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(54) Title: RNAI CONSTRUCTS FOR INHIBITING ASGR1 EXPRESSION AND METHODS OF USE THEREOF

(57) Abstract: The present invention relates to RNAi constructs for reducing expression of the ASGR1 gene. Methods of using such RNAi constructs to treat or prevent cardiovascular disease, such as coronary artery disease and myocardial infarction, and to reduce serum non-HDL cholesterol levels are also described.

RNAI CONSTRUCTS FOR INHIBITING ASGR1 EXPRESSION AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/380,216, filed August 26, 2016, which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[0002] The present application contains a Sequence Listing, which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. The computer readable format copy of the Sequence Listing, which was created on August 25, 2017, is named A-2094-WO-PCT_ST25 and is 1.49 megabytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to compositions and methods for modulating liver expression of asialoglycoprotein receptor 1 (ASGR1). In particular, the present invention relates to nucleic acid-based therapeutics for reducing ASGR1 expression via RNA interference and methods of using such nucleic acid-based therapeutics to treat or prevent cardiovascular disease.

BACKGROUND OF THE INVENTION

[0004] Despite the many advancements and new therapeutics that have emerged over the last several years, cardiovascular disease remains the leading cause of death worldwide. One out of every three adults in America has some form of cardiovascular disease, including coronary artery disease, myocardial infarction, angina, heart failure, and stroke (Heart disease and stroke statistics−2016 update: a report from the American Heart Association. *Circulation*, Vol.133:e38-e360, 2016). In 2013, over 17.3 million people globally and 1.4 million people in the United States died from some form of cardiovascular disease, accounting for 31% of all global deaths and 54% of all deaths in the U.S. that year (Heart disease and stroke statistics−2016 update). Cardiovascular disease currently claims more lives each year than the next two leading causes of death, cancer and chronic lower respiratory disease, combined (Heart disease and stroke

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statistics−2016 update). Thus, there remains a need for additional therapeutic agents for the treatment of cardiovascular disease.

[0005] The asialoglycoprotein receptor is a calcium-dependent receptor expressed on the surface of hepatocytes that contributes to the removal and degradation of desialylated glycoproteins from the serum by binding to ligands with terminal galactose and N-acetylgalactosamine residues (Weigel, Bioessays, Vol. 16:519-524, 1994; Stockert, Physiol. Rev., Vol. 75: 591-609, 1995). The hetero-oligomeric asialoglycoprotein receptor is comprised of two different proteins, a 48 kDa asialoglycoprotein receptor 1 (ASGR1) major subunit and a 40 kDa asialoglycoprotein receptor 2 (ASGR2) minor subunit (*see, e.g.*, Stockert, 1995). The asialogylcoprotein receptor has been implicated in the clearance of low density lipoproteins and chylomicron remnants, suggesting a role for the receptor in lipoprotein metabolism (Windler *et al.*, Biochem J., Vol. 276(Pt 1):79–87, 1991; Ishibashi *et al.*, J Biol Chem., Vol. 271:22422–22427, 1996). Recently, human carriers of loss of function variant alleles of the ASGR1 subunit of the asialoglycoprotein receptor were reported to have lower serum levels of non-high-density lipoprotein (HDL) cholesterol and a lower risk of coronary artery disease and myocardial infarction as compared to non-carriers (Nioi *et al.*, New England Journal of Medicine, Vol. 374(22):2131-2141, 2016). Accordingly, therapeutics targeting ASGR1 function represent a novel approach to reducing non-HDL cholesterol levels and treating cardiovascular disease, particularly coronary artery disease.

[0005a] Reference to any prior art in the specification is not an acknowledgement or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be combined with any other piece of prior art by a skilled person in the art.

SUMMARY OF THE INVENTION

[0006] The present invention is based, in part, on the design and generation of RNAi constructs that target the ASGR1 gene and reduce expression of ASGR1 in liver cells. The sequence-specific inhibition of ASGR1 expression is useful for treating or preventing conditions associated with ASGR1 expression, such as cardiovascular disease. Accordingly, in one embodiment, the present invention provides an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is complementary to an

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ASGR1 mRNA sequence. In certain embodiments, the antisense strand comprises a region having at least 15 contiguous nucleotides from an antisense sequence listed in Table 1, Table 6, or Table 8.

[0006a] In another embodiment, there is provided an RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is complementary to an ASGR1 mRNA sequence, and wherein said region comprises (i) the sequence of nucleotides 1-19 of SEQ ID NO: 2651, (ii) the sequence of nucleotides 2-19 of SEQ ID NO: 2651, or (iii) the sequence of SEQ ID NO: 2651.

[0006b] In another embodiment, there is provided a pharmaceutical composition comprising the RNAi construct described herein and a pharmaceutically acceptable carrier, excipient, or diluent.

[0006c] In an embodiment, there is provided a method for reducing the expression of ASGR1 in a patient in need thereof comprising administering to the patient the RNAi construct described herein.

[0006d] In an embodiment, there is provided a method for reducing non-HDL cholesterol in a patient in need thereof comprising administering to the patient the RNAi construct described herein.

[0006e] In an embodiment, there is provided a method for treating or preventing cardiovascular disease in a patient in need thereof comprising administering to the patient the RNAi construct described herein.

[0006f] In an embodiment, there is provided a method for reducing the risk of myocardial infarction in a patient in need thereof comprising administering to the patient the RNAi construct described herein.

[0006g] In an embodiment, there is provided the use of the RNAi construct described herein in the manufacture of a medicament for reducing the expression of ASGR1 in a patient.

[0006h] In an embodiment, there is provided the use of the RNAi construct described herein in the manufacture of a medicament for reducing non-HDL cholesterol in a patient.

[0006i] In an embodiment, there is provided the use of the RNAi construct described herein in the manufacture of a medicament for treating or preventing cardiovascular disease in a patient.

[0006j] In an embodiment, there is provided the use of the RNAi construct described herein in the manufacture of a medicament for reducing the risk of myocardial infarction in a patient.

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[0007] In some embodiments, the sense strand of the RNAi constructs described herein comprises a sequence that is sufficiently complementary to the sequence of the antisense strand

to form a duplex region of about 15 to about 30 base pairs in length. In these and other embodiments, the sense and antisense strands each are about 15 to about 30 nucleotides in length. In some embodiments, the RNAi constructs comprise at least one blunt end. In other embodiments, the RNAi constructs comprise at least one nucleotide overhang. Such nucleotide overhangs may comprise 1 to 6 unpaired nucleotides and can be located at the 3′ end of the sense strand, the 3′ end of the antisense strand, or the 3′ end of both the sense and antisense strand. In certain embodiments, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3′ end of the sense strand and the 3′ end of the antisense strand. In other embodiments, the RNAi constructs comprise an overhang of two unpaired nucleotides at the 3′ end of the antisense strand and a blunt end of the 3′ end of the sense strand/5′ end of the antisense strand.

[0008] The RNAi constructs of the invention may comprise one or more modified nucleotides, including nucleotides having modifications to the ribose ring, nucleobase, or phosphodiester backbone. In some embodiments, the RNAi constructs comprise one or more 2′-modified nucleotides. Such 2′-modified nucleotides can include 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides, 2′-O-methoxyethyl modified nucleotides, 2′-O-allyl modified nucleotides, bicyclic nucleic acids (BNA), or combinations thereof. In one particular embodiment, the RNAi constructs comprise one or more 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides, or combinations thereof. In some embodiments, all of the nucleotides in the sense and antisense strand of the RNAi construct are modified nucleotides.

[0009] In some embodiments, the RNAi constructs comprise at least one backbone modification, such as a modified internucleotide or internucleoside linkage. In certain embodiments, the RNAi constructs described herein comprise at least one phosphorothioate internucleotide linkage. In particular embodiments, the phosphorothioate internucleotide linkages may be positioned at the 3′ or 5′ ends of the sense and/or antisense strands.

[0010] In some embodiments, the antisense strand and/or the sense strand of the RNAi constructs of the invention may comprise or consist of a sequence from the antisense and sense sequences listed in Tables 1, 6, or 8. In certain embodiments, the RNAi construct may be any one of the duplex compounds listed in any one of Tables 1 to 10. In one embodiment, the RNAi construct is D-1098, D-1176, D-1200, D-1206, D-1235, D-1246, D-1373, D-1389, D-1813, D-1815, D-1983, D-2000, D-2045, D-2142, D-2143, D-1438, D-1494, D-2357, D-2359, D-2361, D-2365, D-2461, D-3036, D-3037, D-3051, D-3053, D-3057, D-3779, D-3780, D-3782, D-3788,

D-3791, D-3795, D-3799, or D-3800. In another embodiment, the RNAi construct is D-1200, D-1206, D-1235, D-1815, D-2143, D-2359, D-2361, D-2365, D-2142, D-1176, D-3779, D-3782, D-3788, D-3799, or D-3800. In another embodiment, the RNAi construct is D-2359. In another embodiment, the RNAi construct is D-1815. In yet another embodiment, the RNAi construct is D-1235. In still another embodiment, the RNAi construct is D-2143. In another embodiment, the RNAi construct is D-2361. In some embodiments, the RNAi construct is D-3782. In other embodiments, the RNAi construct is D-3799.

