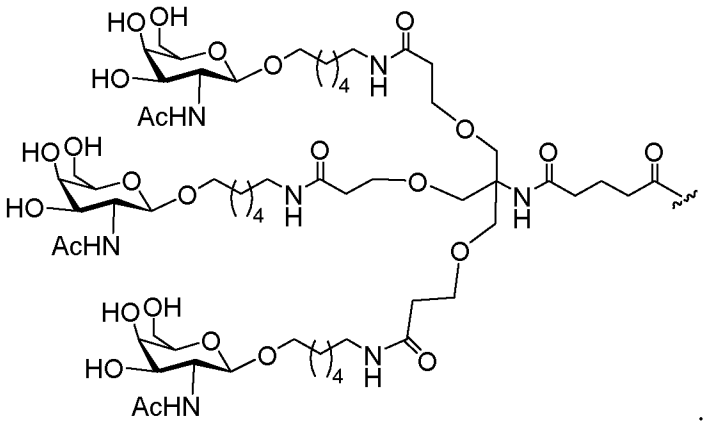
The oligonucleotides listed in Table 90 were tested for splicing modulation of human survival of motor neuron (SMN) in mice.

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	2271
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	2271
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	2271
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	2272
703421	X-ATT^{m}CA^{m}CTTT^{m}CATAATG^{m}CTGG	n/a	n/a	2271
703422	**$GalNAc_3$-7_{b}-**X-ATT^{m}CA^{m}CTTT^{m}CATAATG^{m}CTGG	$GalNAc_3$-7b	n/a	2271

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	2271
387954	288	5.00	n/a	n/a	2271
699819	32	7.84	$GalNAc_3$-7a	PO	2271
699821	32	7.22	$GalNAc_3$-7a	PO	2271
700000	32	6.91	$GalNAc_3$-1a	A_d	2272
703421	32	1.27	n/a	n/a	2271
703422	32	4.12	$GalNAc_3$-7b	n/a	2271

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	2281
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	2281

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

Treatment

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

normalized to the baseline (BL) value for the PBS group. Average absolute transaminase levels and body weights (% relative to baseline averages) are reported in Table 94.

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

Table 93

Apo(a) liver mRNA and plasma protein levels

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

Table 94

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

Example 90: Antisense inhibition *in vivo* by oligonucleotides targeting TTR comprising a $GalNAc_3$ cluster

Oligonucleotides listed in Table 95 below were tested in a dose-dependent study for antisense inhibition of human transthyretin (TTR) in transgenic mice that express the human TTR gene.

Treatment

TTR transgenic mice were each injected subcutaneously once per week for three weeks, for a total of three doses, with an oligonucleotide and dosage listed in Table 96 or with PBS. Each treatment group consisted of 4 animals. Prior to the first dose, a tail bleed was performed to determine plasma TTR protein

levels at baseline (BL). The mice were sacrificed 72 hours following the final administration. TTR protein levels were measured using a clinical analyzer (AU480, Beckman Coulter, CA). Real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc. Eugene, OR) were used according to standard protocols to determine liver human TTR mRNA levels. The results presented in Table 96 are the average values for each treatment group. The mRNA levels are the average values relative to the average for the PBS group. Plasma protein levels are the average values relative to the average value for the PBS group at baseline. "BL" indicates baseline, measurements that were taken just prior to the first dose. As illustrated in Table 96, treatment with antisense oligonucleotides lowered TTR expression levels in a dose-dependent manner. The oligonucleotides comprising a GalNAc conjugate were more potent than the parent lacking a GalNAc conjugate (ISIS 420915), and oligonucleotides comprising a phosphodiester or deoxyadenosine cleavable moiety showed significant improvements in potency compared to the parent lacking a conjugate (see ISIS numbers 682883 and 666943 vs 420915 and see Examples 86 and 87).

Table 95

Oligonucleotides targeting human TTR

Isis No.	Sequence 5' to 3'	Linkages	GalNAc cluster	CM	SEQ ID No.
420915	$T_{es}{}^{m}C_{es}T_{es}T_{es}G_{es}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{es}T_{es}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS	n/a	n/a	2269
682883	**$GalNAc_3$-$3_{a\text{-}o}$**,$T_{es}{}^{m}C_{eo}T_{eo}T_{eo}G_{eo}G_{ds}T_{ds}T_{ds}A_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}A_{ds}A_{eo}T_{eo}{}^{m}C_{es}{}^{m}C_{es}{}^{m}C_{e}$	PS/PO	$GalNAc_3$-3a	PO	2269
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	2273
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	2273
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	2273
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	2273

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	2274
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	2274

The legend for Table 97 can be found in Example 74. The structure of $GalNAc_3$-10_a was shown in Example 46.

Table 98

Factor VII plasma protein levels

ISIS No.	Day	Dose (mg/kg)	Factor VII (% BL)
407935	0	n/a	100
	15	10	87
	22	n/a	92
	29	30	77
	36	n/a	46
	43	n/a	43
686892	0	3	100
	15	10	56
	22	n/a	29
	29	30	19
	36	n/a	15
	43	n/a	11

Example 92: Antisense inhibition in primary hepatocytes by antisense oligonucleotides targeting Apo-CIII comprising a $GalNAc_3$ conjugate

Primary mouse hepatocytes were seeded in 96-well plates at 15,000 cells per well, and the oligonucleotides listed in Table 99, targeting mouse ApoC-III, were added at 0.46, 1.37, 4.12, or 12.35, 37.04, 111.11, or 333.33 nM or 1.00 μM. After incubation with the oligonucleotides for 24 hours, the cells were lysed and total RNA was purified using RNeasy (Qiagen). ApoC-III mRNA levels were determined using real-time PCR and RIBOGREEN® RNA quantification reagent (Molecular Probes, Inc.) according to standard protocols. IC_{50} values were determined using Prism 4 software (GraphPad). The results show that regardless of whether the cleavable moiety was a phosphodiester or a phosphodiester-linked deoxyadensoine, the oligonucleotides comprising a GalNAc conjugate were significantly more potent than the parent oligonucleotide lacking a conjugate.

Table 99

Inhibition of mouse APOC-III expression in mouse primary hepatocytes

ISIS No.	Sequence (5' to 3')	CM	IC_{50} (nM)	SEQ ID No.
440670	$^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}T_{es}T_{ds}T_{ds}A_{ds}T_{ds}T_{ds}A_{ds}G_{ds}G_{ds}G_{ds}A_{ds}{}^{m}C_{es}A_{es}G_{es}{}^{m}C_{es}A_{e}$	n/a	13.20	2275
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	2276
680771	**$GalNAc_3$-3_{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	0.70	2275
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	1.70	2275
680773	**$GalNAc_3$-10_{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	2.00	2275

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	2275
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	2275
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	2277
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	2276

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	2278
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	2278
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	2278
699809	**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} $A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{e}$	GalNAc$_3$-7a	PO	2278
699811	**GalNAc$_3$-7$_{a\text{-}o}$**,$T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{k}$	GalNAc$_3$-7a	PO	2278
699813	**GalNAc$_3$-7$_{a\text{-}o}$**,$T_{ks}T_{ds}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ks}{}^{m}C_{ds}{}^{m}C_{k}$	GalNAc$_3$-7a	PO	2278
699815	**GalNAc$_3$-7$_{a\text{-}o}$**,$T_{es}T_{ks}{}^{m}C_{ks}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}$ $A_{ds}T_{ds}$ $G_{ds}A_{ds}{}^{m}C_{ds}$ $T_{ds}T_{ks}{}^{m}C_{ks}{}^{m}C_{e}$	GalNAc$_3$-7a	PO	2278

The structure of GalNAc$_3$-3$_a$ was shown previously in Example 39, and the structure of GalNAc$_3$-7a was shown previously in Example 48. Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "k" indicates 6'-*(S)*-CH$_3$ bicyclic nucleoside (cEt); "s" indicates phosphorothioate internucleoside linkages (PS); "o" indicates phosphodiester internucleoside linkages (PO). Supersript "m" indicates 5-methylcytosines.

Treatment

Six to eight week old C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were injected subcutaneously once at the dosage shown below with an oligonucleotide listed in Table 100 or with saline.

Each treatment group consisted of 4 animals. The mice were sacrificed 72 hours following the final administration. Liver SRB-1 mRNA levels were measured using real-time PCR. SRB-1 mRNA levels were normalized to cyclophilin mRNA levels according to standard protocols. The results are presented as the average percent of SRB-1 mRNA levels for each treatment group relative to the saline control group. As illustrated in Table 101, treatment with antisense oligonucleotides lowered SRB-1 mRNA levels in a dose-dependent manner, and the gapmer oligonucleotides comprising a GalNAc conjugate and having wings that were either full cEt or mixed sugar modifications were significantly more potent than the parent oligonucleotide lacking a conjugate and comprising full cEt modified wings.

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

Table 101

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

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

Example 94: Antisense inhibition *in vivo* by oligonucleotides targeting SRB-1 comprising 2'-sugar modifications and a 5'-GalNAc$_3$ conjugate

The oligonucleotides listed in Table 102 were tested in a dose-dependent study for antisense inhibition of SRB-1 in mice.

Table 102

Modified ASOs targeting SRB-1

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
353382	$G_{es}{}^{m}C_{es}T_{es}T_{es}{}^{m}C_{es}A_{ds}G_{ds}T_{ds}{}^{m}C_{ds}A_{ds}T_{ds}G_{ds}A_{ds}{}^{m}C_{ds}T_{ds}T_{es}{}^{m}C_{es}{}^{m}C_{es}T_{es}T_{e}$	n/a	n/a	2256
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	2279
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	2256
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	2279

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	2250
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	2250
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	2250
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	2250
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$_d$	2251
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	2250
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	2250

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	2281
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	2281
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	2281
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	2281

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-o}-A_{do}** T_{es} $^mC_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^mC_{es}$ $^mC_{es}$ ^mC_e	$GalNAc_3$-3	A_d	2273
666942	T_{es} $^mC_{eo}$ T_{eo} T_{eo} G_{eo} G_{ds} T_{ds} T_{ds} A_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{eo} T_{eo} $^mC_{es}$ $^mC_{es}$ $^mC_{eo}$ **A_{do}-$GalNAc_3$-3_a**	$GalNAc_3$-1	A_d	2270
682876	**$GalNAc_3$-3_{a-o}-**T_{es} $^mC_{es}$ T_{es} T_{es} G_{es} G_{ds} T_{ds} T_{ds} A_{ds} $^mC_{ds}$ A_{ds} T_{ds} G_{ds} A_{ds} A_{ds} A_{es} T_{es} $^mC_{es}$ $^mC_{es}$ ^mC_e	$GalNAc_3$-3	PO	2269

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	2269
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	2269
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	2269
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$_d$	2273
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$_d$	2273
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$_d$	2273
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$_d$	2270

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	2281
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	2281

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	2275
			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	2275
			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	2275
			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	2248
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$_d$	2264
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$_d$	2249

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.

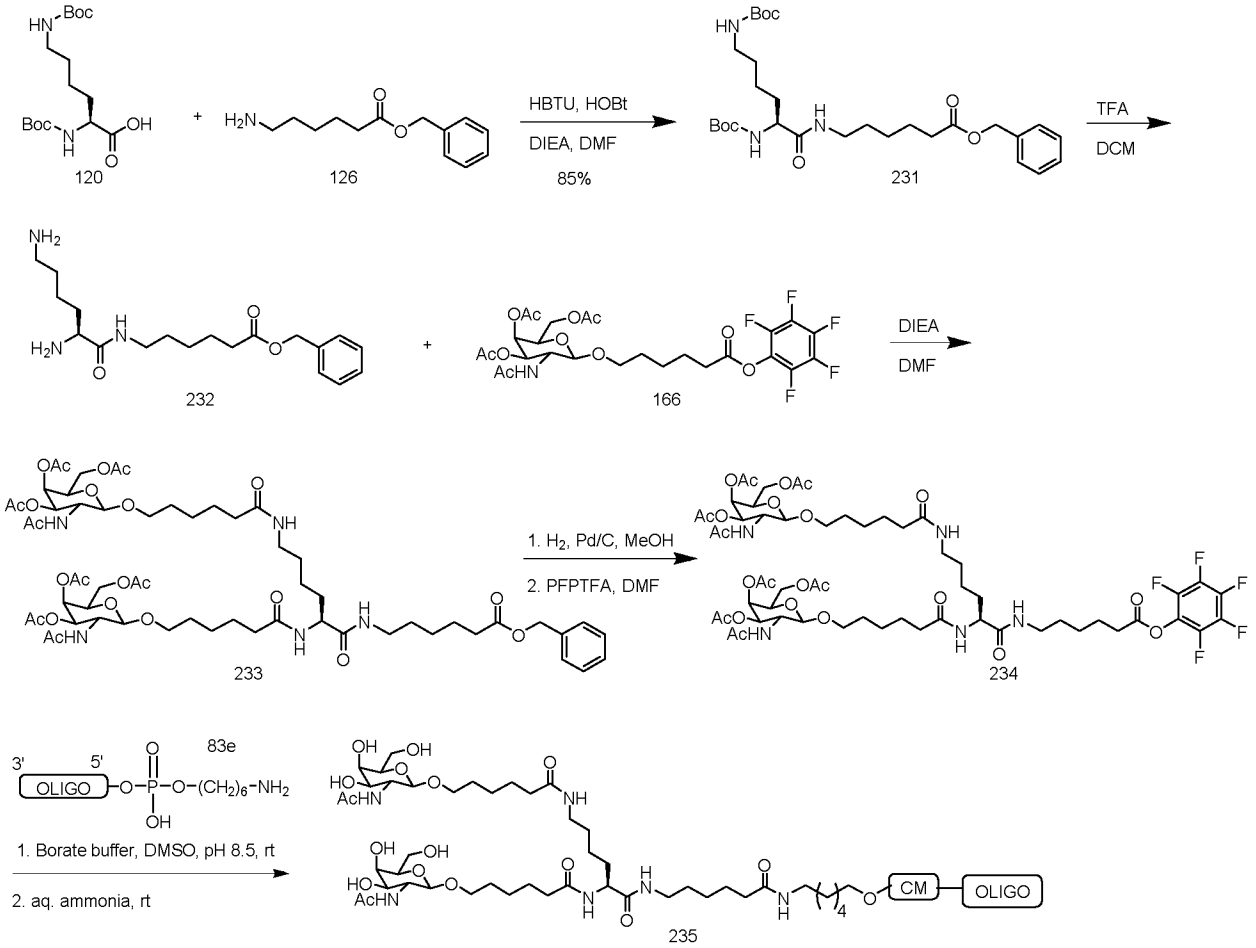
Table 115

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		

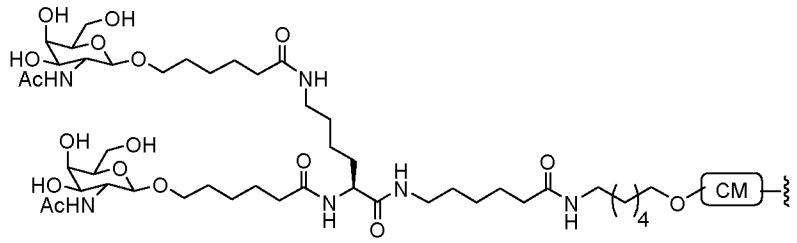
304801	30	3	42	46	n/a	n/a
		7	42	51		
		14	59	69		
		21	67	81		
		28	79	76		
		35	72	95		
		42	82	92		
663084	10	3	35	28	$GalNAc_3$-3a	A_d
		7	23	24		
		14	23	26		
		21	23	29		
		28	30	22		
		35	32	36		
		42	37	47		
679241	10	3	38	30	$GalNAc_3$-19a	A_d
		7	31	28		
		14	30	22		
		21	36	34		
		28	48	34		
		35	50	45		
		42	72	64		

Example 104: Synthesis of oligonucleotides comprising a 5'-GalNAc$_2$ conjugate

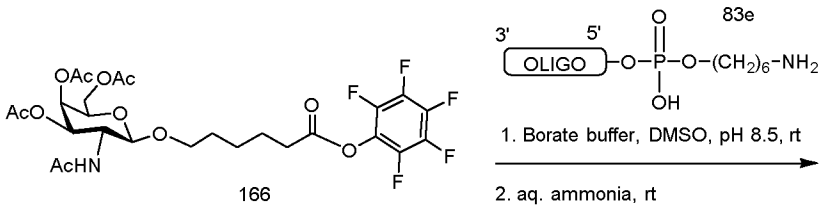


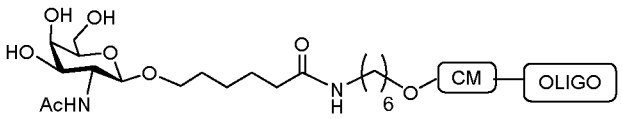
Compound 120 is commercially available, and the synthesis of compound 126 is described in Example 49. Compound 120 (1 g, 2.89 mmol), HBTU (0.39 g, 2.89 mmol), and HOBt (1.64 g, 4.33 mmol) were dissolved in DMF (10 mL. and *N,N*-diisopropylethylamine (1.75 mL, 10.1 mmol) were added. After about 5 min,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

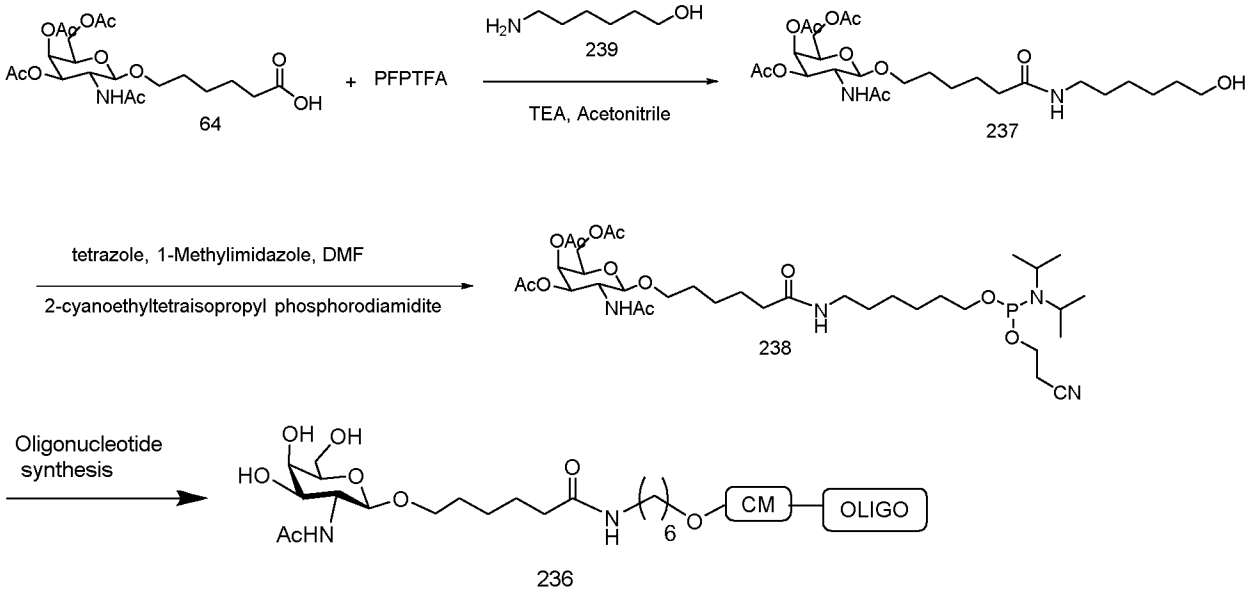




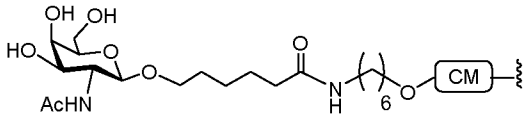
236

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	2250
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	2254
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	2254

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	2250
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	2250

See Example 93 for table legend. The structure of $GalNAc_1$-25a was shown in Example 105.

The concentrations of the oligonucleotides in Tables 116 and 117 in liver were also assessed, using procedures described in Example 75. The results shown in Tables 117a and 117b below are the average total antisense oligonucleotide tissues levels for each treatment group, as measured by UV in units of μg oligonucleotide per gram of liver tissue. The results show that the oligonucleotides comprising a GalNAc conjugate group accumulated in the liver at significantly higher levels than the same dose of the oligonucleotide lacking a GalNAc conjugate group. Furthermore, the antisense oligonucleotides comprising one, two, or three GalNAc ligands in their respective conjugate groups all accumulated in the liver at similar levels. This result is surprising in view of the Khorev et al. literature reference cited above and is consistent with the activity data shown in Tables 116 and 117 above.

Table 117a

Liver concentrations of oligonucleotides comprising a $GalNAc_2$ or $GalNAc_3$ conjugate group

ISIS No.	Dosage (mg/kg)	[Antisense oligonucleotide] (μg/g)	GalNAc cluster	CM
440762	2	2.1	n/a	n/a
	7	13.1		
	20	31.1		
686221	0.2	0.9	$GalNAc_2$-24_a	A_d
	0.6	2.7		
	2	12.0		

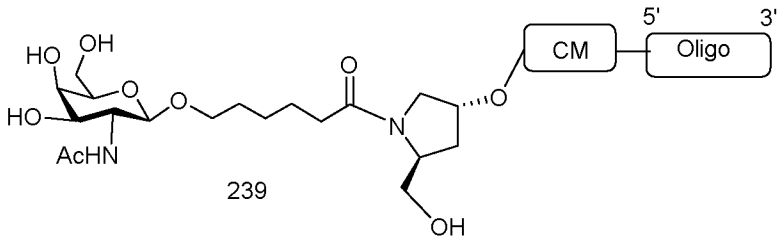
	6	26.5		
686222	0.2	0.5	$GalNAc_3$-13_a	A_d
	0.6	1.6		
	2	11.6		
	6	19.8		

Table 117b

Liver concentrations of oligonucleotides comprising a $GalNAc_1$ conjugate group

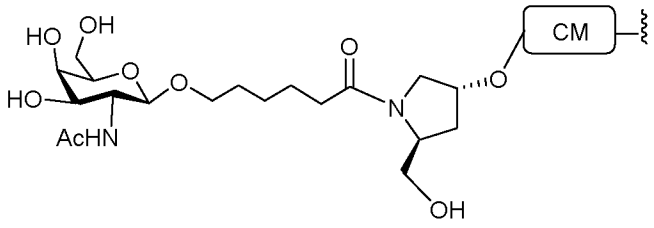
ISIS No.	Dosage (mg/kg)	[Antisense oligonucleotide] (μg/g)	GalNAc cluster	CM
440762	2	2.3	n/a	n/a
	7	8.9		
	20	23.7		
708561	0.2	0.4	$GalNAc_1$-25_a	PO
	0.6	1.1		
	2	5.9		
	6	23.7		
	20	53.9		

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

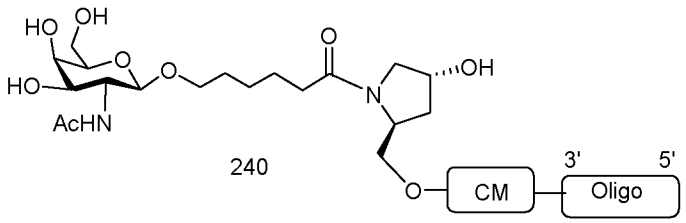


239

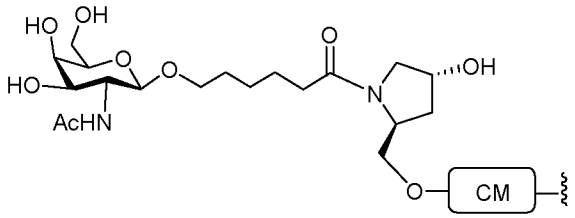
Oligonucleotide 239 is synthesized via coupling of compound 47 (see Example 15) to acid 64 (see Example 32) using HBTU and DIEA in DMF. The resulting amide containing compound is phosphitylated, then added to the 5'-end of an oligonucleotide using procedures described in Example 10. The $GalNAc_1$ cluster portion ($GalNAc_1$-26_a) of the conjugate group $GalNAc_1$-26 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-26 ($GalNAc_1$-26_a-CM) is shown below:



In order to add the $GalNAc_1$ conjugate group to the 3'-end of an oligonucleotide, the amide formed from the reaction of compounds 47 and 64 is added to a solid support using procedures described in Example 7. The oligonucleotide synthesis is then completed using procedures described in Example 9 in order to form oligonucleotide 240.



The $GalNAc_1$ cluster portion ($GalNAc_1$-27_a) of the conjugate group $GalNAc_1$-27 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-27 ($GalNAc_1$-27_a-CM) is shown below:



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

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

Table 118

Modified ASOs targeting APO(a)

ISIS No.	Sequences (5' to 3')	$GalNAc_3$ Cluster	CM	SEQ ID No.
494372	$T_{es}G_{es}{}^{m}C_{es}T_{es}{}^{m}C_{es}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}$ $T_{ds}T_{es}G_{es}T_{es}T_{es}{}^{m}C_{e}$	n/a	n/a	2281
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	2281
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	2281
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	2281
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	2281
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	2281

681260	$T_{es}G_{eo}{}^{m}C_{eo}T_{eo}{}^{m}C_{eo}{}^{m}C_{ds}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}G_{ds}{}^{m}C_{ds}T_{ds}T_{eo}G_{eo}T_{es}T_{es}{}^{m}C_{e0}\mathbf{A_{d0}}$-**GalNAc$_3$-19**	GalNAc$_3$-19a	A_d	2280

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

Treatment

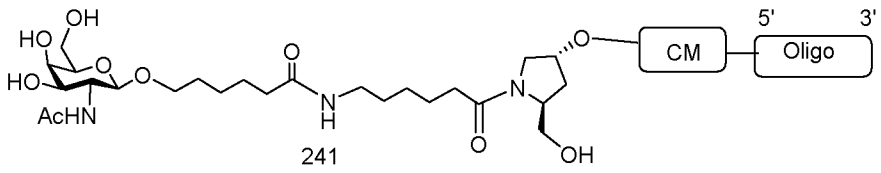
Male transgenic mice that express human Apo(a) were each injected subcutaneously once with an oligonucleotide and dosage listed in Table 119 or with PBS. Each treatment group consisted of 4 animals. Blood was drawn the day before dosing to determine baseline levels of Apo(a) protein in plasma and at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

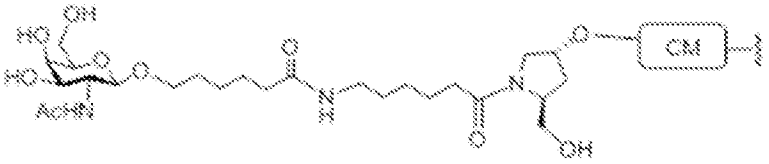
ISIS No.	Dosage (mg/kg)	Apo(a) at 1 week (% BL)
PBS	n/a	143
494372	50	58
681251	10	15
681255	10	14
681256	10	17
681257	10	24
681258	10	22
681260	10	26

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

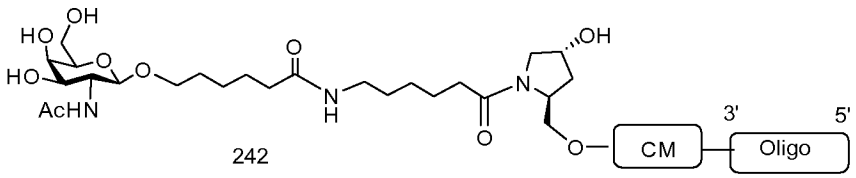


Oligonucleotide 241 is synthesized using procedures similar to those described in Example 71 to form the phosphoramidite intermediate, followed by procedures described in Example 10 to synthesize the oligonucleotide. The GalNAc$_1$ cluster portion (GalNAc$_1$-28$_a$) of the conjugate group GalNAc$_1$-28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

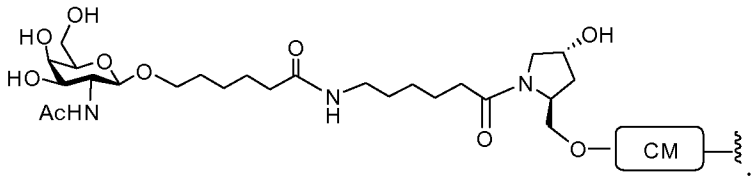


In order to add the $GalNAc_1$ conjugate group to the 3'-end of an oligonucleotide, procedures similar to those described in Example 71 are used to form the hydroxyl intermediate, which is then added to the solid support using procedures described in Example 7. The oligonucleotide synthesis is then completed using procedures described in Example 9 in order to form oligonucleotide 242.

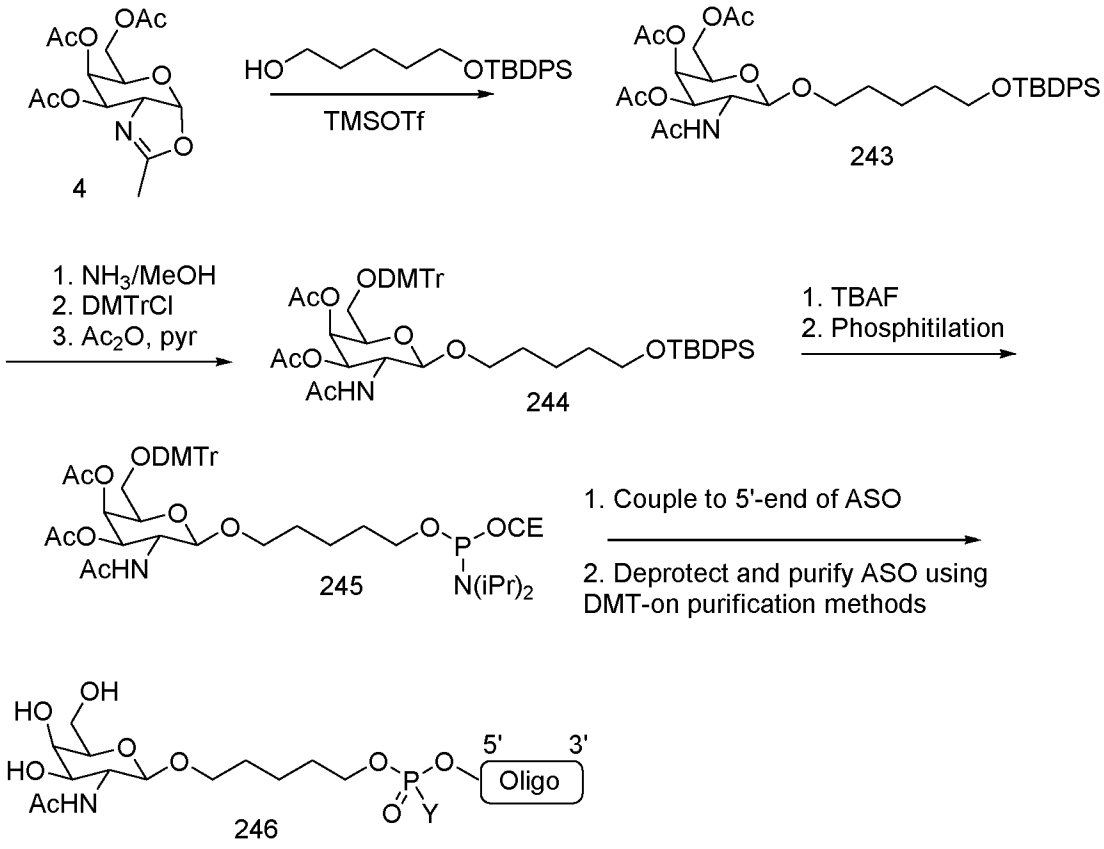


242

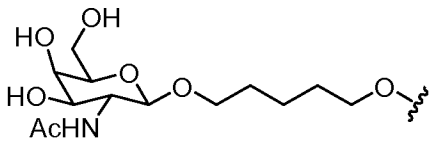
The $GalNAc_1$ cluster portion ($GalNAc_1$-29_a) of the conjugate group $GalNAc_1$-29 can be combined with any cleavable moiety present on the oligonucleotide to provide a variety of conjugate groups. The structure of $GalNAc_1$-29 ($GalNAc_1$-29_a-CM) is shown below:



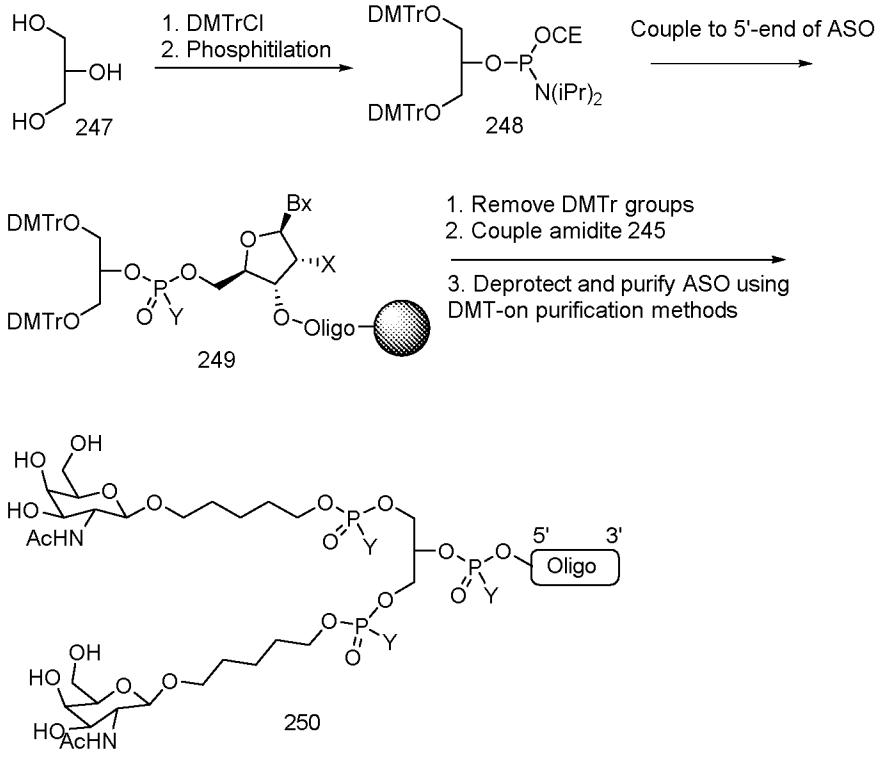
Example 110: Synthesis of oligonucleotides comprising a GalNAc$_1$-30 conjugate



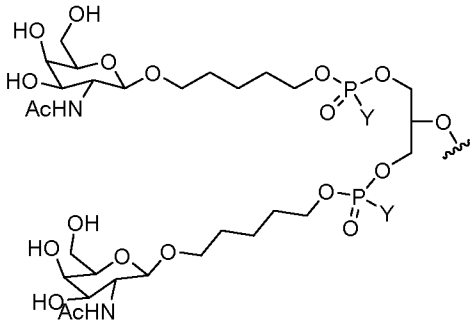
Oligonucleotide 246 comprising a GalNAc$_1$-30 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The GalNAc$_1$ cluster portion (GalNAc$_1$-30$_a$) of the conjugate group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



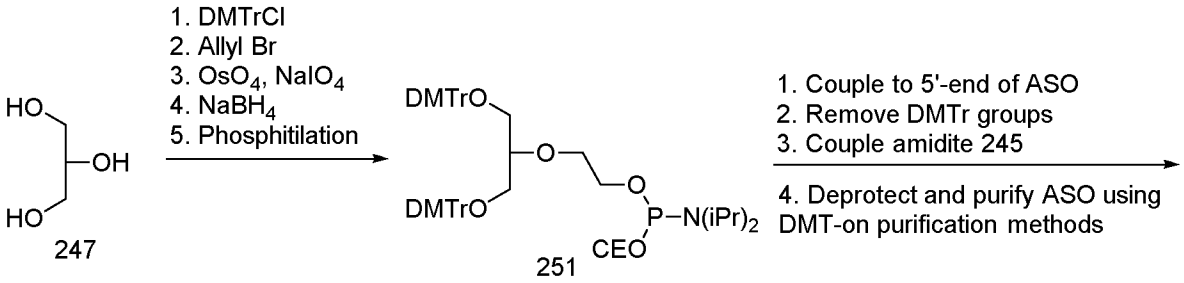
Example 111: Synthesis of oligonucleotides comprising a GalNAc$_2$-31 or GalNAc$_2$-32 conjugate

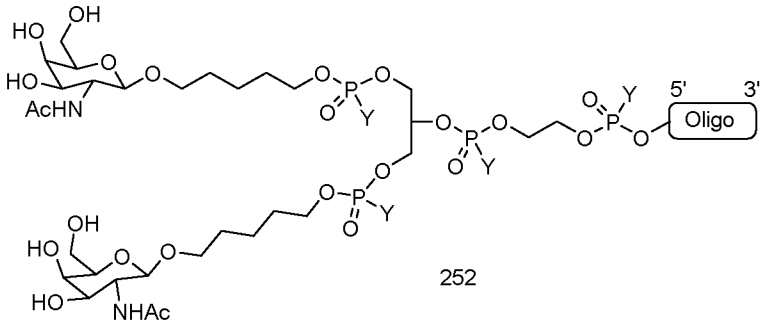


Oligonucleotide 250 comprising a GalNAc$_2$-31 conjugate group, wherein Y is selected from O, S, a substituted or unsubstituted C_1-C_{10} alkyl, amino, substituted amino, azido, alkenyl or alkynyl, is synthesized as shown above. The GalNAc$_2$ cluster portion (GalNAc$_2$-31$_a$) of the conjugate group 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:

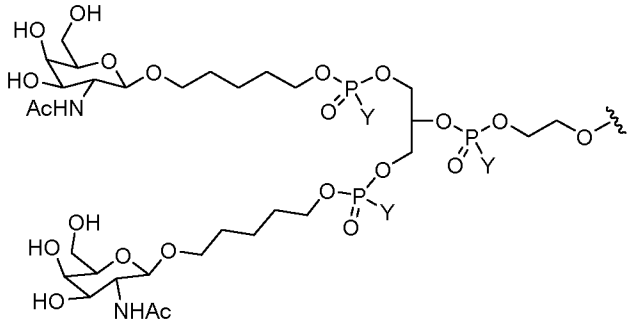


The synthesis of an oligonucleotide comprising a $GalNAc_2$-32 conjugate is shown below.





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}** $G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-25_a	A_d	2258
711462	**$GalNAc_1$-$25_{a\text{-}o}$,** $G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-25_a	PO	2256
711463	**$GalNAc_1$-$25_{a\text{-}o}$,** $G_{es}\ ^mC_{eo}\ T_{eo}\ T_{eo}\ ^mC_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{eo}\ ^mC_{eo}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-25_a	PO	2256
711465	**$GalNAc_1$-$26_{a\text{-}o}$,A_{do}** $G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-26_a	A_d	2258
711466	**$GalNAc_1$-$26_{a\text{-}o}$,** $G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-26_a	PO	2256
711467	**$GalNAc_1$-$26_{a\text{-}o}$,** $G_{es}\ ^mC_{eo}\ T_{eo}\ T_{eo}\ ^mC_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{eo}\ ^mC_{eo}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-26_a	PO	2256
711468	**$GalNAc_1$-$28_{a\text{-}o}$,A_{do}** $G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-28_a	A_d	2258
711469	**$GalNAc_1$-$28_{a\text{-}o}$,** $G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-28_a	PO	2256
711470	**$GalNAc_1$-$28_{a\text{-}o}$,** $G_{es}\ ^mC_{eo}\ T_{eo}\ T_{eo}\ ^mC_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{eo}\ ^mC_{eo}\ ^mC_{es}\ T_{es}\ T_e$	$GalNAc_1$-28_a	PO	2256
713844	$G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_{eo}$**'-$GalNAc_1$-$27_a$**	$GalNAc_1$-27_a	PO	2256
713845	$G_{es}\ ^mC_{eo}\ T_{eo}\ T_{eo}\ ^mC_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{eo}\ ^mC_{eo}\ ^mC_{es}\ T_{es}\ T_{eo}$**'-$GalNAc_1$-$27_a$**	$GalNAc_1$-27_a	PO	2256
713846	$G_{es}\ ^mC_{eo}\ T_{eo}\ T_{eo}\ ^mC_{eo}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{eo}\ ^mC_{eo}\ ^mC_{es}\ T_{es}\ T_{eo}$ **A_{do}'-$GalNAc_1$-27_a**	$GalNAc_1$-27_a	A_d	2257
713847	$G_{es}\ ^mC_{es}\ T_{es}\ T_{es}\ ^mC_{es}\ A_{ds}\ G_{ds}\ T_{ds}\ ^mC_{ds}\ A_{ds}\ T_{ds}\ G_{ds}\ A_{ds}\ ^mC_{ds}\ T_{ds}\ T_{es}\ ^mC_{es}\ ^mC_{es}\ T_{es}\ T_{eo}$**'-$GalNAc_1$-$29_a$**	$GalNAc_1$-29_a	PO	2256

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	2256
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$_d$	2257
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$_d$	2257

Example 113: Antisense oligonucleotides targeting kallikrein B, plasma (Fletcher factor) 1 comprising a GalNAc cluster

The oligonucleotides in Table 121 were designed to target human kallikrein B, plasma (Fletcher factor) 1, or prekallikrein (PKK).

Table 121

Sequences (5' to 3')	SEQ ID No.
GalNAc$_3$-3-$T_{es}G_{es}\ ^{m}C_{es}A_{es}A_{es}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{es}A_{es}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-3-$T_{es}G_{eo}\ ^{m}C_{eo}A_{eo}A_{eo}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{eo}A_{eo}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-7-$T_{es}G_{es}\ ^{m}C_{es}A_{es}A_{es}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{es}A_{es}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-7-$T_{es}G_{eo}\ ^{m}C_{eo}A_{eo}A_{eo}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{eo}A_{eo}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-10-$T_{es}G_{es}\ ^{m}C_{es}A_{es}A_{es}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{es}A_{es}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-10-$T_{es}G_{eo}\ ^{m}C_{eo}A_{eo}A_{eo}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{eo}A_{eo}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-13-$T_{es}G_{es}\ ^{m}C_{es}A_{es}A_{es}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{es}A_{es}A_{es}\ ^{m}C_{es}A_{e}$	570
GalNAc$_3$-13-$T_{es}G_{eo}\ ^{m}C_{eo}A_{eo}A_{eo}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{eo}A_{eo}A_{es}\ ^{m}C_{es}A_{e}$	570
$T_{es}G_{es}\ ^{m}C_{es}A_{es}A_{es}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{es}A_{es}A_{es}\ ^{m}C_{es}A_{e}$-**GalNAc$_3$-19**	570
$T_{es}G_{eo}\ ^{m}C_{eo}A_{eo}A_{eo}G_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{eo}A_{eo}A_{es}\ ^{m}C_{es}A_{e}$-**GalNAc$_3$-19**	570
GalNAc$_3$-7$_{a-o}$-$T_{es}G_{es}\ ^{m}C_{eo}A_{eo}A_{es}\ G_{ds}\ T_{ds}\ ^{m}C_{ds}T_{ds}\ ^{m}C_{ds}T_{ds}T_{ds}G_{ds}G_{ds}\ ^{m}C_{ds}A_{eo}A_{eo}A_{es}\ ^{m}C_{es}A_{e}$	570

Example 114: Antisense inhibition of human PKK in HepaRG™^{T} cells by antisense oligonucleotides with 2'-MOE sugar modifications

Antisense oligonucleotides were designed targeting a PKK nucleic acid and were tested for their effects on PKK mRNA *in vitro*. HepaRG™ cells, which are terminally differentiated hepatic cells derived from a human hepatic progenitor cell line and retain many characteristics of primary human hepatocytes (Lubberstedt M. et al., J. Pharmacol. Toxicol. Methods 2011 63: 59-68), were used in the screen.

The chimeric antisense oligonucleotides in the tables below were designed as 5-10-5 MOE gapmers. The 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. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-O-methoxyethyl modification. The internucleoside linkages throughout each gapmer are phosphorothioate 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 in the human gene sequence. Each gapmer listed in the tables below is targeted to either the human PKK mRNA, designated herein as SEQ ID NO: 1 (GENBANK

Accession No. NM_000892.3) or the human PKK genomic sequence, designated herein as SEQ ID NO: 10 (GENBANK Accession No. NT_016354.19 truncated from nucleotides 111693001 to 111730000). 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence.

Cultured HepaRG™ cells at a density of 20,000 cells per well were transfected using electroporation with 3,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PKK mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3454 (forward sequence CCAAAAAAGGTGCACCAGTAACA, designated herein as SEQ ID NO: 20; reverse sequence CCTCCGGGACTGTACTTTAATAGG, designated herein as SEQ ID NO: 21; probe sequence CACGCAAACATTTCACAAGGCAGAGTACC, designated herein as SEQ ID NO: 22) was used to measure mRNA levels. PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. 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. Results are presented as percent inhibition of PKK, relative to untreated control cells.

Table 122

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
530929	1	20	AACGGTCTTCAAGCTGTTCT	59	3393	3412	30
530930	6	25	AAATGAACGGTCTTCAAGCT	17	3398	3417	31
530931	11	30	CTTAAAAATGAACGGTCTTC	29	3403	3422	32
530932	16	35	TGTCACTTAAAAATGAACGG	52	3408	3427	33
530933	31	50	TGGAGGTGAGTCTCTTGTCA	76	3423	3442	34
530934	36	55	CTTCTTGGAGGTGAGTCTCT	54	3428	3447	35
530935	68	87	GCTTGAATAAAATCATTCTG	0	n/a	n/a	36
530936	73	92	TGCTTGCTTGAATAAAATCA	27	4072	4091	37
530937	78	97	TAAGTTGCTTGCTTGAATAA	0	4077	4096	38
530938	88	107	GGAAATGAAATAAGTTGCTT	11	4087	4106	39
530939	93	112	AACAAGGAAATGAAATAAGT	0	4092	4111	40
530940	98	117	TAGCAAACAAGGAAATGAAA	7	4097	4116	41
530941	103	122	AACTGTAGCAAACAAGGAAA	22	4102	4121	42
530942	108	127	CAGGAAACTGTAGCAAACAA	22	4107	4126	43
530943	113	132	ATCCACAGGAAACTGTAGCA	56	n/a	n/a	44
530944	118	137	CAGACATCCACAGGAAACTG	0	n/a	n/a	45
530945	157	176	ATCCCCACCTCTGAAGAAGG	0	8029	8048	46
530946	160	179	TACATCCCCACCTCTGAAGA	0	8032	8051	47
530947	165	184	GAAGCTACATCCCCACCTCT	27	8037	8056	48
530948	170	189	ACATGGAAGCTACATCCCCA	35	8042	8061	49
530949	175	194	GGTGTACATGGAAGCTACAT	31	8047	8066	50
530950	221	240	ACCTTGGGTGGAATGTGCAC	47	8093	8112	51

530951	226	245	CAAACACCTTGGGTGGAATG	49	8098	8117	52
530952	234	253	CTGAATAGCAAACACCTTGG	38	8106	8125	53
530953	239	258	GAAAACTGAATAGCAAACAC	7	8111	8130	54
530954	244	263	TGGAAGAAAACTGAATAGCA	47	8116	8135	55
530955	278	297	CAAACCTTTTCTCCATGTCA	55	n/a	n/a	56
530956	300	319	ACACTATCTTTCAAGAAGCA	57	9834	9853	57
530957	386	405	GGCAAGCACTTATTTGATGA	56	n/a	n/a	58
530958	432	451	TTAAAATTGACTCCTCTCAT	60	12688	12707	59
530959	456	475	TCAACACTGCTAACCTTAGA	60	12712	12731	60
530960	461	480	ATTCTTCAACACTGCTAACC	58	12717	12736	61
530961	466	485	TTGGCATTCTTCAACACTGC	88	12722	12741	62
530962	472	491	CCTTTTTTGGCATTCTTCAA	64	12728	12747	63
530963	479	498	TGGTGCACCTTTTTTGGCAT	78	12735	12754	64
530964	628	647	CTTCAGTGAGAATCCAGATT	44	14199	14218	65
530965	637	656	GGCACAGGGCTTCAGTGAGA	73	14208	14227	66
530966	649	668	AATTTCTGAAAGGGCACAGG	58	14220	14239	67
530967	654	673	CAACCAATTTCTGAAAGGGC	69	n/a	n/a	68
530968	680	699	CAAGATGCTGGAAGATGTTC	18	26128	26147	69
530969	846	865	GTGCCACTTTCAGATGTTTT	0	27110	27129	70
530970	851	870	TTGGTGTGCCACTTTCAGAT	74	27115	27134	71
530971	856	875	GGAACTTGGTGTGCCACTTT	85	27120	27139	72
530972	861	880	GTAGAGGAACTTGGTGTGCC	42	27125	27144	73
530973	866	885	GAGGAGTAGAGGAACTTGGT	52	27130	27149	74
530974	871	890	TTCTTGAGGAGTAGAGGAAC	18	27135	27154	75
530975	876	895	GTGTTTTCTTGAGGAGTAGA	41	27140	27159	76
530976	881	900	ATATGGTGTTTTCTTGAGGA	26	27145	27164	77
530977	886	905	TCCAGATATGGTGTTTTCTT	55	27150	27169	78
530978	891	910	CTATATCCAGATATGGTGTT	0	27155	27174	79
530979	901	920	GGTTAAAAGGCTATATCCAG	35	27165	27184	80
530980	906	925	TTGCAGGTTAAAAGGCTATA	29	27170	27189	81
530981	911	930	TTCTTTTGCAGGTTAAAAGG	0	27175	27194	82
530982	916	935	TAAAGTTCTTTTGCAGGTTA	0	27180	27199	83
530983	931	950	ATGGCAGGGTTCAGGTAAAG	9	n/a	n/a	84
530984	936	955	TTAGAATGGCAGGGTTCAGG	25	n/a	n/a	85
530985	941	960	AAATTTTAGAATGGCAGGGT	32	27363	27382	86
530986	946	965	CGGGTAAATTTTAGAATGGC	62	27368	27387	87
530987	951	970	ACTCCCGGGTAAATTTTAGA	0	27373	27392	88
530988	961	980	TCCAAAGTCAACTCCCGGGT	76	27383	27402	89
530989	966	985	TCTCCTCCAAAGTCAACTCC	28	27388	27407	90
530990	971	990	ATTCTTCTCCTCCAAAGTCA	32	27393	27412	91
530991	976	995	ATTCAATTCTTCTCCTCCAA	43	27398	27417	92
530992	981	1000	GTCACATTCAATTCTTCTCC	70	27403	27422	93
530993	1005	1024	CAAACATTCACTCCTTTAAC	30	27427	27446	94

530994	1010	1029	CTTGGCAAACATTCACTCCT	50	27432	27451	95
530995	1015	1034	AGTCTCTTGGCAAACATTCA	49	27437	27456	96
530996	1038	1057	TGACAGCGAATCATCTTTGT	51	27460	27479	97
530997	1043	1062	AAAACTGACAGCGAATCATC	39	27465	27484	98
530998	1048	1067	AGTGAAAAACTGACAGCGAA	0	27470	27489	99
530999	1071	1090	CAGTCTTCTGGGAGTAAAGA	31	27493	27512	100
531000	1098	1117	AAGAAACACTTACACTTCTC	1	n/a	n/a	101
531001	1108	1127	AGATAATCTTAAGAAACACT	44	27629	27648	102
531002	1155	1174	GAGCTCCCTTGTGTCCCATA	85	27676	27695	103
531003	1160	1179	AACCAGAGCTCCCTTGTGTC	49	27681	27700	104
531004	1165	1184	AGAGTAACCAGAGCTCCCTT	76	27686	27705	105
531005	1170	1189	CTCAAAGAGTAACCAGAGCT	76	27691	27710	106
531006	1216	1235	GCTTGTTTTTGTTGTGCAGA	49	27892	27911	107

Table 123

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
482586	1608	1627	ACCCAACAGTTGGTATAAAT	0	31914	31933	108
486847	1563	1582	AGGCATATTGGTTTTTGGAA	78	31869	31888	109
531007	46	65	AACACAATTGCTTCTTGGAG	51	3438	3457	110
531008	675	694	TGCTGGAAGATGTTCATGTG	51	26123	26142	111
531009	1239	1258	TTTGTTCCTCCAACAATGCG	65	27915	27934	112
531010	1244	1263	AAGAGTTTGTTCCTCCAACA	52	27920	27939	113
531011	1249	1268	CCAAGAAGAGTTTGTTCCTC	0	27925	27944	114
531012	1254	1273	TCTCCCCAAGAAGAGTTTGT	48	27930	27949	115
531013	1264	1283	CCAGGGCCACTCTCCCCAAG	56	27940	27959	116
531014	1287	1306	AGCTTCACCTGCAGGCTCAC	0	27963	27982	117
531015	1324	1343	TATGAGTGACCCTCCACACA	52	28000	28019	118
531016	1329	1348	TGTCCTATGAGTGACCCTCC	39	28005	28024	119
531017	1334	1353	ACTGGTGTCCTATGAGTGAC	31	28010	28029	120
531018	1339	1358	GACCCACTGGTGTCCTATGA	54	28015	28034	121
531019	1344	1363	GTGAGGACCCACTGGTGTCC	28	28020	28039	122
531020	1369	1388	AAGCCCATCAAAGCAGTGGG	0	n/a	n/a	123
531021	1420	1439	GTCTGACAGATTTAAAATGC	50	30498	30517	124
531022	1425	1444	GTAATGTCTGACAGATTTAA	74	30503	30522	125
531023	1430	1449	CTTTTGTAATGTCTGACAGA	71	30508	30527	126
531024	1452	1471	TTTATTTGTGAGAAAGGTGT	69	30530	30549	127
531025	1457	1476	TCTCTTTTATTTGTGAGAAA	34	30535	30554	128
531026	1501	1520	ATCATGATTCCCTTCTGAGA	73	30579	30598	129
531027	1530	1549	AAAGGAGCCTGGAGTTTTAT	0	30608	30627	130

531028	1535	1554	AATTCAAAGGAGCCTGGAGT	56	30613	30632	131
531029	1540	1559	AGTGTAATTCAAAGGAGCCT	59	30618	30637	132
531030	1545	1564	AATTCAGTGTAATTCAAAGG	24	n/a	n/a	133
531031	1550	1569	TTTGGAATTCAGTGTAATTC	59	n/a	n/a	134
531032	1555	1574	TGGTTTTTGGAATTCAGTGT	67	n/a	n/a	135
531033	1557	1576	ATTGGTTTTTGGAATTCAGT	53	n/a	n/a	136
531034	1560	1579	CATATTGGTTTTTGGAATTC	36	31866	31885	137
531035	1565	1584	GTAGGCATATTGGTTTTTGG	46	31871	31890	138
531036	1581	1600	GTGTCACCTTTGGAAGGTAG	71	31887	31906	139
531037	1604	1623	AACAGTTGGTATAAATTGTG	35	31910	31929	140
531038	1605	1624	CAACAGTTGGTATAAATTGT	22	31911	31930	141
531039	1609	1628	TACCCAACAGTTGGTATAAA	36	31915	31934	142
531040	1632	1651	TCCTTCGAGAAGCCCCATCC	27	31938	31957	143
531041	1677	1696	AAAGGAATATTTACCTTTTG	68	33121	33140	144
531042	1682	1701	TTACCAAAGGAATATTTACC	11	33126	33145	145
531043	1687	1706	ATTTGTTACCAAAGGAATAT	27	33131	33150	146
531044	1697	1716	GGCATTCTTCATTTGTTACC	68	33141	33160	147
531045	1702	1721	TTTCTGGCATTCTTCATTTG	37	33146	33165	148
531046	1709	1728	GATATCTTTTCTGGCATTCT	54	33153	33172	149
531047	1714	1733	ATCTTGATATCTTTTCTGGC	68	33158	33177	150
531048	1719	1738	TTATAATCTTGATATCTTTT	42	33163	33182	151
531049	1724	1743	TTATTTTATAATCTTGATAT	2	33168	33187	152
531050	1729	1748	TTGGGTTATTTTATAATCTT	18	33173	33192	153
531051	1734	1753	ATCCGTTGGGTTATTTTATA	51	33178	33197	154
531052	1739	1758	AGACCATCCGTTGGGTTATT	60	33183	33202	155
531053	1744	1763	AGCACAGACCATCCGTTGGG	49	33188	33207	156
531054	1754	1773	CTTTATAGCCAGCACAGACC	48	33198	33217	157
531055	1759	1778	CCCTTCTTTATAGCCAGCAC	68	33203	33222	158
531056	1764	1783	TTTCCCCCTTCTTTATAGCC	45	33208	33227	159
531057	1769	1788	CATCTTTTCCCCCTTCTTTA	48	33213	33232	160
531058	1779	1798	CCCTTACAAGCATCTTTTCC	60	n/a	n/a	161
531059	1820	1839	ACATTCCATTGTGTTTGCAA	55	33919	33938	162
531060	1841	1860	TGGTGATGCCCACCAAACGC	35	33940	33959	163
531061	1872	1891	TGCTCCCTGCGGGCACAGCC	52	33971	33990	164
531062	1877	1896	CAGGTTGCTCCCTGCGGGCA	39	33976	33995	165
531063	1882	1901	GACACCAGGTTGCTCCCTGC	51	33981	34000	166
531064	1887	1906	GTGTAGACACCAGGTTGCTC	56	33986	34005	167
531065	1892	1911	CTTTGGTGTAGACACCAGGT	57	33991	34010	168
531066	1897	1916	AGCGACTTTGGTGTAGACAC	67	33996	34015	169
531067	1902	1921	TACTCAGCGACTTTGGTGTA	31	34001	34020	170
531068	1907	1926	CCATGTACTCAGCGACTTTG	59	34006	34025	171
531069	1912	1931	CCAGTCCATGTACTCAGCGA	56	34011	34030	172
531070	1930	1949	CTGTGTTTTCTCTAAAATCC	68	34029	34048	173