[0011] The RNAi constructs may further comprise a ligand to facilitate delivery or uptake of the RNAi constructs to specific tissues or cells, such as liver cells. In certain embodiments, the ligand targets delivery of the RNAi constructs to hepatocytes. In these and other embodiments, the ligand may comprise galactose, galactosamine, or N-acetyl-galactosamine (GalNAc). In certain embodiments, the ligand comprises a multivalent galactose or multivalent GalNAc moiety, such as a trivalent or tetravalent galactose or GalNAc moiety. The ligand may be covalently attached to the 5′ or 3′ end of the sense strand of the RNAi construct, optionally through a linker. In some embodiments, the RNAi constructs comprise a ligand and linker having a structure according to any of Formulas I to XXIX described herein. In certain embodiments, the RNAi constructs comprise a ligand and linker having a structure according to Formula VII, Formula VIII, Formula XVI, Formula XXVI, or Formula XXIX. In one embodiment, the RNAi constructs comprise a ligand and linker having a structure according to Formula XVI, wherein n =1 and k =3.

[0012] In certain embodiments, the ligand may comprise an antibody or antigen-binding fragment thereof that specifically binds to ASGR1. The 5′ or 3′ end of the sense strand of the RNAi construct may be covalently linked to the antibody or antigen-binding fragment through the side chain of an amino acid residue in the light chain or heavy chain of the antibody or antigen-binding fragment. In some embodiments, the sense strand of the RNAi construct is covalently attached, optionally through a linker, to the side chain of a cysteine residue present in the heavy chain or light chain of the antibody or antigen-binding fragment thereof. In one embodiment, the anti-ASGR1 antibody-RNA molecule conjugate comprises at least one copy of the interfering RNA molecule (e.g. siRNA or shRNA). In another embodiment, the anti-ASGR1 antibody-RNA molecule conjugate comprises two copies of the interfering RNA molecule (e.g. siRNA or shRNA).

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[0013] The present invention also provides pharmaceutical compositions comprising any of the RNAi constructs described herein and a pharmaceutically acceptable carrier, excipient, or diluent. Such pharmaceutical compositions are particularly useful for reducing expression of ASGR1 in the cells (e.g. liver cells) of a patient in need thereof. Patients who may be administered a pharmaceutical composition of the invention can include patients with a history of myocardial infarction, patients diagnosed with or at risk for coronary artery disease or other form of cardiovascular disease, and patients with elevated levels of non-HDL cholesterol. Accordingly, the present invention includes methods of treating or preventing cardiovascular disease in a patient in need thereof by administering an RNAi construct or pharmaceutical composition described herein. In certain embodiments, the present invention provides methods for reducing non-HDL cholesterol in a patient in need thereof by administering an RNAi construct or pharmaceutical composition described herein.

[0014] The use of ASGR1-targeting RNAi constructs in any of the methods described herein or for preparation of medicaments for administration according to the methods described herein is specifically contemplated. For instance, the present invention includes an ASGR1-targeting RNAi construct for use in a method for treating or preventing cardiovascular disease, including coronary artery disease or myocardial infarction, in a patient in need thereof. The present invention also includes an ASGR1-targeting RNAi construct for use in a method for reducing non-HDL cholesterol in a patient in need thereof. In some embodiments, the present invention provides an ASGR1-targeting RNAi construct for use in a method for reducing the risk of myocardial infarction in a patient in need thereof.

[0015] The present invention also encompasses the use of an ASGR1-targeting RNAi construct in the preparation of a medicament for treating or preventing cardiovascular disease, including coronary artery disease or myocardial infarction, in a patient in need thereof. In certain embodiments, the present invention provides the use of an ASGR1-targeting RNAi construct in the preparation of a medicament for reducing non-HDL cholesterol in a patient in need thereof. In certain other embodiments, the present invention provides the use of an ASGR1-targeting RNAi construct in the preparation of a medicament for reducing the risk of myocardial infarction in a patient in need thereof.

[0015a] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any

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other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1A shows the nucleotide sequence of transcript variant 1 of human *ASGR1* (NCBI Reference Sequence No. NM_001671.4; SEQ ID NO: 1). The transcript sequence is depicted as the complementary DNA (cDNA) sequence with thymine bases replacing uracil bases.

[0017] Figure 1B shows the nucleotide sequence of transcript variant 2 of human *ASGR1* (NCBI Reference Sequence No. NM_001197216.2; SEQ ID NO: 2). The transcript sequence is depicted as the cDNA sequence with thymine bases replacing uracil bases.

[0018] Figure 2 shows the nucleotide sequence of transcript variant 1 of mouse *Asgr1* (NCBI Reference Sequence No. NM_009714.2; SEQ ID NO: 3011). The transcript sequence is depicted as the complementary DNA (cDNA) sequence with thymine bases replacing uracil bases.

[0019] Figure 3 shows the nucleotide sequence of a transcript of rat *Asgr1* (SEQ ID NO: 3012). The transcript sequence is depicted as the complementary DNA (cDNA) sequence with thymine bases replacing uracil bases.

[0020] Figure 4 shows the nucleotide sequence of a transcript of macaque (*Macaca fascicularis*) *ASGR1* (NCBI Reference Sequence No. XM_005582698.1; SEQ ID NO: 3013). The transcript sequence is depicted as the complementary DNA (cDNA) sequence with thymine bases replacing uracil bases.

[0021] Figure 5 depicts the synthetic scheme for a tetravalent GalNAc moiety that can be incorporated into any of the RNAi constructs of the invention.

[0022] Figure 6A is a bar graph of human ASGR1 expression levels in livers of ASGR1 knockout mice injected with an AAV encoding human ASGR1 and treated with 5 mg/kg subcutaneous injections of the indicated GalNAc-ASGR1 siRNA conjugates. Human ASGR1 expression was measured by qPCR and is reported as expression levels relative to the AAV only control animals, which were ASGR1 knockout animals injected with the AAV encoding human ASGR1, but were otherwise untreated. Expression levels are shown at day 8 (d8) and day 15 (d15) after GalNAc-siRNA conjugate administration. Wild-type (WT) mice and ASGR1 knockout (KO) animals were included as controls.

[0023] Figure 6B is a bar graph of serum levels of alkaline phosphatase (ALP) from the animals described in Figure 6A. Serum was obtained at day 8 (d8) and day 15 (d15) following administration of the indicated GalNAc-siRNA conjugates.

[0024] Figure 7A is a schematic illustrating the reaction to add a bromoacetyl linker to the 3′ end of the sense strand of a siRNA duplex.

[0025] Figure 7B is a schematic depicting the conjugation reaction to attach a siRNA duplex to an anti-ASGR1 antibody.

[0026] Figure 8 is a bar graph showing a dose-dependent knockdown of ASGR1 mRNA in human primary hepatocytes observed with the 3549 (RNA-Ab ratio of 1) and 3550 (RNA-Ab ratio of 2) anti-ASGR1 mAb-siRNA conjugates. The unconjugated anti-ASGR1 cys mAb (PL-53515) was used as a control.

[0027] Figure 9A is a bar graph showing the ASGR1 mRNA level in livers from wild-type mice in all dosing groups measured at the indicated time points (days 2, 4, 8, and 15). The same siRNA conjugated to a GalNAc moiety (compound 1418) was used as a positive control. The amount of siRNA in 5 mpk of 1418 is equivalent to that in 30 mpk of the 3550 compound, which has 2 siRNAs/mAb.

[0028] Figure 9B is a line graph depicting ASGR1 protein expression in livers from wild-type mice in all dosing groups measured at the indicated time points (days 2, 4, 8, and 15). The same siRNA conjugated to a GalNAc moiety (compound 1418) was used as a positive control. The amount of siRNA in 5 mpk of 1418 is equivalent to that in 30 mpk of the 3550 compound, which has 2 siRNAs/mAb.

[0029] Figure 10 is a bar graph showing serum alkaline phosphatase (ALP) from wild-type mice in all dosing groups measured at the indicated time points (days 2, 4, 8, and 15). The same siRNA conjugated to a GalNAc moiety (compound 1418) was used as a positive control. The amount of siRNA in 5 mpk of 1418 is equivalent to that in 30 mpk of the 3550 compound, which has 2 siRNAs/mAb.

DETAILED DESCRIPTION

[0030] The present invention is directed to compositions and methods for regulating the expression of the asialoglycoprotein receptor in a cell or mammal. In some embodiments, compositions of the invention comprise RNAi constructs that target an ASGR1 mRNA and reduce ASGR1 expression in a cell or mammal. Such RNAi constructs are useful for treating or preventing various forms of cardiovascular disease, such as, for example, by reducing non-HDL

cholesterol serum levels and reducing the risk of developing coronary artery disease or myocardial infarction.

[0031] As used herein, the term "RNAi construct" refers to an agent comprising a RNA molecule that is capable of downregulating expression of a target gene (e.g. ASGR1) via a RNA interference mechanism when introduced into a cell. RNA interference is the process by which a nucleic acid molecule induces the cleavage and degradation of a target RNA molecule (e.g. messenger RNA or mRNA molecule) in a sequence-specific manner, e.g. through a RNA-induced silencing complex (RISC) pathway. In some embodiments, the RNAi construct comprises a double-stranded RNA molecule comprising two antiparallel strands of contiguous nucleotides that are sufficiently complementary to each other to hybridize to form a duplex region. "Hybridize" or "hybridization" refers to the pairing of complementary polynucleotides, typically via hydrogen bonding (e.g. Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary bases in the two polynucleotides. The strand comprising a region having a sequence that is substantially complementary to a target sequence (e.g. target mRNA) is referred to as the "antisense strand." The "sense strand" refers to the strand that includes a region that is substantially complementary to a region of the antisense strand. In some embodiments, the sense strand may comprise a region that has a sequence that is substantially identical to the target sequence.

[0032] A double-stranded RNA molecule may include chemical modifications to ribonucleotides, including modifications to the ribose sugar, base, or backbone components of the ribonucleotides, such as those described herein or known in the art. Any such modifications, as used in a double-stranded RNA molecule (e.g. siRNA, shRNA, or the like), are encompassed by the term "double-stranded RNA" for the purposes of this disclosure.

[0033] As used herein, a first sequence is "complementary" to a second sequence if a polynucleotide comprising the first sequence can hybridize to a polynucleotide comprising the second sequence to form a duplex region under certain conditions, such as physiological conditions. Other such conditions can include moderate or stringent hybridization conditions, which are known to those of skill in the art. A first sequence is considered to be fully complementary (100% complementary) to a second sequence if a polynucleotide comprising the first sequence base pairs with a polynucleotide comprising the second sequence over the entire length of one or both nucleotide sequences without any mismatches. A sequence is "substantially

complementary" to a target sequence if the sequence is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% complementary to a target sequence. Percent complementarity can be calculated by dividing the number of bases in a first sequence that are complementary to bases at corresponding positions in a second or target sequence by the total length of the first sequence. A sequence may also be said to be substantially complementary to another sequence if there are no more than 5, 4, 3, or 2 mismatches over a 30 base pair duplex region when the two sequences are hybridized. Generally, if any nucleotide overhangs, as defined herein, are present, the sequence of such overhangs is not considered in determining the degree of complementarity between two sequences. By way of example, a sense strand of 21 nucleotides in length and an antisense strand of 21 nucleotides in length that hybridize to form a 19 base pair duplex region with a 2 nucleotide overhang at the 3′ end of each strand would be considered to be fully complementary as the term is used herein.

[0034] In some embodiments, a region of the antisense strand comprises a sequence that is fully complementary to a region of the target RNA sequence (e.g. ASGR1 mRNA). In such embodiments, the sense strand may comprise a sequence that is fully complementary to the sequence of the antisense strand. In other such embodiments, the sense strand may comprise a sequence that is substantially complementary to the sequence of the antisense strand, e.g. having 1, 2, 3, 4, or 5 mismatches in the duplex region formed by the sense and antisense strands. In certain embodiments, it is preferred that any mismatches occur within the terminal regions (e.g. within 6, 5, 4, 3, or 2 nucleotides of the 5′ and/or 3′ ends of the strands). In one embodiment, any mismatches in the duplex region formed from the sense and antisense strands occur within 6, 5, 4, 3, or 2 nucleotides of the 5′ end of the antisense strand.

[0035] In certain embodiments, the sense strand and antisense strand of the double-stranded RNA may be two separate molecules that hybridize to form a duplex region, but are otherwise unconnected. Such double-stranded RNA molecules formed from two separate strands are referred to as "small interfering RNAs" or "short interfering RNAs" (siRNAs). Thus, in some embodiments, the RNAi constructs of the invention comprise a siRNA.

[0036] In other embodiments, the sense strand and the antisense strand that hybridize to form a duplex region may be part of a single RNA molecule, i.e. the sense and antisense strands are part of a self-complementary region of a single RNA molecule. In such cases, a single RNA molecule comprises a duplex region (also referred to as a stem region) and a loop region. The 3′

end of the sense strand is connected to the 5′ end of the antisense strand by a contiguous sequence of unpaired nucleotides, which will form the loop region. The loop region is typically of a sufficient length to allow the RNA molecule to fold back on itself such that the antisense strand can base pair with the sense strand to form the duplex or stem region. The loop region can comprise from about 3 to about 25, from about 5 to about 15, or from about 8 to about 12 unpaired nucleotides. Such RNA molecules with at least partially self-complementary regions are referred to as "short hairpin RNAs" (shRNAs). In certain embodiments, the RNAi constructs of the invention comprise a shRNA. The length of a single, at least partially self-complementary RNA molecule can be from about 35 nucleotides to about 100 nucleotides, from about 45 nucleotides to about 85 nucleotides, or from about 50 to about 60 nucleotides and comprise a duplex region and loop region each having the lengths recited herein.

[0037] In some embodiments, the RNAi constructs of the invention comprise a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is substantially or fully complementary to an ASGR1 messenger RNA (mRNA) sequence. As used herein, an "ASGR1 mRNA sequence" refers to any messenger RNA sequence, including splice variants, encoding an ASGR1 protein, including ASGR1 protein variants or isoforms from any species (e.g. mouse, rat, non-human primate, human). ASGR1 protein (also known as HL-1, ASGPR H1, ASGPR1, and CLEC4H1), as used herein, refers to the major subunit of the asialoglycoprotein receptor. In humans, ASGR1 is found on chromosome 17p13.2 and is expressed as two different isoforms, a long isoform (H1a or isoform A) of about 291 amino acids and a short soluble isoform (H1b or isoform B) of about 252 amino acids.

[0038] An ASGR1 mRNA sequence also includes the transcript sequence expressed as its complementary DNA (cDNA) sequence. A cDNA sequence refers to the sequence of an mRNA transcript expressed as DNA bases (e.g. guanine, adenine, thymine, and cytosine) rather than RNA bases (e.g. guanine, adenine, uracil, and cytosine). Thus, the antisense strand of the RNAi constructs of the invention may comprise a region having a sequence that is substantially or fully complementary to a target ASGR1 mRNA sequence or ASGR1 cDNA sequence. An ASGR1 mRNA or cDNA sequence can include, but is not limited to, any ASGR1 mRNA or cDNA sequence selected from the NCBI Reference sequences NM_001671.4 (human; Figure 1A, SEQ ID NO: 1), NM_001197216.2 (human; Figure 1B, SEQ ID NO: 2), NM_009714.2 (mouse; Figure 2, SEQ ID NO: 3011), and XM_005582698.1 (cynomolgus monkey; Figure 4, SEQ ID

NO: 3013) or the rat sequence in Figure 3 (SEQ ID NO: 3012). In one embodiment, the ASGR1 mRNA sequence is human transcript variant 1 listed in the NCBI database as Reference Sequence NM_001671.4 (see Figure 1A; SEQ ID NO: 1). In another embodiment, the ASGR1 mRNA sequence is human transcript variant 2 listed in the NCBI database as Reference Sequence NM_001197216.2 (see Figure 1B; SEQ ID NO: 2).

[0039] A region of the antisense strand can be substantially complementary or fully complementary to at least 15 consecutive nucleotides of the ASGR1 mRNA sequence. In some embodiments, the target region of the ASGR1 mRNA sequence to which the antisense strand comprises a region of complementarity can range from about 15 to about 30 consecutive nucleotides, from about 16 to about 28 consecutive nucleotides, from about 18 to about 26 consecutive nucleotides, from about 17 to about 24 consecutive nucleotides, from about 19 to about 25 consecutive nucleotides, from about 19 to about 23 consecutive nucleotides, or from about 19 to about 21 consecutive nucleotides. In certain embodiments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to an ASGR1 mRNA sequence may, in some embodiments, comprise at least 15 contiguous nucleotides from an antisense sequence listed in Table 1, Table 6, or Table 8. In other embodiments, the antisense sequence comprises at least 16, at least 17, at least 18, or at least 19 contiguous nucleotides from an antisense sequence listed in Table 1, Table 6, or Table 8. For instance, in some embodments, the region of the antisense strand comprising a sequence that is substantially or fully complementary to an ASGR1 mRNA sequence comprises at least 15 contiguous nucleotides from a sequence selected from SEQ ID NO: 1606, SEQ ID NO: 1684, SEQ ID NO: 1708, SEQ ID NO: 1714, SEQ ID NO: 1743, SEQ ID NO: 1754, SEQ ID NO: 1881, SEQ ID NO: 1897, SEQ ID NO: 2321, SEQ ID NO: 2323, SEQ ID NO: 2491, SEQ ID NO: 2508, SEQ ID NO: 2553, SEQ ID NO: 2650, SEQ ID NO: 2651, SEQ ID NO: 1946, SEQ ID NO: 2002, SEQ ID NO: 2865, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 2873, SEQ ID NO: 2969, SEQ ID NO: 3701, SEQ ID NO: 3702, SEQ ID NO: 3716, SEQ ID NO: 3718, SEQ ID NO: 3722, SEQ ID NO: 4618, SEQ ID NO: 4619, SEQ ID NO: 4621, SEQ ID NO: 4627, SEQ ID NO: 4630, SEQ ID NO: 4634, SEQ ID NO: 4638, or SEQ ID NO: 4639.