531071	1935	1954	CTGCTCTGTGTTTTCTCTAA	73	34034	34053	174
531072	2026	2045	GCTCAGAATTTGACTTGAAC	64	34125	34144	175
531073	2031	2050	CCCAGGCTCAGAATTTGACT	51	34130	34149	176
531074	2049	2068	CTTTGCAGATGAGGACCCCC	67	34148	34167	177
531075	2054	2073	CCATGCTTTGCAGATGAGGA	64	34153	34172	178
531076	2059	2078	ACTCTCCATGCTTTGCAGAT	68	34158	34177	179
531077	2064	2083	ATGCCACTCTCCATGCTTTG	51	34163	34182	180
531078	2111	2130	AGCAGCTCTGAGTGCACTGT	77	34210	34229	181
531079	2116	2135	TCCTCAGCAGCTCTGAGTGC	58	34215	34234	182
531080	2121	2140	CATTGTCCTCAGCAGCTCTG	55	34220	34239	183
531081	n/a	n/a	TGGTTTTTGGAATTCTGAAA	14	31861	31880	184
531082	n/a	n/a	ATATTGGTTTTTGGAATTCT	31	31865	31884	185

Table 124

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531083	n/a	n/a	TGTACTAGTTTCCTATAACT	60	14738	14757	186
					14809	14828	
					14880	14899	
					14939	14958	
					15071	15090	
					15214	15233	
					15286	15305	
					15345	15364	
					15477	15496	
					15549	15568	
					15607	15626	
					15679	15698	
					15809	15828	
					15881	15900	
					15939	15958	
531084	n/a	n/a	ATAGGGACACAACCAAGGAA	25	16296	16315	187
531085	n/a	n/a	AGGCACAGAGCCAGCACCCA	9	16495	16514	188
531086	n/a	n/a	CCTGCCTCCTGGCAGCCTTC	48	16696	16715	189
531087	n/a	n/a	CCAGGTGTGGACAGCAGCTG	52	16821	16840	190
531088	n/a	n/a	GGTTTTGTTTGTAAAATTAG	27	17159	17178	191
531089	n/a	n/a	AAAACACCATTAAATCCATT	45	17306	17325	192
531090	n/a	n/a	ACAGAAACCATGATGTTGCT	59	17644	17663	193
531091	n/a	n/a	TCAGCCCAATGTCCTAACCT	35	17793	17812	194
531092	n/a	n/a	CCTTCACTGACTCTCTTTTC	24	17922	17941	195

531093	n/a	n/a	TTCTCCTGGCTCAGAAGCTC	60	18053	18072	196
					23315	23334	
531094	n/a	n/a	GAATGTCAGGCCTCTGGGCC	48	18181	18200	197
531095	n/a	n/a	CTAACAACCCCACAATATCA	20	18390	18409	198
531096	n/a	n/a	CCCAATTCTTAGTCCTTTAA	45	18523	18542	199
531097	n/a	n/a	ACCAAGCTCAGCCTCCAACT	41	18648	18667	200
531098	n/a	n/a	TTATTAGTCAAATCACCCAA	19	18773	18792	201
531099	n/a	n/a	TGGATGGGTAGAGGCCTTTC	64	18898	18917	202
531100	n/a	n/a	CCCCCTCCCTTCCCTACACA	0	19023	19042	203
531101	n/a	n/a	ATGTAAGTTACAAGCCACTA	37	19153	19172	204
531102	n/a	n/a	TGCCTCTTTAATAAAAACTC	42	19484	19503	205
531103	n/a	n/a	ACTCATTGCCTTAACTCAGG	40	19636	19655	206
531104	n/a	n/a	ACTTGACCTTACTGTTTTAG	20	19886	19905	207
531105	n/a	n/a	CTCCTCCCCAGGCTGCTCCT	16	22092	22111	208
531106	n/a	n/a	AAGATCTAGATAATTCTTGT	31	22332	22351	209
531107	n/a	n/a	TCAACTCACACCTGACCTAA	30	22457	22476	210
531108	n/a	n/a	TGAACCCAAAACTCTGGCAC	50	22771	22790	211
531109	n/a	n/a	AGCCCAAGGAACATCTCACC	52	22959	22978	212
531110	n/a	n/a	GCCTGTTTGGTGGTCTCTTC	86	23110	23129	213
531111	n/a	n/a	CTTCTCCTGGCTCAGAAGCT	68	18054	18073	214
					23316	23335	
531112	n/a	n/a	ATGTATGATTCTAAGAACTT	14	23479	23498	215
531113	n/a	n/a	AACAGACACATTATTTATAT	0	23604	23623	216
531114	n/a	n/a	AGAGTCAAGTCCACAGACAT	40	24246	24265	217
531115	n/a	n/a	TCCTAAATAGGAACAAAGTA	0	24372	24391	218
531116	n/a	n/a	TTGTTAAGGTTGTAGAGAGA	23	24688	24707	219
531117	n/a	n/a	ACCCAATTATTTTTAATGGC	62	24876	24895	220
531118	n/a	n/a	GCCTAAATGTAAGAGCTAAA	26	25157	25176	221
531119	n/a	n/a	TAAACTCTTACATTTATAGA	0	25293	25312	222
531120	n/a	n/a	AAATAAAAGCACTCAGACTG	0	25418	25437	223
531121	n/a	n/a	TTGGTCTACAGATTCAATGC	72	25550	25569	224
531122	n/a	n/a	TAACAAAAATGCCTTGTGCC	33	25710	25729	225
531123	n/a	n/a	TCCCAGCTCCAGTCACCACC	74	25866	25885	226
531124	n/a	n/a	GTACTAAACATCCTAAGTGA	2	25992	26011	227
531125	n/a	n/a	ACTCGCCTTTGTGACTCGAT	23	26264	26283	228
531126	n/a	n/a	TTTTGAATCTTCATTCAAAG	0	26551	26570	229
531127	n/a	n/a	CAGAGCCTTGATCAGAATAA	12	26676	26695	230
531128	n/a	n/a	AAGTTCCACCTTCTAACTGG	18	26831	26850	231
531129	n/a	n/a	AGCAGCTCACACCCAAAAAG	0	27005	27024	232
531130	n/a	n/a	TTCTGTGTCAATTATAAACA	0	27344	27363	233
531131	n/a	n/a	TAGAAAGAGTAAGCCTTCAC	0	27587	27606	234
531132	n/a	n/a	AGTGAGGTTACTCACCAGAG	0	27732	27751	235
531133	n/a	n/a	TTTTGTTGTGCAGACTGAAA	19	27886	27905	236

531134	n/a	n/a	TTACCCATCAAAGCAGTGGG	6	28045	28064	237
531135	n/a	n/a	AATGTTGTGAATACCATCCC	16	28174	28193	238
531136	n/a	n/a	TAACATTTCTATGGGCCTGA	6	28670	28689	239
531137	n/a	n/a	TGTCTACTATTTGACCAATA	19	28795	28814	240
531138	n/a	n/a	TTTAAATGTGTCACTTAATC	0	28987	29006	241
531139	n/a	n/a	TCACTAAAACAAAAATACTT	0	29156	29175	242
531140	n/a	n/a	TCTTCCAGGCCAACCACCTT	22	29321	29340	243
531141	n/a	n/a	TGCAAGGCATGTGTGCACAA	47	29532	29551	244
531142	n/a	n/a	TGTTTAAAATATCTCTATAC	8	30008	30027	245
531143	n/a	n/a	CATGGAAAAATTAAGCTCAT	0	30133	30152	246
531144	n/a	n/a	TGAAGATTCTATTTAACAAA	0	30266	30285	247
531145	n/a	n/a	GCCTAGGAGAGAAAAATAAA	0	30445	30464	248
531146	n/a	n/a	CCAGTGTAATTCAAAGGAGC	40	30620	30639	249
531147	n/a	n/a	CCATTATTTCCATCACCTGC	18	30871	30890	250
531148	n/a	n/a	TACCCAAATTATACCTGGAA	8	31015	31034	251
531149	n/a	n/a	AGAGGTAAAGCAACTTGCCC	45	31429	31448	252
531150	n/a	n/a	TCCTTAATAGTCATAGCAGG	48	31558	31577	253
531151	n/a	n/a	TCACCACCATTTTTCACATG	44	31683	31702	254
531152	n/a	n/a	GTTATGGATATAGACTTTAA	0	31808	31827	255
531153	n/a	n/a	CTAGAAGCAATATTTAAAGC	0	31974	31993	256
531154	n/a	n/a	ATGAAGTAAGATGCTTAAAA	16	32162	32181	257
531155	n/a	n/a	CTTCTTGTCTCAGATTACCA	79	32464	32483	258
531156	n/a	n/a	TCTGAAAAGCCCTCCGAGCT	0	32589	32608	259
531157	n/a	n/a	AAGTGAATCAGAGCAGTGTA	46	32961	32980	260
531158	n/a	n/a	ACCTTACAAGCATCTTTTCC	41	33223	33242	261
531159	n/a	n/a	ATTTGTTAAAAGTTGCTTAT	0	33368	33387	262
531160	n/a	n/a	TGATATCATCATCCCAATGA	13	33510	33529	263

Table 125

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531083	n/a	n/a	TGTACTAGTTTCCTATAACT	68	14738	14757	264
					14809	14828	
					14880	14899	
					14939	14958	
					15071	15090	
					15214	15233	
					15286	15305	
					15345	15364	
					15477	15496	

					15549	15568	
					15607	15626	
					15679	15698	
					15809	15828	
					15881	15900	
					15939	15958	
531161	n/a	n/a	CAGACACCTTCTTCACAAGG	40	898	917	264
531162	n/a	n/a	AATTTCCCAGATGTATTAGT	43	1054	1073	265
531163	n/a	n/a	TCAGCAGAAATCATGTAGGC	60	1181	1200	266
531164	n/a	n/a	TTAAATATAAAGAGATCCTC	38	1609	1628	267
531165	n/a	n/a	GTAATAAAAGGAATGATAAA	0	1825	1844	268
531166	n/a	n/a	AGACAGTAAACAAAATCAGG	12	2046	2065	269
531167	n/a	n/a	CAAGAAACCACCAAAGGAAG	37	2176	2195	270
531168	n/a	n/a	ACCCCAACAGACAGCCCACC	55	2314	2333	271
531169	n/a	n/a	TGGGCTCACCCCAGTGGACC	54	2580	2599	272
531170	n/a	n/a	GCCTGGCCCCCAAGACTCTA	54	2743	2762	273
531171	n/a	n/a	AGGCCTGCCACAGGCCAGAC	40	2873	2892	274
531172	n/a	n/a	TTCAAGCCTGGGCAGCACAG	71	3004	3023	275
531173	n/a	n/a	AAAATAACTTCACTAGAGCT	22	3131	3150	276
531174	n/a	n/a	TGTTAAGTATATTAACTATT	10	3256	3275	277
531175	n/a	n/a	TACTCAGGAAATTAGAATAT	25	3550	3569	278
531176	n/a	n/a	TTATGAAACCTCTTGATTTG	0	3753	3772	279
531177	n/a	n/a	TTCTTGTAAATGTCTGAATT	61	3971	3990	280
531178	n/a	n/a	ACCACAGGAAACTGTAGCAA	72	4111	4130	281
531179	n/a	n/a	GATTGGACCCAGACACTATA	57	4506	4525	282
531180	n/a	n/a	CCTCTTAAGTCACCATAGAC	45	4785	4804	283
531181	n/a	n/a	GGTTGAGGGACAGACACAGG	36	4940	4959	284
531182	n/a	n/a	ATAATCATGATTTATTTTGC	34	5099	5118	285
531183	n/a	n/a	CATAAGAATGTGCACACAAA	39	5382	5401	286
531184	n/a	n/a	ACTCTTATTAGCTGGTAGAA	74	5538	5557	287
531185	n/a	n/a	GGACCAAAACTGAGAGGCAG	63	5663	5682	288
531186	n/a	n/a	CCATTACTCTCAAGCTCCAC	75	5890	5909	289
531187	n/a	n/a	ATCTATTGGTTCAGGAGCCA	72	6015	6034	290
531188	n/a	n/a	GTTAAAACAACTAGAAGCCA	67	6146	6165	291
531189	n/a	n/a	AGGTGTTCTTGCTTATCCTC	63	6484	6503	292
531190	n/a	n/a	GCAGTCACTCCTCTTCCAGC	59	6659	6678	293
531191	n/a	n/a	AAGTGTATTGCCTAGATTTC	37	6784	6803	294
531192	n/a	n/a	GAGTGCCATCTTCTCTGCAC	61	6968	6987	295
531193	n/a	n/a	TTATTCCCAGCTCTAAAATA	23	7274	7293	296
531194	n/a	n/a	CTCACAATTCTGTAAGGGAA	64	7596	7615	297
531195	n/a	n/a	ATAAAATATATTAAGGCAAC	61	7846	7865	298
531196	n/a	n/a	TTGAGTCAGACATCCTGTGA	38	7996	8015	299
531197	n/a	n/a	TACCTTTTCTCCATGTCATT	42	8148	8167	300

531198	n/a	n/a	GGGATTTTGCTGAAGCTGGT	73	8273	8292	301
531199	n/a	n/a	CTTTGAATAGAAAATGACTA	1	8415	8434	302
531200	n/a	n/a	CAAAATCACAAGTTCTAGAT	51	8617	8636	303
531201	n/a	n/a	TTTCCAATACTTTTACAAAT	52	8760	8779	304
531202	n/a	n/a	ATTAATAAGCATCTCTCTGA	31	9109	9128	305
531203	n/a	n/a	TGACTATCCAATTTCTAGTT	67	9253	9272	306
531204	n/a	n/a	CTTGTAGTCTGCACTTAATG	60	9418	9437	307
531205	n/a	n/a	ACATTTTTTAAGTACAGGAA	0	9602	9621	308
531206	n/a	n/a	GAAATGTCTAGCATTTTCTA	28	9755	9774	309
531207	n/a	n/a	CCACTTATTTGATGACCACA	64	9915	9934	310
531208	n/a	n/a	TCCAGAATACTGCCCCATCT	23	10050	10069	311
531209	n/a	n/a	TGGATTCATTTTCTGCAAAT	81	10175	10194	312
531210	n/a	n/a	AGACATTGTCAAATGTCCCC	60	10322	10341	313
531211	n/a	n/a	TTGATGTCAGCACTGTTGAC	77	10480	10499	314
531212	n/a	n/a	ACATCAGTAGCTTCAGATGT	56	10618	10637	315
531213	n/a	n/a	CAAAATTAATTGTGCATAAT	13	10820	10839	316
531214	n/a	n/a	TTTTTCTTTAAATTTTGCTA	37	11120	11139	317
531215	n/a	n/a	TAGAGATTTTATGTACTTGG	63	11245	11264	318
531216	n/a	n/a	AAACACAGGAATTTGCAGAC	33	11408	11427	319
531217	n/a	n/a	GTGGAATAAACCATAATCTA	47	11579	11598	320
531218	n/a	n/a	GATAATTCTTTTCACAGACA	72	12028	12047	321
531219	n/a	n/a	CTTCTCTATCTCCCAGTGTT	61	12227	12246	322
531220	n/a	n/a	CAATACAGGTAAATTTCACG	56	12374	12393	323
531221	n/a	n/a	AAGGGATTTAAAATTTTTAT	0	12507	12526	324
531222	n/a	n/a	GGCAAGCTGTACAAGAAAAA	19	12642	12661	325
531223	n/a	n/a	TGTACTCACCGGTACTCTGC	58	12805	12824	326
531224	n/a	n/a	AAGAGAATGCTCAGAAATGG	25	13435	13454	327
531225	n/a	n/a	ACACTTGTACCCCATACATC	45	13560	13579	328
531226	n/a	n/a	GACAGTAGAGACTGGGAAGG	12	13708	13727	329
531227	n/a	n/a	TACCAATTTCTGAAAGGGCA	72	14224	14243	330
531228	n/a	n/a	CAGAGTAAACTCCCCATCTC	33	14387	14406	331
531229	n/a	n/a	CTTCAAAGCCAGCAGTGTAA	69	14514	14533	332
531230	n/a	n/a	CTTACTGGGCTAAAATCAAG	46	14639	14658	333
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	94	14744	14763	334
					14815	14834	
					14886	14905	
					14945	14964	
					15005	15024	
					15077	15096	
					15220	15239	
					15292	15311	
					15351	15370	
					15411	15430	

					15483	15502	
					15555	15574	
					15613	15632	
					15685	15704	
					15815	15834	
					15887	15906	
					15945	15964	
531232	n/a	n/a	CTGTACTAGTTTCCTATAAC	85	14739	14758	335
					14810	14829	
					14881	14900	
					14940	14959	
					15000	15019	
					15072	15091	
					15215	15234	
					15287	15306	
					15346	15365	
					15406	15425	
					15478	15497	
					15550	15569	
					15608	15627	
					15680	15699	
					15810	15829	
					15882	15901	
					15940	15959	
531233	n/a	n/a	ACTGTACTAGTTTCCTATAA	86	14740	14759	336
					14811	14830	
					14882	14901	
					14941	14960	
					15001	15020	
					15073	15092	
					15216	15235	
					15288	15307	
					15347	15366	
					15407	15426	
					15479	15498	
					15551	15570	
					15609	15628	
					15681	15700	
					15811	15830	
					15883	15902	
					15941	15960	
531234	n/a	n/a	CACTGTACTAGTTTCCTATA	86	14741	14760	337
					14812	14831	

					14883	14902	
					14942	14961	
					15002	15021	
					15074	15093	
					15217	15236	
					15289	15308	
					15348	15367	
					15408	15427	
					15480	15499	
					15552	15571	
					15610	15629	
					15682	15701	
					15812	15831	
					15884	15903	
					15942	15961	
531235	n/a	n/a	TCACTGTACTAGTTTCCTAT	86	14742	14761	338
					14813	14832	
					14884	14903	
					14943	14962	
					15003	15022	
					15075	15094	
					15218	15237	
					15290	15309	
					15349	15368	
					15409	15428	
					15481	15500	
					15553	15572	
					15611	15630	
					15683	15702	
					15813	15832	
					15885	15904	
					15943	15962	
531236	n/a	n/a	ATCACTGTACTAGTTTCCTA	87	14743	14762	339
					14814	14833	
					14885	14904	
					14944	14963	
					15004	15023	
					15076	15095	
					15219	15238	
					15291	15310	
					15350	15369	
					15410	15429	
					15482	15501	

					15554	15573	
					15612	15631	
					15684	15703	
					15814	15833	
					15886	15905	
					15944	15963	
531237	n/a	n/a	GTGGAATGTCATGGCAATTT	56	16399	16418	340

Example 115: Antisense inhibition of human PKK in HepaRG™ cells by antisense oligonucleotides with 2'-MOE sugar modifications

Additional antisense oligonucleotides were designed targeting a PKK nucleic acid and were tested for their effects on PKK mRNA *in vitro*.

The chimeric antisense oligonucleotides in the tables below were designed as 5-10-5 MOE gapmers, 4-9-4 MOE gapmers, 4-10-4 MOE gapmers, 4-10-3 MOE gapmers, 3-10-4 MOE gapmers, or 3-10-3 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 4-9-4 MOE gapmers are 17 nucleosides in length, wherein the central gap segment comprises of nine 2'-deoxynucleosides and is flanked by wing segments on the 5' direction and the 3' direction comprising four nucleosides each. The 4-10-4 MOE gapmers are 18 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 four nucleosides each. The 4-10-3 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 four and three nucleosides respectively. 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. The 3-10-3 MOE gapmers are 16 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 nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-O-methoxyethyl modification. The internucleoside linkages throughout each gapmer are phosphorothioate 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 in the human gene sequence. Each gapmer listed in the tables below is targeted to either SEQ ID NO: 1 or SEQ ID NO: 10. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence.

Cultured HepaRG™ 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 PKK mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3454 was used to measure mRNA levels. PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. 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. Results are presented as percent inhibition of PKK, relative to untreated control cells.

Table 126

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	98	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
546131	4	23	ATGAACGGTCTTCAAGCTGT	5-10-5	75	3396	3415	341
547269	5	24	AATGAACGGTCTTCAAGCTG	5-10-5	56	3397	3416	342
547270	7	26	AAAATGAACGGTCTTCAAGC	5-10-5	68	3399	3418	343
547271	10	29	TTAAAAATGAACGGTCTTCA	5-10-5	60	3402	3421	344
547272	13	32	CACTTAAAAATGAACGGTCT	5-10-5	82	3405	3424	345
547273	25	44	TGAGTCTCTTGTCACTTAAA	5-10-5	93	3417	3436	346
547274	29	48	GAGGTGAGTCTCTTGTCACT	5-10-5	70	3421	3440	347
546136	30	49	GGAGGTGAGTCTCTTGTCAC	5-10-5	86	3422	3441	348
547275	32	51	TTGGAGGTGAGTCTCTTGTC	5-10-5	87	3424	3443	349
546137	40	59	ATTGCTTCTTGGAGGTGAGT	5-10-5	76	3432	3451	350
547276	42	61	CAATTGCTTCTTGGAGGTGA	5-10-5	93	3434	3453	351

547277	44	63	CACAATTGCTTCTTGGAGGT	5-10-5	75	3436	3455	352
547278	45	64	ACACAATTGCTTCTTGGAGG	5-10-5	70	3437	3456	353
546138	47	66	AAACACAATTGCTTCTTGGA	5-10-5	69	3439	3458	354
547279	48	67	AAAACACAATTGCTTCTTGG	5-10-5	69	3440	3459	355
547280	49	68	GAAAACACAATTGCTTCTTG	5-10-5	47	3441	3460	356
547281	70	89	TTGCTTGAATAAAATCATTC	5-10-5	41	4069	4088	357
546140	72	91	GCTTGCTTGAATAAAATCAT	5-10-5	60	4071	4090	358
547282	74	93	TTGCTTGCTTGAATAAAATC	5-10-5	53	4073	4092	359
547283	76	95	AGTTGCTTGCTTGAATAAAA	5-10-5	67	4075	4094	360
546141	82	101	GAAATAAGTTGCTTGCTTGA	5-10-5	56	4081	4100	361
547284	86	105	AAATGAAATAAGTTGCTTGC	5-10-5	26	4085	4104	362
547285	102	121	ACTGTAGCAAACAAGGAAAT	5-10-5	51	4101	4120	363
546143	106	125	GGAAACTGTAGCAAACAAGG	5-10-5	46	4105	4124	364
546144	110	129	CACAGGAAACTGTAGCAAAC	5-10-5	75	4109	4128	365
547286	117	136	AGACATCCACAGGAAACTGT	5-10-5	68	n/a	n/a	366
547287	120	139	GTCAGACATCCACAGGAAAC	5-10-5	69	n/a	n/a	367
546146	123	142	TGAGTCAGACATCCACAGGA	5-10-5	72	n/a	n/a	368
547288	131	150	CATAGAGTTGAGTCAGACAT	5-10-5	80	8003	8022	369
546147	132	151	TCATAGAGTTGAGTCAGACA	5-10-5	76	8004	8023	370
547289	133	152	TTCATAGAGTTGAGTCAGAC	5-10-5	74	8005	8024	371
546148	137	156	CGTTTTCATAGAGTTGAGTC	5-10-5	68	8009	8028	372
546149	155	174	CCCCACCTCTGAAGAAGGCG	5-10-5	83	8027	8046	373
546150	158	177	CATCCCCACCTCTGAAGAAG	5-10-5	58	8030	8049	374
547290	163	182	AGCTACATCCCCACCTCTGA	5-10-5	76	8035	8054	375
546151	166	185	GGAAGCTACATCCCCACCTC	5-10-5	76	8038	8057	376
547291	168	187	ATGGAAGCTACATCCCCACC	5-10-5	74	8040	8059	377
547292	171	190	TACATGGAAGCTACATCCCC	5-10-5	60	8043	8062	378
546152	172	191	GTACATGGAAGCTACATCCC	5-10-5	73	8044	8063	379
546153	176	195	GGGTGTACATGGAAGCTACA	5-10-5	76	8048	8067	380
546154	195	214	TGGCAGTATTGGGCATTTGG	5-10-5	85	8067	8086	381
547293	199	218	CATCTGGCAGTATTGGGCAT	5-10-5	92	8071	8090	382
547294	201	220	CTCATCTGGCAGTATTGGGC	5-10-5	85	8073	8092	383
546155	202	221	CCTCATCTGGCAGTATTGGG	5-10-5	47	8074	8093	384
547295	203	222	ACCTCATCTGGCAGTATTGG	5-10-5	88	8075	8094	385
547296	206	225	TGCACCTCATCTGGCAGTAT	5-10-5	72	8078	8097	386
546156	211	230	GAATGTGCACCTCATCTGGC	5-10-5	81	8083	8102	387
547297	213	232	TGGAATGTGCACCTCATCTG	5-10-5	84	8085	8104	388
546157	216	235	GGGTGGAATGTGCACCTCAT	5-10-5	85	8088	8107	389
547298	218	237	TTGGGTGGAATGTGCACCTC	5-10-5	90	8090	8109	390
546158	219	238	CTTGGGTGGAATGTGCACCT	5-10-5	95	8091	8110	391
546159	229	248	TAGCAAACACCTTGGGTGGA	5-10-5	76	8101	8120	392
546160	235	254	ACTGAATAGCAAACACCTTG	5-10-5	78	8107	8126	393
547299	237	256	AAACTGAATAGCAAACACCT	5-10-5	76	8109	8128	394

546163	250	269	ACTTGCTGGAAGAAAACTGA	5-10-5	42	8122	8141	395
547300	252	271	GAACTTGCTGGAAGAAAACT	5-10-5	37	8124	8143	396
546164	257	276	TGATTGAACTTGCTGGAAGA	5-10-5	33	8129	8148	397
546165	260	279	CATTGATTGAACTTGCTGGA	5-10-5	71	8132	8151	398
547301	261	280	TCATTGATTGAACTTGCTGG	5-10-5	80	8133	8152	399
546166	263	282	TGTCATTGATTGAACTTGCT	5-10-5	70	8135	8154	400
547302	266	285	CCATGTCATTGATTGAACTT	5-10-5	58	8138	8157	401
546167	268	287	CTCCATGTCATTGATTGAAC	5-10-5	73	8140	8159	402
547303	270	289	TTCTCCATGTCATTGATTGA	5-10-5	72	8142	8161	403
547304	273	292	CTTTTCTCCATGTCATTGAT	5-10-5	71	8145	8164	404
547305	280	299	ACCAAACCTTTTCTCCATGT	5-10-5	47	n/a	n/a	405
546170	283	302	GCAACCAAACCTTTTCTCCA	5-10-5	54	n/a	n/a	406
547306	284	303	AGCAACCAAACCTTTTCTCC	5-10-5	62	n/a	n/a	407
547307	286	305	GAAGCAACCAAACCTTTTCT	5-10-5	58	n/a	n/a	408
547308	290	309	TCAAGAAGCAACCAAACCTT	5-10-5	66	n/a	n/a	409
547309	293	312	CTTTCAAGAAGCAACCAAAC	5-10-5	71	9827	9846	410
547310	295	314	ATCTTTCAAGAAGCAACCAA	5-10-5	81	9829	9848	411
546171	297	316	CTATCTTTCAAGAAGCAACC	5-10-5	81	9831	9850	412
547311	299	318	CACTATCTTTCAAGAAGCAA	5-10-5	71	9833	9852	413
546172	301	320	AACACTATCTTTCAAGAAGC	5-10-5	81	9835	9854	414
547312	325	344	ATGTACTTTTGGCAGGGTTC	5-10-5	46	9859	9878	415
546173	327	346	CGATGTACTTTTGGCAGGGT	5-10-5	84	9861	9880	416
547313	330	349	GTTCGATGTACTTTTGGCAG	5-10-5	73	9864	9883	417

Table 127

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	86	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	

						15685 15815 15887 15945	15704 15834 15906 15964	
546174	333	352	CCTGTTCGATGTACTTTTGG	5-10-5	74	9867	9886	418
547314	336	355	GCACCTGTTCGATGTACTTT	5-10-5	73	9870	9889	419
546175	338	357	CTGCACCTGTTCGATGTACT	5-10-5	78	9872	9891	420
547315	340	359	AACTGCACCTGTTCGATGTA	5-10-5	50	9874	9893	421
547316	342	361	GAAACTGCACCTGTTCGATG	5-10-5	75	9876	9895	422
547317	344	363	CAGAAACTGCACCTGTTCGA	5-10-5	75	9878	9897	423
547318	345	364	CCAGAAACTGCACCTGTTCG	5-10-5	74	9879	9898	424
546177	348	367	TGTCCAGAAACTGCACCTGT	5-10-5	75	9882	9901	425
547319	351	370	GAATGTCCAGAAACTGCACC	5-10-5	62	9885	9904	426
547320	353	372	AGGAATGTCCAGAAACTGCA	5-10-5	73	9887	9906	427
547321	356	375	TCAAGGAATGTCCAGAAACT	5-10-5	53	9890	9909	428
547322	358	377	CTTCAAGGAATGTCCAGAAA	5-10-5	65	9892	9911	429
547323	361	380	TTGCTTCAAGGAATGTCCAG	5-10-5	56	9895	9914	430
547324	363	382	CATTGCTTCAAGGAATGTCC	5-10-5	76	9897	9916	431
547325	368	387	GACCACATTGCTTCAAGGAA	5-10-5	67	9902	9921	432
546181	369	388	TGACCACATTGCTTCAAGGA	5-10-5	75	9903	9922	433
547326	370	389	ATGACCACATTGCTTCAAGG	5-10-5	48	9904	9923	434
547327	373	392	TTGATGACCACATTGCTTCA	5-10-5	45	9907	9926	435
547328	375	394	ATTTGATGACCACATTGCTT	5-10-5	40	9909	9928	436
547329	377	396	TTATTTGATGACCACATTGC	5-10-5	24	9911	9930	437
547330	378	397	CTTATTTGATGACCACATTG	5-10-5	60	9912	9931	438
546183	380	399	CACTTATTTGATGACCACAT	5-10-5	69	9914	9933	439
547331	382	401	AGCACTTATTTGATGACCAC	5-10-5	47	n/a	n/a	440
546184	384	403	CAAGCACTTATTTGATGACC	5-10-5	65	n/a	n/a	441
547332	390	409	CGATGGCAAGCACTTATTTG	5-10-5	44	n/a	n/a	442
547333	395	414	TGTCTCGATGGCAAGCACTT	5-10-5	76	n/a	n/a	443
546186	396	415	ATGTCTCGATGGCAAGCACT	5-10-5	84	n/a	n/a	444
547334	397	416	AATGTCTCGATGGCAAGCAC	5-10-5	74	n/a	n/a	445
547335	402	421	TTATAAATGTCTCGATGGCA	5-10-5	93	12658	12677	446
547336	403	422	TTTATAAATGTCTCGATGGC	5-10-5	81	12659	12678	447
546188	407	426	CTCCTTTATAAATGTCTCGA	5-10-5	95	12663	12682	448
547337	409	428	AACTCCTTTATAAATGTCTC	5-10-5	84	12665	12684	449
547338	411	430	TCAACTCCTTTATAAATGTC	5-10-5	71	12667	12686	450
547339	413	432	TATCAACTCCTTTATAAATG	5-10-5	42	12669	12688	451
546190	419	438	CTCTCATATCAACTCCTTTA	5-10-5	92	12675	12694	452
547340	422	441	CTCCTCTCATATCAACTCCT	5-10-5	93	12678	12697	453
547341	424	443	GACTCCTCTCATATCAACTC	5-10-5	87	12680	12699	454
546192	428	447	AATTGACTCCTCTCATATCA	5-10-5	51	12684	12703	455
547342	433	452	ATTAAAATTGACTCCTCTCA	5-10-5	66	12689	12708	456

546193	434	453	CATTAAAATTGACTCCTCTC	5-10-5	57	12690	12709	457
547343	436	455	CACATTAAAATTGACTCCTC	5-10-5	78	12692	12711	458
547344	438	457	GACACATTAAAATTGACTCC	5-10-5	80	12694	12713	459
547345	439	458	AGACACATTAAAATTGACTC	5-10-5	80	12695	12714	460
547346	444	463	ACCTTAGACACATTAAAATT	5-10-5	57	12700	12719	461
546195	448	467	GCTAACCTTAGACACATTAA	5-10-5	83	12704	12723	462
547347	451	470	ACTGCTAACCTTAGACACAT	5-10-5	82	12707	12726	463
546196	452	471	CACTGCTAACCTTAGACACA	5-10-5	83	12708	12727	464
547348	453	472	ACACTGCTAACCTTAGACAC	5-10-5	83	12709	12728	465
547349	458	477	CTTCAACACTGCTAACCTTA	5-10-5	88	12714	12733	466
546198	459	478	TCTTCAACACTGCTAACCTT	5-10-5	85	12715	12734	467
547350	464	483	GGCATTCTTCAACACTGCTA	5-10-5	96	12720	12739	468
546199	465	484	TGGCATTCTTCAACACTGCT	5-10-5	97	12721	12740	469
547351	467	486	TTTGGCATTCTTCAACACTG	5-10-5	92	12723	12742	470
546200	500	519	AAAACTGGCAGCGAATGTTA	5-10-5	91	12756	12775	471
547352	541	560	CCGGTACTCTGCCTTGTGAA	5-10-5	94	12797	12816	472
547354	547	566	ATTGTTCCGGTACTCTGCCT	5-10-5	89	n/a	n/a	473
546203	548	567	AATTGTTCCGGTACTCTGCC	5-10-5	76	n/a	n/a	474
547355	549	568	CAATTGTTCCGGTACTCTGC	5-10-5	77	n/a	n/a	475
546204	555	574	AATAGGCAATTGTTCCGGTA	5-10-5	91	n/a	n/a	476
547356	556	575	TAATAGGCAATTGTTCCGGT	5-10-5	83	n/a	n/a	477
547357	559	578	CTTTAATAGGCAATTGTTCC	5-10-5	78	14130	14149	478
546205	562	581	GTACTTTAATAGGCAATTGT	5-10-5	83	14133	14152	479
547359	569	588	CGGGACTGTACTTTAATAGG	5-10-5	81	14140	14159	480
546208	605	624	CGTTACTCAGCACCTTTATA	5-10-5	92	14176	14195	481
546209	629	648	GCTTCAGTGAGAATCCAGAT	5-10-5	73	14200	14219	482
546210	651	670	CCAATTTCTGAAAGGGCACA	5-10-5	79	14222	14241	483
547360	653	672	AACCAATTTCTGAAAGGGCA	5-10-5	88	n/a	n/a	484
547361	655	674	GCAACCAATTTCTGAAAGGG	5-10-5	46	n/a	n/a	485
546211	656	675	GGCAACCAATTTCTGAAAGG	5-10-5	42	n/a	n/a	486
546212	678	697	AGATGCTGGAAGATGTTCAT	5-10-5	48	26126	26145	487
547362	701	720	CAACATCCACATCTGAGAAC	5-10-5	47	26149	26168	488
547363	703	722	GGCAACATCCACATCTGAGA	5-10-5	84	26151	26170	489
546213	707	726	CCCTGGCAACATCCACATCT	5-10-5	82	26155	26174	490

Table 128

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	88	14744	14763	334
						14815	14834	

						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547364	710	729	GAACCCTGGCAACATCCACA	5-10-5	92	26158	26177	491
546214	712	731	GAGAACCCTGGCAACATCCA	5-10-5	88	26160	26179	492
547365	713	732	TGAGAACCCTGGCAACATCC	5-10-5	81	26161	26180	493
547366	717	736	GGAGTGAGAACCCTGGCAAC	5-10-5	86	26165	26184	494
546216	719	738	CTGGAGTGAGAACCCTGGCA	5-10-5	93	26167	26186	495
547367	721	740	ATCTGGAGTGAGAACCCTGG	5-10-5	76	26169	26188	496
547368	723	742	GCATCTGGAGTGAGAACCCT	5-10-5	89	26171	26190	497
547369	725	744	AAGCATCTGGAGTGAGAACC	5-10-5	76	26173	26192	498
547370	728	747	CAAAAGCATCTGGAGTGAGA	5-10-5	73	26176	26195	499
546217	730	749	CACAAAAGCATCTGGAGTGA	5-10-5	83	26178	26197	500
546218	740	759	TGGTCCGACACACAAAAGCA	5-10-5	71	26188	26207	501
547371	741	760	ATGGTCCGACACACAAAAGC	5-10-5	66	26189	26208	502
547372	742	761	GATGGTCCGACACACAAAAG	5-10-5	32	26190	26209	503
547373	745	764	GCAGATGGTCCGACACACAA	5-10-5	90	26193	26212	504
546220	750	769	TAGGTGCAGATGGTCCGACA	5-10-5	71	26198	26217	505
547374	752	771	GATAGGTGCAGATGGTCCGA	5-10-5	81	26200	26219	506
547375	754	773	GTGATAGGTGCAGATGGTCC	5-10-5	72	26202	26221	507
546222	756	775	GGGTGATAGGTGCAGATGGT	5-10-5	12	26204	26223	508
547376	778	797	GAATGTAAAGAAGAGGCAGT	5-10-5	43	26226	26245	509
546224	780	799	TAGAATGTAAAGAAGAGGCA	5-10-5	65	26228	26247	510
547377	788	807	CATTTGTATAGAATGTAAAG	5-10-5	6	26236	26255	511
547378	790	809	TACATTTGTATAGAATGTAA	5-10-5	0	26238	26257	512
546226	793	812	CCATACATTTGTATAGAATG	5-10-5	37	26241	26260	513
547379	802	821	CTCGATTTTCCATACATTTG	5-10-5	37	26250	26269	514
547380	805	824	TGACTCGATTTTCCATACAT	5-10-5	42	26253	26272	515
546228	806	825	GTGACTCGATTTTCCATACA	5-10-5	60	26254	26273	516
547381	807	826	TGTGACTCGATTTTCCATAC	5-10-5	49	26255	26274	517
547382	810	829	CTTTGTGACTCGATTTTCCA	5-10-5	62	26258	26277	518

547383	812	831	TTCTTTGTGACTCGATTTTC	5-10-5	37	n/a	n/a	519
546229	816	835	ACATTTCTTTGTGACTCGAT	5-10-5	19	n/a	n/a	520
547384	818	837	AAACATTTCTTTGTGACTCG	5-10-5	50	n/a	n/a	521
547385	847	866	TGTGCCACTTTCAGATGTTT	5-10-5	80	27111	27130	522
546230	848	867	GTGTGCCACTTTCAGATGTT	5-10-5	70	27112	27131	523
546231	852	871	CTTGGTGTGCCACTTTCAGA	5-10-5	79	27116	27135	524
547386	853	872	ACTTGGTGTGCCACTTTCAG	5-10-5	78	27117	27136	525
546232	857	876	AGGAACTTGGTGTGCCACTT	5-10-5	86	27121	27140	526
547387	878	897	TGGTGTTTTCTTGAGGAGTA	5-10-5	73	27142	27161	527
546233	879	898	ATGGTGTTTTCTTGAGGAGT	5-10-5	69	27143	27162	528
547388	880	899	TATGGTGTTTTCTTGAGGAG	5-10-5	55	27144	27163	529
547389	884	903	CAGATATGGTGTTTTCTTGA	5-10-5	61	27148	27167	530
546234	885	904	CCAGATATGGTGTTTTCTTG	5-10-5	69	27149	27168	531
547390	887	906	ATCCAGATATGGTGTTTTCT	5-10-5	63	27151	27170	532
547391	889	908	ATATCCAGATATGGTGTTTT	5-10-5	32	27153	27172	533
546235	893	912	GGCTATATCCAGATATGGTG	5-10-5	77	27157	27176	534
547392	895	914	AAGGCTATATCCAGATATGG	5-10-5	81	27159	27178	535
546236	900	919	GTTAAAAGGCTATATCCAGA	5-10-5	50	27164	27183	536
546237	903	922	CAGGTTAAAAGGCTATATCC	5-10-5	64	27167	27186	537
547393	905	924	TGCAGGTTAAAAGGCTATAT	5-10-5	73	27169	27188	538
547394	907	926	TTTGCAGGTTAAAAGGCTAT	5-10-5	29	27171	27190	539
546238	909	928	CTTTTGCAGGTTAAAAGGCT	5-10-5	63	27173	27192	540
546239	912	931	GTTCTTTTGCAGGTTAAAAG	5-10-5	47	27176	27195	541
547395	914	933	AAGTTCTTTTGCAGGTTAAA	5-10-5	15	27178	27197	542
546240	917	936	GTAAAGTTCTTTTGCAGGTT	5-10-5	23	27181	27200	543
546241	920	939	CAGGTAAAGTTCTTTTGCAG	5-10-5	69	27184	27203	544
547396	921	940	TCAGGTAAAGTTCTTTTGCA	5-10-5	49	n/a	n/a	545
547397	923	942	GTTCAGGTAAAGTTCTTTTG	5-10-5	27	n/a	n/a	546
546242	925	944	GGGTTCAGGTAAAGTTCTTT	5-10-5	8	n/a	n/a	547
547398	927	946	CAGGGTTCAGGTAAAGTTCT	5-10-5	16	n/a	n/a	548
547399	928	947	GCAGGGTTCAGGTAAAGTTC	5-10-5	10	n/a	n/a	549
547400	930	949	TGGCAGGGTTCAGGTAAAGT	5-10-5	0	n/a	n/a	550
547401	933	952	GAATGGCAGGGTTCAGGTAA	5-10-5	22	n/a	n/a	551
546243	934	953	AGAATGGCAGGGTTCAGGTA	5-10-5	16	n/a	n/a	552
547402	937	956	TTTAGAATGGCAGGGTTCAG	5-10-5	59	n/a	n/a	553
547403	939	958	ATTTTAGAATGGCAGGGTTC	5-10-5	10	27361	27380	554
546244	942	961	TAAATTTTAGAATGGCAGGG	5-10-5	27	27364	27383	555
547404	956	975	AGTCAACTCCCGGGTAAATT	5-10-5	64	27378	27397	556
547405	959	978	CAAAGTCAACTCCCGGGTAA	5-10-5	47	27381	27400	557
546247	960	979	CCAAAGTCAACTCCCGGGTA	5-10-5	90	27382	27401	558
546248	963	982	CCTCCAAAGTCAACTCCCGG	5-10-5	86	27385	27404	559
547406	965	984	CTCCTCCAAAGTCAACTCCC	5-10-5	81	27387	27406	560
546249	968	987	CTTCTCCTCCAAAGTCAACT	5-10-5	68	27390	27409	561

547407	975	994	TTCAATTCTTCTCCTCCAAA	5-10-5	59	27397	27416	562
546250	977	996	CATTCAATTCTTCTCCTCCA	5-10-5	65	27399	27418	563
547408	980	999	TCACATTCAATTCTTCTCCT	5-10-5	84	27402	27421	564
547409	982	1001	AGTCACATTCAATTCTTCTC	5-10-5	67	27404	27423	565
546251	1007	1026	GGCAAACATTCACTCCTTTA	5-10-5	92	27429	27448	566

Table 129

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	95	14744	14763	344
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
546252	1011	1030	TCTTGGCAAACATTCACTCC	5-10-5	73	27433	27452	567
546253	1014	1033	GTCTCTTGGCAAACATTCAC	5-10-5	98	27436	27455	568
547410	1017	1036	CAAGTCTCTTGGCAAACATT	5-10-5	88	27439	27458	569
546254	1019	1038	TGCAAGTCTCTTGGCAAACA	5-10-5	95	27441	27460	570
546255	1024	1043	CTTTGTGCAAGTCTCTTGGC	5-10-5	92	27446	27465	571
547411	1027	1046	CATCTTTGTGCAAGTCTCTT	5-10-5	79	27449	27468	572
546256	1028	1047	TCATCTTTGTGCAAGTCTCT	5-10-5	83	27450	27469	573
547412	1029	1048	ATCATCTTTGTGCAAGTCTC	5-10-5	73	27451	27470	574
546258	1036	1055	ACAGCGAATCATCTTTGTGC	5-10-5	74	27458	27477	575
546259	1040	1059	ACTGACAGCGAATCATCTTT	5-10-5	86	27462	27481	576
546260	1045	1064	GAAAAACTGACAGCGAATCA	5-10-5	84	27467	27486	577
547413	1047	1066	GTGAAAAACTGACAGCGAAT	5-10-5	94	27469	27488	578
546263	1061	1080	GGAGTAAAGAATAAGTGAAA	5-10-5	0	27483	27502	579
547414	1063	1082	TGGGAGTAAAGAATAAGTGA	5-10-5	76	27485	27504	580

547415	1065	1084	TCTGGGAGTAAAGAATAAGT	5-10-5	71	27487	27506	581
546265	1069	1088	GTCTTCTGGGAGTAAAGAAT	5-10-5	65	27491	27510	582
546266	1072	1091	ACAGTCTTCTGGGAGTAAAG	5-10-5	63	27494	27513	583
547416	1075	1094	CTTACAGTCTTCTGGGAGTA	5-10-5	79	27497	27516	584
546267	1076	1095	CCTTACAGTCTTCTGGGAGT	5-10-5	72	27498	27517	585
547417	1077	1096	TCCTTACAGTCTTCTGGGAG	5-10-5	68	27499	27518	586
546268	1079	1098	CTTCCTTACAGTCTTCTGGG	5-10-5	93	27501	27520	587
547418	1092	1111	CACTTACACTTCTCTTCCTT	5-10-5	0	n/a	n/a	588
546270	1093	1112	ACACTTACACTTCTCTTCCT	5-10-5	32	n/a	n/a	589
546271	1097	1116	AGAAACACTTACACTTCTCT	5-10-5	60	n/a	n/a	590
547419	1101	1120	CTTAAGAAACACTTACACTT	5-10-5	51	n/a	n/a	591
547420	1112	1131	CCATAGATAATCTTAAGAAA	5-10-5	8	27633	27652	592
547421	1115	1134	CATCCATAGATAATCTTAAG	5-10-5	69	27636	27655	593
547422	1117	1136	ACCATCCATAGATAATCTTA	5-10-5	70	27638	27657	594
546275	1119	1138	GAACCATCCATAGATAATCT	5-10-5	87	27640	27659	595
546276	1123	1142	TGGAGAACCATCCATAGATA	5-10-5	74	27644	27663	596
546277	1146	1165	TGTGTCCCATACGCAATCCT	5-10-5	90	27667	27686	597
547423	1150	1169	CCCTTGTGTCCCATACGCAA	5-10-5	95	27671	27690	598
546279	1153	1172	GCTCCCTTGTGTCCCATACG	5-10-5	82	27674	27693	599
547424	1156	1175	AGAGCTCCCTTGTGTCCCAT	5-10-5	90	27677	27696	600
546280	1158	1177	CCAGAGCTCCCTTGTGTCCC	5-10-5	86	27679	27698	601
547425	1161	1180	TAACCAGAGCTCCCTTGTGT	5-10-5	85	27682	27701	602
546281	1162	1181	GTAACCAGAGCTCCCTTGTG	5-10-5	85	27683	27702	603
547426	1164	1183	GAGTAACCAGAGCTCCCTTG	5-10-5	92	27685	27704	604
547427	1166	1185	AAGAGTAACCAGAGCTCCCT	5-10-5	79	27687	27706	605
547428	1169	1188	TCAAAGAGTAACCAGAGCTC	5-10-5	78	27690	27709	606
546283	1171	1190	TCTCAAAGAGTAACCAGAGC	5-10-5	88	27692	27711	607
547429	1173	1192	AATCTCAAAGAGTAACCAGA	5-10-5	81	27694	27713	608
547430	1174	1193	CAATCTCAAAGAGTAACCAG	5-10-5	70	27695	27714	609
546284	1176	1195	CACAATCTCAAAGAGTAACC	5-10-5	89	27697	27716	610
546285	1180	1199	GTTACACAATCTCAAAGAGT	5-10-5	76	27701	27720	611
547431	1184	1203	CAGTGTTACACAATCTCAAA	5-10-5	67	27705	27724	612
547432	1186	1205	CCCAGTGTTACACAATCTCA	5-10-5	90	27707	27726	613
547433	1189	1208	GTCCCCAGTGTTACACAATC	5-10-5	63	27710	27729	614
546287	1192	1211	GTTGTCCCCAGTGTTACACA	5-10-5	82	27713	27732	615
546288	1240	1259	GTTTGTTCCTCCAACAATGC	5-10-5	78	27916	27935	616
547434	1243	1262	AGAGTTTGTTCCTCCAACAA	5-10-5	54	27919	27938	617
547435	1248	1267	CAAGAAGAGTTTGTTCCTCC	5-10-5	85	27924	27943	618
546290	1251	1270	CCCCAAGAAGAGTTTGTTCC	5-10-5	86	27927	27946	619
547436	1253	1272	CTCCCCAAGAAGAGTTTGTT	5-10-5	0	27929	27948	620
547437	1255	1274	CTCTCCCCAAGAAGAGTTTG	5-10-5	50	27931	27950	621
547438	1261	1280	GGGCCACTCTCCCCAAGAAG	5-10-5	82	27937	27956	622
546291	1263	1282	CAGGGCCACTCTCCCCAAGA	5-10-5	81	27939	27958	623

547439	1298	1317	TCTGAGCTGTCAGCTTCACC	5-10-5	85	27974	27993	624
546293	1301	1320	GCCTCTGAGCTGTCAGCTTC	5-10-5	64	27977	27996	625
547440	1327	1346	TCCTATGAGTGACCCTCCAC	5-10-5	67	28003	28022	626
546294	1328	1347	GTCCTATGAGTGACCCTCCA	5-10-5	72	28004	28023	627
547441	1331	1350	GGTGTCCTATGAGTGACCCT	5-10-5	62	28007	28026	628
547442	1332	1351	TGGTGTCCTATGAGTGACCC	5-10-5	42	28008	28027	629
547443	1336	1355	CCACTGGTGTCCTATGAGTG	5-10-5	70	28012	28031	630
546295	1337	1356	CCCACTGGTGTCCTATGAGT	5-10-5	67	28013	28032	631
546296	1370	1389	GAAGCCCATCAAAGCAGTGG	5-10-5	27	n/a	n/a	632
546297	1397	1416	TATAGATGCGCCAAACATCC	5-10-5	82	30475	30494	633
547444	1398	1417	CTATAGATGCGCCAAACATC	5-10-5	71	30476	30495	634
547445	1402	1421	GCCACTATAGATGCGCCAAA	5-10-5	97	30480	30499	635
546299	1404	1423	ATGCCACTATAGATGCGCCA	5-10-5	84	30482	30501	636
546300	1424	1443	TAATGTCTGACAGATTTAAA	5-10-5	58	30502	30521	637
546301	1427	1446	TTGTAATGTCTGACAGATTT	5-10-5	93	30505	30524	638
546302	1444	1463	TGAGAAAGGTGTATCTTTTG	5-10-5	87	30522	30541	639
547446	1447	1466	TTGTGAGAAAGGTGTATCTT	5-10-5	84	30525	30544	640
546303	1448	1467	TTTGTGAGAAAGGTGTATCT	5-10-5	77	30526	30545	641
547447	1449	1468	ATTTGTGAGAAAGGTGTATC	5-10-5	80	30527	30546	642

Table 130

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	96	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	

547448	1451	1470	TTATTTGTGAGAAAGGTGTA	5-10-5	75	30529	30548	643
547449	1453	1472	TTTTATTTGTGAGAAAGGTG	5-10-5	71	30531	30550	644
546304	1454	1473	CTTTTATTTGTGAGAAAGGT	5-10-5	94	30532	30551	645
547450	1456	1475	CTCTTTTATTTGTGAGAAAG	5-10-5	71	30534	30553	646
547451	1471	1490	TTGGTGAATAATAATCTCTT	5-10-5	75	30549	30568	647
546306	1472	1491	TTTGGTGAATAATAATCTCT	5-10-5	65	30550	30569	648
547452	1474	1493	GTTTTGGTGAATAATAATCT	5-10-5	47	30552	30571	649
546307	1478	1497	TATAGTTTTGGTGAATAATA	5-10-5	12	30556	30575	650
546308	1482	1501	ACTTTATAGTTTTGGTGAAT	5-10-5	57	30560	30579	651
546309	1492	1511	CCCTTCTGAGACTTTATAGT	5-10-5	88	30570	30589	652
546310	1496	1515	GATTCCCTTCTGAGACTTTA	5-10-5	78	30574	30593	653
546311	1499	1518	CATGATTCCCTTCTGAGACT	5-10-5	79	30577	30596	654
547453	1500	1519	TCATGATTCCCTTCTGAGAC	5-10-5	81	30578	30597	655
547454	1502	1521	TATCATGATTCCCTTCTGAG	5-10-5	92	30580	30599	656
547455	1503	1522	ATATCATGATTCCCTTCTGA	5-10-5	88	30581	30600	657
547456	1506	1525	GCGATATCATGATTCCCTTC	5-10-5	89	30584	30603	658
546313	1507	1526	GGCGATATCATGATTCCCTT	5-10-5	60	30585	30604	659
547457	1509	1528	AAGGCGATATCATGATTCCC	5-10-5	89	30587	30606	660
547458	1513	1532	TATCAAGGCGATATCATGAT	5-10-5	84	30591	30610	661
547459	1519	1538	GAGTTTTATCAAGGCGATAT	5-10-5	28	30597	30616	662
547460	1522	1541	CTGGAGTTTTATCAAGGCGA	5-10-5	72	30600	30619	663
546316	1524	1543	GCCTGGAGTTTTATCAAGGC	5-10-5	51	30602	30621	664
546317	1528	1547	AGGAGCCTGGAGTTTTATCA	5-10-5	12	30606	30625	665
546318	1534	1553	ATTCAAAGGAGCCTGGAGTT	5-10-5	47	30612	30631	666
547461	1537	1556	GTAATTCAAAGGAGCCTGGA	5-10-5	49	30615	30634	667
547462	1539	1558	GTGTAATTCAAAGGAGCCTG	5-10-5	59	30617	30636	668
546319	1541	1560	CAGTGTAATTCAAAGGAGCC	5-10-5	50	30619	30638	669
547463	1564	1583	TAGGCATATTGGTTTTTGGA	5-10-5	74	31870	31889	670
546320	1566	1585	GGTAGGCATATTGGTTTTTG	5-10-5	72	31872	31891	671
546321	1569	1588	GAAGGTAGGCATATTGGTTT	5-10-5	53	31875	31894	672
546322	1584	1603	CTTGTGTCACCTTTGGAAGG	5-10-5	74	31890	31909	673
547464	1585	1604	GCTTGTGTCACCTTTGGAAG	5-10-5	95	31891	31910	674
546323	1587	1606	GTGCTTGTGTCACCTTTGGA	5-10-5	94	31893	31912	675
547465	1592	1611	AAATTGTGCTTGTGTCACCT	5-10-5	88	31898	31917	676
547466	1596	1615	GTATAAATTGTGCTTGTGTC	5-10-5	82	31902	31921	677
546324	1597	1616	GGTATAAATTGTGCTTGTGT	5-10-5	73	31903	31922	678
547467	1598	1617	TGGTATAAATTGTGCTTGTG	5-10-5	80	31904	31923	679
547468	1600	1619	GTTGGTATAAATTGTGCTTG	5-10-5	61	31906	31925	680
546325	1602	1621	CAGTTGGTATAAATTGTGCT	5-10-5	74	31908	31927	681
546326	1607	1626	CCCAACAGTTGGTATAAATT	5-10-5	62	31913	31932	682
547469	1610	1629	TTACCCAACAGTTGGTATAA	5-10-5	67	31916	31935	683
546327	1612	1631	GGTTACCCAACAGTTGGTAT	5-10-5	95	31918	31937	684
546328	1624	1643	GAAGCCCCATCCGGTTACCC	5-10-5	84	31930	31949	685