[0040] The sense strand of the RNAi construct typically comprises a sequence that is sufficiently complementary to the sequence of the antisense strand such that the two strands hybridize under physiological conditions to form a duplex region. A “duplex region” refers to the region in two

complementary or substantially complementary polynucleotides that form base pairs with one another, either by Watson-Crick base pairing or other hydrogen bonding interaction, to create a duplex between the two polynucleotides. The duplex region of the RNAi construct should be of sufficient length to allow the RNAi construct to enter the RNA interference pathway, e.g. by engaging the Dicer enzyme and/or the RISC complex. For instance, in some embodiments, the duplex region is about 15 to about 30 base pairs in length. Other lengths for the duplex region within this range are also suitable, such as about 15 to about 28 base pairs, about 15 to about 26 base pairs, about 15 to about 24 base pairs, about 15 to about 22 base pairs, about 17 to about 28 base pairs, about 17 to about 26 base pairs, about 17 to about 24 base pairs, about 17 to about 23 base pairs, about 17 to about 21 base pairs, about 19 to about 25 base pairs, about 19 to about 23 base pairs, or about 19 to about 21 base pairs. In one embodiment, the duplex region is about 17 to about 24 base pairs in length. In another embodiment, the duplex region is about 19 to about 21 base pairs in length.

[0041] For embodiments in which the sense strand and antisense strand are two separate molecules (e.g. RNAi construct comprises a siRNA), the sense strand and antisense strand need not be the same length as the length of the duplex region. For instance, one or both strands may be longer than the duplex region and have one or more unpaired nucleotides or mismatches flanking the duplex region. Thus, in some embodiments, the RNAi construct comprises at least one nucleotide overhang. As used herein, a "nucleotide overhang" refers to the unpaired nucleotide or nucleotides that extend beyond the duplex region at the terminal ends of the strands. Nucleotide overhangs are typically created when the 3′ end of one strand extends beyond the 5′ end of the other strand or when the 5′ end of one strand extends beyond the 3′ end of the other strand. The length of a nucleotide overhang is generally between 1 and 6 nucleotides, 1 and 5 nucleotides, 1 and 4 nucleotides, 1 and 3 nucleotides, 2 and 6 nucleotides, 2 and 5 nucleotides, or 2 and 4 nucleotides. In some embodiments, the nucleotide overhang comprises 1, 2, 3, 4, 5, or 6 nucleotides. In one particular embodiment, the nucleotide overhang comprises 1 to 4 nucleotides. In certain embodiments, the nucleotide overhang comprises 2 nucleotides. The nucleotides in the overhang can be ribonucleotides, deoxyribonucleotides, or modified nucleotides as described herein. In some embodiments, the overhang comprises a 5′-uridine-uridine-3′ (5′-UU-3′) dinucleotide. In such embodiments, the UU dinucleotide may comprise

ribonucleotides or modified nucleotides, e.g. 2′-modified nucleotides. In other embodiments, the overhang comprises a 5′-deoxythymidine-deoxythymidine-3′ (5′-dTdT-3′) dinucleotide.

[0042] The nucleotide overhang can be at the 5′ end or 3′ end of one or both strands. For example, in one embodiment, the RNAi construct comprises a nucleotide overhang at the 5′ end and the 3′ end of the antisense strand. In another embodiment, the RNAi construct comprises a nucleotide overhang at the 5′ end and the 3′ end of the sense strand. In some embodiments, the RNAi construct comprises a nucleotide overhang at the 5′ end of the sense strand and the 5′ end of the antisense strand. In other embodiments, the RNAi construct comprises a nucleotide overhang at the 3′ end of the sense strand and the 3′ end of the antisense strand.

[0043] The RNAi constructs may comprise a single nucleotide overhang at one end of the double-stranded RNA molecule and a blunt end at the other. A "blunt end" means that the sense strand and antisense strand are fully base-paired at the end of the molecule and there are no unpaired nucleotides that extend beyond the duplex region. In some embodiments, the RNAi construct comprises a nucleotide overhang at the 3′ end of the sense strand and a blunt end at the 5′ end of the sense strand and 3′ end of the antisense strand. In other embodiments, the RNAi construct comprises a nucleotide overhang at the 3′ end of the antisense strand and a blunt end at the 5′ end of the antisense strand and the 3′ end of the sense strand. In certain embodiments, the RNAi construct comprises a blunt end at both ends of the double-stranded RNA molecule. In such embodiments, the sense strand and antisense strand have the same length and the duplex region is the same length as the sense and antisense strands (i.e. the molecule is double-stranded over its entire length).

[0044] The sense strand and antisense strand can each independently be about 15 to about 30 nucleotides in length, about 18 to about 28 nucleotides in length, about 19 to about 27 nucleotides in length, about 19 to about 25 nucleotides in length, about 19 to about 23 nucleotides in length, about 21 to about 25 nucleotides in length, or about 21 to about 23 nucleotides in length. In certain embodiments, the sense strand and antisense strand are each about 18, about 19, about 20, about 21, about 22, about 23, about 24, or about 25 nucleotides in length. In some embodiments, the sense strand and antisense strand have the same length but form a duplex region that is shorter than the strands such that the RNAi construct has two nucleotide overhangs. For instance, in one embodiment, the RNAi construct comprises (i) a sense strand and an antisense strand that are each 21 nucleotides in length, (ii) a duplex region

that is 19 base pairs in length, and (iii) nucleotide overhangs of 2 unpaired nucleotides at both the 3′ end of the sense strand and the 3′ end of the antisense strand. In another embodiment, the RNAi construct comprises (i) a sense strand and an antisense strand that are each 23 nucleotides in length, (ii) a duplex region that is 21 base pairs in length, and (iii) nucleotide overhangs of 2 unpaired nucleotides at both the 3′ end of the sense strand and the 3′ end of the antisense strand. In other embodiments, the sense strand and antisense strand have the same length and form a duplex region over their entire length such that there are no nucleotide overhangs on either end of the double-stranded molecule. In one such embodiment, the RNAi construct is blunt ended and comprises (i) a sense strand and an antisense strand, each of which is 21 nucleotides in length, and (ii) a duplex region that is 21 base pairs in length. In another such embodiment, the RNAi construct is blunt ended and comprises (i) a sense strand and an antisense strand, each of which is 23 nucleotides in length, and (ii) a duplex region that is 23 base pairs in length.

[0045] In other embodiments, the sense strand or the antisense strand is longer than the other strand and the two strands form a duplex region having a length equal to that of the shorter strand such that the RNAi construct comprises at least one nucleotide overhang. For example, in one embodiment, the RNAi construct comprises (i) a sense strand that is 19 nucleotides in length, (ii) an antisense strand that is 21 nucleotides in length, (iii) a duplex region of 19 base pairs in length, and (iv) a single nucleotide overhang of 2 unpaired nucleotides at the 3′ end of the antisense strand. In another embodiment, the RNAi construct comprises (i) a sense strand that is 21 nucleotides in length, (ii) an antisense strand that is 23 nucleotides in length, (iii) a duplex region of 21 base pairs in length, and (iv) a single nucleotide overhang of 2 unpaired nucleotides at the 3′ end of the antisense strand.

[0046] The antisense strand of the RNAi constructs of the invention can comprise the sequence of any one of the antisense sequences listed in Table 1, Table 6, or Table 8, the sequence of nucleotides 1-19 of any of these antisense sequences, or the sequence of nucleotides 2-19 of any of these antisense sequences. Each of the antisense sequences listed in Tables 1, 6, and 8 comprises a sequence of at least 19 consecutive nucleotides (first 19 nucleotides counting from the 5′ end) that is complementary to an ASGR1 mRNA sequence plus a two nucleotide overhang sequence. Thus, in some embodiments, the antisense strand comprises a sequence of nucleotides 1-19 of any one of SEQ ID NOs: 1508-3010, 3665-4315, or 4513-4687. In other embodiments, the antisense strand comprises a sequence of nucleotides 2-19 of any one of SEQ ID NOs: 1508-

3010, 3665-4315, or 4513-4687. In still other embodiments, the antisense strand comprises a sequence selected from SEQ ID NOs: 1508-3010, 3665-4315, or 4513-4687. In certain embodiments, the antisense strand comprises, or consists of, a sequence selected from SEQ ID NO: 1606, SEQ ID NO: 1684, SEQ ID NO: 1708, SEQ ID NO: 1714, SEQ ID NO: 1743, SEQ ID NO: 1754, SEQ ID NO: 1881, SEQ ID NO: 1897, SEQ ID NO: 2321, SEQ ID NO: 2323, SEQ ID NO: 2491, SEQ ID NO: 2508, SEQ ID NO: 2553, SEQ ID NO: 2650, SEQ ID NO: 2651, SEQ ID NO: 1946, SEQ ID NO: 2002, SEQ ID NO: 2865, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 2873, SEQ ID NO: 2969, SEQ ID NO: 3701, SEQ ID NO: 3702, SEQ ID NO: 3716, SEQ ID NO: 3718, SEQ ID NO: 3722, SEQ ID NO: 4618, SEQ ID NO: 4619, SEQ ID NO: 4621, SEQ ID NO: 4627, SEQ ID NO: 4630, SEQ ID NO: 4634, SEQ ID NO: 4638, or SEQ ID NO: 4639. In some embodiments, the antisense strand comprises, or consists of, a sequence selected from SEQ ID NO: 1684, SEQ ID NO: 1708, SEQ ID NO: 1714, SEQ ID NO: 1743, SEQ ID NO: 2323, SEQ ID NO: 2650, SEQ ID NO: 2651, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 2873, SEQ ID NO: 4618, SEQ ID NO: 4621, SEQ ID NO: 4627, SEQ ID NO: 4638, or SEQ ID NO: 4639. In other embodiments, the antisense strand comprises, or consists of, a sequence selected from SEQ ID NO: 1743, SEQ ID NO: 2323, SEQ ID NO: 2651, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 4621, or SEQ ID NO: 4638.

[0047] In these and other embodiments, the sense strand of the RNAi constructs of the invention can comprise the sequence of any one of the sense sequences listed in Table 1, Table 6, or Table 8, the sequence of nucleotides 1-19 of any of these sense sequences, or the sequence of nucleotides 2-19 of any of these sense sequences. Each of the sense sequences listed in Tables 1, 6, and 8 comprises a sequence of at least 19 consecutive nucleotides (first 19 nucleotides counting from the 5′ end) that is identical to an ASGR1 mRNA sequence and complementary to the corresponding antisense sequence, plus a two nucleotide overhang sequence. Thus, in some embodiments, the sense strand comprises a sequence of nucleotides 1-19 of any one of SEQ ID NOs: 5-1507, 3014-3664, or 4319-4512. In other embodiments, the sense strand comprises a sequence of nucleotides 2-19 of any one of SEQ ID NOs: 5-1507, 3014-3664, or 4319-4512. In still other embodiments, the sense strand comprises a sequence selected from SEQ ID NOs: 5-1507, 3014-3664, or 4319-4512. In certain embodiments, the sense strand comprises, or consists of, a sequence selected from SEQ ID NO: 103, SEQ ID NO: 181, SEQ ID NO: 205, SEQ ID NO: 211, SEQ ID NO: 240, SEQ ID NO: 251, SEQ ID NO: 378, SEQ ID NO: 394, SEQ ID NO:

818, SEQ ID NO: 820, SEQ ID NO: 988, SEQ ID NO: 1005, SEQ ID NO: 1050, SEQ ID NO: 1147, SEQ ID NO: 1148, SEQ ID NO: 443, SEQ ID NO: 499, SEQ ID NO: 1362, SEQ ID NO 1364, SEQ ID NO: 1366, SEQ ID NO: 1370, SEQ ID NO: 1466, SEQ ID NO: 3050, SEQ ID NO: 3051, SEQ ID NO: 3065, SEQ ID NO: 3067, SEQ ID NO: 3071, SEQ ID NO: 4443, SEQ ID NO: 4444, SEQ ID NO: 4446, SEQ ID NO: 4452, SEQ ID NO: 4455, SEQ ID NO: 4459, SEQ ID NO: 4463, or SEQ ID NO: 4464. In certain other embodiments, the sense strand comprises, or consists of, a sequence selected from SEQ ID NO: 181, SEQ ID NO: 205, SEQ ID NO: 211, SEQ ID NO: 240, SEQ ID NO: 820, SEQ ID NO: 1147, SEQ ID NO: 1148, SEQ ID NO: 1364, SEQ ID NO: 1366, SEQ ID NO: 1370, SEQ ID NO: 4443, SEQ ID NO: 4446, SEQ ID NO: 4452, SEQ ID NO: 4463, or SEQ ID NO: 4464. In some embodiments, the sense strand comprises, or consists of, a sequence selected from SEQ ID NO: 240, SEQ ID NO: 820, SEQ ID NO: 1148, SEQ ID NO: 1364, SEQ ID NO: 1366, SEQ ID NO: 4446 or SEQ ID NO: 4463.

[0048] In certain embodiments of the invention, the RNAi constructs comprise (i) a sense strand comprising a sequence selected from SEQ ID NOs: 5-1507, 3014-3664, or 4319-4512, nucleotides 1-19 of any one of SEQ ID NOs: 5-1507, 3014-3664, or 4319-4512, or nucleotides 2-19 of any one of SEQ ID NOs: 5-1507, 3014-3664, or 4319-4512, and (ii) an antisense strand comprising a sequence selected from SEQ ID NOs: 1508-3010, 3665-4315, or 4513-4687, nucleotides 1-19 of any one of SEQ ID NOs: 1508-3010, 3665-4315, or 4513-4687, or nucleotides 2-19 of any one of SEQ ID NOs: 1508-3010, 3665-4315, or 4513-4687. In some embodiments, the RNAi constructs comprise (i) a sense strand comprising, or consisting of, a sequence selected from SEQ ID NO: 103, SEQ ID NO: 181, SEQ ID NO: 205, SEQ ID NO: 211, SEQ ID NO: 240, SEQ ID NO: 251, SEQ ID NO: 378, SEQ ID NO: 394, SEQ ID NO: 818, SEQ ID NO: 820, SEQ ID NO: 988, SEQ ID NO: 1005, SEQ ID NO: 1050, SEQ ID NO: 1147, SEQ ID NO: 1148, SEQ ID NO: 443, SEQ ID NO: 499, SEQ ID NO: 1362, SEQ ID NO 1364, SEQ ID NO: 1366, SEQ ID NO: 1370, SEQ ID NO: 1466, SEQ ID NO: 3050, SEQ ID NO: 3051, SEQ ID NO: 3065, SEQ ID NO: 3067, SEQ ID NO: 3071, SEQ ID NO: 4443, SEQ ID NO: 4444, SEQ ID NO: 4446, SEQ ID NO: 4452, SEQ ID NO: 4455, SEQ ID NO: 4459, SEQ ID NO: 4463, or SEQ ID NO: 4464 and (ii) an antisense strand comprising, or consisting of, a sequence selected from SEQ ID NO: 1606, SEQ ID NO: 1684, SEQ ID NO: 1708, SEQ ID NO: 1714, SEQ ID NO: 1743, SEQ ID NO: 1754, SEQ ID NO: 1881, SEQ ID NO: 1897, SEQ ID NO: 2321, SEQ ID NO: 2323, SEQ ID NO: 2491, SEQ ID NO: 2508, SEQ ID NO: 2553, SEQ

ID NO: 2650, SEQ ID NO: 2651, SEQ ID NO: 1946, SEQ ID NO: 2002, SEQ ID NO: 2865, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 2873, SEQ ID NO: 2969, SEQ ID NO: 3701, SEQ ID NO: 3702, SEQ ID NO: 3716, SEQ ID NO: 3718, SEQ ID NO: 3722, SEQ ID NO: 4618, SEQ ID NO: 4619, SEQ ID NO: 4621, SEQ ID NO: 4627, SEQ ID NO: 4630, SEQ ID NO: 4634, SEQ ID NO: 4638, or SEQ ID NO: 4639. In other embodiments, the RNAi constructs comprise (i) a sense strand comprising, or consisting of, a sequence selected from SEQ ID NO: 181, SEQ ID NO: 205, SEQ ID NO: 211, SEQ ID NO: 240, SEQ ID NO: 820, SEQ ID NO: 1147, SEQ ID NO: 1148, SEQ ID NO: 1364, SEQ ID NO: 1366, SEQ ID NO: 1370, SEQ ID NO: 4443, SEQ ID NO: 4446, SEQ ID NO: 4452, SEQ ID NO: 4463, or SEQ ID NO: 4464, and (ii) an antisense strand comprising, or consisting of, a sequence selected from SEQ ID NO: 1684, SEQ ID NO: 1708, SEQ ID NO: 1714, SEQ ID NO: 1743, SEQ ID NO: 2323, SEQ ID NO: 2650, SEQ ID NO: 2651, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 2873, SEQ ID NO: 4618, SEQ ID NO: 4621, SEQ ID NO: 4627, SEQ ID NO: 4638, or SEQ ID NO: 4639. In still other embodiments, the RNAi constructs comprise (i) a sense strand comprising, or consisting of, a sequence selected from SEQ ID NO: 240, SEQ ID NO: 820, SEQ ID NO: 1148, SEQ ID NO: 1364, SEQ ID NO: 1366, SEQ ID NO: 4446 or SEQ ID NO: 4463, and (ii) an antisense strand comprising, or consisting of, a sequence selected from SEQ ID NO: 1743, SEQ ID NO: 2323, SEQ ID NO: 2651, SEQ ID NO: 2867, SEQ ID NO: 2869, SEQ ID NO: 4621, or SEQ ID NO: 4638.