547470	1628	1647	TCGAGAAGCCCCATCCGGTT	5-10-5	70	31934	31953	686
546329	1631	1650	CCTTCGAGAAGCCCCATCCG	5-10-5	18	31937	31956	687
546330	1636	1655	TTTCTCCTTCGAGAAGCCCC	5-10-5	55	31942	31961	688
547471	1638	1657	CCTTTCTCCTTCGAGAAGCC	5-10-5	58	31944	31963	689
547472	1641	1660	TCACCTTTCTCCTTCGAGAA	5-10-5	44	n/a	n/a	690
546331	1642	1661	TTCACCTTTCTCCTTCGAGA	5-10-5	59	n/a	n/a	691
547473	1649	1668	TTTGGATTTCACCTTTCTCC	5-10-5	5	n/a	n/a	692
547474	1659	1678	TGTAGAATATTTTGGATTTC	5-10-5	51	33103	33122	693
547475	1686	1705	TTTGTTACCAAAGGAATATT	5-10-5	44	33130	33149	694
547476	1688	1707	CATTTGTTACCAAAGGAATA	5-10-5	75	33132	33151	695
546336	1689	1708	TCATTTGTTACCAAAGGAAT	5-10-5	66	33133	33152	696
547477	1692	1711	TCTTCATTTGTTACCAAAGG	5-10-5	74	33136	33155	697
547478	1695	1714	CATTCTTCATTTGTTACCAA	5-10-5	85	33139	33158	698
546339	1712	1731	CTTGATATCTTTTCTGGCAT	5-10-5	65	33156	33175	699
546340	1716	1735	TAATCTTGATATCTTTTCTG	5-10-5	30	33160	33179	700
547479	1718	1737	TATAATCTTGATATCTTTTC	5-10-5	48	33162	33181	701
547480	1756	1775	TTCTTTATAGCCAGCACAGA	5-10-5	60	33200	33219	702
547481	1758	1777	CCTTCTTTATAGCCAGCACA	5-10-5	71	33202	33221	703
547482	1760	1779	CCCCTTCTTTATAGCCAGCA	5-10-5	90	33204	33223	704
546343	1761	1780	CCCCCTTCTTTATAGCCAGC	5-10-5	97	33205	33224	705
547483	1762	1781	TCCCCCTTCTTTATAGCCAG	5-10-5	71	33206	33225	706
546345	1773	1792	CAAGCATCTTTTCCCCCTTC	5-10-5	86	33217	33236	707
546346	1796	1815	AGGGACCACCTGAATCTCCC	5-10-5	83	33895	33914	708
547484	1799	1818	CTAAGGGACCACCTGAATCT	5-10-5	69	33898	33917	709
546347	1800	1819	ACTAAGGGACCACCTGAATC	5-10-5	28	33899	33918	710
547485	1803	1822	CAAACTAAGGGACCACCTGA	5-10-5	49	33902	33921	711
546348	1804	1823	GCAAACTAAGGGACCACCTG	5-10-5	79	33903	33922	712
547486	1805	1824	TGCAAACTAAGGGACCACCT	5-10-5	89	33904	33923	713
546349	1810	1829	GTGTTTGCAAACTAAGGGAC	5-10-5	48	33909	33928	714
547487	1811	1830	TGTGTTTGCAAACTAAGGGA	5-10-5	72	33910	33929	715
546350	1868	1887	CCCTGCGGGCACAGCCTTCA	5-10-5	88	33967	33986	716
546351	1873	1892	TTGCTCCCTGCGGGCACAGC	5-10-5	82	33972	33991	717
546352	1880	1899	CACCAGGTTGCTCCCTGCGG	5-10-5	75	33979	33998	718
547488	1881	1900	ACACCAGGTTGCTCCCTGCG	5-10-5	71	33980	33999	719

Table 131

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	72	14744	14763	334
						14815	14834	

						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547448	1451	1470	TTATTTGTGAGAAAGGTGTA	5-10-5	83	30529	30548	643
547449	1453	1472	TTTTATTTGTGAGAAAGGTG	5-10-5	73	30531	30550	644
546304	1454	1473	CTTTTATTTGTGAGAAAGGT	5-10-5	86	30532	30551	645
547450	1456	1475	CTCTTTTATTTGTGAGAAAG	5-10-5	67	30534	30553	646
547451	1471	1490	TTGGTGAATAATAATCTCTT	5-10-5	64	30549	30568	647
546306	1472	1491	TTTGGTGAATAATAATCTCT	5-10-5	71	30550	30569	648
547452	1474	1493	GTTTTGGTGAATAATAATCT	5-10-5	62	30552	30571	649
546307	1478	1497	TATAGTTTTGGTGAATAATA	5-10-5	0	30556	30575	650
546308	1482	1501	ACTTTATAGTTTTGGTGAAT	5-10-5	43	30560	30579	651
546309	1492	1511	CCCTTCTGAGACTTTATAGT	5-10-5	81	30570	30589	652
546310	1496	1515	GATTCCCTTCTGAGACTTTA	5-10-5	67	30574	30593	653
546311	1499	1518	CATGATTCCCTTCTGAGACT	5-10-5	76	30577	30596	654
547453	1500	1519	TCATGATTCCCTTCTGAGAC	5-10-5	81	30578	30597	655
547454	1502	1521	TATCATGATTCCCTTCTGAG	5-10-5	78	30580	30599	656
547455	1503	1522	ATATCATGATTCCCTTCTGA	5-10-5	66	30581	30600	657
547456	1506	1525	GCGATATCATGATTCCCTTC	5-10-5	96	30584	30603	658
546313	1507	1526	GGCGATATCATGATTCCCTT	5-10-5	75	30585	30604	659
547457	1509	1528	AAGGCGATATCATGATTCCC	5-10-5	92	30587	30606	660
547458	1513	1532	TATCAAGGCGATATCATGAT	5-10-5	64	30591	30610	661
547459	1519	1538	GAGTTTTATCAAGGCGATAT	5-10-5	51	30597	30616	662
547460	1522	1541	CTGGAGTTTTATCAAGGCGA	5-10-5	75	30600	30619	663
546316	1524	1543	GCCTGGAGTTTTATCAAGGC	5-10-5	60	30602	30621	664
546317	1528	1547	AGGAGCCTGGAGTTTTATCA	5-10-5	31	30606	30625	665
546318	1534	1553	ATTCAAAGGAGCCTGGAGTT	5-10-5	46	30612	30631	666
547461	1537	1556	GTAATTCAAAGGAGCCTGGA	5-10-5	55	30615	30634	667
547462	1539	1558	GTGTAATTCAAAGGAGCCTG	5-10-5	54	30617	30636	668
546319	1541	1560	CAGTGTAATTCAAAGGAGCC	5-10-5	61	30619	30638	669
547463	1564	1583	TAGGCATATTGGTTTTTGGA	5-10-5	84	31870	31889	670

546320	1566	1585	GGTAGGCATATTGGTTTTTG	5-10-5	69	31872	31891	671
546321	1569	1588	GAAGGTAGGCATATTGGTTT	5-10-5	56	31875	31894	672
546322	1584	1603	CTTGTGTCACCTTTGGAAGG	5-10-5	68	31890	31909	673
547464	1585	1604	GCTTGTGTCACCTTTGGAAG	5-10-5	84	31891	31910	674
546323	1587	1606	GTGCTTGTGTCACCTTTGGA	5-10-5	80	31893	31912	675
547465	1592	1611	AAATTGTGCTTGTGTCACCT	5-10-5	85	31898	31917	676
547466	1596	1615	GTATAAATTGTGCTTGTGTC	5-10-5	43	31902	31921	677
546324	1597	1616	GGTATAAATTGTGCTTGTGT	5-10-5	82	31903	31922	678
547467	1598	1617	TGGTATAAATTGTGCTTGTG	5-10-5	65	31904	31923	679
547468	1600	1619	GTTGGTATAAATTGTGCTTG	5-10-5	46	31906	31925	680
546325	1602	1621	CAGTTGGTATAAATTGTGCT	5-10-5	79	31908	31927	681
546326	1607	1626	CCCAACAGTTGGTATAAATT	5-10-5	64	31913	31932	682
547469	1610	1629	TTACCCAACAGTTGGTATAA	5-10-5	50	31916	31935	683
546327	1612	1631	GGTTACCCAACAGTTGGTAT	5-10-5	84	31918	31937	684
546328	1624	1643	GAAGCCCCATCCGGTTACCC	5-10-5	81	31930	31949	685
547470	1628	1647	TCGAGAAGCCCCATCCGGTT	5-10-5	68	31934	31953	686
546329	1631	1650	CCTTCGAGAAGCCCCATCCG	5-10-5	8	31937	31956	687
546330	1636	1655	TTTCTCCTTCGAGAAGCCCC	5-10-5	67	31942	31961	688
547471	1638	1657	CCTTTCTCCTTCGAGAAGCC	5-10-5	43	31944	31963	689
547472	1641	1660	TCACCTTTCTCCTTCGAGAA	5-10-5	42	n/a	n/a	690
546331	1642	1661	TTCACCTTTCTCCTTCGAGA	5-10-5	44	n/a	n/a	691
547473	1649	1668	TTTGGATTTCACCTTTCTCC	5-10-5	26	n/a	n/a	692
547474	1659	1678	TGTAGAATATTTTGGATTTC	5-10-5	34	33103	33122	693
547475	1686	1705	TTTGTTACCAAAGGAATATT	5-10-5	42	33130	33149	694
547476	1688	1707	CATTTGTTACCAAAGGAATA	5-10-5	71	33132	33151	695
546336	1689	1708	TCATTTGTTACCAAAGGAAT	5-10-5	73	33133	33152	696
547477	1692	1711	TCTTCATTTGTTACCAAAGG	5-10-5	68	33136	33155	697
547478	1695	1714	CATTCTTCATTTGTTACCAA	5-10-5	55	33139	33158	698
546339	1712	1731	CTTGATATCTTTTCTGGCAT	5-10-5	64	33156	33175	699
546340	1716	1735	TAATCTTGATATCTTTTCTG	5-10-5	56	33160	33179	700
547479	1718	1737	TATAATCTTGATATCTTTTC	5-10-5	9	33162	33181	701
547480	1756	1775	TTCTTTATAGCCAGCACAGA	5-10-5	49	33200	33219	702
547481	1758	1777	CCTTCTTTATAGCCAGCACA	5-10-5	77	33202	33221	703
547482	1760	1779	CCCCTTCTTTATAGCCAGCA	5-10-5	65	33204	33223	704
546343	1761	1780	CCCCCTTCTTTATAGCCAGC	5-10-5	91	33205	33224	705
547483	1762	1781	TCCCCCTTCTTTATAGCCAG	5-10-5	77	33206	33225	706
546345	1773	1792	CAAGCATCTTTTCCCCCTTC	5-10-5	80	33217	33236	707
546346	1796	1815	AGGGACCACCTGAATCTCCC	5-10-5	70	33895	33914	708
547484	1799	1818	CTAAGGGACCACCTGAATCT	5-10-5	64	33898	33917	709
546347	1800	1819	ACTAAGGGACCACCTGAATC	5-10-5	22	33899	33918	710
547485	1803	1822	CAAACTAAGGGACCACCTGA	5-10-5	66	33902	33921	711
546348	1804	1823	GCAAACTAAGGGACCACCTG	5-10-5	76	33903	33922	712
547486	1805	1824	TGCAAACTAAGGGACCACCT	5-10-5	78	33904	33923	713

546349	1810	1829	GTGTTTGCAAACTAAGGGAC	5-10-5	35	33909	33928	714
547487	1811	1830	TGTGTTTGCAAACTAAGGGA	5-10-5	61	33910	33929	715
546350	1868	1887	CCCTGCGGGCACAGCCTTCA	5-10-5	74	33967	33986	716
546351	1873	1892	TTGCTCCCTGCGGGCACAGC	5-10-5	60	33972	33991	717
546352	1880	1899	CACCAGGTTGCTCCCTGCGG	5-10-5	74	33979	33998	718
547488	1881	1900	ACACCAGGTTGCTCCCTGCG	5-10-5	72	33980	33999	719

Table 132

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	90	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547489	1883	1902	AGACACCAGGTTGCTCCCTG	5-10-5	34	33982	34001	720
547490	1885	1904	GTAGACACCAGGTTGCTCCC	5-10-5	55	33984	34003	721
546353	1900	1919	CTCAGCGACTTTGGTGTAGA	5-10-5	55	33999	34018	722
546354	1903	1922	GTACTCAGCGACTTTGGTGT	5-10-5	47	34002	34021	723
547491	1906	1925	CATGTACTCAGCGACTTTGG	5-10-5	47	34005	34024	724
547492	1911	1930	CAGTCCATGTACTCAGCGAC	5-10-5	62	34010	34029	725
546356	1913	1932	TCCAGTCCATGTACTCAGCG	5-10-5	60	34012	34031	726
546357	1947	1966	GCTTTTCCATCACTGCTCTG	5-10-5	79	34046	34065	727
546358	1951	1970	CTGAGCTTTTCCATCACTGC	5-10-5	83	34050	34069	728
547493	1952	1971	TCTGAGCTTTTCCATCACTG	5-10-5	72	34051	34070	729
546359	1955	1974	GCATCTGAGCTTTTCCATCA	5-10-5	79	34054	34073	730
546360	1958	1977	ACTGCATCTGAGCTTTTCCA	5-10-5	13	34057	34076	731
547494	1963	1982	TGGTGACTGCATCTGAGCTT	5-10-5	70	34062	34081	732

547495	1965	1984	GCTGGTGACTGCATCTGAGC	5-10-5	61	34064	34083	733
547496	1967	1986	ATGCTGGTGACTGCATCTGA	5-10-5	80	34066	34085	734
546362	1969	1988	TCATGCTGGTGACTGCATCT	5-10-5	71	34068	34087	735
546363	1973	1992	CTTCTCATGCTGGTGACTGC	5-10-5	81	34072	34091	736
547497	1977	1996	ACTGCTTCTCATGCTGGTGA	5-10-5	68	34076	34095	737
546364	1979	1998	GGACTGCTTCTCATGCTGGT	5-10-5	61	34078	34097	738
547498	1981	2000	CTGGACTGCTTCTCATGCTG	5-10-5	44	34080	34099	739
547499	1983	2002	CTCTGGACTGCTTCTCATGC	5-10-5	65	34082	34101	740
546365	1986	2005	AGACTCTGGACTGCTTCTCA	5-10-5	64	34085	34104	741
547500	1989	2008	CCTAGACTCTGGACTGCTTC	5-10-5	65	34088	34107	742
546366	1991	2010	TGCCTAGACTCTGGACTGCT	5-10-5	79	34090	34109	743
547501	1993	2012	ATTGCCTAGACTCTGGACTG	5-10-5	55	34092	34111	744
546367	1997	2016	AAAAATTGCCTAGACTCTGG	5-10-5	61	34096	34115	745
546368	2003	2022	GGTTGTAAAAATTGCCTAGA	5-10-5	44	34102	34121	746
547502	2006	2025	TCAGGTTGTAAAAATTGCCT	5-10-5	64	34105	34124	747
546369	2007	2026	CTCAGGTTGTAAAAATTGCC	5-10-5	51	34106	34125	748
547503	2008	2027	ACTCAGGTTGTAAAAATTGC	5-10-5	66	34107	34126	749
547504	2010	2029	GAACTCAGGTTGTAAAAATT	5-10-5	37	34109	34128	750
546370	2014	2033	ACTTGAACTCAGGTTGTAAA	5-10-5	34	34113	34132	751
547505	2015	2034	GACTTGAACTCAGGTTGTAA	5-10-5	69	34114	34133	752
546372	2021	2040	GAATTTGACTTGAACTCAGG	5-10-5	49	34120	34139	753
546373	2025	2044	CTCAGAATTTGACTTGAACT	5-10-5	59	34124	34143	754
547506	2028	2047	AGGCTCAGAATTTGACTTGA	5-10-5	78	34127	34146	755
547507	2029	2048	CAGGCTCAGAATTTGACTTG	5-10-5	56	34128	34147	756
546374	2030	2049	CCAGGCTCAGAATTTGACTT	5-10-5	50	34129	34148	757
547508	2032	2051	CCCCAGGCTCAGAATTTGAC	5-10-5	69	34131	34150	758
547509	2034	2053	CCCCCCAGGCTCAGAATTTG	5-10-5	58	34133	34152	759
546375	2036	2055	GACCCCCCAGGCTCAGAATT	5-10-5	48	34135	34154	760
547510	2041	2060	ATGAGGACCCCCCAGGCTCA	5-10-5	40	34140	34159	761
547511	2042	2061	GATGAGGACCCCCCAGGCTC	5-10-5	53	34141	34160	762
547512	2045	2064	GCAGATGAGGACCCCCCAGG	5-10-5	74	34144	34163	763
547513	2046	2065	TGCAGATGAGGACCCCCCAG	5-10-5	72	34145	34164	764
546378	2048	2067	TTTGCAGATGAGGACCCCCC	5-10-5	79	34147	34166	765
546379	2056	2075	CTCCATGCTTTGCAGATGAG	5-10-5	69	34155	34174	766
546380	2062	2081	GCCACTCTCCATGCTTTGCA	5-10-5	81	34161	34180	767
547514	2066	2085	AGATGCCACTCTCCATGCTT	5-10-5	85	34165	34184	768
546381	2068	2087	GAAGATGCCACTCTCCATGC	5-10-5	73	34167	34186	769
547515	2069	2088	AGAAGATGCCACTCTCCATG	5-10-5	58	34168	34187	770
546382	2072	2091	CAAAGAAGATGCCACTCTCC	5-10-5	58	34171	34190	771
547516	2076	2095	GATGCAAAGAAGATGCCACT	5-10-5	48	34175	34194	772
546383	2077	2096	GGATGCAAAGAAGATGCCAC	5-10-5	57	34176	34195	773
547517	2079	2098	TAGGATGCAAAGAAGATGCC	5-10-5	57	34178	34197	774
547518	2083	2102	TCCTTAGGATGCAAAGAAGA	5-10-5	51	34182	34201	775

546384	2085	2104	CGTCCTTAGGATGCAAAGAA	5-10-5	81	34184	34203	776
546385	2120	2139	ATTGTCCTCAGCAGCTCTGA	5-10-5	67	34219	34238	777
547519	2126	2145	CCAGACATTGTCCTCAGCAG	5-10-5	76	34225	34244	778
546386	2128	2147	AGCCAGACATTGTCCTCAGC	5-10-5	78	34227	34246	779
547520	2130	2149	TCAGCCAGACATTGTCCTCA	5-10-5	76	34229	34248	780
547521	2132	2151	CTTCAGCCAGACATTGTCCT	5-10-5	58	34231	34250	781
546387	2138	2157	AGCGGGCTTCAGCCAGACAT	5-10-5	77	34237	34256	782
547522	2141	2160	GAAAGCGGGCTTCAGCCAGA	5-10-5	73	34240	34259	783
546388	2143	2162	CTGAAAGCGGGCTTCAGCCA	5-10-5	71	34242	34261	784
546389	2147	2166	CGTGCTGAAAGCGGGCTTCA	5-10-5	71	34246	34265	785
546390	2165	2184	GTCAGCCCCTGGTTACGGCG	5-10-5	70	34264	34283	786
547523	2167	2186	TTGTCAGCCCCTGGTTACGG	5-10-5	69	34266	34285	787
547524	2169	2188	CATTGTCAGCCCCTGGTTAC	5-10-5	58	34268	34287	788
546391	2170	2189	GCATTGTCAGCCCCTGGTTA	5-10-5	54	34269	34288	789
547525	2174	2193	CCTCGCATTGTCAGCCCCTG	5-10-5	78	34273	34292	790
546392	2176	2195	GACCTCGCATTGTCAGCCCC	5-10-5	72	34275	34294	791
547526	2178	2197	GCGACCTCGCATTGTCAGCC	5-10-5	59	34277	34296	792
547527	2185	2204	CTCAGTTGCGACCTCGCATT	5-10-5	58	34284	34303	793
546393	2186	2205	TCTCAGTTGCGACCTCGCAT	5-10-5	77	34285	34304	794
546394	2196	2215	GTCATGGAGATCTCAGTTGC	5-10-5	71	34295	34314	795
547528	2200	2219	CACAGTCATGGAGATCTCAG	5-10-5	78	34299	34318	796

Table 133

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	90	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	

						15887	15906	
						15945	15964	
546403	n/a	n/a	CCATGAACATCCTATCCGTG	5-10-5	83	3282	3301	797
546406	n/a	n/a	TGTCCTGTCAACATATTCCA	5-10-5	80	3299	3318	798
546409	n/a	n/a	GGGTTTCTGCCAACAGTTTC	5-10-5	77	3326	3345	799
546410	n/a	n/a	GACTTTGGGTTTCTGCCAAC	5-10-5	83	3332	3351	800
546411	n/a	n/a	ATATTGACTTTGGGTTTCTG	5-10-5	56	3337	3356	801
546412	n/a	n/a	GGCTTCAATATTGACTTTGG	5-10-5	84	3344	3363	802
546416	n/a	n/a	CTGCAGGCAATATTTTGCTT	5-10-5	62	3364	3383	803
546418	n/a	n/a	ATGTGGCACTGCAGGCAATA	5-10-5	72	3372	3391	804
546419	n/a	n/a	TTCTAATGTGGCACTGCAGG	5-10-5	65	3377	3396	805
546421	n/a	n/a	TCAAGCTGTTCTAATGTGGC	5-10-5	71	3385	3404	806
546422	n/a	n/a	ACGGTCTTCAAGCTGTTCTA	5-10-5	72	3392	3411	807
546425	n/a	n/a	GGTCAATCTGACTAGTGAAT	5-10-5	69	2284	2303	808
546426	n/a	n/a	TCTCTGGTCAATCTGACTAG	5-10-5	49	2289	2308	809
546429	n/a	n/a	GCCCACCAACAATCTCTGGT	5-10-5	84	2301	2320	810
546432	n/a	n/a	GACCCCAACAGACAGCCCAC	5-10-5	62	2315	2334	811
546444	n/a	n/a	CCAGAATCATGCCTTGTGGG	5-10-5	61	4765	4784	812
546447	n/a	n/a	GTCACCATAGACCCAGAATC	5-10-5	68	4777	4796	813
546450	n/a	n/a	GTGGCCCTCTTAAGTCACCA	5-10-5	73	4790	4809	814
546453	n/a	n/a	CTCATTGTTGTGTGGCCCTC	5-10-5	82	4801	4820	815
546459	n/a	n/a	GTAGCCATACATCTGAGGAA	5-10-5	46	4830	4849	816
546461	n/a	n/a	ATGTTTATTGTAGCCATACA	5-10-5	53	4839	4858	817
546492	n/a	n/a	CTCGCCTTTGTGACTCGATT	5-10-5	61	26263	26282	818
546493	n/a	n/a	CATACTCGCCTTTGTGACTC	5-10-5	35	26267	26286	819
546494	n/a	n/a	GCATACTCGCCTTTGTGACT	5-10-5	67	26268	26287	820
546495	n/a	n/a	TGCATACTCGCCTTTGTGAC	5-10-5	65	26269	26288	821
546395	2209	2228	TTCACAACACACAGTCATGG	5-10-5	72	34308	34327	822
546397	2233	2252	TTTTTTGATCTTTCACCATT	5-10-5	55	n/a	n/a	823
546496	n/a	n/a	ATGCATACTCGCCTTTGTGA	5-10-5	54	26270	26289	824
						26301	26320	
546497	n/a	n/a	CATGCATACTCGCCTTTGTG	5-10-5	56	26271	26290	825
						26302	26321	
546498	n/a	n/a	CCATGCATACTCGCCTTTGT	5-10-5	65	26272	26291	826
						26303	26322	
547529	2203	2222	ACACACAGTCATGGAGATCT	5-10-5	49	34302	34321	827
547530	2206	2225	ACAACACACAGTCATGGAGA	5-10-5	63	34305	34324	828
547531	2213	2232	TTATTTCACAACACACAGTC	5-10-5	69	34312	34331	829
546499	n/a	n/a	TCCATGCATACTCGCCTTTG	5-10-5	20	26273	26292	830
546500	n/a	n/a	TTCCATGCATACTCGCCTTT	5-10-5	46	26274	26293	831
546501	n/a	n/a	TTTCCATGCATACTCGCCTT	5-10-5	53	26275	26294	832
546502	n/a	n/a	GATTTTCCATGCATACTCGC	5-10-5	37	26278	26297	833
546503	n/a	n/a	GTGATGCGATTTTCCATGCA	5-10-5	53	26285	26304	834

546508	n/a	n/a	GCAGCAAGTGCTCCCCATGC	5-10-5	43	26317	26336	835
546511	n/a	n/a	GTGATGAAAGTACAGCAGCA	5-10-5	50	26331	26350	836
546683	n/a	n/a	TCCTATCCGTGTTCAGCTGT	5-10-5	69	3273	3292	837
546684	n/a	n/a	TACTCTCTACATACTCAGGA	5-10-5	71	3561	3580	838
546687	n/a	n/a	TGAGACCTCCAGACTACTGT	5-10-5	76	3847	3866	839
546690	n/a	n/a	CTCTGCTGGTTTTAGACCAC	5-10-5	44	4027	4046	840
546695	n/a	n/a	GGGACAATCTCCACCCCCGA	5-10-5	36	4225	4244	841
546698	n/a	n/a	TGCAGAGTGTCATCTGCGAA	5-10-5	59	4387	4406	842
546700	n/a	n/a	TGGTTCCCTAGCGGTCCAGA	5-10-5	78	4561	4580	843
546705	n/a	n/a	CCCCTGTAGTTGGCTGTGGT	5-10-5	66	5046	5065	844
546707	n/a	n/a	GCAAGTCAAAGAGTGTCCAC	5-10-5	73	5283	5302	845
546710	n/a	n/a	GAAGCCTGTTAGAGTTGGCC	5-10-5	73	5576	5595	846
546719	n/a	n/a	CCCCCATGTCCATGGACTTT	5-10-5	55	6329	6348	847
547532	n/a	n/a	CTGCCAACAGTTTCAACTTT	5-10-5	65	3320	3339	848
547533	n/a	n/a	TTTTGCTTGGCTTCAATATT	5-10-5	23	3352	3371	849
547534	n/a	n/a	ATCTGACTAGTGAATGGCTT	5-10-5	72	2279	2298	850
547535	n/a	n/a	AGACAGCCCACCAACAATCT	5-10-5	28	2306	2325	851
547536	n/a	n/a	TGCATAGACCCCAACAGACA	5-10-5	48	2321	2340	852
547537	n/a	n/a	CCTGTGCATAGACCCCAACA	5-10-5	65	2325	2344	853
547538	n/a	n/a	CCAGCAGAAATCCTGTGCAT	5-10-5	77	2336	2355	854
547539	n/a	n/a	AGAACTCCAGCAGAAATCCT	5-10-5	43	2342	2361	855
547540	n/a	n/a	TTGTGTGGCCCTCTTAAGTC	5-10-5	44	4794	4813	856
547541	n/a	n/a	TATAGATGTTTATTGTAGCC	5-10-5	36	4844	4863	857
547542	n/a	n/a	ATACTCGCCTTTGTGACTCG	5-10-5	35	26266	26285	858
547543	n/a	n/a	TTTTCCATGCATACTCGCCT	5-10-5	54	26276	26295	859
547544	n/a	n/a	TCGCCTTTGTGATGCGATTT	5-10-5	15	26293	26312	860
547545	n/a	n/a	ATACTCGCCTTTGTGATGCG	5-10-5	43	26297	26316	861
547546	n/a	n/a	CATACTCGCCTTTGTGATGC	5-10-5	11	26298	26317	862
547547	n/a	n/a	GCATACTCGCCTTTGTGATG	5-10-5	42	26299	26318	863
547548	n/a	n/a	TGCATACTCGCCTTTGTGAT	5-10-5	61	26300	26319	864
547549	n/a	n/a	CCCATGCATACTCGCCTTTG	5-10-5	36	26304	26323	865
547550	n/a	n/a	CCCCATGCATACTCGCCTTT	5-10-5	53	26305	26324	866
547551	n/a	n/a	TCCCCATGCATACTCGCCTT	5-10-5	38	26306	26325	867
547552	n/a	n/a	CTCCCCATGCATACTCGCCT	5-10-5	53	26307	26326	868
547553	n/a	n/a	TGCTCCCCATGCATACTCGC	5-10-5	64	26309	26328	869
547554	n/a	n/a	GCTCTGATTGGGTCACCACA	5-10-5	50	5743	5762	870
547555	n/a	n/a	TGTCTCCTTCCACTTGCTCC	5-10-5	58	5923	5942	871
547556	n/a	n/a	GCCATTTTATCCCTGAGATT	5-10-5	55	6130	6149	872
547557	n/a	n/a	CTGTGCTGTATTTTGGAGCC	5-10-5	59	6413	6432	873

Table 134

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	85	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
546732	n/a	n/a	GGATTTGGCCCTGAGCCCCA	5-10-5	14	6933	6952	874
546735	n/a	n/a	CAACCTGTCCATTCCCTGGG	5-10-5	46	7082	7101	875
546739	n/a	n/a	ATTCGGTGTCTTTACTGGCT	5-10-5	89	7228	7247	876
546746	n/a	n/a	TCCTGTTGCCTGACATGCTA	5-10-5	65	7694	7713	877
546747	n/a	n/a	CTCCCACTGACTGACTACTC	5-10-5	64	7904	7923	878
546749	n/a	n/a	GCTGGTCCTTGAACCCCGTG	5-10-5	53	8259	8278	879
546753	n/a	n/a	CTGGCTCACTATAGGCCCCA	5-10-5	91	8655	8674	880
546756	n/a	n/a	ATAAGCATCTCTCTGACCTA	5-10-5	47	9105	9124	881
546763	n/a	n/a	GCTTCCCCAATACTTGCTGG	5-10-5	84	9695	9714	882
546765	n/a	n/a	GTGTCCAGAATACTGCCCCA	5-10-5	82	10053	10072	883
546770	n/a	n/a	GTGGACGACTGCCCTGTGCC	5-10-5	74	10435	10454	884
546773	n/a	n/a	TCTCTAGCATCCTAGTCCTC	5-10-5	67	10586	10605	885
546780	n/a	n/a	ATACTGGCTAAGTCAGGCCC	5-10-5	83	10982	11001	886
546784	n/a	n/a	GGCAGGGAGGTGGATTATTC	5-10-5	58	11440	11459	887
546789	n/a	n/a	GCTTCTCTATCTCCCAGTGT	5-10-5	79	12228	12247	888
546791	n/a	n/a	GATGCATGCAGCAATACAGG	5-10-5	52	12385	12404	889
546795	n/a	n/a	GTCTCGATGGCAAGCTGTAC	5-10-5	72	12650	12669	890
546796	n/a	n/a	GTACTCACCGGTACTCTGCC	5-10-5	82	12804	12823	891
546799	n/a	n/a	ATGAAGGGCGAGGCGCAGTG	5-10-5	5	13258	13277	892
546803	n/a	n/a	CCCCATACATCTATGCAAAT	5-10-5	40	13551	13570	893

546804	n/a	n/a	ACATGACTCCAGTGATGGAT	5-10-5	57	13632	13651	894
546808	n/a	n/a	AAAATGACACCAAAATTCGC	5-10-5	0	13841	13860	895
546811	n/a	n/a	TGGACATCCTTCCCCTCGCA	5-10-5	49	13967	13986	896
546817	n/a	n/a	GCTCTGAGCCTTCCGCCTCT	5-10-5	77	14472	14491	897
546822	n/a	n/a	ACTAGTTTCCTATAACTGCT	5-10-5	32	14735	14754	898
546823	n/a	n/a	TACTAGTTTCCTATAACTGC	5-10-5	44	14736	14755	899
546824	n/a	n/a	GTACTAGTTTCCTATAACTG	5-10-5	79	14737	14756	900
546825	n/a	n/a	GTATCACTGTACTAGTTTCC	5-10-5	96	14745	14764	901
						14816	14835	
						14887	14906	
						14946	14965	
						15006	15025	
						15078	15097	
						15221	15240	
						15293	15312	
						15352	15371	
						15412	15431	
						15484	15503	
						15556	15575	
						15614	15633	
						15686	15705	
						15816	15835	
						15888	15907	
						15946	15965	
546826	n/a	n/a	AGTATCACTGTACTAGTTTC	5-10-5	90	14746	14765	902
						14817	14836	
						14888	14907	
						14947	14966	
						15007	15026	
						15079	15098	
						15222	15241	
						15294	15313	
						15353	15372	
						15413	15432	
						15485	15504	
						15557	15576	
						15615	15634	
						15687	15706	
						15817	15836	
						15889	15908	
						15947	15966	
546827	n/a	n/a	CAGTATCACTGTACTAGTTT	5-10-5	98	14747	14766	903
						14818	14837	

						14889	14908	
						14948	14967	
						15008	15027	
						15080	15099	
						15152	15171	
						15223	15242	
						15295	15314	
						15354	15373	
						15414	15433	
						15486	15505	
						15558	15577	
						15616	15635	
						15688	15707	
						15818	15837	
						15890	15909	
						15948	15967	
546828	n/a	n/a	ACAGTATCACTGTACTAGTT	5-10-5	95	14748	14767	904
						14819	14838	
						14890	14909	
						14949	14968	
						15009	15028	
						15081	15100	
						15153	15172	
						15224	15243	
						15296	15315	
						15355	15374	
						15415	15434	
						15487	15506	
						15559	15578	
						15617	15636	
						15689	15708	
						15819	15838	
						15891	15910	
						15949	15968	
546829	n/a	n/a	AACAGTATCACTGTACTAGT	5-10-5	94	14749	14768	905
						14820	14839	
						14891	14910	
						14950	14969	
						15010	15029	
						15082	15101	
						15154	15173	
						15225	15244	
						15297	15316	

						15356	15375	
						15416	15435	
						15488	15507	
						15560	15579	
						15618	15637	
						15690	15709	
						15820	15839	
						15892	15911	
						15950	15969	
546830	n/a	n/a	TAACAGTATCACTGTACTAG	5-10-5	78	14750	14769	906
						14821	14840	
						14892	14911	
						14951	14970	
						15011	15030	
						15083	15102	
						15155	15174	
						15226	15245	
						15298	15317	
						15357	15376	
						15417	15436	
						15489	15508	
						15561	15580	
						15619	15638	
						15691	15710	
						15821	15840	
						15893	15912	
						15951	15970	
546831	n/a	n/a	TCTAACAGTATCACTGTACT	5-10-5	79	14752	14771	907
						14823	14842	
						14894	14913	
						15013	15032	
						15085	15104	
						15228	15247	
						15300	15319	
						15419	15438	
						15491	15510	
						15621	15640	
						15823	15842	
						15953	15972	
546832	n/a	n/a	CTCTAACAGTATCACTGTAC	5-10-5	88	14753	14772	908
						14824	14843	
						14895	14914	
						15014	15033	

						15086	15105	
						15229	15248	
						15301	15320	
						15420	15439	
						15492	15511	
						15622	15641	
						15824	15843	
						15954	15973	
546833	n/a	n/a	ACTCTAACAGTATCACTGTA	5-10-5	90	14754	14773	909
						14825	14844	
						14896	14915	
						15015	15034	
						15087	15106	
						15230	15249	
						15302	15321	
						15421	15440	
						15493	15512	
						15623	15642	
						15825	15844	
						15955	15974	
546834	n/a	n/a	AACTCTAACAGTATCACTGT	5-10-5	86	14755	14774	910
						14826	14845	
						14897	14916	
						15016	15035	
						15088	15107	
						15231	15250	
						15303	15322	
						15422	15441	
						15494	15513	
						15624	15643	
						15826	15845	
						15956	15975	
546835	n/a	n/a	TAACTCTAACAGTATCACTG	5-10-5	86	14756	14775	911
						14827	14846	
						14898	14917	
						15017	15036	
						15089	15108	
						15232	15251	
						15304	15323	
						15423	15442	
						15495	15514	
						15625	15644	
						15827	15846	

						15957	15976	
546836	n/a	n/a	ATAACTCTAACAGTATCACT	5-10-5	30	14757	14776	912
						14828	14847	
						14899	14918	
						15018	15037	
						15090	15109	
						15233	15252	
						15305	15324	
						15424	15443	
						15496	15515	
						15626	15645	
						15828	15847	
						15958	15977	
546837	n/a	n/a	TATAACTCTAACAGTATCAC	5-10-5	0	14758	14777	913
						14829	14848	
						14900	14919	
						15019	15038	
						15091	15110	
						15234	15253	
						15306	15325	
						15425	15444	
						15497	15516	
						15627	15646	
						15829	15848	
						15959	15978	
546838	n/a	n/a	CTATAACTCTAACAGTATCA	5-10-5	43	14759	14778	914
						14830	14849	
						14901	14920	
						15020	15039	
						15092	15111	
						15235	15254	
						15307	15326	
						15426	15445	
						15498	15517	
						15628	15647	
						15830	15849	
						15960	15979	
546839	n/a	n/a	CCTATAACTCTAACAGTATC	5-10-5	47	14760	14779	915
						14831	14850	
						14902	14921	
						15021	15040	
						15093	15112	
						15236	15255	

						15308	15327	
						15427	15446	
						15499	15518	
						15629	15648	
						15831	15850	
						15961	15980	
546840	n/a	n/a	CTGTCCTATAACTCTAACAG	5-10-5	53	14764	14783	916
						14835	14854	
546841	n/a	n/a	CACTGTCCTATAACTCTAAC	5-10-5	38	14766	14785	917
						14837	14856	
546842	n/a	n/a	TCACTGTCCTATAACTCTAA	5-10-5	54	14767	14786	918
						14838	14857	
546843	n/a	n/a	TATCACTGTCCTATAACTCT	5-10-5	52	14769	14788	919
						14840	14859	
546844	n/a	n/a	GTCCTATATCACTGTCCTAT	5-10-5	75	14775	14794	920
						14846	14865	
						15180	15199	
						15716	15735	
546845	n/a	n/a	TGTCCTATATCACTGTCCTA	5-10-5	75	14776	14795	921
						14847	14866	
						15181	15200	
						15717	15736	
546846	n/a	n/a	CTGTCCTATATCACTGTCCT	5-10-5	95	14777	14796	922
						14848	14867	
						15182	15201	
						15718	15737	
546847	n/a	n/a	ACTGTCCTATATCACTGTCC	5-10-5	88	14778	14797	923
						14849	14868	
						15183	15202	
						15719	15738	
546848	n/a	n/a	TCACTGTCCTATATCACTGT	5-10-5	86	14780	14799	924
						14851	14870	
						14976	14995	
						15185	15204	
						15257	15276	
						15382	15401	
						15520	15539	
						15650	15669	
						15721	15740	
						15852	15871	
						15982	16001	
547558	n/a	n/a	CCCCCAGTTCCCATGCAAGG	5-10-5	52	6640	6659	925
547559	n/a	n/a	GAGCACAGATCTCTTCAAGT	5-10-5	69	6822	6841	926

547560	n/a	n/a	GACGGTCACCCAGCCCTGAC	5-10-5	42	7459	7478	927
547561	n/a	n/a	AAGGGAAATTAGAGGCAGGC	5-10-5	57	7583	7602	928
547562	n/a	n/a	CTTTCTTGAGACAATCCCTT	5-10-5	59	8463	8482	929
547563	n/a	n/a	GTGGGATCAGAGAATGACTA	5-10-5	48	9267	9286	930
547564	n/a	n/a	CCCTCTGTCTTAGATGTCCA	5-10-5	94	9390	9409	931
547565	n/a	n/a	CTTATCAGTCCCAGTCATGT	5-10-5	63	10698	10717	932
547566	n/a	n/a	AAGAGTTGGGATGCGACTCT	5-10-5	76	11335	11354	933
547567	n/a	n/a	TCCACTCCTAAGAAGTATGG	5-10-5	60	11546	11565	934
547568	n/a	n/a	GCACCCTTTTCATTGAGATT	5-10-5	70	12070	12089	935
547569	n/a	n/a	ACTACCATTTGGGTTGGTAG	5-10-5	9	12571	12590	936
547570	n/a	n/a	AAGCCCTGTTTGGTTTTTAG	5-10-5	18	12900	12919	937
547571	n/a	n/a	AAATGACACCAAAATTGAGT	5-10-5	14	13744	13763	938
547572	n/a	n/a	AAATGACACCAAAATTCGCT	5-10-5	40	13840	13859	939
547573	n/a	n/a	TAAGCAAGGCCTATGTGTGG	5-10-5	2	13880	13899	940
547574	n/a	n/a	ACACGCACAGGTCCCAGGGC	5-10-5	51	14314	14333	941
547575	n/a	n/a	GGGAAACTCTTTCCTCGCCC	5-10-5	89	14583	14602	942
547576	n/a	n/a	CTAGTTTCCTATAACTGCTG	5-10-5	29	14734	14753	943
547577	n/a	n/a	CTAACAGTATCACTGTACTA	5-10-5	79	14751	14770	944
						14822	14841	
						14893	14912	
						15012	15031	
						15084	15103	
						15227	15246	
						15299	15318	
						15418	15437	
						15490	15509	
						15620	15639	
						15822	15841	
						15952	15971	
547578	n/a	n/a	GTCCTATAACTCTAACAGTA	5-10-5	30	14762	14781	945
						14833	14852	
547579	n/a	n/a	TGTCCTATAACTCTAACAGT	5-10-5	0	14763	14782	946
						14834	14853	
547580	n/a	n/a	ATCACTGTCCTATAACTCTA	5-10-5	61	14768	14787	947
						14839	14858	
547581	n/a	n/a	ATATCACTGTCCTATAACTC	5-10-5	60	14770	14789	948
						14841	14860	
547582	n/a	n/a	TATATCACTGTCCTATAACT	5-10-5	22	14771	14790	949
						14842	14861	
						15176	15195	
						15712	15731	
						16160	16179	
547583	n/a	n/a	CACTGTCCTATATCACTGTC	5-10-5	80	14779	14798	950

						14850	14869	
						15184	15203	
						15720	15739	

Table 135

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	85	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
546849	n/a	n/a	ATCACTGTCCTATATCACTG	5-10-5	93	14781	14800	951
						14852	14871	
						14977	14996	
						15186	15205	
						15258	15277	
						15383	15402	
						15521	15540	
						15651	15670	
						15722	15741	
						15853	15872	
						15983	16002	
546850	n/a	n/a	TATCACTGTCCTATATCACT	5-10-5	80	14782	14801	952
						14853	14872	
						14978	14997	
						15116	15135	
						15187	15206	

						15259	15278	
						15384	15403	
						15522	15541	
						15652	15671	
						15723	15742	
						15854	15873	
						15984	16003	
546851	n/a	n/a	AGTATCACTGTCCTATATCA	5-10-5	81	14784	14803	953
						14980	14999	
						15118	15137	
						15386	15405	
						15524	15543	
						15986	16005	
546852	n/a	n/a	CAGTATCACTGTCCTATATC	5-10-5	94	14785	14804	954
						14981	15000	
						15119	15138	
						15387	15406	
						15525	15544	
						15987	16006	
546853	n/a	n/a	ACAGTATCACTGTCCTATAT	5-10-5	86	14786	14805	955
						14982	15001	
						15120	15139	
						15388	15407	
						15526	15545	
						15988	16007	
546854	n/a	n/a	TAACAGTATCACTGTCCTAT	5-10-5	90	14788	14807	956
						14984	15003	
						15050	15069	
						15122	15141	
						15390	15409	
						15456	15475	
						15528	15547	
						15990	16009	
546855	n/a	n/a	ATAACAGTATCACTGTCCTA	5-10-5	87	14789	14808	957
						14985	15004	
						15051	15070	
						15123	15142	
						15391	15410	
						15457	15476	
						15529	15548	
						15991	16010	
546856	n/a	n/a	AACTATAACAGTATCACTGT	5-10-5	54	14793	14812	958
						15055	15074	

						15127	15146	
						15160	15179	
						15461	15480	
						15533	15552	
						15566	15585	
						15696	15715	
						15898	15917	
						15995	16014	
546857	n/a	n/a	TATAACTATAACAGTATCAC	5-10-5	7	14796	14815	959
						15058	15077	
						15130	15149	
						15163	15182	
						15464	15483	
						15536	15555	
						15569	15588	
						15699	15718	
						15770	15789	
						15998	16017	
546858	n/a	n/a	CTATAACTATAACAGTATCA	5-10-5	21	14797	14816	960
						15059	15078	
						15131	15150	
						15164	15183	
						15465	15484	
						15537	15556	
						15570	15589	
						15700	15719	
						15771	15790	
						15999	16018	
546859	n/a	n/a	TTTCCTATAACTATAACAGT	5-10-5	7	14801	14820	961
						15063	15082	
						15469	15488	
						15541	15560	
546860	n/a	n/a	CTAGTTTCCTATAACTATAA	5-10-5	36	14805	14824	962
						14876	14895	
						14935	14954	
						15067	15086	
						15210	15229	
						15282	15301	
						15341	15360	
						15473	15492	
						15545	15564	
						15603	15622	
						15675	15694	

						15746	15765	
						15805	15824	
						15877	15896	
						15935	15954	
546861	n/a	n/a	TAACAATATCACTGTCCTAT	5-10-5	68	14859	14878	963
						15193	15212	
						15265	15284	
						15586	15605	
						15658	15677	
						15729	15748	
						15860	15879	
						16086	16105	
						16183	16202	
						16234	16253	
546862	n/a	n/a	AACTATAACAATATCACTGT	5-10-5	0	14864	14883	964
						14923	14942	
						15198	15217	
						15270	15289	
						15329	15348	
						15591	15610	
						15663	15682	
						15734	15753	
						15793	15812	
						15865	15884	
						15923	15942	
						16066	16085	
						16091	16110	
						16144	16163	
						16239	16258	
546863	n/a	n/a	TAACTATAACAATATCACTG	5-10-5	21	14865	14884	965
						14924	14943	
						15199	15218	
						15271	15290	
						15330	15349	
						15592	15611	
						15664	15683	
						15735	15754	
						15794	15813	
						15866	15885	
						15924	15943	
						16067	16086	
						16092	16111	
						16145	16164	

						16240	16259	
546864	n/a	n/a	ATAACTATAACAATATCACT	5-10-5	0	14866 14925 15200 15272 15331 15593 15665 15736 15795 15867 15925 16068 16093 16146 16241	14885 14944 15219 15291 15350 15612 15684 15755 15814 15886 15944 16087 16112 16165 16260	966
546865	n/a	n/a	TATAACTATAACAATATCAC	5-10-5	0	14867 14926 15201 15273 15332 15594 15666 15737 15796 15868 15926 16069 16094 16147 16242	14886 14945 15220 15292 15351 15613 15685 15756 15815 15887 15945 16088 16113 16166 16261	967
546866	n/a	n/a	GTTTCCTATAACTATAACAA	5-10-5	35	14873 14932 15207 15279 15338 15600 15672 15743 15802 15874 15932	14892 14951 15226 15298 15357 15619 15691 15762 15821 15893 15951	968
546867	n/a	n/a	ACCTATAACTCTAACAGTAT	5-10-5	40	14903	14922	969

						15022	15041	
						15094	15113	
						15237	15256	
						15309	15328	
						15428	15447	
						15500	15519	
						15630	15649	
						15832	15851	
						15962	15981	
546868	n/a	n/a	TACCTATAACTCTAACAGTA	5-10-5	51	14904	14923	970
						15023	15042	
						15095	15114	
						15238	15257	
						15310	15329	
						15429	15448	
						15501	15520	
						15631	15650	
						15833	15852	
						15963	15982	
546869	n/a	n/a	TGTACCTATAACTCTAACAG	5-10-5	53	14906	14925	971
						15025	15044	
						15240	15259	
						15312	15331	
						15431	15450	
						15503	15522	
						15633	15652	
						15835	15854	
						15965	15984	
546870	n/a	n/a	CTGTACCTATAACTCTAACA	5-10-5	87	14907	14926	972
						15026	15045	
						15241	15260	
						15313	15332	
						15432	15451	
						15504	15523	
						15634	15653	
						15836	15855	
						15966	15985	
546871	n/a	n/a	ACTGTACCTATAACTCTAAC	5-10-5	73	14908	14927	973
						15027	15046	
						15242	15261	
						15314	15333	
						15433	15452	
						15505	15524	

						15635	15654	
						15837	15856	
						15967	15986	
546872	n/a	n/a	CACTGTACCTATAACTCTAA	5-10-5	87	14909	14928	974
						15028	15047	
						15243	15262	
						15315	15334	
						15434	15453	
						15506	15525	
						15636	15655	
						15838	15857	
						15968	15987	
546873	n/a	n/a	CAATATCACTGTACCTATAA	5-10-5	34	14915	14934	975
						15321	15340	
						15785	15804	
546874	n/a	n/a	ATAACAATATCACTGTACCT	5-10-5	68	14919	14938	976
						15325	15344	
						15789	15808	
						16062	16081	
						16140	16159	
546875	n/a	n/a	ACTATAACAATATCACTGTA	5-10-5	33	14922	14941	977
						15328	15347	
						15792	15811	
						16065	16084	
						16143	16162	
546876	n/a	n/a	GTCCTATATCACTGTACCTG	5-10-5	87	14971	14990	978
546877	n/a	n/a	CACTGTCCTATATCACTGTA	5-10-5	88	14975	14994	979
						15256	15275	
						15381	15400	
						15519	15538	
						15649	15668	
						15851	15870	
						15981	16000	
546878	n/a	n/a	CCTATAACAGTATCACTGTC	5-10-5	81	14988	15007	980
						15394	15413	
546879	n/a	n/a	TTTCCTATAACAGTATCACT	5-10-5	42	14991	15010	981
						15397	15416	
546880	n/a	n/a	GTTTCCTATAACAGTATCAC	5-10-5	41	14992	15011	982
						15398	15417	
546881	n/a	n/a	AGTTTCCTATAACAGTATCA	5-10-5	49	14993	15012	983
						15399	15418	
546882	n/a	n/a	TAGTTTCCTATAACAGTATC	5-10-5	24	14994	15013	984
						15400	15419	

546883	n/a	n/a	CTAGTTTCCTATAACAGTAT	5-10-5	19	14995	15014	985
						15401	15420	
546884	n/a	n/a	ACTAGTTTCCTATAACAGTA	5-10-5	6	14996	15015	986
						15402	15421	
547584	n/a	n/a	GTATCACTGTCCTATATCAC	5-10-5	85	14783	14802	987
						14979	14998	
						15117	15136	
						15385	15404	
						15523	15542	
						15985	16004	
547585	n/a	n/a	AACAGTATCACTGTCCTATA	5-10-5	85	14787	14806	988
						14983	15002	
						15121	15140	
						15389	15408	
						15527	15546	
						15989	16008	
547586	n/a	n/a	TATAACAGTATCACTGTCCT	5-10-5	82	14790	14809	989
						14986	15005	
						15052	15071	
						15124	15143	
						15392	15411	
						15458	15477	
						15530	15549	
						15992	16011	
547587	n/a	n/a	CTATAACAGTATCACTGTCC	5-10-5	96	14791	14810	990
						14987	15006	
						15053	15072	
						15125	15144	
						15393	15412	
						15459	15478	
						15531	15550	
						15993	16012	
547588	n/a	n/a	ACTATAACAGTATCACTGTC	5-10-5	83	14792	14811	991
						15054	15073	
						15126	15145	
						15460	15479	
						15532	15551	
						15994	16013	
547589	n/a	n/a	TAACTATAACAGTATCACTG	5-10-5	36	14794	14813	992
						15056	15075	
						15128	15147	
						15161	15180	
						15462	15481	

						15534	15553	
						15567	15586	
						15697	15716	
						15996	16015	
547590	n/a	n/a	ATAACTATAACAGTATCACT	5-10-5	0	14795	14814	993
						15057	15076	
						15129	15148	
						15162	15181	
						15463	15482	
						15535	15554	
						15568	15587	
						15698	15717	
						15997	16016	
547591	n/a	n/a	CCTATAACTATAACAGTATC	5-10-5	23	14798	14817	994
						15060	15079	
						15165	15184	
						15466	15485	
						15538	15557	
						15571	15590	
						15701	15720	
						15772	15791	
						16000	16019	
547592	n/a	n/a	TCCTATAACTATAACAGTAT	5-10-5	27	14799	14818	995
						15061	15080	
						15166	15185	
						15467	15486	
						15539	15558	
						15572	15591	
						15702	15721	
						16001	16020	
547593	n/a	n/a	TTCCTATAACTATAACAGTA	5-10-5	29	14800	14819	996
						15062	15081	
						15468	15487	
						15540	15559	
547594	n/a	n/a	GTTTCCTATAACTATAACAG	5-10-5	19	14802	14821	997
						15064	15083	
						15470	15489	
						15542	15561	
547595	n/a	n/a	ACTAGTTTCCTATAACTATA	5-10-5	21	14806	14825	998
						14877	14896	
						14936	14955	
						15068	15087	
						15211	15230	

						15283	15302	
						15342	15361	
						15474	15493	
						15546	15565	
						15604	15623	
						15676	15695	
						15747	15766	
						15806	15825	
						15878	15897	
						15936	15955	
547596	n/a	n/a	TACTAGTTTCCTATAACTAT	5-10-5	14	14807	14826	999
						14878	14897	
						14937	14956	
						15069	15088	
						15212	15231	
						15284	15303	
						15343	15362	
						15475	15494	
						15547	15566	
						15605	15624	
						15677	15696	
						15748	15767	
						15807	15826	
						15879	15898	
						15937	15956	
547597	n/a	n/a	CAATATCACTGTCCTATATC	5-10-5	29	14856	14875	1000
						15190	15209	
						15262	15281	
						15655	15674	
						15726	15745	
						15857	15876	
547598	n/a	n/a	ACTATAACAATATCACTGTC	5-10-5	59	14863	14882	1001
						15197	15216	
						15269	15288	
						15590	15609	
						15662	15681	
						15733	15752	
						15864	15883	
						15922	15941	
						16090	16109	
						16238	16257	
547599	n/a	n/a	TTCCTATAACTATAACAATA	5-10-5	4	14871	14890	1002
						14930	14949	

						15205	15224	
						15277	15296	
						15336	15355	
						15598	15617	
						15670	15689	
						15741	15760	
						15800	15819	
						15872	15891	
						15930	15949	
547600	n/a	n/a	TTTCCTATAACTATAACAAT	5-10-5	26	14872	14891	1003
						14931	14950	
						15206	15225	
						15278	15297	
						15337	15356	
						15599	15618	
						15671	15690	
						15742	15761	
						15801	15820	
						15873	15892	
						15931	15950	
547601	n/a	n/a	GTACCTATAACTCTAACAGT	5-10-5	75	14905	14924	1004
						15024	15043	
						15239	15258	
						15311	15330	
						15430	15449	
						15502	15521	
						15632	15651	
						15834	15853	
						15964	15983	
547602	n/a	n/a	TCACTGTACCTATAACTCTA	5-10-5	93	14910	14929	1005
						15029	15048	
						15244	15263	
						15316	15335	
						15435	15454	
						15507	15526	
						15637	15656	
						15839	15858	
						15969	15988	
547603	n/a	n/a	TATCACTGTACCTATAACTC	5-10-5	41	14912	14931	1006
						15246	15265	
						15318	15337	
						15509	15528	
						15639	15658	