[0049] In certain embodiments, the RNAi constructs comprise: (a) a sense strand comprising the sequence of SEQ ID NO: 181 and an antisense strand comprising the sequence of SEQ ID NO: 1684; (b) a sense strand comprising the sequence of SEQ ID NO: 205 and an antisense strand comprising the sequence of SEQ ID NO: 1708; (c) a sense strand comprising the sequence of SEQ ID NO: 211 and an antisense strand comprising the sequence of SEQ ID NO: 1714; (d) a sense strand comprising the sequence of SEQ ID NO: 240 and an antisense strand comprising the sequence of SEQ ID NO: 1743; (e) a sense strand comprising the sequence of SEQ ID NO: 820 and an antisense strand comprising the sequence of SEQ ID NO: 2323; (f) a sense strand comprising the sequence of SEQ ID NO: 1147 and an antisense strand comprising the sequence of SEQ ID NO: 2650; (g) a sense strand comprising the sequence of SEQ ID NO: 1148 and an antisense strand comprising the sequence of SEQ ID NO: 2651; (h) a sense strand comprising the sequence of SEQ ID NO: 1364 and an antisense strand comprising the sequence of SEQ ID NO:

2867; (i) a sense strand comprising the sequence of SEQ ID NO: 1366 and an antisense strand comprising the sequence of SEQ ID NO: 2869; or (j) a sense strand comprising the sequence of SEQ ID NO: 1370 and an antisense strand comprising the sequence of SEQ ID NO: 2873.

[0050] The RNAi construct of the invention can be any of the duplex compounds listed in Tables 1 to 10 (including the nucleotide sequences and/or chemical modifications of the compounds). In some embodiments, the RNAi construct is any of the duplex compounds listed in Table 1. In other embodiments, the RNAi construct is any of the duplex compounds listed in Table 6 (including the nucleotide sequences and/or chemical modifications of the compounds). In still other embodiments, the RNAi construct is any of the duplex compounds listed in Table 8 (including the nucleotide sequences and/or chemical modifications of the compounds). In certain embodiments, the RNAi construct is D-1098, D-1176, D-1200, D-1206, D-1235, D-1246, D-1373, D-1389, D-1813, D-1815, D-1983, D-2000, D-2045, D-2142, D-2143, D-1438, D-1494, D-2357, D-2359, D-2361, D-2365, D-2461, D-3036, D-3037, D-3051, D-3053, D-3057, D-3779, D-3780, D-3782, D-3788, D-3791, D-3795, D-3799, or D-3800. In some embodiments, the RNAi construct is D-1200, D-1206, D-1235, D-1815, D-2143, D-2359, D-2361, D-2365, D-2142, D-1176, D-3779, D-3782, D-3788, D-3799, or D-3800. In one particular embodiment, the RNAi construct is D-1235. In another particular embodiment, the RNAi construct is D-2143. In another embodiment, the RNAi construct is D-2361. In another embodiment, the RNAi construct is D-1815. In another embodiment, the RNAi construct is D-2359. In still another embodiment, the RNAi construct is D-3782. In yet another embodiment, the RNAi construct is D-3799.

[0051] In certain embodiments, the antisense strands of the RNAi constructs of the invention may target certain regions of the ASGR1 mRNA sequence. For instance, in some embodiments, the antisense strand of an RNAi construct of the invention comprises a sequence that is substantially complementary or fully complementary to nucleotides 692 to 721 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1, nucleotides 692 to 716 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1, or nucleotides 692 to 710 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1. In such embodiments, the RNAi construct may comprise a sense strand that is substantially complementary or fully complementary to the antisense strand targeting this region. Thus, in these embodiments, the sense strand may

comprise a sequence identical to nucleotides 692 to 721, nucleotides 692 to 716, or nucleotides 692 to 710 of SEQ ID NO: 1.

[0052] In other embodiments, the antisense strand of an RNAi construct of the invention comprises a sequence that is substantially complementary or fully complementary to nucleotides 396 to 425 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1, nucleotides 396 to 420 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1, or nucleotides 396 to 414 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1. In such embodiments, the RNAi construct may comprise a sense strand that is substantially complementary or fully complementary to the antisense strand targeting this region. Thus, in these embodiments, the sense strand may comprise a sequence identical to nucleotides 396 to 425, nucleotides 396 to 420, or nucleotides 396 to 414 of SEQ ID NO: 1.

[0053] In still other embodiments, the antisense strand of an RNAi construct of the invention comprises a sequence that is substantially complementary or fully complementary to nucleotides 886 to 915 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1, nucleotides 886 to 910 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1, or nucleotides 886 to 904 of the human ASGR1 mRNA transcript set forth in SEQ ID NO: 1. In such embodiments, the RNAi construct may comprise a sense strand that is substantially complementary or fully complementary to the antisense strand targeting this region. Thus, in these embodiments, the sense strand may comprise a sequence identical to nucleotides 886 to 915, nucleotides 886 to 910, or nucleotides 886 to 904 of SEQ ID NO: 1.

[0054] The RNAi constructs of the invention may comprise one or more modified nucleotides. A "modified nucleotide" refers to a nucleotide that has one or more chemical modifications to the nucleoside, nucleobase, pentose ring, or phosphate group. As used herein, modified nucleotides do not encompass ribonucleotides containing adenosine monophosphate, guanosine monophosphate, uridine monophosphate, and cytidine monophosphate, and deoxyribonucleotides containing deoxyadenosine monophosphate, deoxyguanosine monophosphate, deoxythymidine monophosphate, and deoxycytidine monophosphate. However, the RNAi constructs may comprise combinations of modified nucleotides, ribonucleotides, and deoxyribonucleotides. Incorporation of modified nucleotides into one or both strands of double-stranded RNA molecules can improve the *in vivo* stability of the RNA molecules, e.g., by reducing the molecules' susceptibility to nucleases and other degradation

processes. The potency of RNAi constructs for reducing expression of the target gene can also be enhanced by incorporation of modified nucleotides.

[0055] In certain embodiments, the modified nucleotides have a modification of the ribose sugar. These sugar modifications can include modifications at the 2′ and/or 5′ position of the pentose ring as well as bicyclic sugar modifications. A 2′-modified nucleotide refers to a nucleotide having a pentose ring with a substituent at the 2′ position other than H or OH. Such 2′-modifications include, but are not limited to, 2′-O-alkyl (e.g. O-C_1-C_{10} or O-C_1-C_{10} substituted alkyl), 2′-O-allyl (O-$CH_2CH{=}CH_2$), 2′-C-allyl, 2′-fluoro, 2′-O-methyl (OCH_3), 2′-O-methoxyethyl (O-$(CH_2)_2OCH_3$), 2′-OCF_3, 2′-O$(CH_2)_2SCH_3$, 2′-O-aminoalkyl, 2′-amino (e.g. NH_2), 2′-O-ethylamine, and 2′-azido. Modifications at the 5′ position of the pentose ring include, but are not limited to, 5′-methyl (R or S); 5′-vinyl, and 5′-methoxy.

[0056] A “bicyclic sugar modification” refers to a modification of the pentose ring where a bridge connects two atoms of the ring to form a second ring resulting in a bicyclic sugar structure. In some embodiments the bicyclic sugar modification comprises a bridge between the 4′ and 2′ carbons of the pentose ring. Nucleotides comprising a sugar moiety with a bicyclic sugar modification are referred to herein as bicyclic nucleic acids or BNAs. Exemplary bicyclic sugar modifications include, but are not limited to, α-L-Methyleneoxy (4′-CH_2—O-2′) bicyclic nucleic acid (BNA); β-D-Methyleneoxy (4′-CH_2—O-2′) BNA (also referred to as a locked nucleic acid or LNA); Ethyleneoxy (4′-$(CH_2)_2$—O-2′) BNA; Aminooxy (4′-CH_2—O—N(R)- 2′) BNA; Oxyamino (4′-CH_2—N(R) —O-2′) BNA; Methyl(methyleneoxy) (4′-$CH(CH_3)$ —O-2′) BNA (also referred to as constrained ethyl or cEt); methylene-thio (4′-CH_2—S-2′) BNA; methylene-amino (4′-CH2-N(R)- 2′) BNA; methyl carbocyclic (4′-CH_2—$CH(CH_3)$- 2′) BNA; propylene carbocyclic (4′-$(CH_2)_3$-2′) BNA; and Methoxy(ethyleneoxy) (4′-$CH(CH_2OMe)$-O-2′) BNA (also referred to as constrained MOE or cMOE). These and other sugar-modified nucleotides that can be incorporated into the RNAi constructs of the invention are described in U.S. Patent No. 9,181,551, U.S. Patent Publication No. 2016/0122761, and Deleavey and Damha, Chemistry and Biology, Vol. 19: 937-954, 2012, all of which are hereby incorporated by reference in their entireties.