						15841	15860	
						15971	15990	
547604	n/a	n/a	ATATCACTGTACCTATAACT	5-10-5	0	14913	14932	1007
						15247	15266	
						15319	15338	
						15510	15529	
						15640	15659	
						15783	15802	
						15842	15861	
						15972	15991	
547605	n/a	n/a	ACAATATCACTGTACCTATA	5-10-5	43	14916	14935	1008
						15322	15341	
						15786	15805	
						16137	16156	
547606	n/a	n/a	AACAATATCACTGTACCTAT	5-10-5	43	14917	14936	1009
						15323	15342	
						15787	15806	
						16138	16157	
547607	n/a	n/a	TAACAATATCACTGTACCTA	5-10-5	49	14918	14937	1010
						15324	15343	
						15788	15807	
						16139	16158	
547608	n/a	n/a	TATAACAATATCACTGTACC	5-10-5	35	14920	14939	1011
						15326	15345	
						15790	15809	
						16063	16082	
						16141	16160	
547609	n/a	n/a	CTATAACAATATCACTGTAC	5-10-5	23	14921	14940	1012
						15327	15346	
						15791	15810	
						16064	16083	
						16142	16161	
547610	n/a	n/a	TGTAACAGTATCACTGTACT	5-10-5	45	14953	14972	1013
547611	n/a	n/a	CTGTAACAGTATCACTGTAC	5-10-5	71	14954	14973	1014
547612	n/a	n/a	CCTGTAACAGTATCACTGTA	5-10-5	68	14955	14974	1015
547613	n/a	n/a	CTATATCACTGTACCTGTAA	5-10-5	39	14968	14987	1016
547614	n/a	n/a	CCTATATCACTGTACCTGTA	5-10-5	81	14969	14988	1017
547615	n/a	n/a	TCCTATATCACTGTACCTGT	5-10-5	84	14970	14989	1018
547616	n/a	n/a	TGTCCTATATCACTGTACCT	5-10-5	86	14972	14991	1019
						15253	15272	
						15378	15397	
						15516	15535	
						15646	15665	

						15848	15867	
						15978	15997	
547617	n/a	n/a	CTGTCCTATATCACTGTACC	5-10-5	91	14973	14992	1020
						15254	15273	
						15379	15398	
						15517	15536	
						15647	15666	
						15849	15868	
						15979	15998	
547618	n/a	n/a	ACTGTCCTATATCACTGTAC	5-10-5	87	14974	14993	1021
						15255	15274	
						15380	15399	
						15518	15537	
						15648	15667	
						15850	15869	
						15980	15999	
547619	n/a	n/a	TCCTATAACAGTATCACTGT	5-10-5	70	14989	15008	1022
						15395	15414	
547620	n/a	n/a	TTCCTATAACAGTATCACTG	5-10-5	65	14990	15009	1023
						15396	15415	
547621	n/a	n/a	TACTAGTTTCCTATAACAGT	5-10-5	12	14997	15016	1024
						15403	15422	
547622	n/a	n/a	GTCACTGTACCTATAACTCT	5-10-5	88	15030	15049	1025
						15436	15455	
547623	n/a	n/a	TGTCACTGTACCTATAACTC	5-10-5	81	15031	15050	1026
						15437	15456	
547624	n/a	n/a	ATGTCACTGTACCTATAACT	5-10-5	64	15032	15051	1027
						15438	15457	

Table 136

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	% inhibition	Motif	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	93	5-10-5	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	

						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
546885	n/a	n/a	TATGTCACTGTACCTATAAC	46	5-10-5	15033	15052	1028
						15439	15458	
546886	n/a	n/a	CTATGTCACTGTACCTATAA	80	5-10-5	15034	15053	1029
						15440	15459	
546887	n/a	n/a	CCTATGTCACTGTACCTATA	82	5-10-5	15035	15054	1030
						15441	15460	
546888	n/a	n/a	TCCTATGTCACTGTACCTAT	78	5-10-5	15036	15055	1031
						15442	15461	
546889	n/a	n/a	GTCCTATGTCACTGTACCTA	93	5-10-5	15037	15056	1032
						15443	15462	
546890	n/a	n/a	TGTCCTATGTCACTGTACCT	78	5-10-5	15038	15057	1033
						15444	15463	
546891	n/a	n/a	CTGTCCTATGTCACTGTACC	81	5-10-5	15039	15058	1034
						15445	15464	
546892	n/a	n/a	ACTGTCCTATGTCACTGTAC	82	5-10-5	15040	15059	1035
						15446	15465	
546893	n/a	n/a	CACTGTCCTATGTCACTGTA	70	5-10-5	15041	15060	1036
						15447	15466	
546894	n/a	n/a	TCACTGTCCTATGTCACTGT	91	5-10-5	15042	15061	1037
						15448	15467	
546895	n/a	n/a	TATCACTGTCCTATGTCACT	77	5-10-5	15044	15063	1038
						15450	15469	
546896	n/a	n/a	GTATCACTGTCCTATGTCAC	75	5-10-5	15045	15064	1039
						15451	15470	
546897	n/a	n/a	AGTATCACTGTCCTATGTCA	90	5-10-5	15046	15065	1040
						15452	15471	
546898	n/a	n/a	AACAGTATCACTGTCCTATG	91	5-10-5	15049	15068	1041
						15455	15474	
546899	n/a	n/a	CTACCTATAACTCTAACAGT	27	5-10-5	15096	15115	1042
546901	n/a	n/a	ACTGTCCTATAACTATAACA	56	5-10-5	15170	15189	1043
						15576	15595	
						15706	15725	
						16005	16024	
						16076	16095	

						16101	16120	
						16154	16173	
546902	n/a	n/a	CACTGTCCTATAACTATAAC	71	5-10-5	15171	15190	1044
						15577	15596	
						15707	15726	
						16006	16025	
						16077	16096	
						16102	16121	
						16155	16174	
546903	n/a	n/a	CCTATATCACTGTACCTATA	91	5-10-5	15250	15269	1045
						15375	15394	
						15513	15532	
						15643	15662	
						15845	15864	
						15975	15994	
546904	n/a	n/a	TCCTATATCACTGTACCTAT	80	5-10-5	15251	15270	1046
						15376	15395	
						15514	15533	
						15644	15663	
						15846	15865	
						15976	15995	
546905	n/a	n/a	TACCTATAACAGTATCACTG	65	5-10-5	15363	15382	1047
546907	n/a	n/a	ATAACTATAACAGTATCACC	37	5-10-5	15769	15788	1048
546908	n/a	n/a	TCACTGTACCTATAACTATA	77	5-10-5	15780	15799	1049
						16252	16271	
546909	n/a	n/a	AACAATATCACTGTACCTTT	44	5-10-5	16060	16079	1050
546910	n/a	n/a	TAACAATATCACTGTACCTT	82	5-10-5	16061	16080	1051
546911	n/a	n/a	GTCCTATAACTATAACAATA	52	5-10-5	16073	16092	1052
						16098	16117	
						16151	16170	
547625	n/a	n/a	CAGTATCACTGTCCTATGTC	79	5-10-5	15047	15066	1053
						15453	15472	
547626	n/a	n/a	ACAGTATCACTGTCCTATGT	91	5-10-5	15048	15067	1054
						15454	15473	
547627	n/a	n/a	TCTACCTATAACTCTAACAG	71	5-10-5	15097	15116	1055
547628	n/a	n/a	CTCTACCTATAACTCTAACA	34	5-10-5	15098	15117	1056
547629	n/a	n/a	ACTCTACCTATAACTCTAAC	0	5-10-5	15099	15118	1057
547630	n/a	n/a	ACTGTCCTATATCACTCTAC	76	5-10-5	15112	15131	1058
547631	n/a	n/a	CACTGTCCTATATCACTCTA	85	5-10-5	15113	15132	1059
547632	n/a	n/a	TCACTGTCCTATATCACTCT	87	5-10-5	15114	15133	1060
547633	n/a	n/a	ATCACTGTCCTATATCACTC	87	5-10-5	15115	15134	1061
547634	n/a	n/a	ATCACTGTACTAGTTTTCTA	72	5-10-5	15148	15167	1062
547635	n/a	n/a	TATCACTGTACTAGTTTTCT	53	5-10-5	15149	15168	1063

547636	n/a	n/a	GTATCACTGTACTAGTTTTC	86	5-10-5	15150	15169	1064
547637	n/a	n/a	AGTATCACTGTACTAGTTTT	88	5-10-5	15151	15170	1065
547638	n/a	n/a	ATAACAGTATCACTGTACTA	87	5-10-5	15156	15175	1066
						15358	15377	
						15562	15581	
						15692	15711	
						15894	15913	
547639	n/a	n/a	GTCCTATAACTATAACAGTA	72	5-10-5	15167	15186	1067
						15573	15592	
						15703	15722	
						16002	16021	
547640	n/a	n/a	TGTCCTATAACTATAACAGT	13	5-10-5	15168	15187	1068
						15574	15593	
						15704	15723	
						16003	16022	
547641	n/a	n/a	CTGTCCTATAACTATAACAG	43	5-10-5	15169	15188	1069
						15575	15594	
						15705	15724	
						16004	16023	
547642	n/a	n/a	TCACTGTCCTATAACTATAA	72	5-10-5	15172	15191	1070
						15578	15597	
						15708	15727	
						16007	16026	
						16078	16097	
						16103	16122	
						16156	16175	
547643	n/a	n/a	ATCACTGTCCTATAACTATA	72	5-10-5	15173	15192	1071
						15579	15598	
						15709	15728	
						16008	16027	
						16079	16098	
						16104	16123	
						16157	16176	
						16176	16195	
547644	n/a	n/a	TATCACTGTCCTATAACTAT	51	5-10-5	15174	15193	1072
						15580	15599	
						15710	15729	
						16009	16028	
						16080	16099	
						16158	16177	
						16177	16196	
						16228	16247	
547645	n/a	n/a	ATATCACTGTCCTATAACTA	60	5-10-5	15175	15194	1073

						15581	15600	
						15711	15730	
						16010	16029	
						16081	16100	
						16159	16178	
						16178	16197	
						16229	16248	
547646	n/a	n/a	CTATATCACTGTACCTATAA	23	5-10-5	15249	15268	1074
						15374	15393	
						15512	15531	
						15642	15661	
						15844	15863	
						15974	15993	
547647	n/a	n/a	GTCCTATATCACTGTACCTA	92	5-10-5	15252	15271	1075
						15377	15396	
						15515	15534	
						15645	15664	
						15847	15866	
						15977	15996	
547648	n/a	n/a	CCTATAACAGTATCACTGTA	83	5-10-5	15361	15380	1076
547649	n/a	n/a	ACCTATAACAGTATCACTGT	73	5-10-5	15362	15381	1077
547650	n/a	n/a	GTACCTATAACAGTATCACT	32	5-10-5	15364	15383	1078
547651	n/a	n/a	TGTACCTATAACAGTATCAC	48	5-10-5	15365	15384	1079
547652	n/a	n/a	TCACTGTACCTATAACAGTA	59	5-10-5	15369	15388	1080
547653	n/a	n/a	ATCACTGTACCTATAACAGT	57	5-10-5	15370	15389	1081
547654	n/a	n/a	TATCACTGTACCTATAACAG	53	5-10-5	15371	15390	1082
547655	n/a	n/a	AATATCACTGTCCTATAACT	37	5-10-5	15582	15601	1083
						16011	16030	
						16082	16101	
						16179	16198	
						16230	16249	
547656	n/a	n/a	CAATATCACTGTCCTATAAC	42	5-10-5	15583	15602	1084
						16083	16102	
						16180	16199	
						16231	16250	
547657	n/a	n/a	ACAATATCACTGTCCTATAA	43	5-10-5	15584	15603	1085
						16084	16103	
						16181	16200	
						16232	16251	
547658	n/a	n/a	CGTACTAGTTTCCTATAACT	68	5-10-5	15750	15769	1086
547659	n/a	n/a	ACTATAACAGTATCACCGTA	80	5-10-5	15766	15785	1087
547660	n/a	n/a	AACTATAACAGTATCACCGT	68	5-10-5	15767	15786	1088
547661	n/a	n/a	TAACTATAACAGTATCACCG	80	5-10-5	15768	15787	1089

547662	n/a	n/a	ACCTATAACTATAACAGTAT	0	5-10-5	15773	15792	1090
547663	n/a	n/a	TACCTATAACTATAACAGTA	10	5-10-5	15774	15793	1091
547664	n/a	n/a	GTACCTATAACTATAACAGT	2	5-10-5	15775	15794	1092
547665	n/a	n/a	TGTACCTATAACTATAACAG	10	5-10-5	15776	15795	1093
547666	n/a	n/a	ATCACTGTACCTATAACTAT	71	5-10-5	15781	15800	1094
						16253	16272	
547667	n/a	n/a	TATCACTGTACCTATAACTA	55	5-10-5	15782	15801	1095
547668	n/a	n/a	CAACTATAACAGTATCACTG	44	5-10-5	15899	15918	1096
547669	n/a	n/a	ACAACTATAACAGTATCACT	0	5-10-5	15900	15919	1097
547670	n/a	n/a	TACAACTATAACAGTATCAC	0	5-10-5	15901	15920	1098
547671	n/a	n/a	CTACAACTATAACAGTATCA	0	5-10-5	15902	15921	1099
547672	n/a	n/a	CAATATCACTGTCCTACAAC	36	5-10-5	15915	15934	1100
547673	n/a	n/a	GAATATCACTGTCCTATAAC	21	5-10-5	16012	16031	1101
547674	n/a	n/a	ACAATATCACTGTACCTTTA	53	5-10-5	16059	16078	1102
547675	n/a	n/a	TGTCCTATAACTATAACAAT	10	5-10-5	16074	16093	1103
						16099	16118	
						16152	16171	
547676	n/a	n/a	CTGTCCTATAACTATAACAA	41	5-10-5	16075	16094	1104
						16100	16119	
						16153	16172	

Table 137

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	93	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	

						15945	15964	
546529	n/a	n/a	GCACCTGGCAGAACAGTACC	5-10-5	65	26419	26438	1105
546578	n/a	n/a	GACAGTGGGCCAGAGCCTTG	5-10-5	73	26686	26705	1106
546912	n/a	n/a	ACATCACTGTCCTATAACTA	5-10-5	26	16106	16125	1107
546913	n/a	n/a	GTACCTATATCACTGTAACT	5-10-5	38	16126	16145	1108
546914	n/a	n/a	ATATCACTGTACCTATATCA	5-10-5	52	16134	16153	1109
546915	n/a	n/a	TCACTGTCCTATAACTATAT	5-10-5	39	16175	16194	1110
546916	n/a	n/a	CGTCACTGTACCTATAACTG	5-10-5	92	16203	16222	1111
546917	n/a	n/a	ATCACTGTCCTATAACTATT	5-10-5	63	16227	16246	1112
546918	n/a	n/a	AACATCACTGTACCTATAAC	5-10-5	14	16256	16275	1113
546926	n/a	n/a	GCCATCCAGGGTGCTCTCCC	5-10-5	81	16839	16858	1114
546931	n/a	n/a	GCCCCCGGAGCACCTTCACT	5-10-5	58	17205	17224	1115
546935	n/a	n/a	CGTGGTTAGCCTGACATCTC	5-10-5	86	17412	17431	1116
546939	n/a	n/a	GCCATCTGGTTAGCCTCCGA	5-10-5	89	17664	17683	1117
546942	n/a	n/a	TACACTGAACCCCCTTAGGC	5-10-5	56	18570	18589	1118
546943	n/a	n/a	CAGTTTGGCCTTTCCATCTC	5-10-5	54	18819	18838	1119
546944	n/a	n/a	GCCACTAACCCACCTCTTAA	5-10-5	42	19140	19159	1120
546946	n/a	n/a	ACTCCCATCTACTCCCCCAT	5-10-5	41	19291	19310	1121
546954	n/a	n/a	CTGCTGATTGTGTCTGGCTC	5-10-5	71	20235	20254	1122
546955	n/a	n/a	ACAAGGCTTCGAGGACAGCC	5-10-5	49	20339	20358	1123
546964	n/a	n/a	GCGATTCCTTGCCTCTGCTG	5-10-5	53	21550	21569	1124
546967	n/a	n/a	CACCGCGCGAATGCCTGCCT	5-10-5	93	22657	22676	1125
546969	n/a	n/a	ATCCAACCTCTCTCCCTATC	5-10-5	53	22901	22920	1126
546970	n/a	n/a	GCCCAAGCCTACATGCATAC	5-10-5	61	23426	23445	1127
546975	n/a	n/a	GGCCTGGATACAGCCTTTCT	5-10-5	70	23825	23844	1128
546977	n/a	n/a	GTCCCGAAGAGTCAAGTCCA	5-10-5	76	24253	24272	1129
546979	n/a	n/a	ACTGTTGTCCATAGCAGCAT	5-10-5	71	24504	24523	1130
546980	n/a	n/a	AGCCCTCAATTGTTGCTGGT	5-10-5	79	24664	24683	1131
546983	n/a	n/a	GATGACCTGCAGATGCACAG	5-10-5	74	24978	24997	1132
546986	n/a	n/a	CAGGATAGAACTGATGGTCC	5-10-5	91	25318	25337	1133
546990	n/a	n/a	AGAACAGGAGACAATCCACT	5-10-5	49	25680	25699	1134
546994	n/a	n/a	GTTCATGTGGCAACCTGTGA	5-10-5	58	26112	26131	1135
547677	n/a	n/a	CATCACTGTCCTATAACTAT	5-10-5	62	16105	16124	1136
547678	n/a	n/a	TACCTATATCACTGTAACTA	5-10-5	21	16125	16144	1137
547679	n/a	n/a	TGTACCTATATCACTGTAAC	5-10-5	28	16127	16146	1138
547680	n/a	n/a	TATCACTGTACCTATATCAC	5-10-5	41	16133	16152	1139
547681	n/a	n/a	AATATCACTGTACCTATATC	5-10-5	6	16135	16154	1140
547682	n/a	n/a	CAATATCACTGTACCTATAT	5-10-5	20	16136	16155	1141
547683	n/a	n/a	ACTATATCACTGTCCTATAA	5-10-5	33	16162	16181	1142
547684	n/a	n/a	TAACTATATCACTGTCCTAT	5-10-5	43	16164	16183	1143
547685	n/a	n/a	ATAACTATATCACTGTCCTA	5-10-5	35	16165	16184	1144
547686	n/a	n/a	CTGTCCTATAACTATATCAC	5-10-5	36	16172	16191	1145
547687	n/a	n/a	ACTGTCCTATAACTATATCA	5-10-5	41	16173	16192	1146

547688	n/a	n/a	CACTGTCCTATAACTATATC	5-10-5	47	16174	16193	1147
547689	n/a	n/a	GTAACAATATCACTGTCCTA	5-10-5	73	16184	16203	1148
547690	n/a	n/a	CTGTAACAATATCACTGTCC	5-10-5	76	16186	16205	1149
547691	n/a	n/a	ACTGTAACAATATCACTGTC	5-10-5	36	16187	16206	1150
547692	n/a	n/a	CACTGTACCTATAACTGTAA	5-10-5	47	16200	16219	1151
547693	n/a	n/a	TCACTGTACCTATAACTGTA	5-10-5	61	16201	16220	1152
547694	n/a	n/a	GTCACTGTACCTATAACTGT	5-10-5	92	16202	16221	1153
547695	n/a	n/a	ACTGTCCTATAACTATTACA	5-10-5	31	16224	16243	1154
547696	n/a	n/a	CACTGTCCTATAACTATTAC	5-10-5	26	16225	16244	1155
547697	n/a	n/a	TCACTGTCCTATAACTATTA	5-10-5	63	16226	16245	1156
547698	n/a	n/a	ACCTATAACTATAACAATAT	5-10-5	0	16245	16264	1157
547699	n/a	n/a	TACCTATAACTATAACAATA	5-10-5	10	16246	16265	1158
547700	n/a	n/a	GTACCTATAACTATAACAAT	5-10-5	0	16247	16266	1159
547701	n/a	n/a	CATCACTGTACCTATAACTA	5-10-5	49	16254	16273	1160
547702	n/a	n/a	ACATCACTGTACCTATAACT	5-10-5	44	16255	16274	1161
547703	n/a	n/a	CAACATCACTGTACCTATAA	5-10-5	25	16257	16276	1162
547704	n/a	n/a	ACATCTTGTCATTAACATCC	5-10-5	61	16435	16454	1163
547705	n/a	n/a	GCACCCAATACAGGGCCAGG	5-10-5	69	16512	16531	1164
547706	n/a	n/a	TGCCTCCTGGCAGCCTTCAA	5-10-5	73	16694	16713	1165
547707	n/a	n/a	TGAAAAGCCACGCCCTTAGC	5-10-5	32	16975	16994	1166
547708	n/a	n/a	GCCAGGAGACAGCCCTACTC	5-10-5	67	17055	17074	1167
547709	n/a	n/a	AGCCCAATGTCCTAACCTGT	5-10-5	76	17791	17810	1168
547710	n/a	n/a	TGCGGTTATATGGGCTGAAG	5-10-5	85	19540	19559	1169
547711	n/a	n/a	CCTTTAGCCACTCCTCTTGC	5-10-5	45	20061	20080	1170
547712	n/a	n/a	CCCCATGGTACCAAAGCCAT	5-10-5	79	20528	20547	1171
547713	n/a	n/a	CTCAATGCCACCCTTTCCCC	5-10-5	37	20880	20899	1172
547714	n/a	n/a	CTGTCTAACTGGCCTGGCTG	5-10-5	19	21326	21345	1173
547715	n/a	n/a	GGTCAGAAGGCCTCTTATTC	5-10-5	21	21750	21769	1174
547716	n/a	n/a	CCATCTGTCCCCTCAATCCC	5-10-5	9	22197	22216	1175
547717	n/a	n/a	ACTCTGGCACTGGTCATGGA	5-10-5	54	22761	22780	1176
547718	n/a	n/a	ATAAAGTGCGATTAAGCCCC	5-10-5	86	23515	23534	1177
547719	n/a	n/a	TACCAAGCTTGTAGAAGGGA	5-10-5	69	23633	23652	1178
547720	n/a	n/a	GAAAGACGGCCAATGGGAAA	5-10-5	8	24177	24196	1179
547721	n/a	n/a	CTCTATCAAAATCCTGCTGC	5-10-5	68	25527	25546	1180
547722	n/a	n/a	CTCCAGTCACCACCATTGCC	5-10-5	80	25860	25879	1181

Table 138

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	91	14744	14763	334

						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
546599	n/a	n/a	AAGAGTAAGCCTTCACAGGG	5-10-5	82	27583	27602	1182
546606	n/a	n/a	CTCACCAGAGTTGTCCCCAG	5-10-5	0	27722	27741	1183
546999	n/a	n/a	GCAGCTCACACCCAAAAAGC	5-10-5	29	27004	27023	1184
547000	n/a	n/a	TCTGTTACCTTGAGGATTGT	5-10-5	63	27276	27295	1185
547006	n/a	n/a	CGCCATCTGCCCTGTACAGA	5-10-5	39	28248	28267	1186
547008	n/a	n/a	TTGGTGGTGGGATTGGTGGT	5-10-5	81	28333	28352	1187
						28388	28407	
						28443	28462	
						28608	28627	
						28620	28639	
547009	n/a	n/a	AATTGGTGGTGGGATTGGTG	5-10-5	73	28335	28354	1188
547010	n/a	n/a	GAATTGGTGGTGGGATTGGT	5-10-5	39	28336	28355	1189
547011	n/a	n/a	GGCAGGATTGGTGGTGGAAT	5-10-5	22	28352	28371	1190
547013	n/a	n/a	TGAGATTGGTGGTGGGTGGC	5-10-5	0	28369	28388	1191
547015	n/a	n/a	GGTGGTGGGATTGGTGCTGA	5-10-5	55	28429	28448	1192
547016	n/a	n/a	GTAGGTGGTGGGATTGGTGG	5-10-5	62	28456	28475	1193
						28535	28554	
547017	n/a	n/a	GGTAGGTGGTGGGATTGGTG	5-10-5	61	28457	28476	1194
						28536	28555	
547018	n/a	n/a	GGTGGCGGGATTGGTGGTGG	5-10-5	58	28477	28496	1195
						28556	28575	
547019	n/a	n/a	GATCGGTGGTGGGATTGGTC	5-10-5	83	28500	28519	1196
						28579	28598	
547020	n/a	n/a	GGATCGGTGGTGGGATTGGT	5-10-5	47	28501	28520	1197
						28580	28599	
547021	n/a	n/a	TTGGTGGCGGGATCGGTGGT	5-10-5	57	28510	28529	1198
						28589	28608	

547022	n/a	n/a	ATTGGTGGCGGGATCGGTGG	5-10-5	69	28511	28530	1199
547023	n/a	n/a	GATTGGTGGCGGGATCGGTG	5-10-5	91	28512	28531	1200
547024	n/a	n/a	GGATTGGTGGCGGGATCGGT	5-10-5	56	28513	28532	1201
547025	n/a	n/a	TGGTGGTGGGATTGGTGGTT	5-10-5	72	28607	28626	1202
547029	n/a	n/a	TCTTCTAGGGCCACACCTCT	5-10-5	50	28891	28910	1203
547035	n/a	n/a	TGGTCCCAAATTGGAGTGCA	5-10-5	40	29383	29402	1204
547039	n/a	n/a	TCTCTATACAGCTGGGCACA	5-10-5	0	29997	30016	1205
547049	n/a	n/a	CACTTCCCAGCAACCCTCAC	5-10-5	20	30765	30784	1206
547055	n/a	n/a	GCTCCTGGCAGCAATGACCC	5-10-5	70	31104	31123	1207
547059	n/a	n/a	GGGTATCTTCACTGTTCCAG	5-10-5	12	31540	31559	1208
547063	n/a	n/a	CGTCATGCTTACCTTTCTCC	5-10-5	23	31955	31974	1209
547069	n/a	n/a	GCCCTCCGAGCTTTGGCAAC	5-10-5	35	32581	32600	1210
547071	n/a	n/a	GCAGCCCCCCAGAAATCCCA	5-10-5	27	32708	32727	1211
547076	n/a	n/a	TCTCAAGCAGCCTATTGTGT	5-10-5	14	33263	33282	1212
547080	n/a	n/a	GTGCAAGACCTTGCTTGCCA	5-10-5	54	33657	33676	1213
547081	n/a	n/a	CTGTAGTCCACTACACAGCA	5-10-5	83	33801	33820	1214
547082	n/a	n/a	TCTCCCTGAGTCACAGTGGA	5-10-5	64	33881	33900	1215
547085	n/a	n/a	CCAGGTGCAGCACGGAGAGG	5-10-5	44	34479	34498	1216
547723	n/a	n/a	TAGAATGGCAGGGTTCTGTG	5-10-5	53	27357	27376	1217
547724	n/a	n/a	GATGCATCCAACACTTACCC	5-10-5	16	28059	28078	1218
547725	n/a	n/a	ATTGGTGGTGGGATTGGTGG	5-10-5	26	28334	28353	1219
						28389	28408	
						28444	28463	
						28523	28542	
						28609	28628	
						28621	28640	
547726	n/a	n/a	GCAGGATTGGTGGTGGAATT	5-10-5	0	28351	28370	1220
547727	n/a	n/a	TGGCAGGATTGGTGGTGGAA	5-10-5	0	28353	28372	1221
547728	n/a	n/a	GAGATTGGTGGTGGGTGGCA	5-10-5	88	28368	28387	1222
547729	n/a	n/a	GTGAGATTGGTGGTGGGTGG	5-10-5	45	28370	28389	1223
547730	n/a	n/a	GATTGGTGGTGGGATTGGTG	5-10-5	60	28390	28409	1224
						28433	28452	
						28445	28464	
						28524	28543	
						28610	28629	
						28622	28641	
547731	n/a	n/a	GGATTGGTGGTGGGATTGGT	5-10-5	49	28391	28410	1225
						28434	28453	
						28446	28465	
						28525	28544	
						28611	28630	
						28623	28642	
547732	n/a	n/a	AGGATTGGTGGTGGGATTGG	5-10-5	0	28392	28411	1226

547733	n/a	n/a	TAGGATTGGTGGTGGGATTG	5-10-5	0	28393	28412	1227
547734	n/a	n/a	GTAGGATTGGTGGTGGGATT	5-10-5	14	28394	28413	1228
547735	n/a	n/a	GGTAGGATTGGTGGTGGGAT	5-10-5	39	28395	28414	1229
547736	n/a	n/a	TGGTAGGATTGGTGGTGGGA	5-10-5	54	28396	28415	1230
547737	n/a	n/a	TGGTGGTGGGATTGGTGCTG	5-10-5	59	28430	28449	1231
547738	n/a	n/a	TTGGTGGTGGGATTGGTGCT	5-10-5	41	28431	28450	1232
547739	n/a	n/a	ATTGGTGGTGGGATTGGTGC	5-10-5	12	28432	28451	1233
547740	n/a	n/a	AGGTGGTGGGATTGGTGGTG	5-10-5	30	28454	28473	1234
						28533	28552	
547741	n/a	n/a	TAGGTGGTGGGATTGGTGGT	5-10-5	47	28455	28474	1235
						28534	28553	
547742	n/a	n/a	ATCGGTGGTGGGATTGGTCG	5-10-5	57	28499	28518	1236
						28578	28597	
547743	n/a	n/a	GGTGGTGGGATTGGTGGCGG	5-10-5	61	28520	28539	1237
547744	n/a	n/a	TGGTGGTGGGATTGGTGGCG	5-10-5	65	28521	28540	1238
547745	n/a	n/a	TTGGTGGTGGGATTGGTGGC	5-10-5	55	28522	28541	1239
547746	n/a	n/a	GTTGGTGGCGGGATCGGTGG	5-10-5	0	28590	28609	1240
547748	n/a	n/a	GGTTGGTGGCGGGATCGGTG	5-10-5	78	28591	28610	1241
547750	n/a	n/a	TGGTTGGTGGCGGGATCGGT	5-10-5	41	28592	28611	1242
547752	n/a	n/a	GTGGTTGGTGGCGGGATCGG	5-10-5	41	28593	28612	1243
547754	n/a	n/a	GGGATTGGTGGTTGGTGGCG	5-10-5	47	28600	28619	1244
547756	n/a	n/a	GGGTCTTGCTCCACCCACAT	5-10-5	49	29244	29263	1245
547758	n/a	n/a	CCAAGTAGTGCAAGGCATGT	5-10-5	24	29540	29559	1246
547760	n/a	n/a	ATCATGCTTACTGCAAGTGA	5-10-5	19	30219	30238	1247
547762	n/a	n/a	TGAAACTGGGCAGTCCTTCC	5-10-5	0	30417	30436	1248
547764	n/a	n/a	CCACCTTCTTACATATGCTA	5-10-5	24	30644	30663	1249
547766	n/a	n/a	GCCTCTCAGACGGCACAGAC	5-10-5	0	30902	30921	1250
547768	n/a	n/a	TTGCCCTCACACATTCGAAT	5-10-5	0	30977	30996	1251
547770	n/a	n/a	TGCTTTCTGCCCAACCTCTA	5-10-5	48	31727	31746	1252
547772	n/a	n/a	CTGTGCTCCCGGCCATTAGC	5-10-5	0	32312	32331	1253
547774	n/a	n/a	GAGACAGTTTGGCAAGCTAC	5-10-5	46	32389	32408	1254
547776	n/a	n/a	GGAGAGAGACGGCACCCTGT	5-10-5	48	32828	32847	1255
547778	n/a	n/a	TCACCTGTGAGTAACCAATA	5-10-5	53	33085	33104	1256
547780	n/a	n/a	CCCCTCTTAAATAGCACATG	5-10-5	67	33441	33460	1257
547782	n/a	n/a	CCAAGTATCTCATGTGCCTG	5-10-5	67	33580	33599	1258

Table 139

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Motif	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	5-10-5	90	14744	14763	334

						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
548706	n/a	n/a	CTAGTTTCCTATAACT	3-10-3	0	14738	14753	1259
						14809	14824	
						14880	14895	
						14939	14954	
						15071	15086	
						15214	15229	
						15286	15301	
						15345	15360	
						15477	15492	
						15549	15564	
						15607	15622	
						15679	15694	
						15750	15765	
						15809	15824	
						15881	15896	
						15939	15954	
548707	n/a	n/a	ACTAGTTTCCTATAAC	3-10-3	10	14739	14754	1260
						14810	14825	
						14881	14896	
						14940	14955	
						15000	15015	
						15072	15087	
						15215	15230	
						15287	15302	
						15346	15361	
						15406	15421	
						15478	15493	

						15550	15565	
						15608	15623	
						15680	15695	
						15751	15766	
						15810	15825	
						15882	15897	
						15940	15955	
548708	n/a	n/a	TACTAGTTTCCTATAA	3-10-3	0	14740	14755	1261
						14811	14826	
						14882	14897	
						14941	14956	
						15001	15016	
						15073	15088	
						15216	15231	
						15288	15303	
						15347	15362	
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						15479	15494	
						15551	15566	
						15609	15624	
						15681	15696	
						15752	15767	
						15811	15826	
						15883	15898	
						15941	15956	
548709	n/a	n/a	GTACTAGTTTCCTATA	3-10-3	0	14741	14756	1262
						14812	14827	
						14883	14898	
						14942	14957	
						15002	15017	
						15074	15089	
						15217	15232	
						15289	15304	
						15348	15363	
						15408	15423	
						15480	15495	
						15552	15567	
						15610	15625	
						15682	15697	
						15753	15768	
						15812	15827	
						15884	15899	
						15942	15957	

548710	n/a	n/a	TGTACTAGTTTCCTAT	3-10-3	0	14742	14757	1263
						14813	14828	
						14884	14899	
						14943	14958	
						15003	15018	
						15075	15090	
						15218	15233	
						15290	15305	
						15349	15364	
						15409	15424	
						15481	15496	
						15553	15568	
						15611	15626	
						15683	15698	
						15813	15828	
						15885	15900	
						15943	15958	
548711	n/a	n/a	CTGTACTAGTTTCCTA	3-10-3	21	14743	14758	1264
						14814	14829	
						14885	14900	
						14944	14959	
						15004	15019	
						15076	15091	
						15219	15234	
						15291	15306	
						15350	15365	
						15410	15425	
						15482	15497	
						15554	15569	
						15612	15627	
						15684	15699	
						15814	15829	
						15886	15901	
						15944	15959	
548712	n/a	n/a	ACTGTACTAGTTTCCT	3-10-3	9	14744	14759	1265
						14815	14830	
						14886	14901	
						14945	14960	
						15005	15020	
						15077	15092	
						15220	15235	
						15292	15307	
						15351	15366	

						15411	15426	
						15483	15498	
						15555	15570	
						15613	15628	
						15685	15700	
						15815	15830	
						15887	15902	
						15945	15960	
548713	n/a	n/a	CACTGTACTAGTTTCC	3-10-3	33	14745	14760	1266
						14816	14831	
						14887	14902	
						14946	14961	
						15006	15021	
						15078	15093	
						15221	15236	
						15293	15308	
						15352	15367	
						15412	15427	
						15484	15499	
						15556	15571	
						15614	15629	
						15686	15701	
						15816	15831	
						15888	15903	
						15946	15961	
548714	n/a	n/a	TCACTGTACTAGTTTC	3-10-3	15	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548715	n/a	n/a	ATCACTGTACTAGTTT	3-10-3	0	14747	14762	1268

						14818	14833	
						14889	14904	
						14948	14963	
						15008	15023	
						15080	15095	
						15152	15167	
						15223	15238	
						15295	15310	
						15354	15369	
						15414	15429	
						15486	15501	
						15558	15573	
						15616	15631	
						15688	15703	
						15818	15833	
						15890	15905	
						15948	15963	
548716	n/a	n/a	TATCACTGTACTAGTT	3-10-3	10	14748	14763	1269
						14819	14834	
						14890	14905	
						14949	14964	
						15009	15024	
						15081	15096	
						15153	15168	
						15224	15239	
						15296	15311	
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						15415	15430	
						15487	15502	
						15559	15574	
						15617	15632	
						15689	15704	
						15819	15834	
						15891	15906	
						15949	15964	
548717	n/a	n/a	ACTAGTTTCCTATAACT	3-10-4	0	14738	14754	1270
						14809	14825	
						14880	14896	
						14939	14955	
						15071	15087	
						15214	15230	
						15286	15302	
						15345	15361	

						15477	15493	
						15549	15565	
						15607	15623	
						15679	15695	
						15750	15766	
						15809	15825	
						15881	15897	
						15939	15955	
548718	n/a	n/a	TACTAGTTTCCTATAAC	3-10-4	0	14739	14755	1271
						14810	14826	
						14881	14897	
						14940	14956	
						15000	15016	
						15072	15088	
						15215	15231	
						15287	15303	
						15346	15362	
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						15478	15494	
						15550	15566	
						15608	15624	
						15680	15696	
						15751	15767	
						15810	15826	
						15882	15898	
						15940	15956	
548719	n/a	n/a	GTACTAGTTTCCTATAA	3-10-4	0	14740	14756	1272
						14811	14827	
						14882	14898	
						14941	14957	
						15001	15017	
						15073	15089	
						15216	15232	
						15288	15304	
						15347	15363	
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						15479	15495	
						15551	15567	
						15609	15625	
						15681	15697	
						15752	15768	
						15811	15827	
						15883	15899	

						15941	15957	
548720	n/a	n/a	TGTACTAGTTTCCTATA	3-10-4	0	14741	14757	1273
						14812	14828	
						14883	14899	
						14942	14958	
						15002	15018	
						15074	15090	
						15217	15233	
						15289	15305	
						15348	15364	
						15408	15424	
						15480	15496	
						15552	15568	
						15610	15626	
						15682	15698	
						15812	15828	
						15884	15900	
						15942	15958	
548721	n/a	n/a	CTGTACTAGTTTCCTAT	3-10-4	27	14742	14758	1274
						14813	14829	
						14884	14900	
						14943	14959	
						15003	15019	
						15075	15091	
						15218	15234	
						15290	15306	
						15349	15365	
						15409	15425	
						15481	15497	
						15553	15569	
						15611	15627	
						15683	15699	
						15813	15829	
						15885	15901	
						15943	15959	
548722	n/a	n/a	ACTGTACTAGTTTCCTA	3-10-4	26	14743	14759	1275
						14814	14830	
						14885	14901	
						14944	14960	
						15004	15020	
						15076	15092	
						15219	15235	
						15291	15307	

						15350	15366	
						15410	15426	
						15482	15498	
						15554	15570	
						15612	15628	
						15684	15700	
						15814	15830	
						15886	15902	
						15944	15960	
548723	n/a	n/a	CACTGTACTAGTTTCCT	3-10-4	62	14744	14760	1276
						14815	14831	
						14886	14902	
						14945	14961	
						15005	15021	
						15077	15093	
						15220	15236	
						15292	15308	
						15351	15367	
						15411	15427	
						15483	15499	
						15555	15571	
						15613	15629	
						15685	15701	
						15815	15831	
						15887	15903	
						15945	15961	
548724	n/a	n/a	TCACTGTACTAGTTTCC	3-10-4	61	14745	14761	1277
						14816	14832	
						14887	14903	
						14946	14962	
						15006	15022	
						15078	15094	
						15221	15237	
						15293	15309	
						15352	15368	
						15412	15428	
						15484	15500	
						15556	15572	
						15614	15630	
						15686	15702	
						15816	15832	
						15888	15904	
						15946	15962	

548725	n/a	n/a	ATCACTGTACTAGTTTC	3-10-4	32	14746	14762	1278
						14817	14833	
						14888	14904	
						14947	14963	
						15007	15023	
						15079	15095	
						15222	15238	
						15294	15310	
						15353	15369	
						15413	15429	
						15485	15501	
						15557	15573	
						15615	15631	
						15687	15703	
						15817	15833	
						15889	15905	
						15947	15963	
548726	n/a	n/a	TATCACTGTACTAGTTT	3-10-4	21	14747	14763	1279
						14818	14834	
						14889	14905	
						14948	14964	
						15008	15024	
						15080	15096	
						15152	15168	
						15223	15239	
						15295	15311	
						15354	15370	
						15414	15430	
						15486	15502	
						15558	15574	
						15616	15632	
						15688	15704	
						15818	15834	
						15890	15906	
						15948	15964	
548727	n/a	n/a	ACTAGTTTCCTATAACT	4-10-3	0	14738	14754	1270
						14809	14825	
						14880	14896	
						14939	14955	
						15071	15087	
						15214	15230	
						15286	15302	
						15345	15361	

						15477	15493	
						15549	15565	
						15607	15623	
						15679	15695	
						15750	15766	
						15809	15825	
						15881	15897	
						15939	15955	
548728	n/a	n/a	TACTAGTTTCCTATAAC	4-10-3	0	14739	14755	1271
						14810	14826	
						14881	14897	
						14940	14956	
						15000	15016	
						15072	15088	
						15215	15231	
						15287	15303	
						15346	15362	
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						15550	15566	
						15608	15624	
						15680	15696	
						15751	15767	
						15810	15826	
						15882	15898	
						15940	15956	
548729	n/a	n/a	GTACTAGTTTCCTATAA	4-10-3	13	14740	14756	1272
						14811	14827	
						14882	14898	
						14941	14957	
						15001	15017	
						15073	15089	
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						15752	15768	
						15811	15827	
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						15941	15957	
548730	n/a	n/a	TGTACTAGTTTCCTATA	4-10-3	0	14741	14757	1273
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						14883	14899	
						14942	14958	
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						15074	15090	
						15217	15233	
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						15812	15828	
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						15942	15958	
548731	n/a	n/a	CTGTACTAGTTTCCTAT	4-10-3	49	14742	14758	1274
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						14884	14900	
						14943	14959	
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						15075	15091	
						15218	15234	
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						15349	15365	
						15409	15425	
						15481	15497	
						15553	15569	
						15611	15627	
						15683	15699	
						15813	15829	
						15885	15901	
						15943	15959	
548732	n/a	n/a	ACTGTACTAGTTTCCTA	4-10-3	36	14743	14759	1275
						14814	14830	
						14885	14901	
						14944	14960	
						15004	15020	
						15076	15092	
						15219	15235	
						15291	15307	

						15350	15366	
						15410	15426	
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						15554	15570	
						15612	15628	
						15684	15700	
						15814	15830	
						15886	15902	
						15944	15960	
548733	n/a	n/a	CACTGTACTAGTTTCCT	4-10-3	84	14744	14760	1276
						14815	14831	
						14886	14902	
						14945	14961	
						15005	15021	
						15077	15093	
						15220	15236	
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						15351	15367	
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						15555	15571	
						15613	15629	
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						15815	15831	
						15887	15903	
						15945	15961	
548734	n/a	n/a	TCACTGTACTAGTTTCC	4-10-3	51	14745	14761	1277
						14816	14832	
						14887	14903	
						14946	14962	
						15006	15022	
						15078	15094	
						15221	15237	
						15293	15309	
						15352	15368	
						15412	15428	
						15484	15500	
						15556	15572	
						15614	15630	
						15686	15702	
						15816	15832	
						15888	15904	
						15946	15962	

548735	n/a	n/a	ATCACTGTACTAGTTTC	4-10-3	48	14746	14762	1278
						14817	14833	
						14888	14904	
						14947	14963	
						15007	15023	
						15079	15095	
						15222	15238	
						15294	15310	
						15353	15369	
						15413	15429	
						15485	15501	
						15557	15573	
						15615	15631	
						15687	15703	
						15817	15833	
						15889	15905	
						15947	15963	
548736	n/a	n/a	TATCACTGTACTAGTTT	4-10-3	21	14747	14763	1279
						14818	14834	
						14889	14905	
						14948	14964	
						15008	15024	
						15080	15096	
						15152	15168	
						15223	15239	
						15295	15311	
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						15414	15430	
						15486	15502	
						15558	15574	
						15616	15632	
						15688	15704	
						15818	15834	
						15890	15906	
						15948	15964	
548737	n/a	n/a	ACTAGTTTCCTATAACT	4-9-4	11	14738	14754	1270
						14809	14825	
						14880	14896	
						14939	14955	
						15071	15087	
						15214	15230	
						15286	15302	
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						15607	15623	
						15679	15695	
						15750	15766	
						15809	15825	
						15881	15897	
						15939	15955	
548738	n/a	n/a	TACTAGTTTCCTATAAC	4-9-4	0	14739	14755	1271
						14810	14826	
						14881	14897	
						14940	14956	
						15000	15016	
						15072	15088	
						15215	15231	
						15287	15303	
						15346	15362	
						15406	15422	
						15478	15494	
						15550	15566	
						15608	15624	
						15680	15696	
						15751	15767	
						15810	15826	
						15882	15898	
						15940	15956	
548739	n/a	n/a	GTACTAGTTTCCTATAA	4-9-4	0	14740	14756	1272
						14811	14827	
						14882	14898	
						14941	14957	
						15001	15017	
						15073	15089	
						15216	15232	
						15288	15304	
						15347	15363	
						15407	15423	
						15479	15495	
						15551	15567	
						15609	15625	
						15681	15697	
						15752	15768	
						15811	15827	
						15883	15899	

						15941	15957	
548740	n/a	n/a	TGTACTAGTTTCCTATA	4-9-4	0	14741	14757	1273
						14812	14828	
						14883	14899	
						14942	14958	
						15002	15018	
						15074	15090	
						15217	15233	
						15289	15305	
						15348	15364	
						15408	15424	
						15480	15496	
						15552	15568	
						15610	15626	
						15682	15698	
						15812	15828	
						15884	15900	
						15942	15958	
548741	n/a	n/a	CTGTACTAGTTTCCTAT	4-9-4	69	14742	14758	1274
						14813	14829	
						14884	14900	
						14943	14959	
						15003	15019	
						15075	15091	
						15218	15234	
						15290	15306	
						15349	15365	
						15409	15425	
						15481	15497	
						15553	15569	
						15611	15627	
						15683	15699	
						15813	15829	
						15885	15901	
						15943	15959	
548742	n/a	n/a	ACTGTACTAGTTTCCTA	4-9-4	50	14743	14759	1275
						14814	14830	
						14885	14901	
						14944	14960	
						15004	15020	
						15076	15092	
						15219	15235	
						15291	15307	

						15350	15366	
						15410	15426	
						15482	15498	
						15554	15570	
						15612	15628	
						15684	15700	
						15814	15830	
						15886	15902	
						15944	15960	
548743	n/a	n/a	CACTGTACTAGTTTCCT	4-9-4	80	14744	14760	1276
						14815	14831	
						14886	14902	
						14945	14961	
						15005	15021	
						15077	15093	
						15220	15236	
						15292	15308	
						15351	15367	
						15411	15427	
						15483	15499	
						15555	15571	
						15613	15629	
						15685	15701	
						15815	15831	
						15887	15903	
						15945	15961	
548744	n/a	n/a	TCACTGTACTAGTTTCC	4-9-4	83	14745	14761	1277
						14816	14832	
						14887	14903	
						14946	14962	
						15006	15022	
						15078	15094	
						15221	15237	
						15293	15309	
						15352	15368	
						15412	15428	
						15484	15500	
						15556	15572	
						15614	15630	
						15686	15702	
						15816	15832	
						15888	15904	
						15946	15962	

548745	n/a	n/a	ATCACTGTACTAGTTTC	4-9-4	71	14746	14762	1278
						14817	14833	
						14888	14904	
						14947	14963	
						15007	15023	
						15079	15095	
						15222	15238	
						15294	15310	
						15353	15369	
						15413	15429	
						15485	15501	
						15557	15573	
						15615	15631	
						15687	15703	
						15817	15833	
						15889	15905	
						15947	15963	
548746	n/a	n/a	TATCACTGTACTAGTTT	4-9-4	40	14747	14763	1279
						14818	14834	
						14889	14905	
						14948	14964	
						15008	15024	
						15080	15096	
						15152	15168	
						15223	15239	
						15295	15311	
						15354	15370	
						15414	15430	
						15486	15502	
						15558	15574	
						15616	15632	
						15688	15704	
						15818	15834	
						15890	15906	
						15948	15964	
548747	n/a	n/a	TACTAGTTTCCTATAACT	4-10-4	2	14738	14755	1280
						14809	14826	
						14880	14897	
						14939	14956	
						15071	15088	
						15214	15231	
						15286	15303	
						15345	15362	

						15477	15494	
						15549	15566	
						15607	15624	
						15679	15696	
						15750	15767	
						15809	15826	
						15881	15898	
						15939	15956	
548748	n/a	n/a	GTACTAGTTTCCTATAAC	4-10-4	0	14739	14756	1281
						14810	14827	
						14881	14898	
						14940	14957	
						15000	15017	
						15072	15089	
						15215	15232	
						15287	15304	
						15346	15363	
						15406	15423	
						15478	15495	
						15550	15567	
						15608	15625	
						15680	15697	
						15751	15768	
						15810	15827	
						15882	15899	
						15940	15957	
548749	n/a	n/a	TGTACTAGTTTCCTATAA	4-10-4	0	14740	14757	1282
						14811	14828	
						14882	14899	
						14941	14958	
						15001	15018	
						15073	15090	
						15216	15233	
						15288	15305	
						15347	15364	
						15407	15424	
						15479	15496	
						15551	15568	
						15609	15626	
						15681	15698	
						15811	15828	
						15883	15900	
						15941	15958	

548750	n/a	n/a	CTGTACTAGTTTCCTATA	4-10-4	62	14741	14758	1283
						14812	14829	
						14883	14900	
						14942	14959	
						15002	15019	
						15074	15091	
						15217	15234	
						15289	15306	
						15348	15365	
						15408	15425	
						15480	15497	
						15552	15569	
						15610	15627	
						15682	15699	
						15812	15829	
						15884	15901	
						15942	15959	
548751	n/a	n/a	ACTGTACTAGTTTCCTAT	4-10-4	53	14742	14759	1284
						14813	14830	
						14884	14901	
						14943	14960	
						15003	15020	
						15075	15092	
						15218	15235	
						15290	15307	
						15349	15366	
						15409	15426	
						15481	15498	
						15553	15570	
						15611	15628	
						15683	15700	
						15813	15830	
						15885	15902	
						15943	15960	
548752	n/a	n/a	CACTGTACTAGTTTCCTA	4-10-4	89	14743	14760	1285
						14814	14831	
						14885	14902	
						14944	14961	
						15004	15021	
						15076	15093	
						15219	15236	
						15291	15308	
						15350	15367	

						15410	15427	
						15482	15499	
						15554	15571	
						15612	15629	
						15684	15701	
						15814	15831	
						15886	15903	
						15944	15961	
548753	n/a	n/a	TCACTGTACTAGTTTCCT	4-10-4	82	14744	14761	1286
						14815	14832	
						14886	14903	
						14945	14962	
						15005	15022	
						15077	15094	
						15220	15237	
						15292	15309	
						15351	15368	
						15411	15428	
						15483	15500	
						15555	15572	
						15613	15630	
						15685	15702	
						15815	15832	
						15887	15904	
						15945	15962	
548754	n/a	n/a	ATCACTGTACTAGTTTCC	4-10-4	77	14745	14762	1287
						14816	14833	
						14887	14904	
						14946	14963	
						15006	15023	
						15078	15095	
						15221	15238	
						15293	15310	
						15352	15369	
						15412	15429	
						15484	15501	
						15556	15573	
						15614	15631	
						15686	15703	
						15816	15833	
						15888	15905	
						15946	15963	
548755	n/a	n/a	TATCACTGTACTAGTTTC	4-10-4	20	14746	14763	1288

						14817	14834	
						14888	14905	
						14947	14964	
						15007	15024	
						15079	15096	
						15222	15239	
						15294	15311	
						15353	15370	
						15413	15430	
						15485	15502	
						15557	15574	
						15615	15632	
						15687	15704	
						15817	15834	
						15889	15906	
						15947	15964	
548756	n/a	n/a	GTATCACTGTACTAGTT	4-9-4	81	14748	14764	1289
						14819	14835	
						14890	14906	
						14949	14965	
						15009	15025	
						15081	15097	
						15153	15169	
						15224	15240	
						15296	15312	
						15355	15371	
						15415	15431	
						15487	15503	
						15559	15575	
						15617	15633	
						15689	15705	
						15819	15835	
						15891	15907	
						15949	15965	
548757	n/a	n/a	AGTATCACTGTACTAGT	4-9-4	87	14749	14765	1290
						14820	14836	
						14891	14907	
						14950	14966	
						15010	15026	
						15082	15098	
						15154	15170	
						15225	15241	
						15297	15313	

						15356	15372	
						15416	15432	
						15488	15504	
						15560	15576	
						15618	15634	
						15690	15706	
						15820	15836	
						15892	15908	
						15950	15966	
548758	n/a	n/a	CAGTATCACTGTACTAG	4-9-4	97	14750	14766	1291
						14821	14837	
						14892	14908	
						14951	14967	
						15011	15027	
						15083	15099	
						15155	15171	
						15226	15242	
						15298	15314	
						15357	15373	
						15417	15433	
						15489	15505	
						15561	15577	
						15619	15635	
						15691	15707	
						15821	15837	
						15893	15909	
						15951	15967	
548759	n/a	n/a	AACAGTATCACTGTACT	4-9-4	68	14752	14768	1292
						14823	14839	
						14894	14910	
						14953	14969	
						15013	15029	
						15085	15101	
						15157	15173	
						15228	15244	
						15300	15316	
						15359	15375	
						15419	15435	
						15491	15507	
						15563	15579	
						15621	15637	
						15693	15709	
						15823	15839	

						15895	15911	
						15953	15969	
548760	n/a	n/a	TAACAGTATCACTGTAC	4-9-4	53	14753	14769	1293
						14824	14840	
						14895	14911	
						14954	14970	
						15014	15030	
						15086	15102	
						15158	15174	
						15229	15245	
						15301	15317	
						15360	15376	
						15420	15436	
						15492	15508	
						15564	15580	
						15622	15638	
						15694	15710	
						15824	15840	
						15896	15912	
						15954	15970	
548761	n/a	n/a	CTAACAGTATCACTGTA	4-9-4	49	14754	14770	1294
						14825	14841	
						14896	14912	
						15015	15031	
						15087	15103	
						15230	15246	
						15302	15318	
						15421	15437	
						15493	15509	
						15623	15639	
						15825	15841	
						15955	15971	
548762	n/a	n/a	TCTAACAGTATCACTGT	4-9-4	16	14755	14771	1295
						14826	14842	
						14897	14913	
						15016	15032	
						15088	15104	
						15231	15247	
						15303	15319	
						15422	15438	
						15494	15510	
						15624	15640	
						15826	15842	

						15956	15972	
548763	n/a	n/a	CTCTAACAGTATCACTG	4-9-4	44	14756	14772	1296
						14827	14843	
						14898	14914	
						15017	15033	
						15089	15105	
						15232	15248	
						15304	15320	
						15423	15439	
						15495	15511	
						15625	15641	
						15827	15843	
						15957	15973	
548764	n/a	n/a	TATCACTGTCCTATAAC	4-9-4	31	14772	14788	1297
						14843	14859	
						15177	15193	
						15583	15599	
						15713	15729	
						16012	16028	
						16083	16099	
						16161	16177	
						16180	16196	
						16231	16247	
548765	n/a	n/a	ATATCACTGTCCTATAA	4-9-4	0	14773	14789	1298
						14844	14860	
						15178	15194	
						15584	15600	
						15714	15730	
						16013	16029	
						16084	16100	
						16162	16178	
						16181	16197	
						16232	16248	
548766	n/a	n/a	TATATCACTGTCCTATA	4-9-4	36	14774	14790	1299
						14845	14861	
						15179	15195	
						15715	15731	
						16163	16179	
548767	n/a	n/a	TATCACTGTCCTATATC	4-9-4	59	14785	14801	1300
						14856	14872	
						14981	14997	
						15119	15135	
						15190	15206	

						15262	15278	
						15387	15403	
						15525	15541	
						15655	15671	
						15726	15742	
						15857	15873	
						15987	16003	
548768	n/a	n/a	GTATCACTGTCCTATAT	4-9-4	56	14786	14802	1301
						14982	14998	
						15120	15136	
						15388	15404	
						15526	15542	
						15988	16004	
548769	n/a	n/a	AGTATCACTGTCCTATA	4-9-4	64	14787	14803	1302
						14983	14999	
						15121	15137	
						15389	15405	
						15527	15543	
						15989	16005	
548770	n/a	n/a	TAACAGTATCACTGTCC	4-9-4	92	14791	14807	1303
						14987	15003	
						15053	15069	
						15125	15141	
						15393	15409	
						15459	15475	
						15531	15547	
						15993	16009	
548771	n/a	n/a	ATAACAGTATCACTGTC	4-9-4	62	14792	14808	1304
						14988	15004	
						15054	15070	
						15126	15142	
						15394	15410	
						15460	15476	
						15532	15548	
						15994	16010	
548772	n/a	n/a	TATAACAGTATCACTGT	4-9-4	0	14793	14809	1305
						14989	15005	
						15055	15071	
						15127	15143	
						15160	15176	
						15362	15378	
						15395	15411	
						15461	15477	

						15533	15549	
						15566	15582	
						15696	15712	
						15898	15914	
						15995	16011	
548773	n/a	n/a	CTATAACAGTATCACTG	4-9-4	0	14794	14810	1306
						14990	15006	
						15056	15072	
						15128	15144	
						15161	15177	
						15363	15379	
						15396	15412	
						15462	15478	
						15534	15550	
						15567	15583	
						15697	15713	
						15899	15915	
						15996	16012	
548774	n/a	n/a	CCTATAACTATAACAGT	4-9-4	0	14801	14817	1307
						15063	15079	
						15168	15184	
						15469	15485	
						15541	15557	
						15574	15590	
						15704	15720	
						15775	15791	
						16003	16019	
548775	n/a	n/a	TCCTATAACTATAACAG	4-9-4	0	14802	14818	1308
						15064	15080	
						15169	15185	
						15470	15486	
						15542	15558	
						15575	15591	
						15705	15721	
						16004	16020	
548776	n/a	n/a	CCTATAACTATAACAAT	4-9-4	0	14872	14888	1309
						14931	14947	
						15206	15222	
						15278	15294	
						15337	15353	
						15599	15615	
						15671	15687	
						15742	15758	

						15801	15817	
						15873	15889	
						15931	15947	
						16074	16090	
						16099	16115	
						16152	16168	
						16247	16263	
548777	n/a	n/a	GTAACAGTATCACTGTA	4-9-4	41	14955	14971	1310
548778	n/a	n/a	ATAACAGTATCACTGTA	4-9-4	20	15159	15175	1311
						15361	15377	
						15565	15581	
						15695	15711	
						15897	15913	
548779	n/a	n/a	GTCCTATAACTATAACA	4-9-4	0	15170	15186	1312
						15576	15592	
						15706	15722	
						16005	16021	
						16076	16092	
						16101	16117	
						16154	16170	
548780	n/a	n/a	TGTCCTATAACTATAAC	4-9-4	22	15171	15187	1313
						15577	15593	
						15707	15723	
						16006	16022	
						16077	16093	
						16102	16118	
						16155	16171	
548781	n/a	n/a	ACCTATAACTATAACAG	4-9-4	0	15776	15792	1314
548782	n/a	n/a	TACCTATAACTATAACA	4-9-4	0	15777	15793	1315
						16249	16265	
548783	n/a	n/a	ACCTATAACTATAACAA	4-9-4	0	16248	16264	1316

Example 116: Antisense inhibition of human PKK in HepaRG™ cells by antisense oligonucleotides with MOE, deoxy and cEt sugar modifications

Additional antisense oligonucleotides were designed targeting a PKK nucleic acid and were tested for their effects on PKK mRNA *in vitro*.