[0057] In some embodiments, the RNAi constructs comprise one or more 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides, 2′-O-methoxyethyl modified nucleotides, 2′-O-allyl modified nucleotides, bicyclic nucleic acids (BNAs), or combinations thereof. In certain

embodiments, the RNAi constructs comprise one or more 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides, 2′-O-methoxyethyl modified nucleotides, or combinations thereof. In one particular embodiment, the RNAi constructs comprise one or more 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides or combinations thereof.

[0058] Both the sense and antisense strands of the RNAi constructs can comprise one or multiple modified nucleotides. For instance, in some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more modified nucleotides. In certain embodiments, all nucleotides in the sense strand are modified nucleotides. In some embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more modified nucleotides. In other embodiments, all nucleotides in the antisense strand are modified nucleotides. In certain other embodiments, all nucleotides in the sense strand and all nucleotides in the antisense strand are modified nucleotides. In these and other embodiments, the modified nucleotides can be 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides, or combinations thereof.

[0059] In some embodiments, all pyrimidine nucleotides preceding an adenosine nucleotide in the sense strand, antisense strand, or both strands are modified nucleotides. For example, where the sequence 5′-CA-3′ or 5′-UA-3′ appears in either strand, the cytidine and uridine nucleotides are modified nucleotides, preferably 2′-O-methyl modified nucleotides. In certain embodiments, all pyrimidine nucleotides in the sense strand are modified nucleotides (e.g. 2′-O-methyl modified nucleotides), and the 5′ nucleotide in all occurrences of the sequence 5′-CA-3′ or 5′-UA-3′ in the antisense strand are modified nucleotides (e.g. 2′-O-methyl modified nucleotides). In other embodiments, all nucleotides in the duplex region are modified nucleotides. In such embodiments, the modified nucleotides are preferably 2′-O-methyl modified nucleotides, 2′-fluoro modified nucleotides or combinations thereof.

[0060] In embodiments in which the RNAi construct comprises a nucleotide overhang, the nucleotides in the overhang can be ribonucleotides, deoxyribonucleotides, or modified nucleotides. In one embodiment, the nucleotides in the overhang are deoxyribonucleotides, e.g. deoxythymidine. In another embodiment, the nucleotides in the overhang are modified nucleotides. For instance, in some embodiments, the nucleotides in the overhang are 2′-O-methyl modified nucleotides, 2′-fluoro modified nucleotides, 2′-methoxyethyl modified nucleotides, or combinations thereof.

[0061] The RNAi constructs of the invention may also comprise one or more modified internucleotide linkages. As used herein, the term "modified internucleotide linkage" refers to an internucleotide linkage other than the natural 3′ to 5′ phosphodiester linkage. In some embodiments, the modified internucleotide linkage is a phosphorous-containing internucleotide linkage, such as a phosphotriester, aminoalkylphosphotriester, an alkylphosphonate (e.g. methylphosphonate, 3′ -alkylene phosphonate), a phosphinate, a phosphoramidate (e.g. 3′-amino phosphoramidate and aminoalkylphosphoramidate), a phosphorothioate (P=S), a chiral phosphorothioate, a phosphorodithioate, a thionophosphoramidate, a thionoalkylphosphonate, a thionoalkylphosphotriester, and a boranophosphate. In one embodiment, a modified internucleotide linkage is a 2′ to 5′ phosphodiester linkage. In other embodiments, the modified internucleotide linkage is a non-phosphorous-containing internucleotide linkage and thus can be referred to as a modified internucleoside linkage. Such non-phosphorous-containing linkages include, but are not limited to, morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane linkages (—O—$Si(H)_2$—O—); sulfide, sulfoxide and sulfone linkages; formacetyl and thioformacetyl linkages; alkene containing backbones; sulfamate backbones; methylenemethylimino (—CH_2—$N(CH_3)$ —O—CH_2—) and methylenehydrazino linkages; sulfonate and sulfonamide linkages; amide linkages; and others having mixed N, O, S and CH_2 component parts. In one embodiment, the modified internucleoside linkage is a peptide-based linkage (e.g. aminoethylglycine) to create a peptide nucleic acid or PNA, such as those described in U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262. Other suitable modified internucleotide and internucleoside linkages that may be employed in the RNAi constructs of the invention are described in U.S. Patent No. 6,693,187, U.S. Patent No. 9,181,551, U.S. Patent Publication No. 2016/0122761, and Deleavey and Damha, Chemistry and Biology, Vol. 19: 937-954, 2012, all of which are hereby incorporated by reference in their entireties.

[0062] In certain embodiments, the RNAi constructs comprise one or more phosphorothioate internucleotide linkages. The phosphorothioate internucleotide linkages may be present in the sense strand, antisense strand, or both strands of the RNAi constructs. For instance, in some embodiments, the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. In other embodiments, the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. In still other embodiments, both strands comprise 1, 2, 3, 4, 5, 6, 7, 8, or more phosphorothioate internucleotide linkages. The RNAi

constructs can comprise one or more phosphorothioate internucleotide linkages at the 3′-end, the 5′-end, or both the 3′- and 5′-ends of the sense strand, the antisense strand, or both strands. For instance, in certain embodiments, the RNAi construct comprises about 1 to about 6 or more (e.g., about 1, 2, 3, 4, 5, 6 or more) consecutive phosphorothioate internucleotide linkages at the 3′-end of the sense strand, the antisense strand, or both strands. In other embodiments, the RNAi construct comprises about 1 to about 6 or more (e.g., about 1, 2, 3, 4, 5, 6 or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In one embodiment, the RNAi construct comprises a single phosphorothioate internucleotide linkage at the 3′ end of the sense strand and a single phosphorothioate internucleotide linkage at the 3′ end of the antisense strand. In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at the 3′ end of the antisense strand (i.e. a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at the 3′ end of the antisense strand). In another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3′ and 5′ ends of the antisense strand. In yet another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3′ and 5′ ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at the 5′ end of the sense strand. In still another embodiment, the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3′ and 5′ ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at both the 3′ and 5′ ends of the sense strand (i.e. a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at both the 5′ and 3′ ends of the antisense strand and a phosphorothioate internucleotide linkage at the first and second internucleotide linkages at both the 5′ and 3′ ends of the sense strand). In any of the embodiments in which one or both strands comprises one or more phosphorothioate internucleotide linkages, the remaining internucleotide linkages within the strands can be the natural 3′ to 5′ phosphodiester linkages. For instance, in some embodiments, each internucleotide linkage of the sense and antisense strands is selected from phosphodiester and phosphorothioate, wherein at least one internucleotide linkage is a phosphorothioate.

[0063] In embodiments in which the RNAi construct comprises a nucleotide overhang, two or more of the unpaired nucleotides in the overhang can be connected by a phosphorothioate internucleotide linkage. In certain embodiments, all the unpaired nucleotides in a nucleotide

overhang at the 3′ end of the antisense strand and/or the sense strand are connected by phosphorothioate internucleotide linkages. In other embodiments, all the unpaired nucleotides in a nucleotide overhang at the 5′ end of the antisense strand and/or the sense strand are connected by phosphorothioate internucleotide linkages. In still other embodiments, all the unpaired nucleotides in any nucleotide overhang are connected by phosphorothioate internucleotide linkages.

[0064] In certain embodiments, the modified nucleotides incorporated into one or both of the strands of the RNAi constructs of the invention have a modification of the nucleobase (also referred to herein as "base"). A "modified nucleobase" or "modified base" refers to a base other than the naturally occurring purine bases adenine (A) and guanine (G) and pyrimidine bases thymine (T), cytosine (C), and uracil (U). Modified nucleobases can be synthetic or naturally occurring modifications and include, but are not limited to, universal bases, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine (X), hypoxanthine (I), 2-aminoadenine, 6-methyladenine, 6-methylguanine, and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine.

[0065] In some embodiments, the modified base is a universal base. A "universal base" refers to a base analog that indiscriminately forms base pairs with all of the natural bases in RNA and DNA without altering the double helical structure of the resulting duplex region. Universal bases are known to those of skill in the art and include, but are not limited to, inosine, C-phenyl, C-naphthyl and other aromatic derivatives, azole carboxamides, and nitroazole derivatives, such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole.

[0066] Other suitable modified bases that can be incorporated into the RNAi constructs of the invention include those described in Herdewijn, Antisense Nucleic Acid Drug Dev., Vol. 10: 297–310, 2000 and Peacock *et al.*, J. Org. Chem., Vol. 76: 7295–7300, 2011, both of which are hereby incorporated by reference in their entireties. The skilled person is well aware that

guanine, cytosine, adenine, thymine, and uracil may be replaced by other nucleobases, such as the modified nucleobases described above, without substantially altering the base pairing properties of a polynucleotide comprising a nucleotide bearing such replacement nucleobase.