The chimeric antisense oligonucleotides in the tables below were designed as deoxy, MOE and cEt gapmers. The gapmers are 16 nucleosides in length wherein the nucleoside have either a MOE sugar modification, a cEt sugar modification, or a deoxy modification. The 'Chemistry' column describes the sugar modifications of each oligonucleotide. 'k' indicates an cEt sugar modification; the number indicates the number of deoxynucleosides; otherwise, 'd' indicates a deoxynucleoside; and 'e' indicates a 2'-O-

methoxyethyl modification. The internucleoside linkages throughout each gapmer are phosphorothioate linkages. All cytosine residues throughout each oligonucleotide 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 in the human gene sequence. Each gapmer listed in the tables below is targeted to either the human PKK mRNA, designated herein as SEQ ID NO: 1 or the human PKK genomic sequence, designated herein as SEQ ID NO: 10. 'n/a' indicates that the antisense oligonucleotide does not target that particular gene sequence.

Cultured HepaRG™ cells at a density of 20,000 cells per well were transfected using electroporation with 1,000 nM antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PKK mRNA levels were measured by quantitative real-time PCR. Human primer probe set RTS3454 was used to measure mRNA levels. ISIS 531231 was also included in this assay. PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. 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. Results are presented as percent inhibition of PKK, relative to untreated control cells.

Table 140

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	95	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548074	1642	1657	CCTTTCTCCTTCGAGA	eekd$_{10}$kke	0	31948	31963	1317

548075	1643	1658	ACCTTTCTCCTTCGAG	eekd$_{10}$kke	0	31949	31964	1318
548076	1644	1659	CACCTTTCTCCTTCGA	eekd$_{10}$kke	26	n/a	n/a	1319
548077	1691	1706	ATTTGTTACCAAAGGA	eekd$_{10}$kke	51	33135	33150	1320
548078	1696	1711	TCTTCATTTGTTACCA	eekd$_{10}$kke	36	33140	33155	1321
548079	1762	1777	CCTTCTTTATAGCCAG	eekd$_{10}$kke	39	33206	33221	1322
548080	1763	1778	CCCTTCTTTATAGCCA	eekd$_{10}$kke	0	33207	33222	1323
548081	1764	1779	CCCCTTCTTTATAGCC	eekd$_{10}$kke	64	33208	33223	1324
548082	1776	1791	AAGCATCTTTTCCCCC	eekd$_{10}$kke	42	33220	33235	1325
548083	1800	1815	AGGGACCACCTGAATC	eekd$_{10}$kke	0	33899	33914	1326
548084	1801	1816	AAGGGACCACCTGAAT	eekd$_{10}$kke	0	33900	33915	1327
548085	1802	1817	TAAGGGACCACCTGAA	eekd$_{10}$kke	8	33901	33916	1328
548086	1803	1818	CTAAGGGACCACCTGA	eekd$_{10}$kke	36	33902	33917	1329
548087	1804	1819	ACTAAGGGACCACCTG	eekd$_{10}$kke	24	33903	33918	1330
548088	1805	1820	AACTAAGGGACCACCT	eekd$_{10}$kke	27	33904	33919	1331
548089	1806	1821	AAACTAAGGGACCACC	eekd$_{10}$kke	34	33905	33920	1332
548090	1807	1822	CAAACTAAGGGACCAC	eekd$_{10}$kke	46	33906	33921	1333
548091	1809	1824	TGCAAACTAAGGGACC	eekd$_{10}$kke	62	33908	33923	1334
548092	1810	1825	TTGCAAACTAAGGGAC	eekd$_{10}$kke	30	33909	33924	1335
548093	1811	1826	TTTGCAAACTAAGGGA	eekd$_{10}$kke	0	33910	33925	1336
548094	1812	1827	GTTTGCAAACTAAGGG	eekd$_{10}$kke	74	33911	33926	1337
548095	1813	1828	TGTTTGCAAACTAAGG	eekd$_{10}$kke	35	33912	33927	1338
548096	1814	1829	GTGTTTGCAAACTAAG	eekd$_{10}$kke	23	33913	33928	1339
548097	1876	1891	TGCTCCCTGCGGGCAC	eekd$_{10}$kke	2	33975	33990	1340
548098	1887	1902	AGACACCAGGTTGCTC	eekd$_{10}$kke	0	33986	34001	1341
548099	1904	1919	CTCAGCGACTTTGGTG	eekd$_{10}$kke	55	34003	34018	1342
548100	1905	1920	ACTCAGCGACTTTGGT	eekd$_{10}$kke	25	34004	34019	1343
548101	1906	1921	TACTCAGCGACTTTGG	eekd$_{10}$kke	47	34005	34020	1344
548102	1907	1922	GTACTCAGCGACTTTG	eekd$_{10}$kke	58	34006	34021	1345
548103	1908	1923	TGTACTCAGCGACTTT	eekd$_{10}$kke	66	34007	34022	1346
548104	1909	1924	ATGTACTCAGCGACTT	eekd$_{10}$kke	59	34008	34023	1347
548105	1910	1925	CATGTACTCAGCGACT	eekd$_{10}$kke	49	34009	34024	1348
548106	1911	1926	CCATGTACTCAGCGAC	eekd$_{10}$kke	79	34010	34025	1349
548107	1912	1927	TCCATGTACTCAGCGA	eekd$_{10}$kke	76	34011	34026	1350
548108	1953	1968	GAGCTTTTCCATCACT	eekd$_{10}$kke	61	34052	34067	1351
548109	1959	1974	GCATCTGAGCTTTTCC	eekd$_{10}$kke	77	34058	34073	1352
548110	1960	1975	TGCATCTGAGCTTTTC	eekd$_{10}$kke	62	34059	34074	1353
548111	1963	1978	GACTGCATCTGAGCTT	eekd$_{10}$kke	53	34062	34077	1354
548112	1965	1980	GTGACTGCATCTGAGC	eekd$_{10}$kke	23	34064	34079	1355
548113	1966	1981	GGTGACTGCATCTGAG	eekd$_{10}$kke	56	34065	34080	1356
548114	1967	1982	TGGTGACTGCATCTGA	eekd$_{10}$kke	70	34066	34081	1357
548115	1972	1987	CATGCTGGTGACTGCA	eekd$_{10}$kke	76	34071	34086	1358
548116	1973	1988	TCATGCTGGTGACTGC	eekd$_{10}$kke	3	34072	34087	1359
548117	1974	1989	CTCATGCTGGTGACTG	eekd$_{10}$kke	73	34073	34088	1360

548118	1975	1990	TCTCATGCTGGTGACT	eekd$_{10}$kke	47	34074	34089	1361
548119	1984	1999	TGGACTGCTTCTCATG	eekd$_{10}$kke	25	34083	34098	1362
548121	1986	2001	TCTGGACTGCTTCTCA	eekd$_{10}$kke	64	34085	34100	1363
548122	1987	2002	CTCTGGACTGCTTCTC	eekd$_{10}$kke	55	34086	34101	1364
548123	1990	2005	AGACTCTGGACTGCTT	eekd$_{10}$kke	49	34089	34104	1365
548124	1991	2006	TAGACTCTGGACTGCT	eekd$_{10}$kke	51	34090	34105	1366
548125	1992	2007	CTAGACTCTGGACTGC	eekd$_{10}$kke	89	34091	34106	1367
548126	1995	2010	TGCCTAGACTCTGGAC	eekd$_{10}$kke	19	34094	34109	1368
548127	1996	2011	TTGCCTAGACTCTGGA	eekd$_{10}$kke	60	34095	34110	1369
548128	1997	2012	ATTGCCTAGACTCTGG	eekd$_{10}$kke	55	34096	34111	1370
548129	2022	2037	TTTGACTTGAACTCAG	eekd$_{10}$kke	35	34121	34136	1371
548130	2023	2038	ATTTGACTTGAACTCA	eekd$_{10}$kke	27	34122	34137	1372
548131	2024	2039	AATTTGACTTGAACTC	eekd$_{10}$kke	45	34123	34138	1373
548132	2025	2040	GAATTTGACTTGAACT	eekd$_{10}$kke	0	34124	34139	1374
548133	2026	2041	AGAATTTGACTTGAAC	eekd$_{10}$kke	23	34125	34140	1375
548134	2027	2042	CAGAATTTGACTTGAA	eekd$_{10}$kke	17	34126	34141	1376
548135	2028	2043	TCAGAATTTGACTTGA	eekd$_{10}$kke	46	34127	34142	1377
548136	2031	2046	GGCTCAGAATTTGACT	eekd$_{10}$kke	39	34130	34145	1378
548137	2032	2047	AGGCTCAGAATTTGAC	eekd$_{10}$kke	62	34131	34146	1379
548138	2036	2051	CCCCAGGCTCAGAATT	eekd$_{10}$kke	52	34135	34150	1380
548139	2047	2062	AGATGAGGACCCCCCA	eekd$_{10}$kke	56	34146	34161	1381
548140	2048	2063	CAGATGAGGACCCCCC	eekd$_{10}$kke	74	34147	34162	1382
548141	2049	2064	GCAGATGAGGACCCCC	eekd$_{10}$kke	66	34148	34163	1383
548142	2063	2078	ACTCTCCATGCTTTGC	eekd$_{10}$kke	44	34162	34177	1384
548143	2064	2079	CACTCTCCATGCTTTG	eekd$_{10}$kke	39	34163	34178	1385
548144	2068	2083	ATGCCACTCTCCATGC	eekd$_{10}$kke	52	34167	34182	1386
548145	2079	2094	ATGCAAAGAAGATGCC	eekd$_{10}$kke	63	34178	34193	1387
548146	2088	2103	GTCCTTAGGATGCAAA	eekd$_{10}$kke	68	34187	34202	1388
548147	2089	2104	CGTCCTTAGGATGCAA	eekd$_{10}$kke	81	34188	34203	1389
548148	2114	2129	GCAGCTCTGAGTGCAC	eekd$_{10}$kke	66	34213	34228	1390
548149	2127	2142	GACATTGTCCTCAGCA	eekd$_{10}$kke	39	34226	34241	1391
548150	2129	2144	CAGACATTGTCCTCAG	eekd$_{10}$kke	60	34228	34243	1392

Table 141

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	84	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	

						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
547843	384	399	CACTTATTTGATGACC	eekd$_{10}$kke	83	9918	9933	1393
547844	385	400	GCACTTATTTGATGAC	eekd$_{10}$kke	13	n/a	n/a	1394
547845	394	409	CGATGGCAAGCACTTA	eekd$_{10}$kke	0	n/a	n/a	1395
547846	395	410	TCGATGGCAAGCACTT	eekd$_{10}$kke	0	n/a	n/a	1396
547847	396	411	CTCGATGGCAAGCACT	eekd$_{10}$kke	46	n/a	n/a	1397
547848	400	415	ATGTCTCGATGGCAAG	eekd$_{10}$kke	93	12656	12671	1398
547849	401	416	AATGTCTCGATGGCAA	eekd$_{10}$kke	79	12657	12672	1399
547850	402	417	AAATGTCTCGATGGCA	eekd$_{10}$kke	51	12658	12673	1400
547851	403	418	TAAATGTCTCGATGGC	eekd$_{10}$kke	93	12659	12674	1401
547852	404	419	ATAAATGTCTCGATGG	eekd$_{10}$kke	67	12660	12675	1402
547853	405	420	TATAAATGTCTCGATG	eekd$_{10}$kke	0	12661	12676	1403
547854	416	431	ATCAACTCCTTTATAA	eekd$_{10}$kke	10	12672	12687	1404
547855	417	432	TATCAACTCCTTTATA	eekd$_{10}$kke	59	12673	12688	1405
547856	419	434	CATATCAACTCCTTTA	eekd$_{10}$kke	93	12675	12690	1406
547858	423	438	CTCTCATATCAACTCC	eekd$_{10}$kke	82	12679	12694	1407
547859	424	439	CCTCTCATATCAACTC	eekd$_{10}$kke	77	12680	12695	1408
547860	425	440	TCCTCTCATATCAACT	eekd$_{10}$kke	71	12681	12696	1409
547861	427	442	ACTCCTCTCATATCAA	eekd$_{10}$kke	0	12683	12698	1410
547862	428	443	GACTCCTCTCATATCA	eekd$_{10}$kke	22	12684	12699	1411
547863	429	444	TGACTCCTCTCATATC	eekd$_{10}$kke	73	12685	12700	1412
547864	430	445	TTGACTCCTCTCATAT	eekd$_{10}$kke	53	12686	12701	1413
547865	434	449	AAAATTGACTCCTCTC	eekd$_{10}$kke	3	12690	12705	1414
547866	436	451	TTAAAATTGACTCCTC	eekd$_{10}$kke	46	12692	12707	1415
547867	447	462	CCTTAGACACATTAAA	eekd$_{10}$kke	34	12703	12718	1416
547868	448	463	ACCTTAGACACATTAA	eekd$_{10}$kke	47	12704	12719	1417
547869	449	464	AACCTTAGACACATTA	eekd$_{10}$kke	45	12705	12720	1418
547870	451	466	CTAACCTTAGACACAT	eekd$_{10}$kke	89	12707	12722	1419

547871	452	467	GCTAACCTTAGACACA	eekd$_{10}$kke	96	12708	12723	1420
547872	453	468	TGCTAACCTTAGACAC	eekd$_{10}$kke	85	12709	12724	1421
547873	454	469	CTGCTAACCTTAGACA	eekd$_{10}$kke	77	12710	12725	1422
547874	455	470	ACTGCTAACCTTAGAC	eekd$_{10}$kke	70	12711	12726	1423
547875	456	471	CACTGCTAACCTTAGA	eekd$_{10}$kke	73	12712	12727	1424
547876	457	472	ACACTGCTAACCTTAG	eekd$_{10}$kke	78	12713	12728	1425
547877	458	473	AACACTGCTAACCTTA	eekd$_{10}$kke	81	12714	12729	1426
547879	460	475	TCAACACTGCTAACCT	eekd$_{10}$kke	69	12716	12731	1427
547880	461	476	TTCAACACTGCTAACC	eekd$_{10}$kke	69	12717	12732	1428
547881	465	480	ATTCTTCAACACTGCT	eekd$_{10}$kke	0	12721	12736	1429
547882	500	515	CTGGCAGCGAATGTTA	eekd$_{10}$kke	91	12756	12771	1430
547883	501	516	ACTGGCAGCGAATGTT	eekd$_{10}$kke	99	12757	12772	1431
547884	518	533	CGTGGCATATGAAAAA	eekd$_{10}$kke	87	12774	12789	1432
547885	539	554	CTCTGCCTTGTGAAAT	eekd$_{10}$kke	45	12795	12810	1433
547886	544	559	CGGTACTCTGCCTTGT	eekd$_{10}$kke	97	12800	12815	1434
547889	547	562	TTCCGGTACTCTGCCT	eekd$_{10}$kke	91	n/a	n/a	1435
547890	550	565	TTGTTCCGGTACTCTG	eekd$_{10}$kke	97	n/a	n/a	1436
547891	551	566	ATTGTTCCGGTACTCT	eekd$_{10}$kke	84	n/a	n/a	1437
547892	553	568	CAATTGTTCCGGTACT	eekd$_{10}$kke	29	n/a	n/a	1438
547893	554	569	GCAATTGTTCCGGTAC	eekd$_{10}$kke	81	n/a	n/a	1439
547894	555	570	GGCAATTGTTCCGGTA	eekd$_{10}$kke	92	n/a	n/a	1440
547898	563	578	CTTTAATAGGCAATTG	eekd$_{10}$kke	0	14134	14149	1441
547899	566	581	GTACTTTAATAGGCAA	eekd$_{10}$kke	49	14137	14152	1442
547900	567	582	TGTACTTTAATAGGCA	eekd$_{10}$kke	93	14138	14153	1443
547901	568	583	CTGTACTTTAATAGGC	eekd$_{10}$kke	77	14139	14154	1444
547902	569	584	ACTGTACTTTAATAGG	eekd$_{10}$kke	20	14140	14155	1445
547903	604	619	CTCAGCACCTTTATAG	eekd$_{10}$kke	62	14175	14190	1446
547904	605	620	ACTCAGCACCTTTATA	eekd$_{10}$kke	56	14176	14191	1447
547905	606	621	TACTCAGCACCTTTAT	eekd$_{10}$kke	20	14177	14192	1448
547906	607	622	TTACTCAGCACCTTTA	eekd$_{10}$kke	59	14178	14193	1449
547907	652	667	ATTTCTGAAAGGGCAC	eekd$_{10}$kke	27	14223	14238	1450
547908	654	669	CAATTTCTGAAAGGGC	eekd$_{10}$kke	94	14225	14240	1451
547909	655	670	CCAATTTCTGAAAGGG	eekd$_{10}$kke	82	14226	14241	1452
547910	656	671	ACCAATTTCTGAAAGG	eekd$_{10}$kke	26	14227	14242	1453
547911	661	676	TGGCAACCAATTTCTG	eekd$_{10}$kke	0	n/a	n/a	1454
547912	701	716	ATCCACATCTGAGAAC	eekd$_{10}$kke	23	26149	26164	1455
547913	706	721	GCAACATCCACATCTG	eekd$_{10}$kke	71	26154	26169	1456
547914	707	722	GGCAACATCCACATCT	eekd$_{10}$kke	74	26155	26170	1457
547915	708	723	TGGCAACATCCACATC	eekd$_{10}$kke	0	26156	26171	1458

547916	710	725	CCTGGCAACATCCACA	eekd$_{10}$kke	70	26158	26173	1459
547917	712	727	ACCCTGGCAACATCCA	eekd$_{10}$kke	33	26160	26175	1460
547918	713	728	AACCCTGGCAACATCC	eekd$_{10}$kke	1	26161	26176	1461
547919	714	729	GAACCCTGGCAACATC	eekd$_{10}$kke	41	26162	26177	1462

Table 142

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	62	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	88	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	

						15817 15889 15947	15832 15904 15962	
547751	7	22	TGAACGGTCTTCAAGC	eekd$_{10}$kke	0	3399	3414	1463
547753	8	23	ATGAACGGTCTTCAAG	eekd$_{10}$kke	3	3400	3415	1464
547755	13	28	TAAAAATGAACGGTCT	eekd$_{10}$kke	0	3405	3420	1465
547757	28	43	GAGTCTCTTGTCACTT	eekd$_{10}$kke	69	3420	3435	1466
547759	29	44	TGAGTCTCTTGTCACT	eekd$_{10}$kke	73	3421	3436	1467
547763	31	46	GGTGAGTCTCTTGTCA	eekd$_{10}$kke	66	3423	3438	1468
547765	32	47	AGGTGAGTCTCTTGTC	eekd$_{10}$kke	20	3424	3439	1469
547767	35	50	TGGAGGTGAGTCTCTT	eekd$_{10}$kke	74	3427	3442	1470
547769	36	51	TTGGAGGTGAGTCTCT	eekd$_{10}$kke	81	3428	3443	1471
547771	37	52	CTTGGAGGTGAGTCTC	eekd$_{10}$kke	60	3429	3444	1472
547773	38	53	TCTTGGAGGTGAGTCT	eekd$_{10}$kke	47	3430	3445	1473
547777	43	58	TTGCTTCTTGGAGGTG	eekd$_{10}$kke	69	3435	3450	1474
547779	44	59	ATTGCTTCTTGGAGGT	eekd$_{10}$kke	41	3436	3451	1475
547781	46	61	CAATTGCTTCTTGGAG	eekd$_{10}$kke	49	3438	3453	1476
547783	48	63	CACAATTGCTTCTTGG	eekd$_{10}$kke	48	3440	3455	1477
547784	72	87	GCTTGAATAAAATCAT	eekd$_{10}$kke	46	4071	4086	1478
547785	79	94	GTTGCTTGCTTGAATA	eekd$_{10}$kke	48	4078	4093	1479
547786	80	95	AGTTGCTTGCTTGAAT	eekd$_{10}$kke	44	4079	4094	1480
547787	81	96	AAGTTGCTTGCTTGAA	eekd$_{10}$kke	22	4080	4095	1481
547788	82	97	TAAGTTGCTTGCTTGA	eekd$_{10}$kke	49	4081	4096	1482
547789	86	101	GAAATAAGTTGCTTGC	eekd$_{10}$kke	20	4085	4100	1483
547790	87	102	TGAAATAAGTTGCTTG	eekd$_{10}$kke	23	4086	4101	1484
547791	106	121	ACTGTAGCAAACAAGG	eekd$_{10}$kke	49	4105	4120	1485
547792	116	131	TCCACAGGAAACTGTA	eekd$_{10}$kke	31	n/a	n/a	1486
547793	117	132	ATCCACAGGAAACTGT	eekd$_{10}$kke	16	n/a	n/a	1487
547794	136	151	TCATAGAGTTGAGTCA	eekd$_{10}$kke	49	8008	8023	1488
547795	155	170	ACCTCTGAAGAAGGCG	eekd$_{10}$kke	66	8027	8042	1489
547796	161	176	ATCCCCACCTCTGAAG	eekd$_{10}$kke	35	8033	8048	1490
547797	167	182	AGCTACATCCCCACCT	eekd$_{10}$kke	33	8039	8054	1491
547799	169	184	GAAGCTACATCCCCAC	eekd$_{10}$kke	41	8041	8056	1492
547800	174	189	ACATGGAAGCTACATC	eekd$_{10}$kke	20	8046	8061	1493
547801	175	190	TACATGGAAGCTACAT	eekd$_{10}$kke	11	8047	8062	1494
547802	176	191	GTACATGGAAGCTACA	eekd$_{10}$kke	41	8048	8063	1495
547803	177	192	TGTACATGGAAGCTAC	eekd$_{10}$kke	0	8049	8064	1496
547804	178	193	GTGTACATGGAAGCTA	eekd$_{10}$kke	22	8050	8065	1497
547805	180	195	GGGTGTACATGGAAGC	eekd$_{10}$kke	54	8052	8067	1498
547807	197	212	GCAGTATTGGGCATTT	eekd$_{10}$kke	75	8069	8084	1499
547808	203	218	CATCTGGCAGTATTGG	eekd$_{10}$kke	56	8075	8090	1500
547809	204	219	TCATCTGGCAGTATTG	eekd$_{10}$kke	33	8076	8091	1501
547810	206	221	CCTCATCTGGCAGTAT	eekd$_{10}$kke	60	8078	8093	1502

547811	207	222	ACCTCATCTGGCAGTA	eekd$_{10}$kke	49	8079	8094	1503
547812	211	226	GTGCACCTCATCTGGC	eekd$_{10}$kke	51	8083	8098	1504
547813	219	234	GGTGGAATGTGCACCT	eekd$_{10}$kke	34	8091	8106	1505
547814	220	235	GGGTGGAATGTGCACC	eekd$_{10}$kke	60	8092	8107	1506
547815	255	270	AACTTGCTGGAAGAAA	eekd$_{10}$kke	3	8127	8142	1507
547816	256	271	GAACTTGCTGGAAGAA	eekd$_{10}$kke	45	8128	8143	1508
547817	257	272	TGAACTTGCTGGAAGA	eekd$_{10}$kke	18	8129	8144	1509
547818	260	275	GATTGAACTTGCTGGA	eekd$_{10}$kke	4	8132	8147	1510
547819	264	279	CATTGATTGAACTTGC	eekd$_{10}$kke	11	8136	8151	1511
547820	265	280	TCATTGATTGAACTTG	eekd$_{10}$kke	0	8137	8152	1512
547821	282	297	CAAACCTTTTCTCCAT	eekd$_{10}$kke	44	n/a	n/a	1513
547822	287	302	GCAACCAAACCTTTTC	eekd$_{10}$kke	71	n/a	n/a	1514
547823	288	303	AGCAACCAAACCTTTT	eekd$_{10}$kke	51	n/a	n/a	1515
547824	331	346	CGATGTACTTTTGGCA	eekd$_{10}$kke	82	9865	9880	1516
547825	332	347	TCGATGTACTTTTGGC	eekd$_{10}$kke	59	9866	9881	1517
547826	333	348	TTCGATGTACTTTTGG	eekd$_{10}$kke	31	9867	9882	1518
547827	334	349	GTTCGATGTACTTTTG	eekd$_{10}$kke	47	9868	9883	1519
547828	337	352	CCTGTTCGATGTACTT	eekd$_{10}$kke	63	9871	9886	1520
547829	338	353	ACCTGTTCGATGTACT	eekd$_{10}$kke	59	9872	9887	1521
547830	340	355	GCACCTGTTCGATGTA	eekd$_{10}$kke	74	9874	9889	1522
547831	342	357	CTGCACCTGTTCGATG	eekd$_{10}$kke	49	9876	9891	1523
547832	343	358	ACTGCACCTGTTCGAT	eekd$_{10}$kke	59	9877	9892	1524
547833	344	359	AACTGCACCTGTTCGA	eekd$_{10}$kke	40	9878	9893	1525
547834	345	360	AAACTGCACCTGTTCG	eekd$_{10}$kke	63	9879	9894	1526
547835	349	364	CCAGAAACTGCACCTG	eekd$_{10}$kke	81	9883	9898	1527
547836	350	365	TCCAGAAACTGCACCT	eekd$_{10}$kke	50	9884	9899	1528
547837	352	367	TGTCCAGAAACTGCAC	eekd$_{10}$kke	51	9886	9901	1529
547838	362	377	CTTCAAGGAATGTCCA	eekd$_{10}$kke	45	9896	9911	1530
547839	363	378	GCTTCAAGGAATGTCC	eekd$_{10}$kke	35	9897	9912	1531
547840	365	380	TTGCTTCAAGGAATGT	eekd$_{10}$kke	36	9899	9914	1532
547841	369	384	CACATTGCTTCAAGGA	eekd$_{10}$kke	42	9903	9918	1533
547842	375	390	GATGACCACATTGCTT	eekd$_{10}$kke	10	9909	9924	1534

Table 143

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	75	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	

						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	91	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
547843	384	399	CACTTATTTGATGACC	eekd$_{10}$kke	83	9918	9933	1393
547844	385	400	GCACTTATTTGATGAC	eekd$_{10}$kke	76	n/a	n/a	1394
547845	394	409	CGATGGCAAGCACTTA	eekd$_{10}$kke	64	n/a	n/a	1395
547846	395	410	TCGATGGCAAGCACTT	eekd$_{10}$kke	42	n/a	n/a	1396
547847	396	411	CTCGATGGCAAGCACT	eekd$_{10}$kke	72	n/a	n/a	1397
547848	400	415	ATGTCTCGATGGCAAG	eekd$_{10}$kke	79	12656	12671	1398
547849	401	416	AATGTCTCGATGGCAA	eekd$_{10}$kke	90	12657	12672	1399
547850	402	417	AAATGTCTCGATGGCA	eekd$_{10}$kke	80	12658	12673	1400
547851	403	418	TAAATGTCTCGATGGC	eekd$_{10}$kke	84	12659	12674	1401
547852	404	419	ATAAATGTCTCGATGG	eekd$_{10}$kke	66	12660	12675	1402
547853	405	420	TATAAATGTCTCGATG	eekd$_{10}$kke	30	12661	12676	1403
547854	416	431	ATCAACTCCTTTATAA	eekd$_{10}$kke	9	12672	12687	1404

547855	417	432	TATCAACTCCTTTATA	eekd$_{10}$kke	38	12673	12688	1405
547856	419	434	CATATCAACTCCTTTA	eekd$_{10}$kke	51	12675	12690	1406
547857	421	436	CTCATATCAACTCCTT	eekd$_{10}$kke	84	12677	12692	1535
547858	423	438	CTCTCATATCAACTCC	eekd$_{10}$kke	76	12679	12694	1407
547859	424	439	CCTCTCATATCAACTC	eekd$_{10}$kke	88	12680	12695	1408
547860	425	440	TCCTCTCATATCAACT	eekd$_{10}$kke	70	12681	12696	1409
547861	427	442	ACTCCTCTCATATCAA	eekd$_{10}$kke	57	12683	12698	1410
547862	428	443	GACTCCTCTCATATCA	eekd$_{10}$kke	88	12684	12699	1411
547863	429	444	TGACTCCTCTCATATC	eekd$_{10}$kke	77	12685	12700	1412
547864	430	445	TTGACTCCTCTCATAT	eekd$_{10}$kke	73	12686	12701	1413
547865	434	449	AAAATTGACTCCTCTC	eekd$_{10}$kke	61	12690	12705	1414
547866	436	451	TTAAAATTGACTCCTC	eekd$_{10}$kke	40	12692	12707	1415
547867	447	462	CCTTAGACACATTAAA	eekd$_{10}$kke	53	12703	12718	1416
547868	448	463	ACCTTAGACACATTAA	eekd$_{10}$kke	71	12704	12719	1417
547869	449	464	AACCTTAGACACATTA	eekd$_{10}$kke	77	12705	12720	1418
547870	451	466	CTAACCTTAGACACAT	eekd$_{10}$kke	83	12707	12722	1419
547871	452	467	GCTAACCTTAGACACA	eekd$_{10}$kke	77	12708	12723	1420
547872	453	468	TGCTAACCTTAGACAC	eekd$_{10}$kke	73	12709	12724	1421
547873	454	469	CTGCTAACCTTAGACA	eekd$_{10}$kke	82	12710	12725	1422
547874	455	470	ACTGCTAACCTTAGAC	eekd$_{10}$kke	60	12711	12726	1423
547875	456	471	CACTGCTAACCTTAGA	eekd$_{10}$kke	57	12712	12727	1424
547876	457	472	ACACTGCTAACCTTAG	eekd$_{10}$kke	59	12713	12728	1425
547877	458	473	AACACTGCTAACCTTA	eekd$_{10}$kke	93	12714	12729	1426
547878	459	474	CAACACTGCTAACCTT	eekd$_{10}$kke	62	12715	12730	1536
547879	460	475	TCAACACTGCTAACCT	eekd$_{10}$kke	65	12716	12731	1427
547880	461	476	TTCAACACTGCTAACC	eekd$_{10}$kke	59	12717	12732	1428
547881	465	480	ATTCTTCAACACTGCT	eekd$_{10}$kke	50	12721	12736	1429
547882	500	515	CTGGCAGCGAATGTTA	eekd$_{10}$kke	96	12756	12771	1430
547883	501	516	ACTGGCAGCGAATGTT	eekd$_{10}$kke	0	12757	12772	1431
547884	518	533	CGTGGCATATGAAAAA	eekd$_{10}$kke	49	12774	12789	1432
547885	539	554	CTCTGCCTTGTGAAAT	eekd$_{10}$kke	57	12795	12810	1433
547886	544	559	CGGTACTCTGCCTTGT	eekd$_{10}$kke	89	12800	12815	1434
547887	545	560	CCGGTACTCTGCCTTG	eekd$_{10}$kke	99	12801	12816	1537
547888	546	561	TCCGGTACTCTGCCTT	eekd$_{10}$kke	99	n/a	n/a	1538
547889	547	562	TTCCGGTACTCTGCCT	eekd$_{10}$kke	97	n/a	n/a	1435
547890	550	565	TTGTTCCGGTACTCTG	eekd$_{10}$kke	90	n/a	n/a	1436
547891	551	566	ATTGTTCCGGTACTCT	eekd$_{10}$kke	88	n/a	n/a	1437
547892	553	568	CAATTGTTCCGGTACT	eekd$_{10}$kke	28	n/a	n/a	1438
547893	554	569	GCAATTGTTCCGGTAC	eekd$_{10}$kke	80	n/a	n/a	1439

547894	555	570	GGCAATTGTTCCGGTA	eekd$_{10}$kke	91	n/a	n/a	1440
547895	556	571	AGGCAATTGTTCCGGT	eekd$_{10}$kke	94	n/a	n/a	1539
547896	557	572	TAGGCAATTGTTCCGG	eekd$_{10}$kke	95	n/a	n/a	1540
547897	558	573	ATAGGCAATTGTTCCG	eekd$_{10}$kke	82	n/a	n/a	1541
547898	563	578	CTTTAATAGGCAATTG	eekd$_{10}$kke	28	14134	14149	1441
547899	566	581	GTACTTTAATAGGCAA	eekd$_{10}$kke	68	14137	14152	1442
547900	567	582	TGTACTTTAATAGGCA	eekd$_{10}$kke	68	14138	14153	1443
547901	568	583	CTGTACTTTAATAGGC	eekd$_{10}$kke	85	14139	14154	1444
547902	569	584	ACTGTACTTTAATAGG	eekd$_{10}$kke	33	14140	14155	1445
547903	604	619	CTCAGCACCTTTATAG	eekd$_{10}$kke	6	14175	14190	1446
547904	605	620	ACTCAGCACCTTTATA	eekd$_{10}$kke	41	14176	14191	1447
547905	606	621	TACTCAGCACCTTTAT	eekd$_{10}$kke	59	14177	14192	1448
547906	607	622	TTACTCAGCACCTTTA	eekd$_{10}$kke	70	14178	14193	1449
547907	652	667	ATTTCTGAAAGGGCAC	eekd$_{10}$kke	27	14223	14238	1450
547908	654	669	CAATTTCTGAAAGGGC	eekd$_{10}$kke	71	14225	14240	1451
547909	655	670	CCAATTTCTGAAAGGG	eekd$_{10}$kke	51	14226	14241	1452
547910	656	671	ACCAATTTCTGAAAGG	eekd$_{10}$kke	34	14227	14242	1453
547911	661	676	TGGCAACCAATTTCTG	eekd$_{10}$kke	15	n/a	n/a	1454
547912	701	716	ATCCACATCTGAGAAC	eekd$_{10}$kke	53	26149	26164	1455
547913	706	721	GCAACATCCACATCTG	eekd$_{10}$kke	61	26154	26169	1456
547914	707	722	GGCAACATCCACATCT	eekd$_{10}$kke	63	26155	26170	1457
547915	708	723	TGGCAACATCCACATC	eekd$_{10}$kke	62	26156	26171	1458
547916	710	725	CCTGGCAACATCCACA	eekd$_{10}$kke	56	26158	26173	1459
547917	712	727	ACCCTGGCAACATCCA	eekd$_{10}$kke	54	26160	26175	1460
547918	713	728	AACCCTGGCAACATCC	eekd$_{10}$kke	65	26161	26176	1461
547919	714	729	GAACCCTGGCAACATC	eekd$_{10}$kke	73	26162	26177	1462

Table 144

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	16	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	

						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	83	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
547920	716	731	GAGAACCCTGGCAACA	eekd$_{10}$kke	52	26164	26179	1542
547921	717	732	TGAGAACCCTGGCAAC	eekd$_{10}$kke	43	26165	26180	1543
547922	722	737	TGGAGTGAGAACCCTG	eekd$_{10}$kke	79	26170	26185	1544
547923	725	740	ATCTGGAGTGAGAACC	eekd$_{10}$kke	68	26173	26188	1545
547924	742	757	GTCCGACACACAAAAG	eekd$_{10}$kke	53	26190	26205	1546
547925	743	758	GGTCCGACACACAAAA	eekd$_{10}$kke	16	26191	26206	1547
547927	745	760	ATGGTCCGACACACAA	eekd$_{10}$kke	79	26193	26208	1548
547928	746	761	GATGGTCCGACACACA	eekd$_{10}$kke	70	26194	26209	1549
547929	747	762	AGATGGTCCGACACAC	eekd$_{10}$kke	65	26195	26210	1550
547930	757	772	TGATAGGTGCAGATGG	eekd$_{10}$kke	48	26205	26220	1551
547931	758	773	GTGATAGGTGCAGATG	eekd$_{10}$kke	58	26206	26221	1552
547932	804	819	CGATTTTCCATACATT	eekd$_{10}$kke	33	26252	26267	1553
547933	805	820	TCGATTTTCCATACAT	eekd$_{10}$kke	44	26253	26268	1554
547934	806	821	CTCGATTTTCCATACA	eekd$_{10}$kke	38	26254	26269	1555
547935	807	822	ACTCGATTTTCCATAC	eekd$_{10}$kke	27	26255	26270	1556

547936	808	823	GACTCGATTTTCCATA	eekd$_{10}$kke	44	26256	26271	1557
547937	811	826	TGTGACTCGATTTTCC	eekd$_{10}$kke	56	26259	26274	1558
547938	812	827	TTGTGACTCGATTTTC	eekd$_{10}$kke	56	26260	26275	1559
547939	813	828	TTTGTGACTCGATTTT	eekd$_{10}$kke	70	26261	26276	1560
547940	817	832	TTTCTTTGTGACTCGA	eekd$_{10}$kke	71	n/a	n/a	1561
547941	852	867	GTGTGCCACTTTCAGA	eekd$_{10}$kke	66	27116	27131	1562
547942	853	868	GGTGTGCCACTTTCAG	eekd$_{10}$kke	85	27117	27132	1563
547943	854	869	TGGTGTGCCACTTTCA	eekd$_{10}$kke	83	27118	27133	1564
547944	857	872	ACTTGGTGTGCCACTT	eekd$_{10}$kke	54	27121	27136	1565
547945	858	873	AACTTGGTGTGCCACT	eekd$_{10}$kke	62	27122	27137	1566
547946	859	874	GAACTTGGTGTGCCAC	eekd$_{10}$kke	81	27123	27138	1567
547947	860	875	GGAACTTGGTGTGCCA	eekd$_{10}$kke	80	27124	27139	1568
547948	861	876	AGGAACTTGGTGTGCC	eekd$_{10}$kke	77	27125	27140	1569
547949	880	895	GTGTTTTCTTGAGGAG	eekd$_{10}$kke	6	27144	27159	1570
547950	881	896	GGTGTTTTCTTGAGGA	eekd$_{10}$kke	49	27145	27160	1571
547951	887	902	AGATATGGTGTTTTCT	eekd$_{10}$kke	25	27151	27166	1572
547952	888	903	CAGATATGGTGTTTTC	eekd$_{10}$kke	46	27152	27167	1573
547953	895	910	CTATATCCAGATATGG	eekd$_{10}$kke	16	27159	27174	1574
547954	902	917	TAAAAGGCTATATCCA	eekd$_{10}$kke	36	27166	27181	1575
547956	904	919	GTTAAAAGGCTATATC	eekd$_{10}$kke	13	27168	27183	1576
547957	905	920	GGTTAAAAGGCTATAT	eekd$_{10}$kke	6	27169	27184	1577
547958	907	922	CAGGTTAAAAGGCTAT	eekd$_{10}$kke	57	27171	27186	1578
547959	908	923	GCAGGTTAAAAGGCTA	eekd$_{10}$kke	60	27172	27187	1579
547960	909	924	TGCAGGTTAAAAGGCT	eekd$_{10}$kke	40	27173	27188	1580
547961	910	925	TTGCAGGTTAAAAGGC	eekd$_{10}$kke	5	27174	27189	1581
547962	911	926	TTTGCAGGTTAAAAGG	eekd$_{10}$kke	16	27175	27190	1582
547963	927	942	GTTCAGGTAAAGTTCT	eekd$_{10}$kke	22	n/a	n/a	1583
547964	928	943	GGTTCAGGTAAAGTTC	eekd$_{10}$kke	0	n/a	n/a	1584
547965	929	944	GGGTTCAGGTAAAGTT	eekd$_{10}$kke	29	n/a	n/a	1585
547966	930	945	AGGGTTCAGGTAAAGT	eekd$_{10}$kke	13	n/a	n/a	1586
547967	933	948	GGCAGGGTTCAGGTAA	eekd$_{10}$kke	25	n/a	n/a	1587
547968	940	955	TTAGAATGGCAGGGTT	eekd$_{10}$kke	37	27362	27377	1588
547969	953	968	TCCCGGGTAAATTTTA	eekd$_{10}$kke	0	27375	27390	1589
547970	954	969	CTCCCGGGTAAATTTT	eekd$_{10}$kke	42	27376	27391	1590
547972	958	973	TCAACTCCCGGGTAAA	eekd$_{10}$kke	49	27380	27395	1591
547973	961	976	AAGTCAACTCCCGGGT	eekd$_{10}$kke	62	27383	27398	1592
547974	962	977	AAAGTCAACTCCCGGG	eekd$_{10}$kke	52	27384	27399	1593
547975	963	978	CAAAGTCAACTCCCGG	eekd$_{10}$kke	44	27385	27400	1594
547976	964	979	CCAAAGTCAACTCCCG	eekd$_{10}$kke	49	27386	27401	1595

547977	967	982	CCTCCAAAGTCAACTC	eekd$_{10}$kke	57	27389	27404	1596
547978	1014	1029	CTTGGCAAACATTCAC	eekd$_{10}$kke	71	27436	27451	1597
547979	1018	1033	GTCTCTTGGCAAACAT	eekd$_{10}$kke	77	27440	27455	1598
547980	1020	1035	AAGTCTCTTGGCAAAC	eekd$_{10}$kke	54	27442	27457	1599
547981	1029	1044	TCTTTGTGCAAGTCTC	eekd$_{10}$kke	76	27451	27466	1600
547982	1034	1049	AATCATCTTTGTGCAA	eekd$_{10}$kke	54	27456	27471	1601
547983	1035	1050	GAATCATCTTTGTGCA	eekd$_{10}$kke	56	27457	27472	1602
547984	1036	1051	CGAATCATCTTTGTGC	eekd$_{10}$kke	55	27458	27473	1603
547985	1037	1052	GCGAATCATCTTTGTG	eekd$_{10}$kke	63	27459	27474	1604
547986	1039	1054	CAGCGAATCATCTTTG	eekd$_{10}$kke	63	27461	27476	1605
547987	1040	1055	ACAGCGAATCATCTTT	eekd$_{10}$kke	64	27462	27477	1606
547988	1042	1057	TGACAGCGAATCATCT	eekd$_{10}$kke	56	27464	27479	1607
547989	1043	1058	CTGACAGCGAATCATC	eekd$_{10}$kke	66	27465	27480	1608
547990	1044	1059	ACTGACAGCGAATCAT	eekd$_{10}$kke	58	27466	27481	1609
547991	1077	1092	TACAGTCTTCTGGGAG	eekd$_{10}$kke	0	27499	27514	1610
547992	1080	1095	CCTTACAGTCTTCTGG	eekd$_{10}$kke	17	27502	27517	1611
547993	1113	1128	TAGATAATCTTAAGAA	eekd$_{10}$kke	26	27634	27649	1612
547994	1120	1135	CCATCCATAGATAATC	eekd$_{10}$kke	53	27641	27656	1613
547995	1149	1164	GTGTCCCATACGCAAT	eekd$_{10}$kke	64	27670	27685	1614
547996	1150	1165	TGTGTCCCATACGCAA	eekd$_{10}$kke	65	27671	27686	1615

Table 145

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	0	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	

						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	80	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
547997	1151	1166	TTGTGTCCCATACGCA	eekd$_{10}$kke	89	27672	27687	1616
547998	1152	1167	CTTGTGTCCCATACGC	eekd$_{10}$kke	82	27673	27688	1617
547999	1153	1168	CCTTGTGTCCCATACG	eekd$_{10}$kke	50	27674	27689	1618
548000	1154	1169	CCCTTGTGTCCCATAC	eekd$_{10}$kke	54	27675	27690	1619
548001	1163	1178	ACCAGAGCTCCCTTGT	eekd$_{10}$kke	64	27684	27699	1620
548002	1164	1179	AACCAGAGCTCCCTTG	eekd$_{10}$kke	56	27685	27700	1621
548003	1165	1180	TAACCAGAGCTCCCTT	eekd$_{10}$kke	66	27686	27701	1622
548004	1167	1182	AGTAACCAGAGCTCCC	eekd$_{10}$kke	80	27688	27703	1623
548005	1169	1184	AGAGTAACCAGAGCTC	eekd$_{10}$kke	77	27690	27705	1624
548006	1172	1187	CAAAGAGTAACCAGAG	eekd$_{10}$kke	54	27693	27708	1625
548007	1174	1189	CTCAAAGAGTAACCAG	eekd$_{10}$kke	70	27695	27710	1626
548008	1175	1190	TCTCAAAGAGTAACCA	eekd$_{10}$kke	71	27696	27711	1627
548009	1184	1199	GTTACACAATCTCAAA	eekd$_{10}$kke	47	27705	27720	1628
548010	1187	1202	AGTGTTACACAATCTC	eekd$_{10}$kke	80	27708	27723	1629
548011	1189	1204	CCAGTGTTACACAATC	eekd$_{10}$kke	14	27710	27725	1630
548012	1192	1207	TCCCCAGTGTTACACA	eekd$_{10}$kke	3	27713	27728	1631
548013	1193	1208	GTCCCCAGTGTTACAC	eekd$_{10}$kke	37	27714	27729	1632
548014	1194	1209	TGTCCCCAGTGTTACA	eekd$_{10}$kke	31	27715	27730	1633
548015	1195	1210	TTGTCCCCAGTGTTAC	eekd$_{10}$kke	50	27716	27731	1634
548016	1248	1263	AAGAGTTTGTTCCTCC	eekd$_{10}$kke	55	27924	27939	1635
548017	1252	1267	CAAGAAGAGTTTGTTC	eekd$_{10}$kke	3	27928	27943	1636

548018	1253	1268	CCAAGAAGAGTTTGTT	eekd$_{10}$kke	22	27929	27944	1637
548019	1255	1270	CCCCAAGAAGAGTTTG	eekd$_{10}$kke	24	27931	27946	1638
548020	1256	1271	TCCCCAAGAAGAGTTT	eekd$_{10}$kke	76	27932	27947	1639
548021	1261	1276	CACTCTCCCCAAGAAG	eekd$_{10}$kke	0	27937	27952	1640
548022	1262	1277	CCACTCTCCCCAAGAA	eekd$_{10}$kke	69	27938	27953	1641
548023	1290	1305	GCTTCACCTGCAGGCT	eekd$_{10}$kke	58	27966	27981	1642
548024	1297	1312	GCTGTCAGCTTCACCT	eekd$_{10}$kke	79	27973	27988	1643
548025	1300	1315	TGAGCTGTCAGCTTCA	eekd$_{10}$kke	66	27976	27991	1644
548026	1332	1347	GTCCTATGAGTGACCC	eekd$_{10}$kke	52	28008	28023	1645
548027	1334	1349	GTGTCCTATGAGTGAC	eekd$_{10}$kke	18	28010	28025	1646
548028	1335	1350	GGTGTCCTATGAGTGA	eekd$_{10}$kke	38	28011	28026	1647
548029	1336	1351	TGGTGTCCTATGAGTG	eekd$_{10}$kke	12	28012	28027	1648
548030	1337	1352	CTGGTGTCCTATGAGT	eekd$_{10}$kke	52	28013	28028	1649
548031	1397	1412	GATGCGCCAAACATCC	eekd$_{10}$kke	73	30475	30490	1650
548032	1398	1413	AGATGCGCCAAACATC	eekd$_{10}$kke	51	30476	30491	1651
548034	1400	1415	ATAGATGCGCCAAACA	eekd$_{10}$kke	31	30478	30493	1652
548035	1404	1419	CACTATAGATGCGCCA	eekd$_{10}$kke	44	30482	30497	1653
548036	1405	1420	CCACTATAGATGCGCC	eekd$_{10}$kke	74	30483	30498	1654
548037	1427	1442	AATGTCTGACAGATTT	eekd$_{10}$kke	70	30505	30520	1655
548038	1428	1443	TAATGTCTGACAGATT	eekd$_{10}$kke	67	30506	30521	1656
548039	1445	1460	GAAAGGTGTATCTTTT	eekd$_{10}$kke	29	30523	30538	1657
548040	1449	1464	GTGAGAAAGGTGTATC	eekd$_{10}$kke	62	30527	30542	1658
548041	1450	1465	TGTGAGAAAGGTGTAT	eekd$_{10}$kke	64	30528	30543	1659
548042	1452	1467	TTTGTGAGAAAGGTGT	eekd$_{10}$kke	63	30530	30545	1660
548043	1453	1468	ATTTGTGAGAAAGGTG	eekd$_{10}$kke	76	30531	30546	1661
548044	1474	1489	TGGTGAATAATAATCT	eekd$_{10}$kke	12	30552	30567	1662
548045	1483	1498	TTATAGTTTTGGTGAA	eekd$_{10}$kke	0	30561	30576	1663
548046	1506	1521	TATCATGATTCCCTTC	eekd$_{10}$kke	84	30584	30599	1664
548047	1508	1523	GATATCATGATTCCCT	eekd$_{10}$kke	83	30586	30601	1665
548048	1509	1524	CGATATCATGATTCCC	eekd$_{10}$kke	84	30587	30602	1666
548049	1510	1525	GCGATATCATGATTCC	eekd$_{10}$kke	62	30588	30603	1667
548050	1512	1527	AGGCGATATCATGATT	eekd$_{10}$kke	37	30590	30605	1668
548051	1513	1528	AAGGCGATATCATGAT	eekd$_{10}$kke	61	30591	30606	1669
548052	1535	1550	CAAAGGAGCCTGGAGT	eekd$_{10}$kke	43	30613	30628	1670
548053	1538	1553	ATTCAAAGGAGCCTGG	eekd$_{10}$kke	36	30616	30631	1671
548054	1539	1554	AATTCAAAGGAGCCTG	eekd$_{10}$kke	45	30617	30632	1672
548055	1541	1556	GTAATTCAAAGGAGCC	eekd$_{10}$kke	78	30619	30634	1673
548056	1543	1558	GTGTAATTCAAAGGAG	eekd$_{10}$kke	40	30621	30636	1674
548057	1564	1579	CATATTGGTTTTTGGA	eekd$_{10}$kke	49	31870	31885	1675

548058	1565	1580	GCATATTGGTTTTTGG	eekd$_{10}$kke	71	31871	31886	1676
548059	1568	1583	TAGGCATATTGGTTTT	eekd$_{10}$kke	50	31874	31889	1677
548060	1588	1603	CTTGTGTCACCTTTGG	eekd$_{10}$kke	76	31894	31909	1678
548061	1589	1604	GCTTGTGTCACCTTTG	eekd$_{10}$kke	86	31895	31910	1679
548062	1598	1613	ATAAATTGTGCTTGTG	eekd$_{10}$kke	19	31904	31919	1680
548063	1600	1615	GTATAAATTGTGCTTG	eekd$_{10}$kke	35	31906	31921	1681
548064	1602	1617	TGGTATAAATTGTGCT	eekd$_{10}$kke	54	31908	31923	1682
548065	1603	1618	TTGGTATAAATTGTGC	eekd$_{10}$kke	22	31909	31924	1683
548067	1606	1621	CAGTTGGTATAAATTG	eekd$_{10}$kke	18	31912	31927	1684
548068	1609	1624	CAACAGTTGGTATAAA	eekd$_{10}$kke	0	31915	31930	1685
548069	1610	1625	CCAACAGTTGGTATAA	eekd$_{10}$kke	57	31916	31931	1686
548070	1611	1626	CCCAACAGTTGGTATA	eekd$_{10}$kke	85	31917	31932	1687
548071	1629	1644	AGAAGCCCCATCCGGT	eekd$_{10}$kke	55	31935	31950	1688
548072	1640	1655	TTTCTCCTTCGAGAAG	eekd$_{10}$kke	33	31946	31961	1689
548073	1641	1656	CTTTCTCCTTCGAGAA	eekd$_{10}$kke	24	31947	31962	1690

Table 146

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	19	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	66	14746	14761	1267
						14817	14832	

						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548151	2139	2154	GGGCTTCAGCCAGACA	eekd$_{10}$kke	35	34238	34253	1691
548152	2140	2155	CGGGCTTCAGCCAGAC	eekd$_{10}$kke	32	34239	34254	1692
548153	2149	2164	TGCTGAAAGCGGGCTT	eekd$_{10}$kke	44	34248	34263	1693
548154	2150	2165	GTGCTGAAAGCGGGCT	eekd$_{10}$kke	7	34249	34264	1694
548155	2151	2166	CGTGCTGAAAGCGGGC	eekd$_{10}$kke	76	34250	34265	1695
548156	2168	2183	TCAGCCCCTGGTTACG	eekd$_{10}$kke	0	34267	34282	1696
548157	2172	2187	ATTGTCAGCCCCTGGT	eekd$_{10}$kke	7	34271	34286	1697
548158	2174	2189	GCATTGTCAGCCCCTG	eekd$_{10}$kke	18	34273	34288	1698
548159	2175	2190	CGCATTGTCAGCCCCT	eekd$_{10}$kke	59	34274	34289	1699
548160	2176	2191	TCGCATTGTCAGCCCC	eekd$_{10}$kke	60	34275	34290	1700
548161	2177	2192	CTCGCATTGTCAGCCC	eekd$_{10}$kke	59	34276	34291	1701
548162	2178	2193	CCTCGCATTGTCAGCC	eekd$_{10}$kke	25	34277	34292	1702
548163	2179	2194	ACCTCGCATTGTCAGC	eekd$_{10}$kke	46	34278	34293	1703
548164	2180	2195	GACCTCGCATTGTCAG	eekd$_{10}$kke	40	34279	34294	1704
548165	2181	2196	CGACCTCGCATTGTCA	eekd$_{10}$kke	53	34280	34295	1705
548166	2182	2197	GCGACCTCGCATTGTC	eekd$_{10}$kke	0	34281	34296	1706
548167	2183	2198	TGCGACCTCGCATTGT	eekd$_{10}$kke	36	34282	34297	1707
548168	2184	2199	TTGCGACCTCGCATTG	eekd$_{10}$kke	61	34283	34298	1708
548169	2185	2200	GTTGCGACCTCGCATT	eekd$_{10}$kke	7	34284	34299	1709
548170	2186	2201	AGTTGCGACCTCGCAT	eekd$_{10}$kke	68	34285	34300	1710
548171	2187	2202	CAGTTGCGACCTCGCA	eekd$_{10}$kke	47	34286	34301	1711
548172	2188	2203	TCAGTTGCGACCTCGC	eekd$_{10}$kke	0	34287	34302	1712
548173	2189	2204	CTCAGTTGCGACCTCG	eekd$_{10}$kke	51	34288	34303	1713
548174	2190	2205	TCTCAGTTGCGACCTC	eekd$_{10}$kke	68	34289	34304	1714
548175	2191	2206	ATCTCAGTTGCGACCT	eekd$_{10}$kke	0	34290	34305	1715

548176	2192	2207	GATCTCAGTTGCGACC	eekd$_{10}$kke	38	34291	34306	1716
548177	2193	2208	AGATCTCAGTTGCGAC	eekd$_{10}$kke	45	34292	34307	1717
548178	2194	2209	GAGATCTCAGTTGCGA	eekd$_{10}$kke	54	34293	34308	1718
548179	2195	2210	GGAGATCTCAGTTGCG	eekd$_{10}$kke	52	34294	34309	1719
548180	2199	2214	TCATGGAGATCTCAGT	eekd$_{10}$kke	79	34298	34313	1720
548181	2200	2215	GTCATGGAGATCTCAG	eekd$_{10}$kke	55	34299	34314	1721
548182	2201	2216	AGTCATGGAGATCTCA	eekd$_{10}$kke	55	34300	34315	1722
548183	2202	2217	CAGTCATGGAGATCTC	eekd$_{10}$kke	43	34301	34316	1723
548184	2203	2218	ACAGTCATGGAGATCT	eekd$_{10}$kke	73	34302	34317	1724
548185	2208	2223	AACACACAGTCATGGA	eekd$_{10}$kke	23	34307	34322	1725
548186	2209	2224	CAACACACAGTCATGG	eekd$_{10}$kke	0	34308	34323	1726
548187	n/a	n/a	CATCCTATCCGTGTTC	eekd$_{10}$kke	33	3279	3294	1727
548189	n/a	n/a	CATGAACATCCTATCC	eekd$_{10}$kke	24	3285	3300	1728
548190	n/a	n/a	TATTCCATGAACATCC	eekd$_{10}$kke	43	3290	3305	1729
548191	n/a	n/a	GTCAACATATTCCATG	eekd$_{10}$kke	0	3297	3312	1730
548192	n/a	n/a	CCTGTCAACATATTCC	eekd$_{10}$kke	65	3300	3315	1731
548193	n/a	n/a	TGTCCTGTCAACATAT	eekd$_{10}$kke	58	3303	3318	1732
548194	n/a	n/a	GCCAACAGTTTCAACT	eekd$_{10}$kke	61	3322	3337	1733
548195	n/a	n/a	TTCTGCCAACAGTTTC	eekd$_{10}$kke	84	3326	3341	1734
548196	n/a	n/a	CAATATTGACTTTGGG	eekd$_{10}$kke	6	3343	3358	1735
548197	n/a	n/a	TGCTTGGCTTCAATAT	eekd$_{10}$kke	68	3353	3368	1736
548198	n/a	n/a	ACTGCAGGCAATATTT	eekd$_{10}$kke	49	3369	3384	1737
548199	n/a	n/a	GCACTGCAGGCAATAT	eekd$_{10}$kke	24	3371	3386	1738
548200	n/a	n/a	CTAATGTGGCACTGCA	eekd$_{10}$kke	19	3379	3394	1739
548201	n/a	n/a	TGTTCTAATGTGGCAC	eekd$_{10}$kke	67	3383	3398	1740
548202	n/a	n/a	GCTGTTCTAATGTGGC	eekd$_{10}$kke	9	3385	3400	1741
548203	n/a	n/a	TGACTAGTGAATGGCT	eekd$_{10}$kke	73	2280	2295	1742
548204	n/a	n/a	TCTGACTAGTGAATGG	eekd$_{10}$kke	25	2282	2297	1743
548205	n/a	n/a	TCAATCTGACTAGTGA	eekd$_{10}$kke	14	2286	2301	1744
548206	n/a	n/a	GGTCAATCTGACTAGT	eekd$_{10}$kke	45	2288	2303	1745
548207	n/a	n/a	CTGGTCAATCTGACTA	eekd$_{10}$kke	60	2290	2305	1746
548208	n/a	n/a	CTCTGGTCAATCTGAC	eekd$_{10}$kke	19	2292	2307	1747
548209	n/a	n/a	CAATCTCTGGTCAATC	eekd$_{10}$kke	57	2296	2311	1748
548210	n/a	n/a	CAACAATCTCTGGTCA	eekd$_{10}$kke	55	2299	2314	1749
548211	n/a	n/a	ACCAACAATCTCTGGT	eekd$_{10}$kke	51	2301	2316	1750
548212	n/a	n/a	AGCCCACCAACAATCT	eekd$_{10}$kke	44	2306	2321	1751
548213	n/a	n/a	GACAGCCCACCAACAA	eekd$_{10}$kke	70	2309	2324	1752
548214	n/a	n/a	CAGACAGCCCACCAAC	eekd$_{10}$kke	55	2311	2326	1753
548215	n/a	n/a	GCATAGACCCCAACAG	eekd$_{10}$kke	61	2324	2339	1754

548216	n/a	n/a	GTGCATAGACCCCAAC	eekd$_{10}$kke	45	2326	2341	1755
548217	n/a	n/a	CTGTGCATAGACCCCA	eekd$_{10}$kke	69	2328	2343	1756
548218	n/a	n/a	TCCTGTGCATAGACCC	eekd$_{10}$kke	59	2330	2345	1757
548219	n/a	n/a	GAAATCCTGTGCATAG	eekd$_{10}$kke	8	2334	2349	1758
548220	n/a	n/a	GCAGAAATCCTGTGCA	eekd$_{10}$kke	69	2337	2352	1759
548221	n/a	n/a	ACTCCAGCAGAAATCC	eekd$_{10}$kke	49	2343	2358	1760
548222	n/a	n/a	AATCATGCCTTGTGGG	eekd$_{10}$kke	32	4765	4780	1761
548223	n/a	n/a	TAGACCCAGAATCATG	eekd$_{10}$kke	50	4774	4789	1762
548224	n/a	n/a	CCATAGACCCAGAATC	eekd$_{10}$kke	20	4777	4792	1763
548225	n/a	n/a	AGTCACCATAGACCCA	eekd$_{10}$kke	48	4782	4797	1764
548226	n/a	n/a	TAAGTCACCATAGACC	eekd$_{10}$kke	39	4784	4799	1765
548227	n/a	n/a	GTGGCCCTCTTAAGTC	eekd$_{10}$kke	0	4794	4809	1766

Table 147

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	42	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	80	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	

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						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548228	n/a	n/a	GTTGTGTGGCCCTCTT	eekd$_{10}$kke	37	4799	4814	1767
548229	n/a	n/a	CATTGTTGTGTGGCCC	eekd$_{10}$kke	31	4803	4818	1768
548230	n/a	n/a	TACTCATTGTTGTGTG	eekd$_{10}$kke	10	4807	4822	1769
548231	n/a	n/a	AATACTCATTGTTGTG	eekd$_{10}$kke	11	4809	4824	1770
548232	n/a	n/a	GCCATACATCTGAGGA	eekd$_{10}$kke	3	4831	4846	1771
548233	n/a	n/a	ATTGTAGCCATACATC	eekd$_{10}$kke	38	4837	4852	1772
548234	n/a	n/a	TTATTGTAGCCATACA	eekd$_{10}$kke	17	4839	4854	1773
548235	n/a	n/a	TCTAGATGACCTGAAG	eekd$_{10}$kke	0	18147	18162	1774
548236	n/a	n/a	TACATCTAGATGACCT	eekd$_{10}$kke	37	18151	18166	1775
548237	n/a	n/a	GTATACATCTAGATGA	eekd$_{10}$kke	22	18154	18169	1776
548238	n/a	n/a	ACTCGCCTTTGTGACT	eekd$_{10}$kke	31	26268	26283	1777
548239	n/a	n/a	TACTCGCCTTTGTGAC	eekd$_{10}$kke	18	26269	26284	1778
548240	n/a	n/a	ATACTCGCCTTTGTGA	eekd$_{10}$kke	3	26270	26285	1779
						26301	26316	
548241	n/a	n/a	CATACTCGCCTTTGTG	eekd$_{10}$kke	1	26271	26286	1780
						26302	26317	
548242	n/a	n/a	GCATACTCGCCTTTGT	eekd$_{10}$kke	25	26272	26287	1781
						26303	26318	
548243	n/a	n/a	ATGCATACTCGCCTTT	eekd$_{10}$kke	0	26274	26289	1782
						26305	26320	
548244	n/a	n/a	CATGCATACTCGCCTT	eekd$_{10}$kke	51	26275	26290	1783
						26306	26321	
548245	n/a	n/a	CCATGCATACTCGCCT	eekd$_{10}$kke	31	26276	26291	1784
						26307	26322	
548246	n/a	n/a	TTCCATGCATACTCGC	eekd$_{10}$kke	46	26278	26293	1785
548247	n/a	n/a	CGATTTTCCATGCATA	eekd$_{10}$kke	56	26283	26298	1786
548248	n/a	n/a	TGCGATTTTCCATGCA	eekd$_{10}$kke	13	26285	26300	1787
548249	n/a	n/a	TGTGATGCGATTTTCC	eekd$_{10}$kke	22	26290	26305	1788

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548250	n/a	n/a	CTTTGTGATGCGATTT	eekd$_{10}$kke	0	26293	26308	1789
548251	n/a	n/a	GCCTTTGTGATGCGAT	eekd$_{10}$kke	13	26295	26310	1790
548252	n/a	n/a	ACTCGCCTTTGTGATG	eekd$_{10}$kke	33	26299	26314	1791
548253	n/a	n/a	TACTCGCCTTTGTGAT	eekd$_{10}$kke	8	26300	26315	1792
548254	n/a	n/a	CCCATGCATACTCGCC	eekd$_{10}$kke	39	26308	26323	1793
548255	n/a	n/a	CCCCATGCATACTCGC	eekd$_{10}$kke	38	26309	26324	1794
548256	n/a	n/a	GCTCCCCATGCATACT	eekd$_{10}$kke	25	26312	26327	1795
548257	n/a	n/a	AGTGCTCCCCATGCAT	eekd$_{10}$kke	2	26315	26330	1796
548258	n/a	n/a	CAAGTGCTCCCCATGC	eekd$_{10}$kke	0	26317	26332	1797
548259	n/a	n/a	GTGATGAAAGTACAGC	eekd$_{10}$kke	45	26335	26350	1798
548260	n/a	n/a	AGGAGTTTGTCAGAAC	eekd$_{10}$kke	28	3210	3225	1799
548261	n/a	n/a	TTCAGGGAGTGATGTC	eekd$_{10}$kke	36	3241	3256	1800
548262	n/a	n/a	CCTATCCGTGTTCAGC	eekd$_{10}$kke	73	3276	3291	1801
548263	n/a	n/a	CTCTACATACTCAGGA	eekd$_{10}$kke	62	3561	3576	1802
548264	n/a	n/a	CAGTCCAAAAATCCCT	eekd$_{10}$kke	60	3701	3716	1803
548265	n/a	n/a	CCTCTTGATTTGGGCA	eekd$_{10}$kke	85	3749	3764	1804
548266	n/a	n/a	TTGGCCAACTCTGTGG	eekd$_{10}$kke	44	3816	3831	1805
548267	n/a	n/a	GACCTCCAGACTACTG	eekd$_{10}$kke	34	3848	3863	1806
548268	n/a	n/a	TGTGTCTAGGGAGTTG	eekd$_{10}$kke	52	3898	3913	1807
548269	n/a	n/a	AGCACACAATTACTGG	eekd$_{10}$kke	62	3946	3961	1808
548270	n/a	n/a	CTGCTGGTTTTAGACC	eekd$_{10}$kke	28	4029	4044	1809
548271	n/a	n/a	TTCACTTACCACAGGA	eekd$_{10}$kke	56	4122	4137	1810
548272	n/a	n/a	GGTGCCACTTGCTTGG	eekd$_{10}$kke	54	4178	4193	1811
548273	n/a	n/a	AATCTCCACCCCCGAA	eekd$_{10}$kke	5	4224	4239	1812
548274	n/a	n/a	TACCTGACAAGTGGTC	eekd$_{10}$kke	0	4287	4302	1813
548275	n/a	n/a	GTCCCAAGACATTCCT	eekd$_{10}$kke	40	4350	4365	1814
548276	n/a	n/a	CAGAGTGTCATCTGCG	eekd$_{10}$kke	49	4389	4404	1815
548277	n/a	n/a	GGATTGGACCCAGACA	eekd$_{10}$kke	57	4511	4526	1816
548278	n/a	n/a	GGTTCCCTAGCGGTCC	eekd$_{10}$kke	74	4564	4579	1817
548279	n/a	n/a	CACCTAGAACTATCCA	eekd$_{10}$kke	39	4632	4647	1818
548280	n/a	n/a	CTCCCTCTGTAATGAT	eekd$_{10}$kke	43	4736	4751	1819
548281	n/a	n/a	GGTTGAGGGACAGACA	eekd$_{10}$kke	0	4944	4959	1820
548282	n/a	n/a	GTGGGTTTGCACATGG	eekd$_{10}$kke	73	4992	5007	1821
548283	n/a	n/a	GGCTTATGCTCCTTCT	eekd$_{10}$kke	56	5017	5032	1822
548284	n/a	n/a	CCCCCTGTAGTTGGCT	eekd$_{10}$kke	35	5051	5066	1823
548285	n/a	n/a	GCTTACTTACATCCCT	eekd$_{10}$kke	52	5132	5147	1824
548286	n/a	n/a	GGGACTACATGCAATA	eekd$_{10}$kke	47	5166	5181	1825
548287	n/a	n/a	GTCAAAGAGTGTCCAC	eekd$_{10}$kke	38	5283	5298	1826
548288	n/a	n/a	GAATAGCAAGCTCCAA	eekd$_{10}$kke	64	5348	5363	1827

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548289	n/a	n/a	CATGATACCACACCAC	eekd$_{10}$kke	28	5484	5499	1828
548290	n/a	n/a	GAGCACTCTTATTAGC	eekd$_{10}$kke	31	5546	5561	1829
548291	n/a	n/a	CCTGTTAGAGTTGGCC	eekd$_{10}$kke	35	5576	5591	1830
548292	n/a	n/a	AGGACACTGTTTCCAG	eekd$_{10}$kke	38	5627	5642	1831
548293	n/a	n/a	GTCACCAGAACCACAT	eekd$_{10}$kke	44	5683	5698	1832
548294	n/a	n/a	GTGTGCACTTTCTGGT	eekd$_{10}$kke	33	5716	5731	1833
548295	n/a	n/a	CTCTGATTGGGTCACC	eekd$_{10}$kke	26	5746	5761	1834
548296	n/a	n/a	ACCAACAACTCAGGCC	eekd$_{10}$kke	34	5858	5873	1835
548297	n/a	n/a	ACTCTCAAGCTCCACG	eekd$_{10}$kke	32	5889	5904	1836
548298	n/a	n/a	GGACAATATGTCTCCT	eekd$_{10}$kke	0	5935	5950	1837
548299	n/a	n/a	CATTGTGCTCAACTGA	eekd$_{10}$kke	35	5961	5976	1838
548300	n/a	n/a	GCCCATGGTGAATCTG	eekd$_{10}$kke	53	5995	6010	1839
548301	n/a	n/a	CCTAGTACAAAGTGGC	eekd$_{10}$kke	65	6050	6065	1840
548302	n/a	n/a	GCCATTTTATCCCTGA	eekd$_{10}$kke	71	6134	6149	1841
548303	n/a	n/a	GGGCCCCCATGTCCAT	eekd$_{10}$kke	0	6336	6351	1842

Table 148

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	72	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	67	14746	14761	1267
						14817	14832	

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						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548305	n/a	n/a	GTTCTTGCTTATCCTC	eekd$_{10}$kke	55	6484	6499	1843
548306	n/a	n/a	ATGTGACAGTCAGGGA	eekd$_{10}$kke	8	6559	6574	1844
548307	n/a	n/a	TTCTGCAACTGAGCCT	eekd$_{10}$kke	6	6587	6602	1845
548308	n/a	n/a	AATGGCAGGTCCTGGC	eekd$_{10}$kke	9	6616	6631	1846
548309	n/a	n/a	AGACAGTTGGTGGTTT	eekd$_{10}$kke	41	6700	6715	1847
548310	n/a	n/a	GAGGAGTTGGTTTAGT	eekd$_{10}$kke	0	6750	6765	1848
548311	n/a	n/a	TGACCACCTCTCGGGT	eekd$_{10}$kke	10	6860	6875	1849
548312	n/a	n/a	ATTTGGCCCTGAGCCC	eekd$_{10}$kke	0	6935	6950	1850
548313	n/a	n/a	GCCTTTGAGGGAGTGG	eekd$_{10}$kke	35	7024	7039	1851
548314	n/a	n/a	ACAACCTGTCCATTCC	eekd$_{10}$kke	43	7087	7102	1852
548315	n/a	n/a	GTTGTCAACTGGGACC	eekd$_{10}$kke	14	7125	7140	1853
548316	n/a	n/a	CTGTTCAGGTAGCACA	eekd$_{10}$kke	64	7150	7165	1854
548317	n/a	n/a	CCGGGAAAGACTGTCT	eekd$_{10}$kke	42	7190	7205	1855
548318	n/a	n/a	ACTGCACCCCACATAT	eekd$_{10}$kke	18	7257	7272	1856
548319	n/a	n/a	CCTCATCTCAGTATGA	eekd$_{10}$kke	26	7398	7413	1857
548320	n/a	n/a	GCACACAGACTTGCCC	eekd$_{10}$kke	0	7508	7523	1858
548321	n/a	n/a	CTGCATCTGGACTATG	eekd$_{10}$kke	38	7559	7574	1859
548322	n/a	n/a	AGGGAAATTAGAGGCA	eekd$_{10}$kke	38	7586	7601	1860
548323	n/a	n/a	CTGTTGCCTGACATGC	eekd$_{10}$kke	43	7696	7711	1861
548324	n/a	n/a	ACATAAATTCCCCACA	eekd$_{10}$kke	29	7741	7756	1862
548325	n/a	n/a	CCCACTGACTGACTAC	eekd$_{10}$kke	27	7906	7921	1863
548326	n/a	n/a	TCCTGTGACAGAACCA	eekd$_{10}$kke	27	7988	8003	1864
548327	n/a	n/a	CTACACCTTTCTGCAC	eekd$_{10}$kke	6	8221	8236	1865
548328	n/a	n/a	GGTCCTTGAACCCCGT	eekd$_{10}$kke	68	8260	8275	1866
548329	n/a	n/a	AGCAGATCTGGGTTGT	eekd$_{10}$kke	59	8328	8343	1867

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548330	n/a	n/a	GACTAGCTTCTACTAC	eekd$_{10}$kke	34	8404	8419	1868
548331	n/a	n/a	ACAATCCCTTAGCCCA	eekd$_{10}$kke	73	8457	8472	1869
548332	n/a	n/a	GATGAAATGTGCACCT	eekd$_{10}$kke	46	8491	8506	1870
548333	n/a	n/a	GACTGTGCTATCCGCT	eekd$_{10}$kke	58	8550	8565	1871
548334	n/a	n/a	GCTCACTATAGGCCCC	eekd$_{10}$kke	69	8656	8671	1872
548335	n/a	n/a	TAGCATCATGCCACAG	eekd$_{10}$kke	51	8684	8699	1873
548336	n/a	n/a	GCACATTAGGAGGTAG	eekd$_{10}$kke	1	9039	9054	1874
548337	n/a	n/a	TACCGCTGGGTGCGGT	eekd$_{10}$kke	10	9075	9090	1875
548338	n/a	n/a	ATGAAACTGTGGCTCG	eekd$_{10}$kke	80	9131	9146	1876
548339	n/a	n/a	ACATGTGGGATCAGAG	eekd$_{10}$kke	37	9275	9290	1877
548340	n/a	n/a	GATGATCCTCACATAC	eekd$_{10}$kke	35	9316	9331	1878
548341	n/a	n/a	TAGAACCTTCCTCCAC	eekd$_{10}$kke	30	9341	9356	1879
548342	n/a	n/a	GGAAGACTTCCCTCTG	eekd$_{10}$kke	0	9403	9418	1880
548343	n/a	n/a	TAGTGATAAGAGCTGG	eekd$_{10}$kke	78	9472	9487	1881
548344	n/a	n/a	GGCAACTATGTTCTCA	eekd$_{10}$kke	76	9536	9551	1882
548345	n/a	n/a	CTAACTCCATCACTGC	eekd$_{10}$kke	55	9637	9652	1883
548346	n/a	n/a	TCCCCAATACTTGCTG	eekd$_{10}$kke	35	9696	9711	1884
548347	n/a	n/a	GCTGTTCTAAGCGAGA	eekd$_{10}$kke	31	9976	9991	1885
548348	n/a	n/a	TGAGTGATGCCTTCCA	eekd$_{10}$kke	82	10024	10039	1886
548349	n/a	n/a	TCCAGAATACTGCCCC	eekd$_{10}$kke	61	10054	10069	1887
548350	n/a	n/a	GCGCTAACCTCATAAA	eekd$_{10}$kke	29	10148	10163	1888
548351	n/a	n/a	CTGGAAACGAGACACA	eekd$_{10}$kke	33	10201	10216	1889
548352	n/a	n/a	GAGAGAGATGTTCCCT	eekd$_{10}$kke	47	10240	10255	1890
548353	n/a	n/a	CTGCTGGTTGAGAATC	eekd$_{10}$kke	48	10287	10302	1891
548354	n/a	n/a	ATGTCCCCAGTGGAAG	eekd$_{10}$kke	41	10314	10329	1892
548355	n/a	n/a	GCATCCTCCCTAGTTG	eekd$_{10}$kke	47	10362	10377	1893
548356	n/a	n/a	TGTTGGTCAGCATTCA	eekd$_{10}$kke	63	10411	10426	1894
548357	n/a	n/a	GACGACTGCCCTGTGC	eekd$_{10}$kke	69	10436	10451	1895
548358	n/a	n/a	ATTTGGGCCTAGTGGT	eekd$_{10}$kke	0	10515	10530	1896
548359	n/a	n/a	CCTAGTCCTCAAGTTT	eekd$_{10}$kke	0	10580	10595	1897
548360	n/a	n/a	CAAGACATCAGTAGCT	eekd$_{10}$kke	45	10626	10641	1898
548361	n/a	n/a	CTTATCAGTCCCAGTC	eekd$_{10}$kke	52	10702	10717	1899
548362	n/a	n/a	GACAACCCATCAGTTG	eekd$_{10}$kke	33	10742	10757	1900
548363	n/a	n/a	CAGCAGGCTCAAAGTG	eekd$_{10}$kke	37	10915	10930	1901
548364	n/a	n/a	TGGCTAAGTCAGGCCC	eekd$_{10}$kke	30	10982	10997	1902
548365	n/a	n/a	TGTACTCCACCTCACG	eekd$_{10}$kke	55	11017	11032	1903
548366	n/a	n/a	AGCAAGCTAAGTGAGT	eekd$_{10}$kke	5	11199	11214	1904
548367	n/a	n/a	GTTCTTGAGTGTAGAG	eekd$_{10}$kke	52	11260	11275	1905
548368	n/a	n/a	GTGTTCATACGGAAGC	eekd$_{10}$kke	59	11299	11314	1906

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548369	n/a	n/a	GTTGGGATGCGACTCT	eekd$_{10}$kke	50	11335	11350	1907
548370	n/a	n/a	ACGAAGTCTCTTTCCT	eekd$_{10}$kke	53	11385	11400	1908
548371	n/a	n/a	CGATGAGTTGGGCAGG	eekd$_{10}$kke	57	11454	11469	1909
548372	n/a	n/a	GATACCTTTCCACTCC	eekd$_{10}$kke	61	11558	11573	1910
548373	n/a	n/a	TCCCCAAGATTATGTG	eekd$_{10}$kke	16	11596	11611	1911
548374	n/a	n/a	GCACCCTTTTCATTGA	eekd$_{10}$kke	41	12074	12089	1912
548375	n/a	n/a	TCGACTTCTCCTGTCT	eekd$_{10}$kke	27	12199	12214	1913
548376	n/a	n/a	GCCTTTGACCTTTCGC	eekd$_{10}$kke	65	12261	12276	1914
548377	n/a	n/a	GTGTGCTGAGGTTTGC	eekd$_{10}$kke	80	12297	12312	1915
548378	n/a	n/a	GCAAGATGCATGCAGC	eekd$_{10}$kke	49	12393	12408	1916
548379	n/a	n/a	ATCGAACTCTGCTTGA	eekd$_{10}$kke	44	12477	12492	1917
548380	n/a	n/a	GCCCAGTTTTGGCAAC	eekd$_{10}$kke	7	12540	12555	1918
548381	n/a	n/a	CCCACTACCATTTGGG	eekd$_{10}$kke	0	12578	12593	1919

Table 149

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	46	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	64	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	

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						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548459	n/a	n/a	CAACTATAACAGTATC	eekd$_{10}$kke	26	15903	15918	1920
548460	n/a	n/a	CTATACCACGGTAACT	eekd$_{10}$kke	0	16036	16051	1921
548461	n/a	n/a	CCTATATCACTGTAAC	eekd$_{10}$kke	0	16127	16142	1922
548462	n/a	n/a	ACCTATATCACTGTAA	eekd$_{10}$kke	0	16128	16143	1923
548463	n/a	n/a	TCACTGTACCTATATC	eekd$_{10}$kke	0	16135	16150	1924
548464	n/a	n/a	GTCCTATAACTATATC	eekd$_{10}$kke	0	16174	16189	1925
548465	n/a	n/a	CTGTACCTATAACTGT	eekd$_{10}$kke	0	16202	16217	1926
548466	n/a	n/a	CGTCACTGTACCTATA	eekd$_{10}$kke	71	16207	16222	1927
548467	n/a	n/a	CATCACTGTACCTATA	eekd$_{10}$kke	20	16258	16273	1928
548468	n/a	n/a	CAACATCACTGTACCT	eekd$_{10}$kke	6	16261	16276	1929
548469	n/a	n/a	TTCCCTACCCCTGGTA	eekd$_{10}$kke	0	16331	16346	1930
548470	n/a	n/a	GGTGGAATGTCATGGC	eekd$_{10}$kke	56	16404	16419	1931
548471	n/a	n/a	GCGGAAAACTGGCCGT	eekd$_{10}$kke	17	16474	16489	1932
548472	n/a	n/a	CCCAATACAGGGCCAG	eekd$_{10}$kke	0	16513	16528	1933
548473	n/a	n/a	CCAACCTTCCCAATCT	eekd$_{10}$kke	0	16554	16569	1934
548474	n/a	n/a	GAAGGTGTGCTGTCGC	eekd$_{10}$kke	33	16602	16617	1935
548475	n/a	n/a	ATCGAGTCCTGCCTCC	eekd$_{10}$kke	17	16707	16722	1936
548476	n/a	n/a	GCAAATCCTTCCAGCA	eekd$_{10}$kke	27	16755	16770	1937
548477	n/a	n/a	GCACGAGCTTGCCTGT	eekd$_{10}$kke	26	16787	16802	1938
548478	n/a	n/a	GAGCCATCCAGGGTGC	eekd$_{10}$kke	53	16845	16860	1939
548479	n/a	n/a	AGGCCATTTGATCCGA	eekd$_{10}$kke	68	16913	16928	1940
548480	n/a	n/a	GCCACGCCCTTAGCAG	eekd$_{10}$kke	20	16973	16988	1941
548481	n/a	n/a	GTTCCCTGAGGAACGG	eekd$_{10}$kke	2	17010	17025	1942
548482	n/a	n/a	GGCAGTTAGGCCAGGA	eekd$_{10}$kke	53	17068	17083	1943
548483	n/a	n/a	CTACAGATCATCCCTA	eekd$_{10}$kke	5	17102	17117	1944
548484	n/a	n/a	CCCCGGAGCACCTTCA	eekd$_{10}$kke	41	17207	17222	1945
548485	n/a	n/a	GTGACCCAAGGGTCGA	eekd$_{10}$kke	17	17252	17267	1946

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548486	n/a	n/a	CGTGGTTAGCCTGACA	eekd$_{10}$kke	68	17416	17431	1947
548487	n/a	n/a	TCCATGTCAGAGTTGC	eekd$_{10}$kke	71	17461	17476	1948
548488	n/a	n/a	CCTCCTTTTGGCTTGA	eekd$_{10}$kke	63	17530	17545	1949
548489	n/a	n/a	TTCCCCAGAGGTGATA	eekd$_{10}$kke	16	17582	17597	1950
548490	n/a	n/a	TCTGGTTAGCCTCCGA	eekd$_{10}$kke	58	17664	17679	1951
548491	n/a	n/a	TGGCCAAGCAACCAGT	eekd$_{10}$kke	57	17715	17730	1952
548492	n/a	n/a	GCCCAATGTCCTAACC	eekd$_{10}$kke	51	17794	17809	1953
548493	n/a	n/a	CCACCGCTGCCCGCCA	eekd$_{10}$kke	37	18013	18028	1954
548494	n/a	n/a	TGTGACCCCCCACCGC	eekd$_{10}$kke	39	18022	18037	1955
548495	n/a	n/a	TTGTGACCCCCCACCG	eekd$_{10}$kke	55	18023	18038	1956
548496	n/a	n/a	ACTGAACCCCCTTAGG	eekd$_{10}$kke	0	18571	18586	1957
548497	n/a	n/a	CCTTCATACCCCTCAC	eekd$_{10}$kke	26	18725	18740	1958
548498	n/a	n/a	CCGATAACAGACCGGC	eekd$_{10}$kke	71	18795	18810	1959
548499	n/a	n/a	ATACCCGGAGTCAGGA	eekd$_{10}$kke	56	18955	18970	1960
548500	n/a	n/a	ATTGCTCAGGCCCCCT	eekd$_{10}$kke	29	19037	19052	1961
548501	n/a	n/a	CAAGCCACTAACCCAC	eekd$_{10}$kke	33	19147	19162	1962
548502	n/a	n/a	AATTCTTGGACCAAGG	eekd$_{10}$kke	25	19234	19249	1963
548503	n/a	n/a	CCATCTACTCCCCCAT	eekd$_{10}$kke	9	19291	19306	1964
548504	n/a	n/a	GCAGCGAGCATTCCAA	eekd$_{10}$kke	28	19352	19367	1965
548505	n/a	n/a	GGACAATGCCTATGCT	eekd$_{10}$kke	21	19386	19401	1966
548506	n/a	n/a	GAAGCCATTCACTGCA	eekd$_{10}$kke	32	19436	19451	1967
548507	n/a	n/a	AAACTCCTCTCAAGGC	eekd$_{10}$kke	53	19474	19489	1968
548508	n/a	n/a	GCACCACCATGCGGTT	eekd$_{10}$kke	43	19553	19568	1969
548509	n/a	n/a	TGCAGGGCTGCGCAGT	eekd$_{10}$kke	41	19960	19975	1970
548510	n/a	n/a	TTAGCCACTCCTCTTG	eekd$_{10}$kke	30	20062	20077	1971
548511	n/a	n/a	AGCTAGCTGACCCCAA	eekd$_{10}$kke	16	20092	20107	1972
548512	n/a	n/a	TCCGCCTTTGGATACT	eekd$_{10}$kke	49	20155	20170	1973
548513	n/a	n/a	CCTGCTGATTGTGTCT	eekd$_{10}$kke	16	20240	20255	1974
548514	n/a	n/a	TCGAGGACAGCCCCCA	eekd$_{10}$kke	40	20335	20350	1975
548515	n/a	n/a	ACCCGTCAGCCTCAGC	eekd$_{10}$kke	59	20381	20396	1976
548516	n/a	n/a	CTTGCCTATTCACCCC	eekd$_{10}$kke	49	20544	20559	1977
548517	n/a	n/a	CGGACAAGCCTTACAG	eekd$_{10}$kke	43	20596	20611	1978
548518	n/a	n/a	CACACTTACCCCGCTC	eekd$_{10}$kke	12	20741	20756	1979
548519	n/a	n/a	CCTCCCCTTGTGTGTC	eekd$_{10}$kke	31	20843	20858	1980
548520	n/a	n/a	CCGCTTCCCTGACTGT	eekd$_{10}$kke	43	20919	20934	1981
548521	n/a	n/a	CAGCTCCCTTACTAGG	eekd$_{10}$kke	61	20958	20973	1982
548522	n/a	n/a	AGGTATTGACCGCCAG	eekd$_{10}$kke	55	21062	21077	1983
548523	n/a	n/a	GGTAAATCCATCCCCT	eekd$_{10}$kke	44	21157	21172	1984
548524	n/a	n/a	GCCCGATCACCTTAGA	eekd$_{10}$kke	45	21220	21235	1985

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548525	n/a	n/a	GTCTAACTGGCCTGGC	eekd$_{10}$kke	2	21328	21343	1986
548526	n/a	n/a	CTAAGCTGTGTCTCAT	eekd$_{10}$kke	26	21373	21388	1987
548527	n/a	n/a	TGTTTCAAGTGCCAGA	eekd$_{10}$kke	50	21434	21449	1988
548528	n/a	n/a	TGCAGTGGTCAAGCAT	eekd$_{10}$kke	32	21478	21493	1989
548529	n/a	n/a	GCGATTCCTTGCCTCT	eekd$_{10}$kke	56	21554	21569	1990
548530	n/a	n/a	ATAATAGAGGCAGCCA	eekd$_{10}$kke	50	21592	21607	1991
548531	n/a	n/a	GTCAGAAGGCCTCTTA	eekd$_{10}$kke	21	21753	21768	1992
548532	n/a	n/a	TATTTATCCGACCTCT	eekd$_{10}$kke	34	21881	21896	1993
548533	n/a	n/a	GAGGTGGTTGGAGCTA	eekd$_{10}$kke	9	21926	21941	1994
548534	n/a	n/a	CAGATCCCAATTCTTC	eekd$_{10}$kke	22	22063	22078	1995
548535	n/a	n/a	GAGTCTTTCCAATCCT	eekd$_{10}$kke	13	22142	22157	1996

Table 150

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	46	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	64	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	

						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548536	n/a	n/a	TCTCAATCCCAACCCC	eekd$_{10}$kke	0	22168	22183	1997
548537	n/a	n/a	CCTCAATCCCAACCCA	eekd$_{10}$kke	0	22191	22206	1998
548538	n/a	n/a	TAGTGGCAAGAACCAC	eekd$_{10}$kke	0	22627	22642	1999
548539	n/a	n/a	CGCGCGAATGCCTGCC	eekd$_{10}$kke	41	22658	22673	2000
548540	n/a	n/a	GACACCTGCTTGATTA	eekd$_{10}$kke	7	22704	22719	2001
548541	n/a	n/a	GGCACTGGTCATGGAC	eekd$_{10}$kke	39	22760	22775	2002
548542	n/a	n/a	GCGCCATCCTTCAATC	eekd$_{10}$kke	7	22857	22872	2003
548543	n/a	n/a	GATCCACCCATGACCT	eekd$_{10}$kke	32	22997	23012	2004
548544	n/a	n/a	GCTGTGACTCAGATCA	eekd$_{10}$kke	62	23070	23085	2005
548545	n/a	n/a	CTCTTCGCATGGACAC	eekd$_{10}$kke	46	23100	23115	2006
548546	n/a	n/a	GCCCAAGCCTACATGC	eekd$_{10}$kke	35	23430	23445	2007
548547	n/a	n/a	GTGCGATTAAGCCCCA	eekd$_{10}$kke	86	23514	23529	2008
548548	n/a	n/a	GCTTGTAGAAGGGATT	eekd$_{10}$kke	54	23631	23646	2009
548549	n/a	n/a	TGTGCAATCAGGTGGA	eekd$_{10}$kke	56	23765	23780	2010
548550	n/a	n/a	CCGGCCTGGATACAGC	eekd$_{10}$kke	0	23831	23846	2011
548551	n/a	n/a	CGGCCAATGGGAAAGG	eekd$_{10}$kke	25	24175	24190	2012
548552	n/a	n/a	TGGAGGAGTAGGGAAT	eekd$_{10}$kke	10	24200	24215	2013
548553	n/a	n/a	CCCGAAGAGTCAAGTC	eekd$_{10}$kke	46	24255	24270	2014
548554	n/a	n/a	GTGCTGCATTGCATGA	eekd$_{10}$kke	42	24290	24305	2015
548555	n/a	n/a	ACACGCCAGGTGAAAA	eekd$_{10}$kke	2	24322	24337	2016
548556	n/a	n/a	ATGCATGCCTACCCAA	eekd$_{10}$kke	43	24526	24541	2017
548557	n/a	n/a	GTTACTCTGTGATCCA	eekd$_{10}$kke	81	24581	24596	2018
548558	n/a	n/a	AACATTGTGTAGCTGC	eekd$_{10}$kke	75	24640	24655	2019
548559	n/a	n/a	GAGACTGAAGCCCTCA	eekd$_{10}$kke	44	24676	24691	2020
548560	n/a	n/a	CACTGCCTAGAAAGGC	eekd$_{10}$kke	16	24734	24749	2021
548561	n/a	n/a	TGTAGTATCCAGAGTA	eekd$_{10}$kke	46	24930	24945	2022
548562	n/a	n/a	AGATGACCTGCAGATG	eekd$_{10}$kke	50	24983	24998	2023
548563	n/a	n/a	AAACCATGAATTAGGT	eekd$_{10}$kke	20	25100	25115	2024
548564	n/a	n/a	TTGCTACTTTACACCA	eekd$_{10}$kke	69	25208	25223	2025

548565	n/a	n/a	GGCATTAGGATAGGCA	eekd$_{10}$kke	63	25350	25365	2026
548566	n/a	n/a	CACTCAGACTGTCTGA	eekd$_{10}$kke	0	25413	25428	2027
548567	n/a	n/a	AGATCCGGAATAACCA	eekd$_{10}$kke	67	25459	25474	2028
548568	n/a	n/a	ATTGACAACCATCCTA	eekd$_{10}$kke	27	25496	25511	2029
548569	n/a	n/a	ACTCATTGGTCTACAG	eekd$_{10}$kke	41	25559	25574	2030
548570	n/a	n/a	ATGCCTTGTGCCTATT	eekd$_{10}$kke	74	25706	25721	2031
548571	n/a	n/a	ACTCTGAGGCCTTAGG	eekd$_{10}$kke	59	25794	25809	2032
548572	n/a	n/a	GCATTACTCAGCATGT	eekd$_{10}$kke	63	25836	25851	2033
548573	n/a	n/a	CCAGTCACCACCATTG	eekd$_{10}$kke	65	25862	25877	2034
548574	n/a	n/a	GGTCTAACTCTAAGGG	eekd$_{10}$kke	0	25920	25935	2035
548575	n/a	n/a	TGTCCTTTAAAGTATC	eekd$_{10}$kke	18	25971	25986	2036
548576	n/a	n/a	TCATGTGGCAACCTGT	eekd$_{10}$kke	41	26114	26129	2037
548577	n/a	n/a	AATCTGCACCTGGCAG	eekd$_{10}$kke	42	26428	26443	2038
548578	n/a	n/a	CATGGCTATTGCTTCC	eekd$_{10}$kke	73	26513	26528	2039
548579	n/a	n/a	GGGCTATATTGCCAGC	eekd$_{10}$kke	46	26614	26629	2040
548580	n/a	n/a	CCAGAGCCTTGATCAG	eekd$_{10}$kke	36	26681	26696	2041
548581	n/a	n/a	GGTGGGTTATCTGAGA	eekd$_{10}$kke	13	26710	26725	2042
548582	n/a	n/a	TAGCTCCATGCTGTGT	eekd$_{10}$kke	59	26735	26750	2043
548583	n/a	n/a	GGGAATTTATGCTGCC	eekd$_{10}$kke	79	26782	26797	2044
548584	n/a	n/a	TGATGAAGTTCCACCT	eekd$_{10}$kke	47	26840	26855	2045
548585	n/a	n/a	TAGGCACAGACAACCT	eekd$_{10}$kke	33	26869	26884	2046
548586	n/a	n/a	TCCAACTACAGGACTC	eekd$_{10}$kke	39	26943	26958	2047
548587	n/a	n/a	TTCTGGGAAACTCTCT	eekd$_{10}$kke	45	26969	26984	2048
548588	n/a	n/a	AGCTCACACCCAAAAA	eekd$_{10}$kke	10	27006	27021	2049
548589	n/a	n/a	TCTGTTACCTTGAGGA	eekd$_{10}$kke	40	27280	27295	2050
548590	n/a	n/a	TGGTCATGTCAACTGT	eekd$_{10}$kke	35	27550	27565	2051
548591	n/a	n/a	GTAAGCCTTCACAGGG	eekd$_{10}$kke	3	27583	27598	2052
548592	n/a	n/a	CTCACCAGAGTTGTCC	eekd$_{10}$kke	7	27726	27741	2053
548593	n/a	n/a	CATCCCTGACAGGTCC	eekd$_{10}$kke	61	27759	27774	2054
548594	n/a	n/a	CCCTTCTAACCAAGGA	eekd$_{10}$kke	30	27825	27840	2055
548595	n/a	n/a	GGATGAGATGCATCCA	eekd$_{10}$kke	8	28069	28084	2056
548596	n/a	n/a	ATGGCGGTGAAGCAGC	eekd$_{10}$kke	20	28127	28142	2057
548597	n/a	n/a	TGAATACCATCCCCGC	eekd$_{10}$kke	50	28171	28186	2058
548598	n/a	n/a	GCGCCATCTGCCCTGT	eekd$_{10}$kke	50	28253	28268	2059
548599	n/a	n/a	TGGGTTGGAGGAGTGG	eekd$_{10}$kke	19	28311	28326	2060
548600	n/a	n/a	TGGTGGTGGGATTGGT	eekd$_{10}$kke	53	28336	28351	2061
						28391	28406	
						28434	28449	
						28446	28461	
						28525	28540	

						28611	28626	
						28623	28638	
548601	n/a	n/a	TTGGTGGTGGGATTGG	eekd$_{10}$kke	18	28337	28352	2062
						28392	28407	
						28435	28450	
						28447	28462	
						28526	28541	
						28612	28627	
						28624	28639	
548602	n/a	n/a	GGTGGTGGAATTGGTG	eekd$_{10}$kke	20	28347	28362	2063
548603	n/a	n/a	GAGATTGGTGGTGGGT	eekd$_{10}$kke	35	28372	28387	2064
548604	n/a	n/a	GTGGTGGGATTGGTGC	eekd$_{10}$kke	22	28432	28447	2065
548605	n/a	n/a	TGGCGGGATTGGTGGT	eekd$_{10}$kke	12	28479	28494	2066
						28558	28573	
548606	n/a	n/a	CGGTGGTGGGATTGGT	eekd$_{10}$kke	41	28501	28516	2067
						28580	28595	
548607	n/a	n/a	TCGGTGGTGGGATTGG	eekd$_{10}$kke	34	28502	28517	2068
						28581	28596	
548608	n/a	n/a	ATCGGTGGTGGGATTG	eekd$_{10}$kke	25	28503	28518	2069
						28582	28597	
548609	n/a	n/a	GATCGGTGGTGGGATT	eekd$_{10}$kke	30	28504	28519	2070
						28583	28598	
548610	n/a	n/a	GGATCGGTGGTGGGAT	eekd$_{10}$kke	2	28505	28520	2071
						28584	28599	
548611	n/a	n/a	GCGGGATCGGTGGTGG	eekd$_{10}$kke	7	28508	28523	2072
						28587	28602	
548612	n/a	n/a	GGCGGGATCGGTGGTG	eekd$_{10}$kke	20	28509	28524	2073
						28588	28603	

Table 151

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	46	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	

						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	64	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	
						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548382	n/a	n/a	GAGCAAATACAGTCCA	eekd$_{10}$kke	19	12620	12635	2074
548383	n/a	n/a	GTCTCGATGGCAAGCT	eekd$_{10}$kke	49	12654	12669	2075
548384	n/a	n/a	CTCACCGGTACTCTGC	eekd$_{10}$kke	49	12805	12820	2076
548385	n/a	n/a	TCCTGGAGGCACCAAT	eekd$_{10}$kke	0	12847	12862	2077
548386	n/a	n/a	AGCCCTGTTTGGTTTT	eekd$_{10}$kke	0	12903	12918	2078
548387	n/a	n/a	TGAAGGGCGAGGCGCA	eekd$_{10}$kke	22	13261	13276	2079
548388	n/a	n/a	AAGAGGATGTCAGGCT	eekd$_{10}$kke	4	13357	13372	2080
548389	n/a	n/a	TTGAGGAAAGACCTGC	eekd$_{10}$kke	11	13399	13414	2081
548390	n/a	n/a	GCTGAGTGTGACTTAA	eekd$_{10}$kke	43	13455	13470	2082
548391	n/a	n/a	GTACATGACTCCAGTG	eekd$_{10}$kke	34	13638	13653	2083
548392	n/a	n/a	GTAGAGCATGGAGCGA	eekd$_{10}$kke	31	13730	13745	2084
548393	n/a	n/a	CGCTTCAGGAAAGCGA	eekd$_{10}$kke	26	13828	13843	2085
548394	n/a	n/a	GGCAGGAGACTCCGTG	eekd$_{10}$kke	25	13919	13934	2086
548395	n/a	n/a	ATCCTTCCCCTCGCAA	eekd$_{10}$kke	0	13966	13981	2087
548396	n/a	n/a	TAATGAGTGGGTTAGG	eekd$_{10}$kke	0	14007	14022	2088
548397	n/a	n/a	GGAGCAGTGCAGGTAA	eekd$_{10}$kke	1	14065	14080	2089

548398	n/a	n/a	ATAGGCAATTGTTCCT	eekd$_{10}$kke	55	14129	14144	2090
548399	n/a	n/a	AGTCCTACAATTACCA	eekd$_{10}$kke	11	14239	14254	2091
548400	n/a	n/a	GGGCTCCTATTCCACC	eekd$_{10}$kke	13	14277	14292	2092
548401	n/a	n/a	GCCAGCTATGGGAACA	eekd$_{10}$kke	71	14333	14348	2093
548402	n/a	n/a	CCCCATCTCGAAGCCC	eekd$_{10}$kke	45	14380	14395	2094
548403	n/a	n/a	GAGTACATTGGGCCCA	eekd$_{10}$kke	25	14418	14433	2095
548404	n/a	n/a	GAGCCTTCCGCCTCTC	eekd$_{10}$kke	37	14471	14486	2096
548405	n/a	n/a	CGGACCTTCATCTTCA	eekd$_{10}$kke	35	14529	14544	2097
548406	n/a	n/a	TCTAGAGGCCGCCTGC	eekd$_{10}$kke	0	14558	14573	2098
548407	n/a	n/a	CCTATAACTGCTGCTC	eekd$_{10}$kke	24	14731	14746	2099
548408	n/a	n/a	TATCACTGTACTAGTT	eekd$_{10}$kke	47	14748	14763	1269
						14819	14834	
						14890	14905	
						14949	14964	
						15009	15024	
						15081	15096	
						15153	15168	
						15224	15239	
						15296	15311	
						15355	15370	
						15415	15430	
						15487	15502	
						15559	15574	
						15617	15632	
						15689	15704	
						15819	15834	
						15891	15906	
						15949	15964	
548409	n/a	n/a	GTATCACTGTACTAGT	eekd$_{10}$kke	81	14749	14764	2100
						14820	14835	
						14891	14906	
						14950	14965	
						15010	15025	
						15082	15097	
						15154	15169	
						15225	15240	
						15297	15312	
						15356	15371	
						15416	15431	
						15488	15503	
						15560	15575	
						15618	15633	
						15690	15705	

						15820	15835	
						15892	15907	
						15950	15965	
548410	n/a	n/a	AGTATCACTGTACTAG	eekd$_{10}$kke	85	14750	14765	2101
						14821	14836	
						14892	14907	
						14951	14966	
						15011	15026	
						15083	15098	
						15155	15170	
						15226	15241	
						15298	15313	
						15357	15372	
						15417	15432	
						15489	15504	
						15561	15576	
						15619	15634	
						15691	15706	
						15821	15836	
						15893	15908	
						15951	15966	
548411	n/a	n/a	CAGTATCACTGTACTA	eekd$_{10}$kke	72	14751	14766	2102
						14822	14837	
						14893	14908	
						14952	14967	
						15012	15027	
						15084	15099	
						15156	15171	
						15227	15242	
						15299	15314	
						15358	15373	
						15418	15433	
						15490	15505	
						15562	15577	
						15620	15635	
						15692	15707	
						15822	15837	
						15894	15909	
						15952	15967	
548412	n/a	n/a	TAACAGTATCACTGTA	eekd$_{10}$kke	17	14754	14769	2103
						14825	14840	
						14896	14911	
						14955	14970	

						15015	15030	
						15087	15102	
						15159	15174	
						15230	15245	
						15302	15317	
						15361	15376	
						15421	15436	
						15493	15508	
						15565	15580	
						15623	15638	
						15695	15710	
						15825	15840	
						15897	15912	
						15955	15970	
548413	n/a	n/a	CTAACAGTATCACTGT	eekd$_{10}$kke	55	14755	14770	2104
						14826	14841	
						14897	14912	
						15016	15031	
						15088	15103	
						15231	15246	
						15303	15318	
						15422	15437	
						15494	15509	
						15624	15639	
						15826	15841	
						15956	15971	
548414	n/a	n/a	TCTAACAGTATCACTG	eekd$_{10}$kke	20	14756	14771	2105
						14827	14842	
						14898	14913	
						15017	15032	
						15089	15104	
						15232	15247	
						15304	15319	
						15423	15438	
						15495	15510	
						15625	15640	
						15827	15842	
						15957	15972	
548415	n/a	n/a	ATAACTCTAACAGTAT	eekd$_{10}$kke	0	14761	14776	2106
						14832	14847	
						14903	14918	
						15022	15037	
						15094	15109	

						15237	15252	
						15309	15324	
						15428	15443	
						15500	15515	
						15630	15645	
						15832	15847	
						15962	15977	
548416	n/a	n/a	CTATAACTCTAACAGT	eekd$_{10}$kke	9	14763	14778	2107
						14834	14849	
						14905	14920	
						15024	15039	
						15096	15111	
						15239	15254	
						15311	15326	
						15430	15445	
						15502	15517	
						15632	15647	
						15834	15849	
						15964	15979	
548417	n/a	n/a	ACTGTCCTATAACTCT	eekd$_{10}$kke	24	14769	14784	2108
						14840	14855	
548418	n/a	n/a	TATATCACTGTCCTAT	eekd$_{10}$kke	39	14775	14790	2109
						14846	14861	
						15180	15195	
						15716	15731	
						16164	16179	
548419	n/a	n/a	CCTATATCACTGTCCT	eekd$_{10}$kke	52	14777	14792	2110
						14848	14863	
						15182	15197	
						15718	15733	
548420	n/a	n/a	TCCTATATCACTGTCC	eekd$_{10}$kke	58	14778	14793	2111
						14849	14864	
						15183	15198	
						15719	15734	
548421	n/a	n/a	CACTGTCCTATATCAC	eekd$_{10}$kke	56	14783	14798	2112
						14854	14869	
						14979	14994	
						15117	15132	
						15188	15203	
						15260	15275	
						15385	15400	
						15523	15538	
						15653	15668	

						15724	15739	
						15855	15870	
						15985	16000	
548422	n/a	n/a	GTATCACTGTCCTATA	eekd$_{10}$kke	69	14787	14802	2113
						14983	14998	
						15121	15136	
						15389	15404	
						15527	15542	
						15989	16004	
548423	n/a	n/a	AGTATCACTGTCCTAT	eekd$_{10}$kke	72	14788	14803	2114
						14984	14999	
						15050	15065	
						15122	15137	
						15390	15405	
						15456	15471	
						15528	15543	
						15990	16005	
548424	n/a	n/a	CAGTATCACTGTCCTA	eekd$_{10}$kke	90	14789	14804	2115
						14985	15000	
						15051	15066	
						15123	15138	
						15391	15406	
						15457	15472	
						15529	15544	
						15991	16006	
548425	n/a	n/a	AACAGTATCACTGTCC	eekd$_{10}$kke	90	14791	14806	2116
						14987	15002	
						15053	15068	
						15125	15140	
						15393	15408	
						15459	15474	
						15531	15546	
						15993	16008	
548426	n/a	n/a	TATAACAGTATCACTG	eekd$_{10}$kke	14	14794	14809	2117
						14990	15005	
						15056	15071	
						15128	15143	
						15161	15176	
						15363	15378	
						15396	15411	
						15462	15477	
						15534	15549	
						15567	15582	

						15697	15712	
						15899	15914	
						15996	16011	
548427	n/a	n/a	CTATAACAGTATCACT	eekd$_{10}$kke	24	14795	14810	2118
						14991	15006	
						15057	15072	
						15129	15144	
						15162	15177	
						15364	15379	
						15397	15412	
						15463	15478	
						15535	15550	
						15568	15583	
						15698	15713	
						15900	15915	
						15997	16012	
548428	n/a	n/a	TAACTATAACAGTATC	eekd$_{10}$kke	0	14798	14813	2119
						15060	15075	
						15132	15147	
						15165	15180	
						15466	15481	
						15538	15553	
						15571	15586	
						15701	15716	
						15772	15787	
						16000	16015	
548429	n/a	n/a	TATAACTATAACAGTA	eekd$_{10}$kke	0	14800	14815	2120
						15062	15077	
						15134	15149	
						15167	15182	
						15468	15483	
						15540	15555	
						15573	15588	
						15703	15718	
						15774	15789	
						16002	16017	
548430	n/a	n/a	CCTATAACTATAACAG	eekd$_{10}$kke	21	14802	14817	2121
						15064	15079	
						15169	15184	
						15470	15485	
						15542	15557	
						15575	15590	
						15705	15720	

						15776	15791	
						16004	16019	
548431	n/a	n/a	TACCTATAACTCTAAC	eekd$_{10}$kke	9	14908	14923	2122
						15027	15042	
						15099	15114	
						15242	15257	
						15314	15329	
						15433	15448	
						15505	15520	
						15635	15650	
						15837	15852	
						15967	15982	
548432	n/a	n/a	ACTGTACCTATAACTC	eekd$_{10}$kke	43	14912	14927	2123
						15031	15046	
						15246	15261	
						15318	15333	
						15437	15452	
						15509	15524	
						15639	15654	
						15841	15856	
						15971	15986	
548433	n/a	n/a	TATCACTGTACCTATA	eekd$_{10}$kke	33	14916	14931	2124
						15250	15265	
						15322	15337	
						15375	15390	
						15513	15528	
						15643	15658	
						15786	15801	
						15845	15860	
						15975	15990	
						16137	16152	
548434	n/a	n/a	ACAATATCACTGTACC	eekd$_{10}$kke	63	14920	14935	2125
						15326	15341	
						15790	15805	
						16063	16078	
						16141	16156	
548435	n/a	n/a	AACAATATCACTGTAC	eekd$_{10}$kke	19	14921	14936	2126
						15327	15342	
						15791	15806	
						16064	16079	
						16142	16157	
548436	n/a	n/a	ATATCACTGTACCTGT	eekd$_{10}$kke	8	14970	14985	2127
548437	n/a	n/a	TATATCACTGTACCTG	eekd$_{10}$kke	74	14971	14986	2128

548438	n/a	n/a	CTATATCACTGTACCT	eekd$_{10}$kke	38	14972	14987	2129
						15253	15268	
						15378	15393	
						15516	15531	
						15646	15661	
						15848	15863	
						15978	15993	
548439	n/a	n/a	CCTATATCACTGTACC	eekd$_{10}$kke	46	14973	14988	2130
						15254	15269	
						15379	15394	
						15517	15532	
						15647	15662	
						15849	15864	
						15979	15994	
548440	n/a	n/a	CCTATAACAGTATCAC	eekd$_{10}$kke	32	14992	15007	2131
						15365	15380	
						15398	15413	
548441	n/a	n/a	TCCTATAACAGTATCA	eekd$_{10}$kke	42	14993	15008	2132
						15399	15414	
548442	n/a	n/a	TTCCTATAACAGTATC	eekd$_{10}$kke	17	14994	15009	2133
						15400	15415	
548443	n/a	n/a	GTTTCCTATAACAGTA	eekd$_{10}$kke	12	14996	15011	2134
						15402	15417	
548444	n/a	n/a	CTATGTCACTGTACCT	eekd$_{10}$kke	43	15038	15053	2135
						15444	15459	
548445	n/a	n/a	CCTATGTCACTGTACC	eekd$_{10}$kke	62	15039	15054	2136
						15445	15460	
548446	n/a	n/a	TCCTATGTCACTGTAC	eekd$_{10}$kke	16	15040	15055	2137
						15446	15461	
548447	n/a	n/a	CACTGTCCTATGTCAC	eekd$_{10}$kke	59	15045	15060	2138
						15451	15466	
548448	n/a	n/a	TCACTGTCCTATGTCA	eekd$_{10}$kke	61	15046	15061	2139
						15452	15467	
548449	n/a	n/a	ATCACTGTCCTATGTC	eekd$_{10}$kke	62	15047	15062	2140
						15453	15468	
548450	n/a	n/a	CTACCTATAACTCTAA	eekd$_{10}$kke	0	15100	15115	2141
548451	n/a	n/a	GTCCTATAACTATAAC	eekd$_{10}$kke	0	15171	15186	2142
						15577	15592	
						15707	15722	
						16006	16021	
						16077	16092	
						16102	16117	
						16155	16170	

548452	n/a	n/a	TATATCACTGTACCTA	eekd$_{10}$kke	65	15252	15267	2143
						15377	15392	
						15515	15530	
						15645	15660	
						15847	15862	
						15977	15992	
548453	n/a	n/a	TACCTATAACAGTATC	eekd$_{10}$kke	12	15367	15382	2144
548454	n/a	n/a	ACTGTACCTATAACAG	eekd$_{10}$kke	17	15371	15386	2145
548455	n/a	n/a	CACCGTACTAGTTTCC	eekd$_{10}$kke	64	15757	15772	2146
548456	n/a	n/a	TATAACAGTATCACCG	eekd$_{10}$kke	52	15768	15783	2147
548457	n/a	n/a	CTATAACAGTATCACC	eekd$_{10}$kke	13	15769	15784	2148
548458	n/a	n/a	ACCTATAACTATAACA	eekd$_{10}$kke	0	15777	15792	2149
						16249	16264	

Table 152

ISIS NO	SEQ ID NO: 1 Start Site	SEQ ID NO: 1 Stop Site	Sequence	Chemistry	% inhibition	SEQ ID NO: 10 Start Site	SEQ ID NO: 10 Stop Site	SEQ ID NO
531231	n/a	n/a	TATCACTGTACTAGTTTCCT	eeeeed$_{10}$eeeee	48	14744	14763	334
						14815	14834	
						14886	14905	
						14945	14964	
						15005	15024	
						15077	15096	
						15220	15239	
						15292	15311	
						15351	15370	
						15411	15430	
						15483	15502	
						15555	15574	
						15613	15632	
						15685	15704	
						15815	15834	
						15887	15906	
						15945	15964	
547747	n/a	n/a	TCACTGTACTAGTTTC	eekd$_{10}$kke	88	14746	14761	1267
						14817	14832	
						14888	14903	
						14947	14962	
						15007	15022	
						15079	15094	

						15222	15237	
						15294	15309	
						15353	15368	
						15413	15428	
						15485	15500	
						15557	15572	
						15615	15630	
						15687	15702	
						15817	15832	
						15889	15904	
						15947	15962	
548613	n/a	n/a	TGGCGGGATCGGTGGT	eekd$_{10}$kke	39	28510	28525	2150
						28589	28604	
548614	n/a	n/a	TGGTGGCGGGATCGGT	eekd$_{10}$kke	0	28513	28528	2151
						28592	28607	
548615	n/a	n/a	TTGGTGGCGGGATCGG	eekd$_{10}$kke	10	28514	28529	2152
						28593	28608	
548616	n/a	n/a	ATTGGTGGCGGGATCG	eekd$_{10}$kke	35	28515	28530	2153
548617	n/a	n/a	GATTGGTGGCGGGATC	eekd$_{10}$kke	44	28516	28531	2154
548618	n/a	n/a	GTTGGTGGCGGGATCG	eekd$_{10}$kke	18	28594	28609	2155
548619	n/a	n/a	GGTTGGTGGCGGGATC	eekd$_{10}$kke	19	28595	28610	2156
548620	n/a	n/a	TGGTTGGTGGCGGGAT	eekd$_{10}$kke	24	28596	28611	2157
548621	n/a	n/a	GAACACATCAGGGATT	eekd$_{10}$kke	33	28638	28653	2158
548622	n/a	n/a	TTTCTATGGGCCTGAC	eekd$_{10}$kke	0	28669	28684	2159
548623	n/a	n/a	GCTGTCACTTAAGCCA	eekd$_{10}$kke	16	28862	28877	2160
548624	n/a	n/a	TCTAGGGCCACACCTC	eekd$_{10}$kke	24	28892	28907	2161
548625	n/a	n/a	GTTCTACACACAGTAC	eekd$_{10}$kke	0	29014	29029	2162
548626	n/a	n/a	GCAGTATGTTCAATCC	eekd$_{10}$kke	36	29202	29217	2163
548627	n/a	n/a	CCCACATGTACCACCG	eekd$_{10}$kke	22	29235	29250	2164
548628	n/a	n/a	GTATGGCAGAGCCCCT	eekd$_{10}$kke	9	29285	29300	2165
548629	n/a	n/a	CCCATCTTGGGACTTT	eekd$_{10}$kke	44	29341	29356	2166
548630	n/a	n/a	TGGTCCCAAATTGGAG	eekd$_{10}$kke	33	29387	29402	2167
548631	n/a	n/a	CTCACAATACTGAGCC	eekd$_{10}$kke	55	29421	29436	2168
548632	n/a	n/a	GGAGATATCAGGTGCA	eekd$_{10}$kke	45	29499	29514	2169
548633	n/a	n/a	CAAGGCATGTGTGCAC	eekd$_{10}$kke	41	29534	29549	2170
548634	n/a	n/a	GCCTTATTCTGTGCAA	eekd$_{10}$kke	0	29583	29598	2171
548635	n/a	n/a	AGGTGTGGCGCGCGCC	eekd$_{10}$kke	18	29853	29868	2172
548636	n/a	n/a	CTCTATACAGCTGGGC	eekd$_{10}$kke	5	30000	30015	2173
548637	n/a	n/a	GCTGATCTTCTAATGC	eekd$_{10}$kke	38	30063	30078	2174
548638	n/a	n/a	CCTCATTGCTCCACTA	eekd$_{10}$kke	26	30103	30118	2175
548639	n/a	n/a	TGGGAAGAAACTAGCA	eekd$_{10}$kke	10	30159	30174	2176
548640	n/a	n/a	GAATGTTGCTGTCCCA	eekd$_{10}$kke	32	30194	30209	2177
548641	n/a	n/a	GCATCATGCTTACTGC	eekd$_{10}$kke	23	30225	30240	2178

548642	n/a	n/a	GCGGCAGTAGTGAATC	eekd$_{10}$kke	23	30288	30303	2179
548643	n/a	n/a	CCTACCTAATTCCTCC	eekd$_{10}$kke	0	30329	30344	2180
548644	n/a	n/a	AACTGGGCAGTCCTTC	eekd$_{10}$kke	14	30418	30433	2181
548645	n/a	n/a	CCAGCGCAATTCTGCT	eekd$_{10}$kke	8	30666	30681	2182
548646	n/a	n/a	CGTTTCCCTCAACTCC	eekd$_{10}$kke	24	30750	30765	2183
548647	n/a	n/a	CACGGCAAGTCGCGGG	eekd$_{10}$kke	39	30790	30805	2184
548648	n/a	n/a	CAGTTGTATCCCTCCC	eekd$_{10}$kke	32	30852	30867	2185
548649	n/a	n/a	GCCTCTCAGACGGCAC	eekd$_{10}$kke	0	30906	30921	2186
548650	n/a	n/a	CTGATCCCACTTGCCC	eekd$_{10}$kke	21	30991	31006	2187
548651	n/a	n/a	AGTCTCTTTCCTACCC	eekd$_{10}$kke	61	31030	31045	2188
548652	n/a	n/a	CCACGATGCTCTGGCC	eekd$_{10}$kke	65	31068	31083	2189
548653	n/a	n/a	TCGGCTCCTGGCAGCA	eekd$_{10}$kke	46	31111	31126	2190
548654	n/a	n/a	ACCATTCCTGACCATG	eekd$_{10}$kke	34	31151	31166	2191
548655	n/a	n/a	CCCGAGGTCACATAAT	eekd$_{10}$kke	56	31416	31431	2192
548656	n/a	n/a	TTACAACAGACCCAGG	eekd$_{10}$kke	35	31497	31512	2193
548657	n/a	n/a	AGCAGGGTATCTTCAC	eekd$_{10}$kke	26	31548	31563	2194
548658	n/a	n/a	GAAGTTCCTGTGTCTT	eekd$_{10}$kke	11	31593	31608	2195
548659	n/a	n/a	CCAACCTCTAAGGCTA	eekd$_{10}$kke	17	31721	31736	2196
548660	n/a	n/a	ATGCTTACCTTTCTCC	eekd$_{10}$kke	0	31955	31970	2197
548661	n/a	n/a	ACGACCCACTCCATGT	eekd$_{10}$kke	18	32016	32031	2198
548662	n/a	n/a	TGCTTAAAAGTCTCCC	eekd$_{10}$kke	5	32155	32170	2199
548663	n/a	n/a	GCCCTAGAAGGGCCCA	eekd$_{10}$kke	20	32219	32234	2200
548664	n/a	n/a	GCGGGTGGTCTTGCAC	eekd$_{10}$kke	38	32245	32260	2201
548665	n/a	n/a	GCTCCCGGCCATTAGC	eekd$_{10}$kke	8	32312	32327	2202
548666	n/a	n/a	TCTCCATAGTGAGACG	eekd$_{10}$kke	1	32342	32357	2203
548667	n/a	n/a	TGGCAAGCTACCTTCT	eekd$_{10}$kke	51	32384	32399	2204
548668	n/a	n/a	GGGAGCTTTCATGGCT	eekd$_{10}$kke	68	32506	32521	2205
548669	n/a	n/a	AATGCAGGCCAGCATC	eekd$_{10}$kke	42	32541	32556	2206
548670	n/a	n/a	GAAAAGCCCTCCGAGC	eekd$_{10}$kke	15	32590	32605	2207
548671	n/a	n/a	CAACAATCCAAAGCCT	eekd$_{10}$kke	3	32674	32689	2208
548672	n/a	n/a	CCCCCCAGAAATCCCA	eekd$_{10}$kke	40	32708	32723	2209
548673	n/a	n/a	GACCTTGCTTCCATGT	eekd$_{10}$kke	40	32753	32768	2210
548674	n/a	n/a	GAGAGACGGCACCCTG	eekd$_{10}$kke	4	32829	32844	2211
548675	n/a	n/a	GGGAAGGTAGTGTTAC	eekd$_{10}$kke	8	32898	32913	2212
548676	n/a	n/a	GTGAATCAGAGCAGTG	eekd$_{10}$kke	63	32963	32978	2213
548677	n/a	n/a	TCACCTGTGAGTAACC	eekd$_{10}$kke	40	33089	33104	2214
548678	n/a	n/a	GAGTTACCTTACAAGC	eekd$_{10}$kke	22	33232	33247	2215
548679	n/a	n/a	TCTCAAGCAGCCTATT	eekd$_{10}$kke	0	33267	33282	2216
548680	n/a	n/a	GCCCCTCTTAAATAGC	eekd$_{10}$kke	9	33446	33461	2217
548681	n/a	n/a	GATATCATCATCCCAA	eekd$_{10}$kke	22	33513	33528	2218
548682	n/a	n/a	GTATCCCCTTTTCTAT	eekd$_{10}$kke	0	33556	33571	2219
548683	n/a	n/a	AGTATCTCATGTGCCT	eekd$_{10}$kke	46	33581	33596	2220
548684	n/a	n/a	CAAGACCTTGCTTGCC	eekd$_{10}$kke	24	33658	33673	2221

548685	n/a	n/a	TAGTCCACTACACAGC	eekd$_{10}$kke	24	33802	33817	2222
548686	n/a	n/a	ACGACAATGGGATTCA	eekd$_{10}$kke	0	33844	33859	2223
548687	n/a	n/a	GAATCTCCCTGAGTCA	eekd$_{10}$kke	20	33888	33903	2224
548688	n/a	n/a	TAGAGGGATCCCAGGA	eekd$_{10}$kke	0	34416	34431	2225
548689	n/a	n/a	CCAGGTGCAGCACGGA	eekd$_{10}$kke	12	34483	34498	2226

Example 117: Dose-dependent antisense inhibition of human PKK in HepaRG™ cells

Gapmers from the studies described above exhibiting significant *in vitro* inhibition of PKK mRNA were selected and tested at various doses in HepaRG™ 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 PKK mRNA levels were measured by quantitative real-time PCR. Human PKK primer probe set RTS3454 was used to measure mRNA levels. PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. 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. Results are presented as percent inhibition of PKK, relative to untreated control cells.

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

Table 153

ISIS No	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
486847	0	34	48	71	87	1.1
530933	15	13	42	67	66	1.7
530959	12	27	53	80	94	0.9
530965	8	5	63	83	91	0.8
530967	30	36	48	82	91	0.7
530970	1	0	66	76	84	1.0
530971	12	40	52	66	70	1.3
530988	0	25	54	86	78	0.9
530992	0	50	63	83	80	0.7
531002	6	28	58	82	86	0.9
531004	0	14	25	71	84	2.1
531005	14	28	61	73	77	0.9
531022	0	0	32	62	77	2.2
531078	10	27	54	69	92	1.1

531231	23	30	76	89	94	0.6

Table 154

ISIS No	0.12 μM	0.37 μM	1.11 μM	3.33 μM	10.00 μM	IC_{50} (μM)
531026	23	26	49	75	85	1.0
531055	3	28	64	76	81	0.9
531069	19	39	48	76	83	0.9
531071	23	37	56	83	83	0.7
531110	14	29	49	76	85	1.1
531121	0	13	47	69	79	1.5
531123	14	43	51	71	64	0.9
531172	0	16	37	60	60	2.1
531198	0	35	62	76	60	0.8
531231	18	0	36	76	84	2.0
531232	15	26	40	62	76	1.7
531233	17	27	50	77	84	1.0
531234	24	21	47	72	82	1.4
531235	27	55	62	84	95	0.4
531236	4	28	59	85	93	0.8

Example 118: Dose-dependent antisense inhibition of human PKK in HepaRG™ cells

Gapmers from the studies described above exhibiting significant *in vitro* inhibition of PKK mRNA were selected and tested at various doses in HepaRG™ cells. Cells were plated at a density of 20,000 cells per well and transfected using electroporation with 0.19 μM, 0.56 μM, 1.67 μM, and 5.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and PKK mRNA levels were measured by quantitative real-time PCR. Human PKK primer probe set RTS3454 was used to measure mRNA levels. PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. 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. Results are presented as percent inhibition of PKK, relative to untreated control cells. 'n/a' indicates that there was no measurement done for that particular antisense oligonucleotide for that particular dose.

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

Table 155

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	32	30	73	89	0.5
546158	5	45	79	83	0.7
546188	36	55	81	83	0.4
546253	1	13	46	81	1.7
546254	51	66	80	91	0.2
546343	28	64	87	87	0.4
546825	46	73	86	88	0.2
546827	32	70	84	90	0.3
546828	39	58	87	93	0.3
546829	3	30	73	88	1.0
546846	36	45	71	82	0.5
547413	0	0	41	83	2.2
547423	37	50	92	90	0.4
547445	41	75	82	88	0.2
547456	12	67	66	80	1.0
547464	21	52	67	97	0.6
547564	51	48	82	90	0.2
547587	20	62	84	86	0.5
548758	41	47	82	94	0.4

Table 156

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	25	34	84	92	0.7
546190	33	65	86	n/a	0.4
546208	16	45	79	91	0.7
546216	62	69	88	88	0.1
546255	32	35	78	87	0.5
546268	56	50	82	93	0.1
546301	25	50	53	87	0.8
546849	23	35	83	91	0.7
546852	19	40	78	85	0.8
546889	23	54	78	91	0.6
546916	43	71	79	89	0.2
546967	20	39	76	71	0.7
547273	44	69	87	87	0.2
547276	35	44	71	77	0.6
547335	8	52	85	92	0.7

547340	46	79	88	n/a	0.2
547602	18	53	92	87	0.5
547647	1	70	72	n/a	0.8
547694	0	29	67	90	1.2

Table 157

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	58	64	77	98	0.1
546247	0	29	71	88	1.1
546251	31	60	99	89	0.5
546753	28	47	83	96	0.5
546826	17	40	87	97	0.7
546833	8	33	74	94	0.9
546854	23	39	83	94	0.6
546894	15	47	50	93	0.9
546897	40	56	71	95	0.4
546903	15	37	74	98	0.8
546986	31	49	77	89	0.5
547293	53	57	80	86	0.2
547298	32	61	74	90	0.4
547364	38	47	54	89	0.6
547373	20	7	49	86	1.1
547426	19	50	84	93	0.6
547454	19	40	58	92	0.9
547617	52	66	77	93	0.2
548770	26	54	77	91	0.5

Table 158

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	34	47	72	n/a	0.5
546214	0	0	68	85	1.3
546304	0	6	51	71	2.1
546739	35	55	57	79	0.6
546832	19	38	70	95	0.8
546847	39	57	75	89	0.4
546855	18	7	30	82	2.2
546877	0	19	75	80	1.3
546939	1	66	86	90	0.6
547349	0	8	66	76	1.6

547360	8	27	76	76	0.8
547368	0	0	31	80	2.5
547483	0	9	49	71	2.1
547575	0	34	82	93	1.1
547618	0	0	73	98	1.3
547622	0	47	79	90	0.9
547637	10	21	36	82	1.8
547731	0	0	17	56	5.0
548752	0	0	51	90	1.9

Table 159

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	21	45	67	96	0.7
546195	34	51	79	92	0.5
546198	7	3	45	92	1.3
546287	0	15	39	89	1.7
546358	0	19	71	80	1.3
546403	0	20	37	41	>5.0
546410	13	43	52	75	1.2
546412	0	1	61	62	2.3
546429	6	10	44	69	2.3
546834	1	0	30	83	2.3
547006	0	0	54	77	1.5
547294	28	59	87	86	0.4
547337	23	41	55	79	1.0
547514	18	8	51	80	1.9
547584	26	34	76	86	0.7
547585	42	57	70	95	0.4
547615	20	26	41	84	1.4
547636	0	24	79	94	1.1
548744	14	35	63	83	1.0

Table 160

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	21	39	90	97	0.6
546232	49	50	94	97	0.2
546248	25	66	87	93	0.4
546835	9	35	68	93	0.9
546848	0	18	91	97	1.0

546853	47	64	84	n/a	0.2
546870	35	42	80	95	0.5
546872	32	33	82	94	0.4
546876	0	50	85	95	0.8
547275	34	66	82	95	0.3
547341	36	58	91	95	0.3
547366	0	45	68	91	1.2
547453	25	40	54	92	0.8
547457	41	65	80	85	0.3
547616	26	50	72	89	0.6
547632	44	47	81	97	0.6
547633	12	46	78	n/a	0.7
547718	36	12	69	74	1.6
548757	18	49	82	93	0.6

Table 161

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	6	38	74	95	0.8
546291	22	32	34	72	2.0
546310	0	36	56	80	1.3
546896	0	45	82	97	0.8
546980	0	18	29	80	2.2
547009	0	9	21	63	3.6
547019	0	6	54	86	1.6
547277	2	32	34	62	2.8
547288	0	0	0	38	>5.0
547374	0	15	24	44	>5.0
547493	0	26	64	77	1.3
547520	0	25	66	64	1.1
547712	0	5	21	62	3.8
547722	0	15	32	73	2.4
547728	0	2	16	61	4.4
547780	0	10	36	55	3.9
548743	25	57	73	88	0.5
548753	0	23	49	84	1.5
548756	0	4	16	86	>5.0

Table 162

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	25	55	89	97	0.5
546188	27	69	88	97	0.4
546216	23	78	95	98	<0.2
546254	40	63	84	95	0.3
546268	0	71	92	92	0.5
546343	37	32	83	95	0.4
546825	38	82	n/a	99	0.2
546827	23	74	98	96	0.4
546828	0	64	89	97	0.2
546846	26	49	85	n/a	0.5
546967	22	45	74	92	0.7
547273	0	60	82	83	0.6
547340	34	84	96	n/a	0.3
547423	78	92	n/a	n/a	<0.2
547445	80	87	98	91	<0.2
547564	46	66	90	97	0.2
547587	38	64	91	97	0.3
547602	1	9	52	93	1.4
548758	0	72	79	n/a	0.6

Table 163

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	7	39	56	97	1.0
546190	21	34	76	98	0.7
546208	5	33	70	97	0.9
546251	19	45	91	97	0.6
546255	5	39	82	96	0.8
546739	4	62	84	86	0.6
546753	17	31	70	91	0.9
546849	13	45	84	98	0.7
546889	25	9	73	92	1.4
546897	16	17	69	97	0.8
546916	0	27	73	97	1.0
546986	7	28	69	86	1.1
547276	6	3	53	68	2.2
547293	0	45	65	70	1.3
547298	0	12	67	87	1.7
547335	0	13	73	95	1.3

547426	18	35	80	95	0.7
547617	17	37	79	98	0.7
548770	9	0	61	92	1.7

Table 164

ISIS No	0.19 μM	0.56 μM	1.67 μM	5.00 μM	IC_{50} (μM)
531231	6	56	68	97	0.8
546195	0	27	91	94	0.9
546232	0	74	95	96	0.2
546248	0	59	73	89	0.8
546832	36	49	85	97	0.4
546847	14	44	83	95	0.7
546853	4	49	74	92	0.8
546870	36	34	61	91	1.0
546872	42	13	59	99	1.4
546896	35	60	83	n/a	0.4
546939	16	71	96	95	0.4
547275	56	16	80	86	1.2
547294	4	70	84	91	0.6
547341	45	44	81	95	0.6
547457	33	42	70	83	0.6
547584	0	21	64	92	1.3
547585	0	46	89	93	0.8
547632	0	0	63	91	1.6
548743	22	47	74	96	0.6

Example 119: Dose-dependent antisense inhibition of human PKK in HepaRG™ cells

Gapmers from the studies described above exhibiting significant *in vitro* inhibition of PKK mRNA were selected and tested at various doses in HepaRG™ cells. 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, and 3.00 μM concentrations of antisense oligonucleotide. After a treatment period of approximately 16 hours, RNA was isolated from the cells and PKK mRNA levels were measured by quantitative real-time PCR. Human PKK primer probe set RTS3454 was used to measure mRNA levels. PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN®. 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. Results are presented as percent inhibition of PKK, relative to untreated control cells. 'n/a' indicates that there was no measurement done for that particular antisense oligonucleotide for that particular dose.

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

Table 165

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
547747	24	29	81	89	0.4
547769	12	17	80	96	0.6
547824	45	73	78	n/a	0.1
547835	44	27	53	79	0.9
547843	0	52	80	91	0.4
547857	36	66	77	93	0.2
547870	0	44	80	97	0.6
547943	33	70	87	90	0.2
547946	0	47	74	n/a	0.5
547947	24	58	81	93	0.3
547998	55	73	91	91	0.1
548004	24	47	80	92	0.3
548010	0	11	49	64	1.4
548047	50	62	76	95	0.1
548147	59	94	80	n/a	0.0
548338	41	58	79	95	0.2
548348	19	46	67	91	0.4
548409	21	60	90	93	0.3
548557	5	47	82	95	0.4

Table 166

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
547747	8	61	90	92	0.3
547807	26	71	61	94	0.4
547922	67	75	81	92	0.0
547927	56	64	92	88	0.1
547948	60	80	88	97	0.0
547979	56	58	94	97	0.1
548005	53	49	71	95	0.4
548024	28	57	84	82	0.3
548043	14	60	90	92	0.3
548055	43	57	50	88	0.3
548106	53	54	82	94	0.1
548109	50	92	79	85	0.1

548155	49	50	70	81	0.3
548180	11	59	71	88	0.4
548278	3	59	78	93	0.4
548343	61	67	88	92	0.0
548558	53	61	78	95	0.1
548570	20	40	70	94	0.4
548583	43	46	93	88	0.2

Table 167

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
547747	3	44	72	90	0.5
547849	36	52	67	n/a	0.3
547851	16	46	83	n/a	0.4
547859	29	56	83	78	0.3
547862	26	71	69	n/a	0.3
547877	29	66	83	n/a	0.2
547942	25	51	91	n/a	0.3
547997	39	68	n/a	82	0.2
548046	7	35	64	77	0.7
548048	49	66	86	92	0.1
548061	26	61	59	n/a	0.4
548070	26	35	48	63	1.1
548125	33	50	81	73	0.3
548195	5	23	61	76	0.8
548265	47	69	78	67	0.1
548410	31	58	85	82	0.2
548424	17	67	86	72	0.3
548425	41	57	68	80	0.2
548547	30	41	76	90	0.4

Table 168

ISIS No	0.11 μM	0.33 μM	1.00 μM	3.00 μM	IC_{50} (μM)
547747	16	59	85	96	0.3
547808	19	22	48	71	1.1
547861	7	40	75	84	0.5
548069	6	0	27	66	1.9
548128	14	29	49	66	1.1
548170	0	8	26	65	2.0
548174	20	18	29	62	2.0

548197	33	37	51	75	0.8
548201	0	7	70	85	0.8
548217	22	24	54	71	0.9
548220	0	0	0	6	>3
548247	16	50	62	82	0.5
548422	0	32	71	93	0.7
548479	2	52	82	97	0.4
548486	20	48	77	92	0.4
548521	21	0	3	1	>3
548655	0	0	8	33	>3
548667	0	37	73	86	0.7
548668	10	30	61	84	0.7

Example 120: Efficacy of antisense oligonucleotides targeting human PKK in transgenic mice

Transgenic mice containing a 37,390 base pair fragment of the human KLKB1 gene sequence (chromosome 4: position 187148672-187179625, accession no: NC_000004.11) were treated with ISIS antisense oligonucleotides selected from studies described above, which were evaluated for efficacy in this model.

Treatment

Groups of transgenic mice were injected subcutaneously twice a week for 3 weeks with 2.5 mg/kg/week, 5.0 mg/kg/week, 10 mg/kg/week or 20 mg/kg/week of ISIS 546232, ISIS 546251, ISIS 546254, ISIS 546343, ISIS 546828, ISIS 547455, ISIS 547457, ISIS 547927, and ISIS 548048. One group of transgenic mice was injected subcutaneously twice a week for 3 weeks with PBS. Mice were euthanized 48 hours after the last dose, and organs and plasma were harvested for further analysis.

RNA analysis

To evaluate the effect of ISIS oligonucleotides on target reduction, RNA was extracted from liver tissue for real-time PCR analysis of human PKK. Results are presented as percent inhibition of PKK mRNA, relative to PBS control. As shown in Table 169, treatment with ISIS antisense oligonucleotides resulted in significant reduction of PKK mRNA in comparison to the PBS control.

Table 169

Percent Inhibition of PKK mRNA in the transgenic mice liver relative to the PBS control

ISIS No	Dose	% inhibition
547927	20	71
	10	93
	5	52

	2.5	35
547455	20	62
	10	45
	5	69
	2.5	0
546232	20	84
	10	30
	5	53
	2.5	57
546254	20	83
	10	84
	5	55
	2.5	31
546343	20	86
	10	66
	5	n/a
	2.5	46
548048	20	80
	10	72
	5	77
	2.5	7
546828	20	83
	10	32
	5	62
	2.5	77
546251	20	79
	10	66
	5	51
	2.5	13
547457	20	62
	10	45
	5	69
	2.5	0

Protein analysis

Plasma PKK protein levels were evaluated in all groups. Results are presented as percent inhibition of PKK protein, relative to PBS control. As shown in Table 170, treatment with ISIS antisense oligonucleotides resulted in significant reduction of PKK protein levels in comparison to the PBS control.

Table 170

Percent reduction of PKK protein levels in the transgenic mice relative to the PBS control

ISIS No	Dose	% inhibition
547927	20	80
	10	n/a

	5	21
	2.5	25
547455	20	78
	10	32
	5	0
	2.5	0
546232	20	79
	10	33
	5	6
	2.5	0
546254	20	76
	10	51
	5	36
	2.5	0
546343	20	79
	10	38
	5	n/a
	2.5	0
548048	20	98
	10	89
	5	70
	2.5	23
546828	20	93
	10	36
	5	25
	2.5	0
546251	20	69
	10	52
	5	30
	2.5	22
547457	20	60
	10	31
	5	4
	2.5	0

Example 121: Effect of ISIS antisense oligonucleotides targeting human PKK in cynomolgus monkeys

Cynomolgus monkeys were treated with ISIS antisense oligonucleotides selected from studies described above. Antisense oligonucleotide efficacy and tolerability were evaluated. The human antisense oligonucleotides tested are cross-reactive with the rhesus genomic sequence (GENBANK Accession No. NW_001118167.1 truncated from nucleotides 2358000 to 2391000 and designated herein as SEQ ID NO: 18). The target start site of each oligonucleotide to SEQ ID NO: 18 is presented in Table 171. 'Mismatches' indicates that the number of nucleotides by which the oligonucleotide is mismatched to the rhesus sequence. 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. 'n/a' indicates that the oligonucleotide is has more than 3 mismatches with the rhesus gene sequence.

Table 171

Antisense oligonucleotides complementary to SEQ ID NO: 18

ISIS No	Target Start Site	Mismatches	Sequence	Chemistry	SEQ ID NO.
547927	22059	1	ATGGTCCGACACACAA	Deoxy, MOE and cEt	1548
546232	n/a	n/a	AGGAACTTGGTGTGCCACTT	5-10-5 MOE	526
547455	27391	0	ATATCATGATTCCCTTCTGA	5-10-5 MOE	657
546254	23858	1	TGCAAGTCTCTTGGCAAACA	5-10-5 MOE	570
546343	30532	0	CCCCCTTCTTTATAGCCAGC	5-10-5 MOE	705
548048	27397	0	CGATATCATGATTCCC	Deoxy, MOE and cEt	1666
546828	13632	1	ACAGTATCACTGTACTAGTT	5-10-5 MOE	904
546251	23846	0	GGCAAACATTCACTCCTTTA	5-10-5 MOE	566
547457	27397	0	AAGGCGATATCATGATTCCC	5-10-5 MOE	660

Treatment

Prior to the study, the monkeys were kept in quarantine for a 30-day period, during which the animals were observed daily for general health. The monkeys were 2-4 years old and weighed between 2 and 4 kg. Ten groups of four randomly assigned male cynomolgus monkeys each were injected subcutaneously with ISIS oligonucleotide or PBS. PBS solution or ISIS oligonucleotides at a dose of 40 mg/kg were administered initially with a loading regimen consisting of four doses on the first week of the study (days 1, 3, 5, and 7), followed by a maintenance regimen consisting of once weekly administration starting on Day 14 (weeks 2 to 13). Subcutaneous injections were performed in clock-wise rotations at 4 sites on the back; one site per dose. The injection sites were delineated by tattoo, while sedated using ketamine, and were separated by a minimum of 3 cm.

During the study period, the monkeys were observed a minimum of once 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 promptly reported to the responsible veterinarian and the Study Director. Any animal in poor health or in a possible moribund condition was identified for further monitoring and possible euthanasia. For example, two monkeys treated with ISIS 547445 were euthanized due to subdued behavior, lateral position, lack of response to stimuli and decreased respiration. The protocols described in the Example were approved by the Institutional Animal Care and Use Committee (IACUC).

Target Reduction

RNA analysis

On day 87 or 88, 48 hours after the final dose, RNA was extracted from liver tissue for real-time PCR analysis of PKK using primer probe set RTS3455 (forward sequence CCTGTGTGGAGGGTCACTCA, designated herein as SEQ ID NO: 23; reverse sequence CCACTATAGATGCGCCAAACATC, designated herein as SEQ ID NO: 24; probe sequence CCCACTGCTTTGATGGGCTTCCC, designated herein as SEQ ID NO: 25). The results were normalized to the housekeeping gene, Cyclophilin. Results are presented as percent inhibition of PKK mRNA, relative to PBS control. As shown in Table 172, treatment with ISIS antisense oligonucleotides resulted in significant reduction of PKK mRNA in comparison to the PBS control.

Table 172

Percent Inhibition of PKK mRNA in the cynomolgus monkey liver relative to the PBS control

ISIS No	% inhibition
546232	88
546251	90
546254	88
546343	74
546828	45
547455	90
547457	89
547927	54
548048	95

Protein analysis

Approximately 0.9 mL of blood was collected each time from all available animals at pre-dose, day 17, day 31, day 45, day 59, and day 73, and placed in tubes containing 3.2% sodium citrate. The tubes were centrifuged (3000 rpm for 10 min at room temperature) to obtain plasma. PKK protein levels were measured in the plasma by ELISA. The results are presented in Table 173, expressed as percentage inhibition compared to the PBS control levels. The results indicate that ISIS oligonucleotides significantly reduced PKK protein levels.

Table 173

PKK protein level reduction (%) in the cynomolgus monkey plasma relative to control levels

	Day 17	Day 31	Day 45	Day 59	Day 73
ISIS 546232	53	58	72	75	70
ISIS 546251	71	75	75	81	77
ISIS 546254	38	51	63	74	73
ISIS 546343	56	74	69	70	70
ISIS 546828	0	8	23	39	39

ISIS 547455	26	33	43	58	58
ISIS 547457	68	75	79	76	80
ISIS 547927	8	0	15	10	18
ISIS 548048	90	93	95	95	95

Tolerability studies

Liver function

To evaluate the effect of ISIS oligonucleotides on hepatic function, the monkeys were fasted overnight. Approximately, 1.5 mL of blood samples were collected from all the study groups. Blood was collected in 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. Levels of various liver function markers were measured using a Toshiba 120FR NEO chemistry analyzer (Toshiba Co., Japan). The results are presented in Table 174 and indicate that antisense oligonucleotides had no effect on liver function outside the expected range for antisense oligonucleotides.

Table 174

Liver function markers in cynomolgus monkey plasma

	Albumin (g/dL)	AST (IU/L)	ALT (IU/L)
PBS	4.2	48	60
ISIS 546232	4.1	63	140
ISIS 546251	3.7	51	58
ISIS 546254	3.8	68	54
ISIS 546343	4.3	49	76
ISIS 546828	3.7	75	67
ISIS 547455	3.8	56	61
ISIS 547457	4.0	54	52
ISIS 547927	4.2	59	61
ISIS 548048	4.2	44	47

Hematology

To evaluate any effect of ISIS oligonucleotides in cynomolgus monkeys on hematologic parameters, blood samples of approximately 1.2 mL of blood was collected pre-dose and on day 87 or day 88 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, platelet count, hemoglobin content and hematocrit, using an ADVIA2120i hematology analyzer (SIEMENS, USA). The data is presented in Table 175.

The data indicate treatment with most of the oligonucleotides did not cause any changes in hematologic parameters outside the expected range for antisense oligonucleotides at this dose.

Table 175

Hematological parameters in cynomolgus monkeys

	RBC (x 10^6/μL)	Platelets (x $10^{3/}$μL)	WBC (x 10^3/μL)	Hemoglobin (g/dL)	HCT (%)
PBS	5.4	458	13	13.1	43
ISIS 546232	5.4	391	11	12.9	42
ISIS 546251	5.7	419	8	12.9	43
ISIS 546254	5.3	436	11	12.4	41
ISIS 546343	5.5	373	14	12.6	42
ISIS 546828	6.0	408	11	12.9	43
ISIS 547455	4.5	448	13	10.2	34
ISIS 547457	6.4	367	10	13.8	45
ISIS 547927	5.2	461	45	12.5	41
ISIS 548048	5.9	393	11	13.4	44

Kidney function

To evaluate the effect of ISIS oligonucleotides on kidney function, the monkeys were fasted overnight. Approximately, 1.5 mL of blood samples were collected from all the study groups. Blood was collected in 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. Levels of BUN and creatinine were measured using a Toshiba 120FR NEO chemistry analyzer (Toshiba Co., Japan). Results are presented in Table 176, expressed in mg/dL. 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 546254 was well tolerated in terms of the kidney function of the monkeys.

Kidney function was also assessed by urinalysis. Fresh urine from all animals was collected using a clean cage pan on wet ice. Food was removed overnight the day before fresh urine collection was done but water was supplied. The total protein and creatinine levels were measured using a Toshiba 120FR NEO automated chemistry analyzer (Toshiba Co., Japan) and the protein to creatinine ratio was calculated. The results are presented in Table 177.

Table 176

Plasma BUN and creatinine levels (mg/dL) in cynomolgus monkeys

	BUN	Creatinine
PBS	22.8	0.9
ISIS 546232	22.7	1.0
ISIS 546251	25.4	1.1
ISIS 546254	25.7	0.9
ISIS 546343	26.2	1.0
ISIS 546828	24.7	0.9
ISIS 547455	29.4	0.9
ISIS 547457	24.3	1.0
ISIS 547927	22.3	1.0
ISIS 548048	21.9	0.9

Table 177

Urine protein/creatinine ratio in cynomolgus monkeys

	Ratio
ISIS 546232	0.03
ISIS 546251	0.12
ISIS 546254	0.04
ISIS 546343	0.01
ISIS 546828	0.03
ISIS 547455	0.70
ISIS 547457	0.03
ISIS 547927	0.04
ISIS 548048	0.03
PBS	0.06

C-reactive protein level analysis

To evaluate any inflammatory effect of ISIS oligonucleotides in cynomolgus monkeys, the monkeys were fasted overnight. Approximately, 1.5 mL of blood samples were collected from all the study groups. Blood was collected in 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. C-reactive protein (CRP), which is synthesized in the liver and which serves as a marker of inflammation, was measured using a Toshiba 120FR NEO chemistry analyzer (Toshiba Co., Japan). Complement C3 was also measured

similarly, and the data is presented as a percentage of baseline values. The results are presented in Table 178 and indicate that treatment with ISIS oligonucleotides did not cause any inflammation in monkeys.

Table 178

C-reactive protein and C3 levels in cynomolgus monkey plasma

	CRP (mg/dL)	C3 (% of baseline)
PBS	0.2	73
ISIS 546232	0.5	50
ISIS 546251	0.7	62
ISIS 546254	0.8	61
ISIS 546343	0.2	60
ISIS 546828	0.6	56
ISIS 547455	1.9	64
ISIS 547457	0.3	53
ISIS 547927	0.2	73
ISIS 548048	0.2	69

Example 122: Antisense inhibition of murine PKK mRNA in mouse primary hepatocytes

Antisense oligonucleotides targeting a murine PKK nucleic acid were designed and tested for their effects on PKK mRNA *in vitro*. Cultured mouse primary hepatocytes at a density of 10,000 cells per well were transfected using Cytofectin reagent with 12.5 nM, 25.0 nM, 50.0 nM, 100.0 nM, and 200.0 nM of antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and mouse PKK mRNA levels were measured by quantitative real-time PCR using the murine primer probe set RTS3313 (forward sequence TGCCTGCTGTTCAGCTTTCTC, designated herein as SEQ ID NO: 2228; reverse sequence TGGCAAAGTCCCTGTAATGCT, designated herein as SEQ ID NO: 2229; probe sequence CGTGACTCCACCCAAAGAGACAAATAAACG, designated herein as SEQ ID NO: 2230). PKK mRNA levels were adjusted according to total RNA content, as measured by RIBOGREEN.

The chimeric antisense oligonucleotides were designed as 5-10-5 MOE gapmers. The gapmers are 20 nucleotides in length, wherein the central gap segment is comprised of ten 2'-deoxynucleosides and is flanked on both sides (in the 5' and 3' directions) by wings comprising 5 nucleosides each. Each nucleoside in the 5' wing segment and each nucleoside in the 3' wing segment has a 2'-O-methoxyethyl modification. The internucleoside linkages throughout each gapmer are phosphorothioate linkages. All cytosine residues throughout each gapmer are 5-methylcytosines. Results demonstrate that PKK mRNA levels were significantly reduced in a dose dependent manner.

In one specific example, ISIS 482584 (GGCATATTGGTTTTTGGAAT; SEQ ID NO: 2244) reduced PKK mRNA in a dose dependent manner yielding a half maximal inhibitory concentration (IC_{50}) of 84 nM (see Table 179). ISIS 482584 is targeted to SEQ ID NO: 11 (GENBANK Accession No. NM_008455.2) and has a target start site of 1586 and a target stop site of 1605. "Target start site" indicates the 5'-most nucleotide to which the gapmer is targeted. "Target stop site" indicates the 3'-most nucleotide to which the gapmer is targeted.

Table 179
Dose-dependent inhibition of mouse PKK mRNA levels by ISIS 482584

Dose	% inhibition
12.5 nM	0
25.0 nM	47
50.0 nM	27
100.0 nM	60
200.0 nM	82

Example 123: Antisense inhibition of PKK mRNA in BALB/c mice

ISIS 482584 was tested for its effect on murine PKK mRNA *in vivo*.

Treatment

Six groups of male BALB/c mice each were treated with 2.5 mg/kg, 5.0 mg/kg, 10.0 mg/kg, 20.0 mg/kg, 40.0 mg/kg, or 80.0mg/kg of ISIS 482584, administered subcutaneously twice a week for 3 weeks (weekly doses of 5.0 mg/kg, 10.0 mg/kg, 20.0 mg/kg, 40.0 mg/kg, 80.0 mg/kg, or 160.0 mg/kg). A control group of BALB/c mice was treated with PBS, administered subcutaneously twice a week for 3 weeks. Two days after the last dose of antisense oligonucleotide or PBS, mice from all groups were anesthetized with 150 mg/kg ketamine mixed with 10 mg/kg xylazine, administered by intraperitoneal injection. Liver was collected for RNA analysis.

RNA Analysis

RNA was extracted from liver tissue for real-time PCR analysis of PKK. PKK mRNA levels were measured using the murine primer probe set (forward sequence ACAAGTGCATTTTACAGACCAGAGTAC, designated herein as SEQ ID NO: 2231; reverse sequence GGTTGTCCGCTGACTTTATGCT, designated herein as SEQ ID NO: 2232; probe sequence AAGCACAGTGCAAGCGGAACACCC, designated herein as SEQ ID NO: 2233). Results are presented as percent inhibition of PKK, relative to PBS control. As shown in Table 180, treatment with ISIS 482584 resulted in significant dose-dependent reduction of PKK mRNA in comparison to the PBS control.

Table 180
Dose-dependent reduction of PKK mRNA in BALB/c mice liver

Dose (mg/kg/wk)	% inhibition
5	3
10	42
20	68
40	85
80	91
160	94

Protein Analysis

Plasma was collected in tubes containing sodium citrate as an anticoagulant. The samples were run on a 4-12% gradient SDS-polyacrylamide gel (Invitrogen), followed by immunoblotting with murine PKK antibody (R&D Systems). Blots were incubated with secondary fluorophore-labeled antibodies (LI-COR) and imaged in an Odyssey Imager (LI-COR). Results are presented as percent inhibition of PKK, relative to PBS control. As shown in Table 181, treatment with ISIS 482584 resulted in significant dose-dependent reduction of PKK plama protein in comparison to the PBS control.

Table 181
Dose-dependent reduction of PKK protein in BALB/c mice plasma

Dose (mg/kg/wk)	% inhibition
5	5
10	24
20	47
40	76
80	81
160	n.d.

n.d. = no data

Example 124: *In vivo* effect of antisense inhibition of murine PKK in an angioedema mouse model

Hereditary angioedema (HAE) is characterized by local swelling and increase in vascular permeability in subcutaneous tissues (Morgan, B.P. N. Engl. J. Med. 363: 581-83, 2010). It is caused by a deficiency of the C1 inhibitor, a protein of the complement system. Two mouse models were used in this study including an established mouse model of C1-INH deficiency and a captopril-induced edema model, both of which cause vascular permeability, a hallmark of HAE. Reversal of vascular permeability is accompanied by increased plasma levels of high molecular weight kininogen (HMWK).

In the first model, angioedema was induced by treatment with Captopril, a known antihypertensive agent, which increases vascular permeability in mice and replicates the pathology of hereditary angioedema.

In the second model, angioedema was induced by treatment with ISIS 461756, an antisense oligonucleotide which targets murine C1 inhibitor mRNA, which increases vascular permeability in mice and replicates the pathology of hereditary angioedema. ISIS 461756 (SEQ ID NO: 2245; AAAGTGGTTGATACCCTGGG) is a 5-10-5 MOE gapmer targeting nucleosides 1730-1749 of NM_009776.3 (SEQ ID NO: 2243).

The effect of HOE-140 and ISIS 482584, an antisense oligonucleotide inhibitor of PKK, were evaluated in the Captopril and ISIS 461756-induced mouse models of vascular permeability. Some of the murine groups were treated with HOE-140, a selective antagonist of the bradykinin B2 receptor, which blocks vasodilation and vascular permeability (Cruden and Newby, Expert Opin. Pharmacol. 9: 2383-90, 2008). Other mice were treated with ISIS 482584, which inhibits PKK mRNA expression. The effect of treatment with HOE-140 was compared with the effect of treatment with ISIS 482584.

Treatment

The various treatment groups for this assay are presented in Table 182.

Group 1 consisted of 4 C57BL/6J-Tyrc-2J mice treated with PBS administered subcutaneously twice a week for 4 weeks. No other treatment was administered to Group 1 which served as a control group to measure the basal level of vascular permeability.

Group 2 consisted of 8 C57BL/6J-Tyrc-2J mice treated with PBS administered subcutaneously twice a week for 4 weeks. At the end of the treatment, the mice were intraperitoneally administered 20 μg of captopril. Group 2 served as a PBS control group for captopril-induced vascular permeability.

Group 3 consisted of 8 C57BL/6J-Tyrc-2J mice treated with PBS administered subcutaneously twice a week for 4 weeks. On day 14, the mice were treated with 50 mg/kg of the antisense oligonucleotide targeting C1 inhibitor, ISIS 461756, administered subcutaneously twice a week for 2 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 3 served as a PBS control group for captopril and ISIS 461756-induced vascular permeability.

Group 4 consisted of 8 C57BL/6J-Tyrc-2J mice treated with PBS administered subcutaneously twice a week for 4 weeks. On day 14, the mice were treated with 50 mg/kg of the antisense oligonucleotide targeting C1 inhibitor, ISIS 461756, administered subcutaneously twice a week for 2 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. The mice were then also intraperitoneally administered 30 μg of HOE-140. Group 4 served as a positive control for inhibition of vascular permeability with HOE-140.

Group 5 consisted of 8 C57BL/6J-Tyrc-2J mice treated with 40 mg/kg of control oligonucleotide ISIS 141923, a 5-10-5 MOE gapmer with no known murine target, (CCTTCCCTGAAGGTTCCTCC; SEQ ID NO: 2246) administered subcutaneously twice a week for 4 weeks. On day 14, the mice were treated with

50 mg/kg of the antisense oligonucleotide targeting C1 inhibitor, ISIS 461756, administered subcutaneously twice a week for 2 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 5 served as a control group for captopril and ISIS 461756-induced vascular permeability.

Group 6 consisted of 8 C57BL/6J-Tyrc-2J mice and was treated with 40 mg/kg of ISIS 482584 administered subcutaneously twice a week for 4 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 6 served as the experimental treatment group for examining the effect of PKK ASO on captopril-induced vascular permeability.

Group 7 consisted of 8 C57BL/6J-Tyrc-2J mice treated with 40 mg/kg of ISIS 482584 administered subcutaneously twice a week for 4 weeks. On day 14, the mice were treated with 50 mg/kg of the antisense oligonucleotide targeting C1 inhibitor, ISIS 461756, administered subcutaneously twice a week for 2 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 7 served as the experimental treatment group for examining the effect of PKK ASO on captopril and ISIS 461756-induced vascular permeability.

All the groups were then injected with 30 mg/kg of Evans Blue solution into the tail vein. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, ears, and intestines were harvested. Blood samples were taken through cardiac puncture.

Table 182
Treatment groups

Group No.	Treatment	Captopril	ISIS 461756	HOE-140
1. (N=4)	PBS	No	No	No
2. (N=8)	PBS	Yes	No	No
3. (N=8)	PBS	Yes	Yes	No
4. (N=8)	PBS	Yes	Yes	Yes
5. (N=8)	ISIS 141923	Yes	Yes	No
6. (N=8)	ISIS 482584	Yes	No	No
7. (N=8)	ISIS 482584	Yes	Yes	No

Quantification of vascular permeability

The harvested tissues from the feet, colon, ears, and intestines were placed separately in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing ear and feet tissue was heated to 55^0C and left overnight. The color intensity of the dye-infused formamide solution was then

measured at OD_{600nm}, and is presented in Table 183. Mice displaying any manifestation of angioedema take up more dye and, therefore, demonstrate high OD values.

As presented in Table 183, treatment with ISIS 482584 prevents vascular permeability in mice treated with captopril (Group 6) and in mice treated with captopril and ISIS 461756 (Group 7) compared to the respective PBS control groups (Groups 2 and 3). Measures of vascular permeability in mice of Groups 6 and 7 were also reduced in most of the tissues in comparison to the mice treated with the control oligonucleotide, ISIS 141923 (Group 5), where vascular permeability was induced with captopril and ISIS 461756. Measures of vascular permeability in the colon and feet tissues of both the treatment groups (Groups 6 and 7) were comparable to basal levels, as observed in mice treated with only PBS (Group 1). Reduction in vascular permeability in mice treated with ISIS 482584 was comparable to that seen in mice treated with the bradykinin 2 receptor antagonist, HOE140, which served as a positive control in this assay.

Therefore, antisense inhibition of PKK mRNA may be beneficial for the treatment and prevention of vascular permeability, which is symptomatic of HAE.

Table 183

OD_{600nm} of Evans Blue dye to measure vascular permeability

Group No.	Treatment	Captopril	ISIS 461756	HOE-140	Colons	Intestines	Feet	Ears
1	PBS	No	No	No	0.26	0.16	0.11	0.02
2	PBS	Yes	No	No	0.49	0.29	0.12	0.07
3	PBS	Yes	Yes	No	0.49	0.34	0.11	0.12
4	PBS	Yes	Yes	Yes	0.14	0.18	0.07	0.09
5	ISIS 141923	Yes	Yes	No	0.44	0.29	0.14	0.08
6	ISIS 482584	Yes	No	No	0.27	0.30	0.07	0.14
7	ISIS 482584	Yes	Yes	No	0.21	0.34	0.07	0.06

Quantification of High Molecular Weight Kininogen (HMWK)

Western blot quantification of HMWK from blood samples are presented in Figure 1.

As shown in Figure 1, samples from Groups 1 and 2 have low levels of HMWK as compared to Groups 6 and 7 indicating that vascular permeability is reversed in Groups 6 and 7. Also as shown in Figure 1, samples from Groups 1 and 2 have increased HMWK cleavage product as compared to Groups 6 and 7. Thus, lack of HMWK is caused by PKK cleavage of HMWK into cleavage products (including bradykinin and HKa).

Example 125: *In vivo* effect of antisense inhibition of murine PKK on basal permeability and captopril-induced permeability in mice

Basal permeability is the level of vascular permeability occurring in the tissues of naïve, untreated mice. The effect of ISIS 482584 in the prevention of vascular permeability, either basal or captopril-induced, was evaluated.

Treatment

The various treatment groups for this assay are presented in Table 184.

Group 1 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 4 weeks. No other treatment was administered to Group 1 which served as a control group to measure the basal levels of vascular permeability.

Group 2 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 4 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 2 served as the negative control group for captopril-induced vascular permeability.

Group 3 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 4 weeks. At the end of the treatment period, the mice were intraperitoneally administered 30 μg of HOE-140. Group 3 served as a positive control for inhibition of basal vascular permeability.

Group 4 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 4 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. The mice were also intraperitoneally administered 30 μg of HOE-140. Group 4 served as a positive control for inhibition of captopril-induced vascular permeability.

Group 5 consisted of 8 mice and was treated with 40 mg/kg of ISIS 482584 administered subcutaneously twice a week for 4 weeks. Group 5 served as an experimental treatment group for examining the effect of ISIS 482584 on basal vascular permeability.

Group 6 consisted of 8 mice and was treated with 40 mg/kg of ISIS 482584 administered subcutaneously twice a week for 4 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 6 served as an experimental treatment group for examining the effect of ISIS 482584 on captopril-induced vascular permeability.

All the groups were then injected with 30 mg/kg of Evans Blue solution. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, ears, and intestines were harvested.

Table 184
Treatment groups

Group No.	Treatment	Captopril	HOE-140
1. (N=8)	PBS	No	No
2. (N=8)	PBS	Yes	No
3. (N=8)	PBS	No	Yes
4. (N=8)	PBS	Yes	Yes
5. (N=8)	ISIS 482584	No	No
6. (N=8)	ISIS 482584	Yes	No

Quantification of vascular permeability

The harvested tissues from the feet, colon, intestine, and ears were placed separately in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing feet and ear tissue was heated to 55^0C and left overnight. The color intensity of the dye-infused formamide solution was then measured at OD_{600nm}, and is presented in Table 185. Mice displaying any manifestation of angioedema take up more dye and, therefore, demonstrate high OD values.

As presented in Table 185, mice treated with ISIS 482584 demonstrated reduced basal vascular permeability compared to the PBS control (Group 5 vs. Group 1). The reduction in basal vascular permeability by treatment with ISIS 482584 was comparable to that caused by treatment with HOE-140 (Group 3, which served as the positive control). Mice treated with ISIS 482584 also demonstrated reduced captopril-induced vascular permeability in most tissues compared to the PBS control (Group 6 vs. Group 2). The reduction in captopril-induced vascular permeability by treatment with ISIS 482584 was comparable to that caused by treatment with HOE-140 (Group 4, which served as the positive control).

Table 185
OD_{600nm} of Evans Blue dye to measure vascular permeability

Group No.	Treatment	Captopril	HOE-140	Colon	Feet	Intestine	Ears
1	PBS	No	No	0.27	0.08	0.23	0.06
2	PBS	Yes	No	0.61	0.08	0.24	0.01
3	PBS	No	Yes	0.18	0.06	0.21	0.03
4	PBS	Yes	Yes	0.29	0.03	0.14	0.00
5	ISIS 482584	No	No	0.19	0.07	0.22	0.04
6	ISIS 482584	Yes	No	0.37	0.05	0.22	0.00

Example 126: Dose-dependent effect of antisense inhibition of murine PKK on captopril-induced vascular permeability

The effect of varying doses on ISIS 482584 on captopril-induced vascular permeability was evaluated.

Treatment

The various treatment groups for this assay are presented in Table 186.

Group 1 consisted of 4 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. No other treatment was administered to Group 1 which served as a control group to measure the basal levels of vascular permeability.

Group 2 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 2 served as the control group for captopril-induced vascular permeability.

Group 3 consisted of 4 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. The mice were also intraperitoneally administered 30 μg of Icatibant (HOE-140). Group 4 served as a positive control for inhibition of captopril-induced vascular permeability.

Groups 4, 5, 6, 7, 8, and 9 consisted of 8 mice each and were treated with 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg (corresponding to 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, or 160 mg/kg per week), respectively of ISIS 482584 administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice of all the groups were intraperitoneally administered 20 μg of captopril. Groups 4-9 served as the experimental treatment groups for examining the effect of varying doses of ISIS 482584 on captopril-induced vascular permeability.

All the groups were then injected with 30 mg/kg of Evans Blue solution in the tail vein. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, ears, and intestines were harvested. Blood samples were taken through cardiac puncture.

Table 186
Treatment groups

Group No.	Treatment	Dose (mg/kg/wk)	Captopril	HOE-140
1. (N=4)	PBS	-	No	No
2. (N=8)	PBS	-	Yes	No
3. (N=4)	PBS	-	Yes	Yes

4. (N=8)	ISIS 482584	160	Yes	No
5. (N=8)	ISIS 482584	80	Yes	No
6. (N=8)	ISIS 482584	40	Yes	No
7. (N=8)	ISIS 482584	20	Yes	No
8. (N=8)	ISIS 482584	10	Yes	No
9. (N=8)	ISIS 482584	5	Yes	No

Quantification of vascular permeability

The harvested tissues were placed in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing feet and ear tissue was heated to 55^{0}C and left overnight. The color intensity of the dye-infused formamide solution was then measured at OD_{600nm}, and is presented in Table 187. Mice displaying any manifestation of angioedema take up more dye and, therefore, demonstrate high OD values.

As presented in Table 187, mice treated with higher doses of ISIS 482584 (Groups 4, 5, and 6) had reduced levels of captopril-induced vascular permeability compared to the corresponding PBS control group (Group 2). The reduction in vascular permeability in mice of these treatment groups (Groups 4 and 5) was comparable to the levels of basal vascular permeability (as shown in Group 1) as well as in mice treated with HOE-140 (Group 3).

Table 187

OD_{600nm} of Evans Blue dye to measure vascular permeability

Group No.	Treatment	Dose (mg/kg)	Captopril	HOE-140	Colon	Feet	Intestine	Ears
1	PBS	-	No	No	0.16	0.07	0.13	0.01
2	PBS	-	Yes	No	0.39	0.12	0.18	0.07
3	PBS	-	Yes	Yes	0.15	0.03	0.10	0.04
4	ISIS 482584	160	Yes	No	0.26	0.10	0.15	0.05
5	ISIS 482584	80	Yes	No	0.21	0.04	0.17	0.03
6	ISIS 482584	40	Yes	No	0.36	0.10	0.20	0.05
7	ISIS 482584	20	Yes	No	0.40	0.11	0.20	0.07
8	ISIS 482584	10	Yes	No	0.41	0.10	0.19	0.05
9	ISIS 482584	5	Yes	No	0.41	0.10	0.17	0.05

Quantification of vascular leakage

The blood drawn through cardiac puncture was immediately mixed with 3 times the volume of ice-cold ethanol. The solution was centrifuged at 15,000 g for 20 minutes at 4^{0}C to remove cell debris and

precipitated plasma proteins. The ethanol extracts were further purified by ultra-filtration through a 10 kDa MWCO filter. The color intensity of the ethanol extracted plasma solution was then measured at OD_{620nm}. The results are presented in Table 188 as percentage increase or decrease of the OD values of the Group 1 PBS control. It was expected that tissues from mice displaying manifestation of angioedema would leak more dye from the plasma and, therefore, demonstrate low OD values, whereas treatment groups may display higher OD values due to reduced vascular leakage. Mice treated with 160 mg/kg/week and 80 mg/kg/week of ISIS 482584 (Groups 4 and 5) demonstrated less vascular leakage compared to the PBS negative control treated with captopril (Group 2). The results from Groups 4 and 5 were comparable to the positive control treated with HOE-140 (Group 3).

Table 188

Percentage of OD_{620nm} of Evans Blue dye compared to the PBS basal control to measure vascular leakage

Group No.	Treatment	Dose (mg/kg)	Captopril	HOE-140	Plasma
2	PBS	-	Yes	No	-43
3	PBS	-	Yes	Yes	5
4	ISIS 482584	160	Yes	No	91
5	ISIS 482584	80	Yes	No	40
6	ISIS 482584	40	Yes	No	-31
7	ISIS 482584	20	Yes	No	-26
8	ISIS 482584	10	Yes	No	-20
9	ISIS 482584	5	Yes	No	-23

Example 127: Dose-dependent effect of antisense inhibition of murine PKK on basal permeability in mice

The effect of varying doses on ISIS 482584 on basal vascular permeability was evaluated.

Treatment

The various treatment groups for this assay are presented in Table 189.

Group 1 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. No other treatment was administered to Group 1 which served as a control group to measure the basal levels of vascular permeability.

Group 2 consisted of 4 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice were intraperitoneally administered 30 μg of HOE-140. Group 2 served as a positive control for inhibition of basal vascular permeability.

Groups 3, 4, 5, 6, 7, and 8 consisted of 8 mice each and were treated with 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg (corresponding to 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, or 160 mg/kg per week), respectively of ISIS 482584 administered subcutaneously twice a week for 3 weeks. Groups 4-9 served as the experimental treatment groups for examining the effect of varying doses of ISIS 482584 on basal vascular permeability.

All the groups were then injected with 30 mg/kg of Evans Blue solution in the tail vein. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, and ears were harvested and examined for permeability defects. Blood samples were taken through cardiac puncture.

Table 189
Treatment groups

Group No.	Treatment	Dose (mg/kg/week)	HOE-140
1. (N=8)	PBS	-	No
2. (N=4)	PBS	-	Yes
3. (N=8)	ISIS 482584	160	No
4. (N=8)	ISIS 482584	80	No
5. (N=8)	ISIS 482584	40	No
6. (N=8)	ISIS 482584	20	No
7. (N=8)	ISIS 482584	10	No
8. (N=8)	ISIS 482584	5	No

Quantification of vascular permeability

The harvested tissues from the feet, colon, and ears were placed in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing feet and ear tissue was heated to 55^{0}C and left overnight. The color intensity of the dye-infused formamide solution was then measured at OD_{600nm}, and is presented in Table 190. Higher OD values are associated with higher levels of permeability.

As presented in Table 190, most of the tissues of mice treated with ISIS 482584 at all doses (Groups 3-8) demonstrated reduced basal vascular permeability compared to the PBS control (Group 1). The reduction in basal vascular permeability of the ISIS oligonucleotide-treated groups was comparable to the same demonstrated in the positive control group treated with HOE-140 (Group 2).

Table 190

OD_{600nm} of Evans Blue dye to measure vascular permeability

Group No.	Treatment	Dose (mg/kg/week)	HOE-140	Colon	Feet	Ears
1	PBS	-	No	0.27	0.17	0.013
2	PBS	-	Yes	0.24	0.09	0.047
3	ISIS 482584	160	No	0.25	0.11	0.019
4	ISIS 482584	80	No	0.24	0.09	0.014
5	ISIS 482584	40	No	0.27	0.11	0.011
6	ISIS 482584	20	No	0.26	0.11	0.009
7	ISIS 482584	10	No	0.31	0.10	0.015
8	ISIS 482584	5	No	0.32	0.11	0.009

Quantification of vascular leakage

The blood drawn through cardiac puncture was immediately mixed with 3 times the volume of ice-cold ethanol. The solution was centrifuged at 15,000 g for 20 minutes at 4^0C to remove cell debris and precipitated plasma proteins. The ethanol extracts were further purified by ultra-filtration through a 10 kDa MWCO filter. The color intensity of the ethanol extracted plasma solution was then measured at OD_{620nm}. The results are presented in Table 191 as percentage increase or decrease of the OD values of the Group 1 PBS control. It was expected that treatment groups may display higher OD values due to reduced vascular leakage. All the mice in the ISIS oligonucleotide-treated groups demonstrated significantly reduced vascular leakage compared to the PBS negative control.

Table 191

Percentage of OD_{620nm} of Evans Blue dye compared to the PBS basal control to measure vascular leakage

Group No.	Treatment	Dose (mg/kg/week)	HOE-140	Plasma
2. (N=8)	ISIS 482584	160	No	95
3. (N=8)	ISIS 482584	80	No	93
4. (N=8)	ISIS 482584	40	No	83
5. (N=8)	ISIS 482584	20	No	56
6. (N=8)	ISIS 482584	10	No	36

Quantification of High Molecular Weight Kininogen (HMWK)

Western blot quantification of HMWK from blood samples are presented in Figure 2 and Tables 192 and 193.

As shown in Table 192, Groups treated with 482584 have higher levels of HMWK as compared to PBS control, increasing in a dose-dependent manner. Treatment with PKK antisense oligonucleotide results in stabilization of HMWK. Thus, vascular permeability is reduced in ISIS 482584-treated groups in a dose-dependent manner. As shown in Table 193, Groups treated with ISIS 482584 have lower HMWK cleavage product as compared to PBS control, decreasing in a dose-dependent manner. Thus, reduced HMWK is caused by PKK cleavage of HMWK into cleavage products (including bradykinin and HKa). Data are presented in Intensity Units as measured by densitometer.

Table 192

Quantification of HMWK by densitometer

Group No	Treatment	Dose (mg/kg/week)	Intensity Units
1	PBS	-	89
3	ISIS 482584	160	21358
4	ISIS 482584	80	7279
5	ISIS 482584	40	873
6	ISIS 482584	20	608
7	ISIS 482584	10	507

Table 193

Quantification of HMWK cleavage product by densitometer

Group No	Treatment	Dose (mg/kg/week)	Intensity Units
1	PBS	-	401738
3	ISIS 482584	160	19936
4	ISIS 482584	80	204482
5	ISIS 482584	40	388135
6	ISIS 482584	20	403360
7	ISIS 482584	10	414774

Example 128: Combination therapy of antisense oligonucleotides targeting PKK and Factor 12 on captopril-induced vascular permeability in mice

Mice were treated varying doses of ISIS 410944, a 5-10-5 MOE gapmer targeting Factor 12 (GCATGGGACAGAGATGGTGC; SEQ ID NO: 2247), and ISIS 482584 in a captopril-induced vascular permeability model.

Treatment

The various treatment groups for this assay are presented in Table 194.

Group 1 consisted of 4 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. No other treatment was administered to Group 1 which served as a control group to measure the basal levels of vascular permeability.

Group 2 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. Group 2 served as the control group for captopril-induced vascular permeability.

Group 3 consisted of 4 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice were intraperitoneally administered 20 μg of captopril. The mice were also intraperitoneally administered 30 μg of HOE-140. Group 3 served as a positive control for inhibition of captopril-induced vascular permeability.

Groups 4, 5, 6, 7, and 8 consisted of 8 mice each and were treated with 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, or 40 mg/kg (corresponding to 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg per week), respectively of ISIS 482584 and ISIS 410944 each administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice of all the groups were intraperitoneally administered 20 μg of captopril. Groups 4-8 served as the experimental treatment groups for examining the effect of ISIS 410944 and ISIS 482584 on captopril-induced vascular permeability.

All the groups were then injected with 30 mg/kg of Evans Blue solution in the tail vein. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, ears, and intestines were harvested.

Table 194
Treatment groups

Group No.	Treatment	Dose (mg/kg/wk) of each ASO	Captopril	HOE-140
1. (N=4)	PBS	-	No	No
2. (N=8)	PBS	-	Yes	No
3. (N=4)	PBS	-	Yes	Yes
4. (N=8)	ISIS 482584+ISIS 410944	80	Yes	No
5. (N=8)	ISIS 482584+ISIS 410944	40	Yes	No

6. (N=8)	ISIS 482584+ISIS 410944	20	Yes	No
7. (N=8)	ISIS 482584+ISIS 410944	10	Yes	No
8. (N=8)	ISIS 482584+ISIS 410944	5	Yes	No

Quantification of vascular permeability

The harvested tissues from the feet, colon, and ears were placed in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing feet and ear tissue was heated to 55^{0}C and left overnight. The color intensity of the dye-infused formamide solution was then measured at OD_{600nm}, and is presented in Table 195. Higher OD values are associated with higher levels of permeability.

As presented in Table 195, most of the tissues of mice treated with a combination of ISIS 482584 and ISIS 410944 at all doses (Groups 3-8) demonstrated reduced vascular permeability compared to the PBS control (Group 1). The reduction in vascular permeability of the ISIS oligonucleotide-treated groups was comparable to the same demonstrated in the basal PBS control (Group 1), as well as the positive control group treated with HOE140 (Group 2). Combination of PKK and Factor 12 antisense oligonucleotides results in synergistic decrease in permeability. As expected, a corresponding synergistic decrease in vascular leakage was also observed.

Table 195

OD_{600nm} of Evans Blue dye to measure vascular permeability

Group No.	Treatment	Dose (mg/kg/wk) of each ASO	Captopril	HOE-140	Colon	Feet	Intestines	Ears
1	PBS	-	No	No	0.24	0.11	0.13	0.01
2	PBS	-	Yes	No	0.38	0.15	0.11	0.05
3	PBS	-	Yes	Yes	0.23	0.06	0.15	0.04
4	ISIS 482584+ISIS 410944	80	Yes	No	0.19	0.07	0.11	0.04
5	ISIS 482584+ISIS 410944	40	Yes	No	0.19	0.07	0.12	0.03
6	ISIS 482584+ISIS 410944	20	Yes	No	0.22	0.08	0.12	0.04
7	ISIS 482584+ISIS 410944	10	Yes	No	0.38	0.13	0.13	0.05

8	ISIS 482584+ISIS 410944	5	Yes	No	0.53	0.12	0.13	0.03

Example 129: Combination therapy of antisense oligonucleotides targeting PKK and Factor 12 on basal vascular permeability in mice

Mice were treated with varying doses of ISIS 410944, an antisense oligonucleotide targeting Factor 12, and ISIS 482584 in a basal vascular permeability model.

Treatment

The various treatment groups for this assay are presented in Table 196.

Group 1 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. No other treatment was administered to Group 1 which served as a control group to measure the basal levels of vascular permeability.

Group 2 consisted of 4 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. At the end of the treatment period, the mice were intraperitoneally administered 30 μg of HOE-140. Group 2 served as a positive control for inhibition of basal vascular permeability.

Groups 3, 4, 5, 6, and 7 consisted of 8 mice each and were treated with 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, or 40 mg/kg (corresponding to 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg per week), respectively of ISIS 482584 and ISIS 410944 each administered subcutaneously twice a week for 3 weeks. Groups 3-7 served as the experimental treatment groups for examining the effect of ISIS 410944 and ISIS 482584 on basal vascular permeability.

All the groups were then injected with 30 mg/kg of Evans Blue solution in the tail vein. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, ears, and intestines were harvested.

Table 196
Treatment groups

Group No.	Treatment	Dose (mg/kg/wk)	HOE-140
1. (N=8)	PBS	-	No
2. (N=4)	PBS	-	Yes
3. (N=8)	ISIS 482584+ISIS 410944	80	No
4. (N=8)	ISIS 482584+ISIS 410944	40	No

5. (N=8)	ISIS 482584+ISIS 410944	20	No
6. (N=8)	ISIS 482584+ISIS 410944	10	No
7. (N=8)	ISIS 482584+ISIS 410944	5	No

Quantification of vascular permeability

The harvested tissues from the feet, colon, intestines, and ears were placed in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing feet and ear tissue was heated to 55^{0}C and left overnight. The color intensity of the dye-infused formamide solution was then measured at OD_{600nm}, and is presented in Table 197. Higher OD values are associated with higher levels of permeability.

As presented in Table 197, most of the tissues of mice treated with a combination of ISIS 482584 and ISIS 410944 at all doses (Groups 2-7) demonstrated reduced vascular permeability compared to the PBS control (Group 1). The reduction in vascular permeability of the ISIS oligonucleotide-treated groups was comparable to the same demonstrated in positive control group treated with HOE140 (Group 2). Combination of PKK and Factor 12 antisense oligonucleotides results in synergistic decrease in permeability. As expected, a corresponding synergistic decrease in vascular leakage was also observed.

Table 197

OD_{600nm} of Evans Blue dye to measure vascular permeability

Group No.	Treatment	Dose (mg/kg/wk)	HOE-140	Colon	Feet	Intestines	Ears
1	PBS	-	No	0.19	0.08	0.10	0.004
2	PBS	-	Yes	0.14	0.04	0.08	0.008
3	ISIS 482584+ISIS 410944	80	No	0.14	0.04	0.09	0.01
4	ISIS 482584+ISIS 410944	40	No	0.15	0.05	0.10	0.006
5	ISIS 482584+ISIS 410944	20	No	0.15	0.04	0.10	0.007
6	ISIS 482584+ISIS 410944	10	No	0.15	0.06	0.10	0.004
7	ISIS 482584+ISIS 410944	5	No	0.14	0.05	0.13	0.002

Example 130: Inhibition of Factor 12 protein activation by ISIS 482584

The effect of antisense inhibition of PKK mRNA on Factor 12 protein activation was evaluated.

Treatment

The various treatment groups for this assay are presented in Table 198.

Group 1 consisted of 8 mice and was treated with PBS administered subcutaneously twice a week for 3 weeks. No other treatment was administered to Group 1 which served as a control group to measure Factor 12 activation.

Groups 2, 3, 4, 5, and 6 consisted of 8 mice each and were treated with 2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, or 40 mg/kg (corresponding to 5 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg per week), respectively of ISIS 482584 administered subcutaneously twice a week for 3 weeks. Groups 2-6 served as the treatment groups for measuring the effect of ISIS 482584 on Factor 12 activation.

At the end of the treatment period, plasma was harvested from the mice for the Spectrozyme® Factor 12a based amidolytic assay for Factor 12 in plasma.

Table 198
Treatment groups

Group No.	Treatment	Dose (mg/kg/wk)
1. (N=8)	PBS	-
2. (N=8)	ISIS 482584	80
3. (N=8)	ISIS 482584	40
4. (N=8)	ISIS 482584	20
5. (N=8)	ISIS 482584	10
6. (N=8)	ISIS 482584	5

Assay for Factor 12 activation in plasma

Plasma (5 µL) was added to 85 µL of PBS with 1ug/ml dextran sulfate (500kDa) in a 96 well polypropelene microplate and the solution was incubated for 5 minutes at room temperature. Spectrozyme® FXIIa (10 µL of a 2 mM solution) and 0.2 mM KALLISTOP™ solution was added and the absorbance kinetic was measured at 405 nm. Factor 12 activation was measured in the linear phase of absorbance accumulation. The results are presented in Table 199 as a percentage of Factor 12 activation measured in the PBS control sample. As observed in Table 199, inhibition of PKK by ISIS 482584 results in decreased activation of Factor 12 by its substrate, implying the that PKK is required for proper factor 12 activation.

Table 199
Percentage Factor 12 activation compared to the PBS control

Dose (mg/kg/wk)	% F12 activation
80	14
40	24
20	47
10	63
5	82

Example 131: *In vivo* effect of antisense inhibition of murine PKK on C1-INH antisense oligonucleotide-induced vascular permeability

Vascular permeability induced by ISIS 461756, an antisense oligonucleotide which targets murine C1 inhibitor mRNA, increases vascular permeability in mice and replicates the pathology of hereditary angioedema. The effect of ISIS 482584 on this model was evaluated.

Treatment

One group of 8 mice was treated with 40 mg/kg ISIS 482584 administered subcutaneously twice a week for 3 weeks (weekly dose of 80 mg/kg). A second group of 8 mice was treated with 40 mg/kg of the control oligonucleotide, ISIS 141923, administered subcutaneously twice a week for 3 weeks (weekly dose of 80 mg/kg). A third group of 8 mice was treated with PBS administered subcutaneously twice a week for 3 weeks. On day 14, all the groups were treated with 12.5 mg/kg ISIS 461756 administered subcutaneously twice a week for 3 weeks (weekly dose of 25 mg/kg). A control group of mice was treated with PBS administered subcutaneously twice a week for 3 weeks but was not administered ISIS 461756.

At the end of the treatment period, all the groups were injected with 30 mg/kg of Evans Blue solution into the tail vein. The mice were sacrificed 30 min after the Evans Blue solution administration and colons, feet, ears, and intestines were harvested. The liver was also harvested for RNA analysis.

RNA analysis

RNA was isolated from the liver for RT-PCR analysis of C1-INH and PKK mRNAs. The primer probe set for C1-INH is RTS3218 (forward sequence GAGTCCCCCAGAGCCTACAGT, designated herein as SEQ ID NO: 2234; reverse sequence TGTCATTTGTTATTGTGATGGCTACA, designated herein as SEQ ID NO: 2235; probe sequence CTGCCCTCTACCTGGCCAACAACCA, designated herein as SEQ ID NO: 2236). The primer probe set for PKK is RTS3287 (forward sequence ACAAGTGCATTTTACAGACCAGAGTAC, designated herein as SEQ ID NO: 2237; reverse sequence GGTTGTCCGCTGACTTTATGCT, designated herein as SEQ ID NO: 2238; probe sequence

AAGCACAGTGCAAGCGGAACACCC, designated herein as SEQ ID NO: 2239). The results are presented in Table 200 as percent inhibition compared to the PBS control not treated with ISIS 461756. The data indicates that ISIS 461756 significantly reduced C1-INH mRNA expression and that treatment with ISIS 482584 significantly reduced PKK expression.

Table 200

Percent inhibition of mRNA expression in mice treated with ISIS 461756 compared to the untreated PBS control

Treatment	C1-INH mRNA	PKK mRNA
PBS	76	0
ISIS 141923	79	0
ISIS 482584	77	78

Quantification of vascular permeability

The harvested tissues from the feet, colon, and intestines were placed in formamide solution overnight to leach out the Evans Blue dye. The formamide solution containing feet tissue was heated to 55^{0}C and left overnight. The color intensity of the dye-infused formamide solution was then measured at OD_{600nm}. The data is presented in Table 201 as percent increase or reduction compared to the PBS control not treated with ISIS 461756. The data indicates that treatment with ISIS 482584 prevented vascular permeability induced by ISIS 461756.

Table 201

Percent change in vascular permeability in mice treated with ISIS 461756 compared to the untreated PBS control

Treatment	**Colon**	**Feet**	**Intestines**
PBS	13	70	27
ISIS 141923	2	80	14
ISIS 482584	-23	2	-25

Example 132: *In vivo* effect of antisense inhibition of murine PKK in the $FeCl_3$-induced inferior vena cava thrombosis model

ISIS 482584, which demonstrated significant *in vitro* and *in vivo* inhibition of PKK, was evaluated in the $FeCl_3$-induced inferior vena cava thrombosis mouse model.

Treatment

Three groups of 8 male BALB/c mice were treated with 10 mg/kg, 20 mg/kg, or 40 mg/kg of ISIS 482584, administered subcutaneously twice a week for 3 weeks (weekly doses of 20 mg/kg, 40 mg/kg, or 80 mg/kg). Two control groups of 12 BALB/c mice each were treated with PBS, administered subcutaneously twice a week for 3 weeks. Two days after the last dose of antisense oligonucleotide or PBS, mice from all groups were anesthetized with 150 mg/kg ketamine mixed with 10 mg/kg xylazine, administered by intraperitoneal injection. Thrombus formation was induced with $FeCl_3$ in all groups of anesthetized mice except the first control group.

In mice undergoing $FeCl_3$ treatment, thrombus formation was induced by applying a piece of filter paper (2 x 4 mm) pre-saturated with 10 % $FeCl_3$ solution directly on the vena cava. After 3 minutes of exposure, the filter paper was removed. Thirty minutes after the filter paper application, a fixed length of the vein containing the thrombus was dissected out for platelet analysis. Liver was collected for RNA analysis.

Quantification of Platelet Composition

Real-time PCR quantification of platelet factor-4 (PF-4) was used to quantify platelets in the vena cava as a measure of thrombus formation. PF-4 mRNA levels were measured using the murine primer probe set mPF4_LTS_00086 (forward sequence AGACCCATTTCCTCAAGGTAGAACT, designated herein as SEQ ID NO: 2240; reverse sequence CGCAGCGACGCTCATG, designated herein as SEQ ID NO: 2241; probe sequence TCTTTGGGTCCAGTGGCACCCTCTT, designated herein as SEQ ID NO: 2242). Results are presented as a percentage of PF-4 in ISIS oligonucleotide-treated mice, as compared to the two PBS-treated control groups. As shown in Table 202, treatment with ISIS 482584 resulted in a significant reduction of PF-4 in comparison to the PBS control. Therefore, reduction of PKK by the compound provided herein is useful for inhibiting thrombus formation.

Table 202

Analysis of thrombus formation by real-time PCR quantification of PF-4 in the $FeCl_3$ induced venous thrombosis model

	Dose in mg/kg/wk	PF-4
PBS-$FeCl_3$	-	0
PBS+$FeCl_3$	-	100
ISIS 482584	20	62
	40	34
	80	25

Example 133: *In vivo* effect of antisense inhibition of murine PKK in a tail bleeding assay

Tail-bleeding was measured to observe whether treatment with ISIS 482584 causes excess bleeding or hemorrhage in mice.

Treatment

Groups of 10 male BALB/c mice were treated with 10 mg/kg, 20 mg/kg, or 40 mg/kg of ISIS 482584, administered subcutaneously twice a week for 3 weeks (weekly doses of 20 mg/kg, 40 mg/kg, or 80 mg/kg). A control group of 8 BALB/c mice was treated with PBS, administered subcutaneously twice a week for 3 weeks.

Tail-bleeding Assay

Two days after the final treatment of ISIS oligonucleotides or PBS, mice were placed in a tail bleeding chamber. Mice were anesthetized in the chamber with isoflurane. Then, a small piece of tail (approximately 4 mm from the tip) was cut with sterile scissors. The cut tail was immediately placed in a 15 mL Falcon tube filled with approximately 10 mL of 0.9 % NaCl buffer solution warmed to 37ºC. The blood was collected over the course of 40 minutes. The saline filled tubes were weighed both before and after bleeding. The results are provided in Table 203.

Treatment with ISIS 482584 did not significantly affect bleeding. These data suggest that the hemorrhagic potential of the compounds provided herein is low. These data taken with the results provided in Example 19 suggest inhibition of PKK with the compounds described herein are useful for providing antithrombotic activity without associated bleeding risk.

Table 203

Tail bleeding assay after treatment with ISIS 482584

	Dose (mg/kg/wk)	Bleeding (mL)
PBS	-	0.03
ISIS 482584	20	0.03
	40	0.14
	80	0.07

Example 134: *In vivo* effect of antisense inhibition of murine PKK in the $FeCl_3$ induced mesenteric thrombosis model

ISIS 482584 was evaluated in the $FeCl_3$ induced mesenteric thrombosis mouse model.

Treatment

A group of 6-8 Swiss-Webster mice was treated with 40 mg/kg of ISIS 482584, administered subcutaneously twice a week for 3 weeks (weekly dose of 80 mg/kg). A control group of 6 Swiss-Webster mice was treated with PBS, administered subcutaneously twice a week for 3 weeks. Two days after the last dose of antisense oligonucleotide or PBS, mice from all groups were anesthetized with 75 mg/kg ketamine mixed with 25 mg/kg xylazine, administered by subcutaneous injection.

Rhodamine 6G dye at a dosage of 5 mg/kg was injected subcutaneously to stain platelets. Alexa-647-labeled anti-fibrinogen antibody at a dosage of 1 mg/kg was injected via tail vein injection to stain fibrin. The abdomen was opened by a middle incision. The visceral mesentery was spread on a glass coverslip and the mesenteric arterioles (70-120 μm) were located by observation under a microscope. Thrombus formation was induced by applying of cotton threads (2 x 0.3 mm) pre-saturated with 6% $FeCl_3$ solution directly on the target vessel. After three minutes of exposure, the thread was removed and the color intensities of both the dyes were recorded by fluorescent microscopy (Olympus FluoView 1000 confocal laser scanning microscope) with appropriate filters for 70 min.

The results for platelet aggregation in the control and treatment groups are presented in Table 204, expressed in arbitrary units (a.u.). Platelet aggregation was reduced in mice treated with ISIS 482584 at a dose of 80 mg/kg/week as compared to mice treated with PBS. The results for fibrin formation in the control and treatment groups are presented in Table 205, also expressed in arbitrary units (a.u.). Fibrin formation was reduced in mice treated with ISIS 482584 at a dose of 80 mg/kg/week as compared to mice treated with PBS. Therefore, these results suggest that ISIS 482584 inhibits thrombus formation.

Table 204

Analysis of platelet aggregation by real-time measurement of fluorescent intensity (a.u.) in a $FeCl_3$ induced mesenteric thrombus model

Time (sec)	PBS	80 mg/kg/wk
752	54	74
1018	315	11
1284	485	7
1550	654	0
1815	1079	0
2081	1164	0
2347	1452	0
2613	1440	38
2879	1689	148
3144	1716	129
3410	1845	169
3676	1865	131
3944	2055	87

Table 205

Analysis of fibrin formation by real-time measurement of fluorescent intensity (a.u.) in a $FeCl_3$ induced mesenteric thrombus model

Time (sec)	PBS	80 mg/kg/wk
752	9	54
1018	86	7
1284	203	1
1550	319	10
1815	521	16
2081	598	15
2347	831	61
2613	959	88
2879	1157	141
3144	1236	150
3410	1374	173
3676	1629	160
3944	1822	128

Example 135: *In vivo* effect of antisense inhibition of murine PKK in the stenosis-induced inferior vena cava thrombosis model

ISIS 482584 was evaluated in the stenosis-induced inferior vena cava (IVC) thrombosis model. Reduced blood flow and endothelial damage are hallmarks of this model, also known as the St. Tomas model.

Treatment

Four groups of 6-8 BALB/c mice were treated with 5 mg/kg, 10 mg/kg, 20 mg/kg, or 40 mg/kg of ISIS 482584, administered subcutaneously twice a week for 3 weeks (weekly doses of 10 mg/kg, 20 mg/kg, 40 mg/kg, or 80 mg/kg). A control group of 8 BALB/c mice was treated with PBS, administered subcutaneously twice a week for 3 weeks. Two days after the last dose of antisense oligonucleotide or PBS was administered, mice from all groups were anesthetized with 2.5% inhalant isoflurane. The IVC of the mice was exposed via a midline abdominal incision below the left renal vein, and was separated from the abdominal aorta by blunt dissection. A 6-0 silk tie (Ethicon, UK) was placed behind the blood vessel just below the left renal vein and a metal 4-0 suture (Ethicon, UK) was placed longitudinally over the IVC to tie the silk tie on top. The metal suture was then removed. Two neurovascular surgical clips (Braun Medical Inc, PA) were placed at two seaparate positions below the ligation for 20 seconds each, after which they were removed. The abdominal cavity contents were then replaced and the abdomen was closed. After 24 hrs, the IVC was exposed and checked for thrombi formation. All thrombi formed were collected and fixed in 10% formalin for 24 hrs.

The thrombi were weighed and the results are presented in Table 206, expressed in miligrams. As demonstrated by the results, treatment with increasing doses of ISIS 482584 resulted in corresponding decrease in thrombus weight. The results indicate that antisense inhibition of PKK is useful for inhibiting thrombus formation.

Table 206

Thrombi weights in the stenosis-induced IVC thrombosis model

	Dose in mg/kg/wk	Weight (mg)
PBS	-	10
ISIS 482584	10	8
	20	6
	40	5
	80	3

Example 136: Inhibition of murine PKK with an antisense oligonucleotide comprising a GalNAc$_3$ conjugate group

ISIS 482584 and ISIS 722059, shown in the table below, were tested for their effects on murine PKK mRNA *in vivo*.

Table 207

ISIS 722059, comprising a GalNAc$_3$ conjugate group and its parent, ISIS 482584

Isis No.	Sequence (5' to 3')	Chemistry	SEQ ID NO.
482584	$G_{es}G_{es}{}^{m}C_{es}A_{es}T_{es}A_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{es}G_{es}A_{es}A_{es}T_{e}$	No conjugate group and full PS	2244
722059	GalNAc$_3$-7$_{a\text{-}o}$$G_{es}G_{es}{}^{m}C_{eo}A_{eo}T_{es}A_{ds}T_{ds}T_{ds}G_{ds}G_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}G_{eo}G_{eo}A_{es}A_{es}T_{e}$	5'-GalNAc$_3$-7 and mixed PS/PO	2244

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$_3$-7" is shown in Example 48.

Treatment

Four groups of four C57Bl/6J-Tyr^{c-2J} mice each were treated with 5.0 mg/kg, 10.0 mg/kg, 20.0 mg/kg, or 40.0 mg/kg of ISIS 482584, administered subcutaneously twice a week for 3 weeks (weekly doses of 10.0 mg/kg, 20.0 mg/kg, 40.0 mg/kg, or 80.0 mg/kg). Four groups of four BALB/c mice each were treated with 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg, or 8.0 mg/kg of ISIS 722059, administered subcutaneously twice a week for 3 weeks (weekly doses of 2.0 mg/kg, 4.0 mg/kg, 8.0 mg/kg, or 16.0 mg/kg). A control group of four BALB/c mice was treated with PBS, administered subcutaneously twice a week for 3 weeks. Three days after the last dose of antisense oligonucleotide or PBS, mice from all groups were anesthetized with vaporized isoflurane in air at 2.5% for induction followed by 1-2% isoflurane by nosecone for maintenance. This was followed by cervical dislocation. Following euthanasia, liver was collected for RNA analysis.

RNA Analysis

RNA was extracted from liver tissue for real-time PCR analysis of PKK. PKK mRNA levels were measured using the murine primer probe set (forward sequence ACAAGTGCATTTTACAGACCAGAGTAC, designated herein as SEQ ID NO: 2231; reverse sequence GGTTGTCCGCTGACTTTATGCT, designated herein as SEQ ID NO: 2232; probe sequence AAGCACAGTGCAAGCGGAACACCC, designated herein as SEQ ID NO: 2233). Results are presented as percent inhibition of PKK, relative to PBS control. As shown in Table 208 below, Isis 722059, comprising a $GalNAc_3$ conjugate group, reduced PKK mRNA significantly more potently than the parent antisense oligonucleotide, Isis 482584. This result is consistent with the results in the above examples, in which antisense oligonucleotides comprising a $GalNAc_3$ conjugate group were significantly more potent than their parent antisense oligonucleotides, for many target genes in both mouse and human. Thus, it is expected that human PKK antisense oligonucleotides comprising a $GalNAc_3$ conjugate group would likewise reduce human PKK mRNA significantly more potently than their parent antisense oligonucleotides that do not comprise a conjugate group.

Table 208

Percent Inhibition of PKK mRNA in liver relative to the PBS control

ISIS No.	Dose (mg/kg/week)	% inhibition	ED_{50} (mg/kg/week)
482584	10	42.6	17.2
	20	53.3	
	40	71.4	
	80	90.8	
722059	2	50.1	2.09
	4	76.7	
	8	80.8	
	16	86.1	

Example 137: Inhibition of human PKK with an antisense oligonucleotide comprising a $GalNAc_3$ conjugate group

ISIS 546254 and ISIS 721744, shown in the table below, were tested for their effects on human PKK mRNA *in vitro*.

Table 209

ISIS 721744, comprising a $GalNAc_3$ conjugate group and its parent, ISIS 546254

Isis No.	Sequence (5' to 3')	Chemistry	SEQ ID NO.
546254	$T_{es}G_{es}{}^{m}C_{es}A_{es}A_{es}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}$ $G_{ds}{}^{m}C_{ds}A_{es}A_{es}A_{es}{}^{m}C_{es}A_{e}$	No conjugate group and full PS	570
721744	$GalNAc_3\text{-}7_{a\text{-}o}T_{es}G_{es}{}^{m}C_{eo}A_{eo}A_{es}G_{ds}T_{ds}{}^{m}C_{ds}T_{ds}{}^{m}C_{ds}T_{ds}T_{ds}G_{ds}$ $G_{ds}{}^{m}C_{ds}A_{eo}A_{eo}A_{es}{}^{m}C_{es}A_{e}$	5'-$GalNAc_3\text{-}7_{a\text{-}o}$, and mixed PS/PO	570

Subscripts: "e" indicates 2'-MOE modified nucleoside; "d" indicates β-D-2'-deoxyribonucleoside; "s" indicates a phosphorothioate internucleoside linkage (PS); and "o" indicates a phosphodiester internucleoside linkage (PO). Superscript "m" indicates 5-methylcytosine. The structure of "$GalNAc_3$-7" is shown in Example 48, and "$GalNAc_3\text{-}7_{a\text{-}o}$" indicates a $GalNAc_3$-7 conjugate group in which the cleavable moiety is -O-P(=O)(OH)-.

Primary human hepatocyte co-cultures that include stromal cells in order to mimic the physiological microenviroment of the liver *in vitro* (HepatoPac kit HPHU-TX-96S, Hepregen, Medford, MA) were used according to the manufacturer's instructions. A concentration of Isis oligonucleotide listed in table below or PBS was added to each well in the absence of any transfection reagent. 96 hours later, cells were lysed and RNA was isolated from the cells. PKK mRNA levels were measured by quantitative real-time PCR using primer probe set RTS3454 and normalized to total RNA content, as measured by RIBOGREEN®. The results are presented in the table below as percent inhibition of PKK mRNA levels, relative to PBS treated cells; and IC_{50} values were calculated using a 4 parameter logistic model (JMP Software, Cary, NC). The results show that, under free uptake conditions in which no reagents or electroporation techniques were used to artificially promote entry of the oligonucleotides into cells, the oligonucleotide comprising a GalNAc conjugate was significantly more potent than the parent oligonucleotide that does not comprise a GalNAc conjugate.

Table 210

Percent Inhibition of PKK mRNA relative to the PBS control

ISIS No.	Concentration (μM)	Inhibition (%)	IC_{50} (μM)
546254	0.1	30	2.12
	0.3	25	
	1.0	24	
	3.0	63	
	10.0	85	
721744	0.03	34	0.07
	0.1	52	
	0.3	81	
	1.0	92	
	3.0	98	

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WHAT IS CLAIMED:

1. A compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide consists of 20 linked nucleosides and has the nucleobase sequence of SEQ ID NO: 570, and wherein the conjugate group is covalently linked to the modified oligonucleotide at the 5' end of the modified oligonucleotide.

2. The compound of claim 1, wherein the compound consists of the modified oligonucleotide and the conjugate group, and wherein the modified oligonucleotide is single-stranded.

3. The compound of claim 1 or claim 2, wherein at least one internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage, optionally wherein the at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.

4. The compound of any preceding claim, wherein the modified oligonucleotide comprises at least 1 phosphodiester internucleoside linkage.

5. The compound of any preceding claim, wherein the modified oligonucleotide comprises at least 2 phosphodiester internucleoside linkages.

6. The compound of any preceding claim, wherein the modified oligonucleotide comprises at least 3 phosphodiester internucleoside linkages.

7. The compound of any preceding claim, wherein the modified oligonucleotide comprises at least 4 phosphodiester internucleoside linkages.

8. The compound of any preceding claim, wherein each internucleoside linkage of the modified oligonucleotide is selected from a phosphodiester internucleoside linkage and a phosphorothioate internucleoside linkage.

9. The compound of any preceding claim, wherein at least one nucleoside comprises a modified nucleobase, optionally wherein the modified nucleobase is a 5-methylcytosine.

10. The compound of any preceding claim, wherein the modified oligonucleotide comprises at least one modified sugar.

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11. The compound of claim 10, wherein the modified sugar is any of a 2'-O-methoxyethyl modified sugar, a 2'-O-methyl modified sugar, a constrained ethyl, a LNA, or a 3'-fluoro-HNA.

12. The compound of any preceding claim, wherein the modified oligonucleotide comprises:

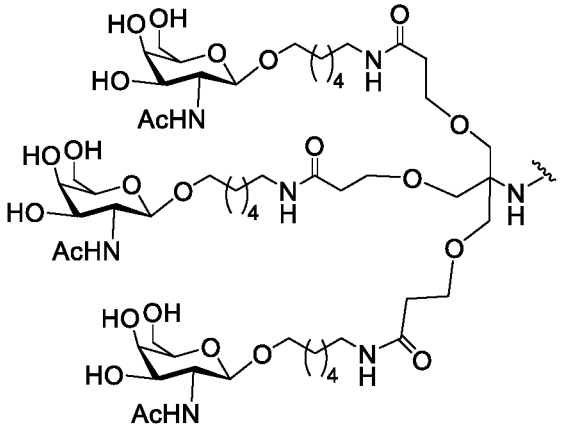
a gap segment consisting of 10 linked deoxynucleosides;

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

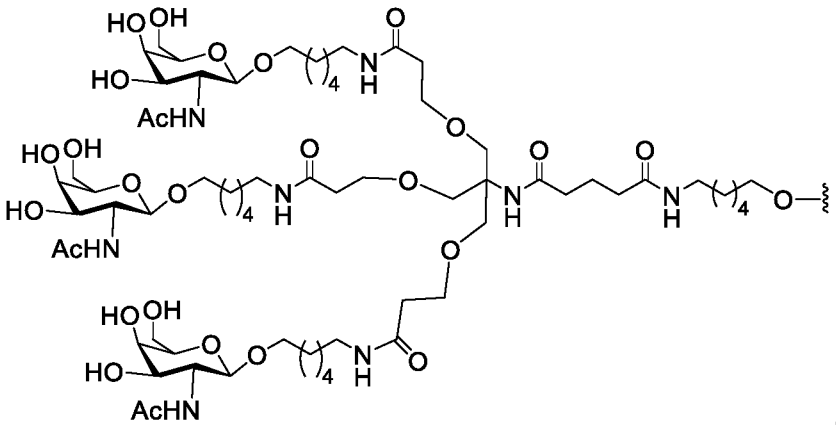
a 3' wing segment consisting of 5 linked nucleosides,

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.

13. The compound of any preceding claim, wherein the conjugate group comprises a cell-targeting moiety, optionally wherein the cell-targeting moiety has the following structure:



14. The compound of any preceding claim, wherein the conjugate group comprises:



15. A compound comprising a modified oligonucleotide and a conjugate group, wherein the modified oligonucleotide is a gapmer consisting of a 5' wing segment, a central gap segment, and a 3' wing segment, wherein:

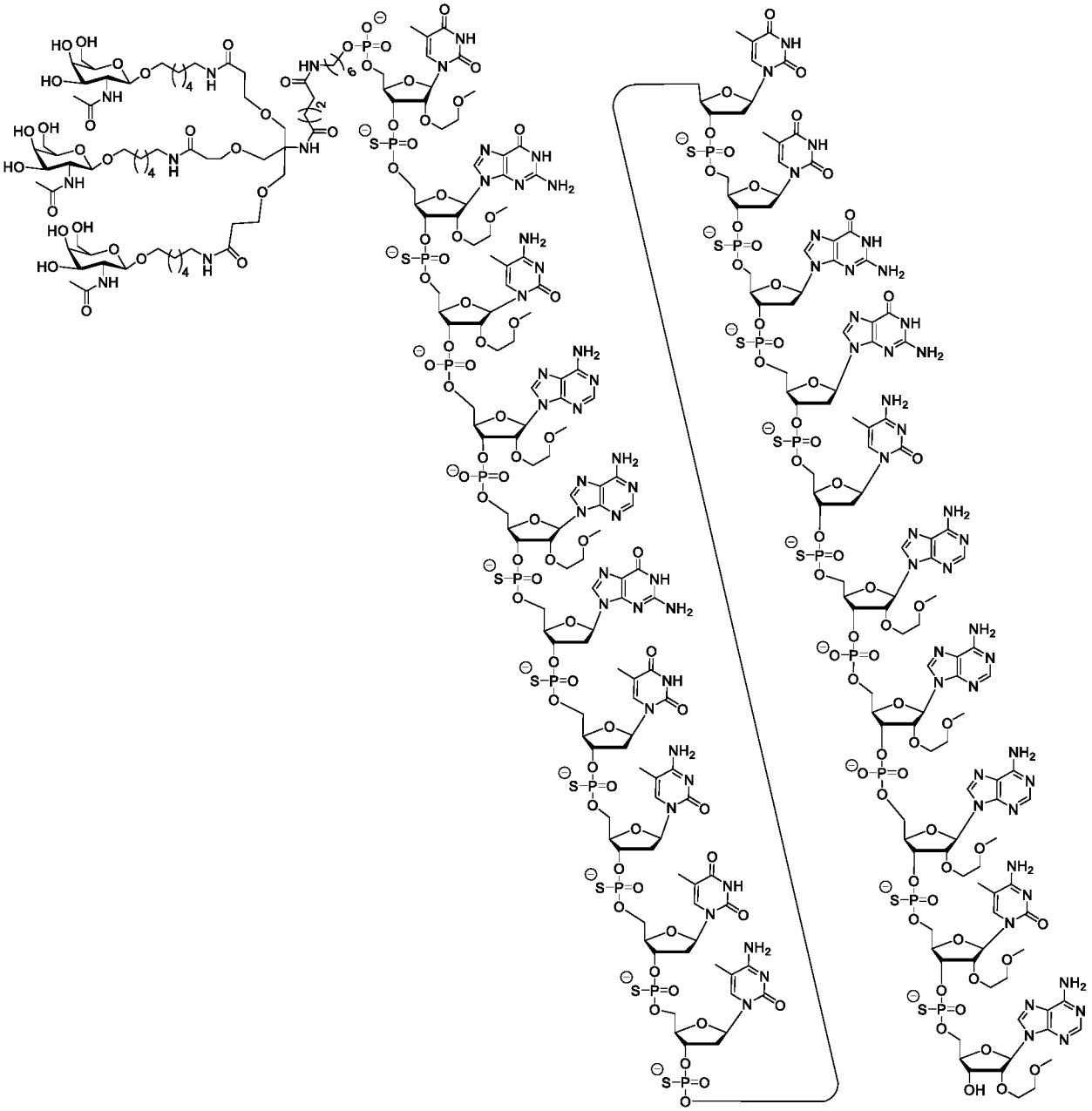
the 5' wing segment consists of five 2'-O-methyoxyethyl nucleosides,

the central gap segment consists of ten β-D-deoxyribonucleosides, and

the 3' wing segment consists of five 2'-O-methyoxyethyl nucleosides,

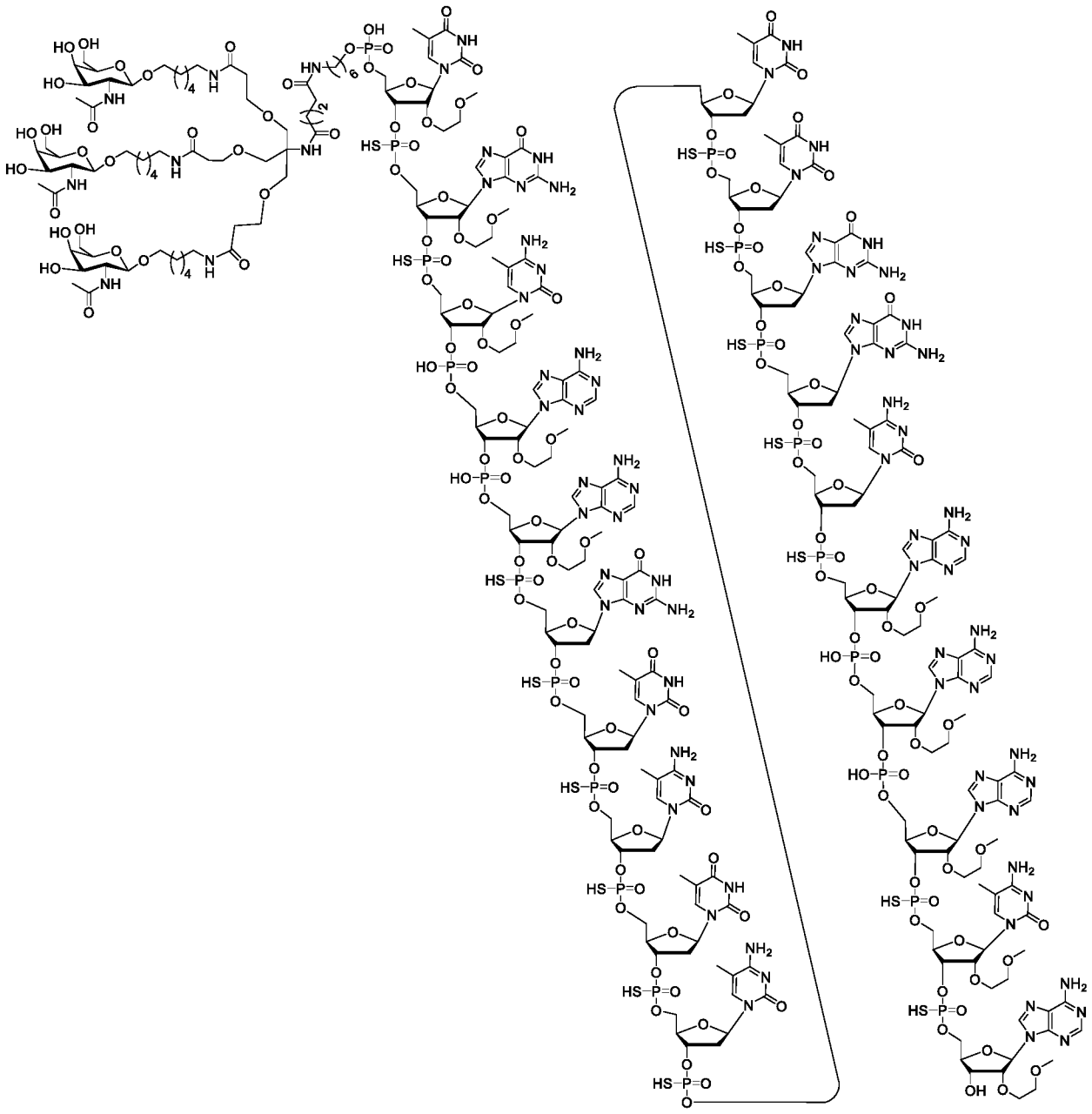
wherein the conjugate group is linked to the modified oligonucleotide at the 5' end of the modified oligonucleotide, wherein the modified oligonucleotide has the nucleobase sequence 5'-TGCAAGTCTCTTGGCAAACA -3' (SEQ ID NO: 570), wherein each cytosine is a 5-methylcytosine, and wherein the internucleoside linkages of the modified oligonucleotide are ssoosssssssssssooss from 5' to 3' wherein each s is a phosphorothioate linkage and each o is a phosphodiester linkage.

16. A salt of a compound consisting of a modified oligonucleotide and a conjugate group, wherein the anion of the compound has the following structure:



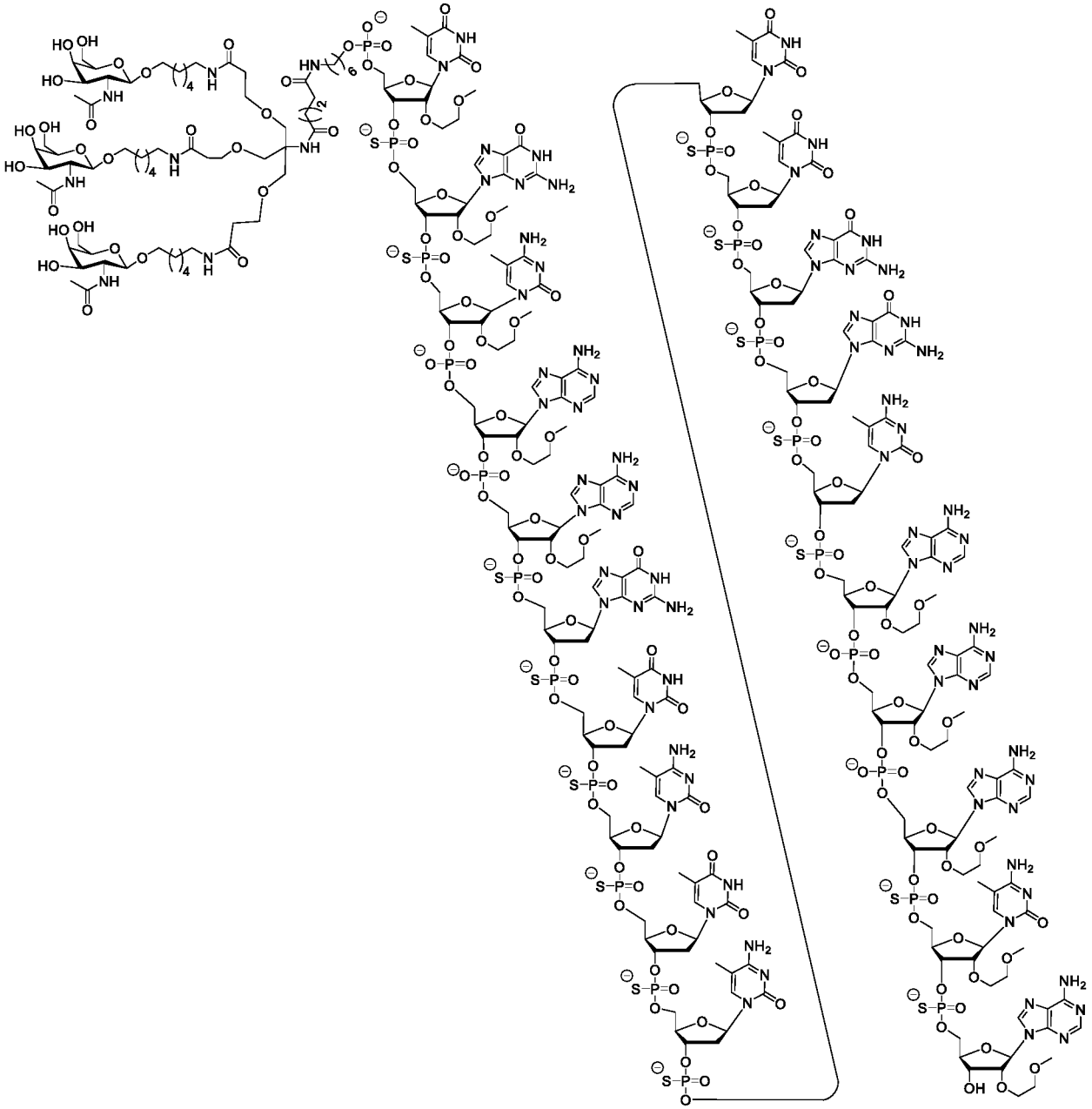
(SEQ ID NO: 570).

17. A compound consisting of a modified oligonucleotide and a conjugate group, according to the following structure:



(SEQ ID 570), or a salt thereof.

18. A pharmaceutical composition comprising a salt of a compound consisting of a modified oligonucleotide and a conjugate group, wherein the anion of the compound has the following structure:



(SEQ ID NO: 570), and a pharmaceutically acceptable carrier or diluent.

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19. A pharmaceutical composition comprising the compound of any one of claims 1-15 and 17, or the salt of claim 16, and at least one of a pharmaceutically acceptable carrier or diluent.

20. The pharmaceutical composition of claim 18 or claim 19, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline (PBS).

21. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition consists essentially of the compound or salt and PBS.

22. The compound of any one of claims 1-15 and 17, or the salt of claim 16, wherein the modified oligonucleotide of the compound is a sodium salt.

23. A method comprising administering to an animal the compound, salt, or pharmaceutical composition of any preceding claim, wherein the animal is a human.

24. The method of claim 23, wherein administering the compound, salt, or pharmaceutial composition prevents, treats, or ameliorates a PKK associated disease, disorder or condition.

25. Use of the compound, salt, or pharmaceutical composition of any one of claims 1-22 in the manufacture of a medicament for preventing, treating, or ameliorating a PKK associated disease, disorder or condition.

SEQUENCE LISTING

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<120> COMPOSITIONS AND METHODS FOR MODULATING PKK EXPRESSION

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