[0067] In some embodiments, the sense and antisense strands of the RNAi constructs may comprise one or more abasic nulceotides. An "abasic nucleotide" or "abasic nucleoside" is a nucleotide or nucleoside that lacks a nucleobase at the 1′ position of the ribose sugar. In certain embodiments, the abasic nucleotides are incorporated into the terminal ends of the sense and/or antisense strands of the RNAi constructs. In one embodiment, the sense strand comprises an abasic nucleotide as the terminal nucleotide at its 3′ end, its 5′ end, or both its 3′ and 5′ ends. In another embodiment, the antisense strand comprises an abasic nucleotide as the terminal nucleotide at its 3′ end, its 5′ end, or both its 3′ and 5′ ends. In such embodiments in which the abasic nucleotide is a terminal nucleotide, it may be linked to the adjacent nucleotide through a 3′-3′ internucleotide linkage (i.e. an inverted nucleotide) rather than the natural 3′-5′ internucleotide linkage.

[0068] In some embodiments of the RNAi constructs of the invention, the 5′ end of the sense strand, antisense strand, or both the antisense and sense strands comprises a phosphate moiety. As used herein, the term "phosphate moiety" refers to a terminal phosphate group that includes unmodified phosphates (—O—P=O)(OH)OH) as well as modified phosphates. Modified phosphates include phosphates in which one or more of the O and OH groups is replaced with H, O, S, N(R) or alkyl where R is H, an amino protecting group or unsubstituted or substituted alkyl. Exemplary phosphate moieties include, but are not limited to, 5′-monophosphate; 5′-diphosphate; 5′-triphosphate; 5′-guanosine cap (7-methylated or non-methylated); 5′-adenosine cap or any other modified or unmodified nucleotide cap structure; 5′-monothiophosphate (phosphorothioate); 5′-monodithiophosphate (phosphorodithioate); 5′-alpha-thiotriphosphate; 5′-gamma-thiotriphosphate, 5′-phosphoramidates; 5′-vinylphosphates; 5′-alkylphosphonates (e.g., alkyl = methyl, ethyl, isopropyl, propyl, etc.); and 5′-alkyletherphosphonates (e.g., alkylether = methoxymethyl, ethoxymethyl, etc.).

[0069] The modified nucleotides that can be incorporated into the RNAi constructs of the invention may have more than one chemical modification described herein. For instance, the modified nucleotide may have a modification to the ribose sugar as well as a modification to the nucleobase. By way of example, a modified nucleotide may comprise a 2′ sugar modification

(e.g. 2′-fluoro or 2′-methyl) and comprise a modified base (e.g. 5-methyl cytosine or pseudouracil). In other embodiments, the modified nucleotide may comprise a sugar modification in combination with a modification to the 5′ phosphate that would create a modified internucleotide or internucleoside linkage when the modified nucleotide was incorporated into a polynucleotide. For instance, in some embodiments, the modified nucleotide may comprise a sugar modification, such as a 2′-fluoro modification, a 2′-O-methyl modification, or a bicyclic sugar modification, as well as a 5′ phosphorothioate group. Accordingly, in some embodiments, one or both strands of the RNAi constructs of the invention comprise a combination of 2′ modified nucleotides or BNAs and phosphorothioate internucleotide linkages. In certain embodiments, both the sense and antisense strands of the RNAi constructs of the invention comprise a combination of 2′-fluoro modified nucleotides, 2′-O-methyl modified nucleotides, and phosphorothioate internucleotide linkages. Exemplary RNAi constructs comprising modified nucleotides and internucleotide linkages are shown in Tables 6 and 8.

[0070] Preferably, the RNAi constructs of the invention reduce or inhibit the expression of ASGR1 in cells, particularly liver cells. Accordingly, in one embodiment, the present invention provides a method of reducing ASGR1 expression in a cell by contacting the cell with any RNAi construct described herein. The cell may be *in vitro* or *in vivo*. ASGR1 expression can be assessed by measuring the amount or level of ASGR1 mRNA, ASGR1 protein, or another biomarker linked to ASGR1 expression, such as serum levels of alkaline phosphatase. The reduction of ASGR1 expression in cells or animals treated with an RNAi construct of the invention can be determined relative to the ASGR1 expression in cells or animals not treated with the RNAi construct or treated with a control RNAi construct. For instance, in some embodiments, reduction of ASGR1 expression is assessed by (a) measuring the amount or level of ASGR1 mRNA in liver cells treated with a RNAi construct of the invention, (b) measuring the amount or level of ASGR1 mRNA in liver cells treated with a control RNAi construct (e.g. RNAi agent directed to a RNA molecule not expressed in liver cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured ASGR1 mRNA levels from treated cells in (a) to the measured ASGR1 mRNA levels from control cells in (b). The ASGR1 mRNA levels in the treated cells and controls cells can be normalized to RNA levels for a control gene (e.g. 18S ribosomal RNA or housekeeping gene) prior to comparison. ASGR1 mRNA levels can be measured by a variety of methods, including Northern

blot analysis, nuclease protection assays, fluorescence *in situ* hybridization (FISH), reverse-transcriptase (RT)-PCR, real-time RT-PCR, quantitative PCR, droplet digital PCR, and the like.

[0071] In other embodiments, reduction of ASGR1 expression is assessed by (a) measuring the amount or level of ASGR1 protein in liver cells treated with a RNAi construct of the invention, (b) measuring the amount or level of ASGR1 protein in liver cells treated with a control RNAi construct (e.g. RNAi agent directed to a RNA molecule not expressed in liver cells or a RNAi construct having a nonsense or scrambled sequence) or no construct, and (c) comparing the measured ASGR1 protein levels from treated cells in (a) to the measured ASGR1 protein levels from control cells in (b). Methods of measuring ASGR1 protein levels are known to those of skill in the art, and include Western Blots, immunoassays (e.g. ELISA), and flow cytometry. An exemplary immunoassay-based method for assessing ASGR1 protein expression is described in Examples 2 and 7. Example 3 describes an exemplary method for measuring ASGR1 mRNA using RNA FISH, and Example 8 describes an exemplary method for assessing ASGR1 mRNA using droplet digital PCR. Any method capable of measuring ASGR1 mRNA or protein can be used to assess the efficacy of the RNAi constructs of the invention.

[0072] In some embodiments, the methods to assess ASGR1 expression levels are performed *in vitro* in cells that natively express ASGR1 (e.g. liver cells) or cells that have been engineered to express ASGR1. In certain embodiments, the methods are performed *in vitro* in liver cells. Suitable liver cells include, but are not limited to, primary hepatocytes (e.g. human, non-human primate, or rodent hepatocytes), HepAD38 cells, HuH-6 cells, HuH-7 cells, HuH-5-2 cells, BNLCL2 cells, Hep3B cells, or HepG2 cells. In one embodiment, the liver cells are Hep3B cells. In another embodiment, the liver cells are human primary hepatopyctes.

[0073] In other embodiments, the methods to assess ASGR1 expression levels are performed *in vivo*. The RNAi constructs and any control RNAi constructs can be administered to an animal (e.g. rodent or non-human primate) and ASGR1 mRNA or protein levels assessed in liver tissue harvested from the animal following treatment. Alternatively or additionally, a biomarker or functional phenotype associated with ASGR1 expression can be assessed in the treated animals. For instance, elevated serum alkaline phosphatase levels correlate with reduced serum levels of non-HDL cholesterol in individuals with loss of function mutations in the ASGR1 gene (Nioi *et al.*, New England Journal of Medicine, Vol. 374(22):2131-2141, 2016, which is hereby incorporated by reference in its entirety). Thus, serum levels of alkaline phosphatase or non-

HDL cholesterol can be measured in animals treated with RNAi constructs of the invention to assess the functional efficacy of reducing ASGR1 expression. Exemplary methods for these analyses are described in Examples 6, 9, and 10.

[0074] In certain embodiments, expression of ASGR1 is reduced in liver cells by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50% by an RNAi construct of the invention. In some embodiments, expression of ASGR1 is reduced in liver cells by at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, or at least 85% by an RNAi construct of the invention. In other embodiments, the expression of ASGR1 is reduced in liver cells by about 90% or more, e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more by an RNAi construct of the invention. The percent reduction of ASGR1 expression can be measured by any of the methods described herein as well as others known in the art. For instance, in certain embodiments, the RNAi constructs of the invention inhibit at least 45% of ASGR1 expression at 5 nM in Hep3B cells *in vitro*. In related embodiments, the RNAi constructs of the invention inhibit at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 75% of ASGR1 expression at 5 nM in Hep3B cells *in vitro*. In other embodiments, the RNAi constructs of the invention inhibit at least 80%, at least 85%, at least 90%, at least 92%, at least 94%, at least 96%, or at least 98% of ASGR1 expression at 5 nM in Hep3B cells *in vitro*.

[0075] In some embodiments, an IC50 value is calculated to assess the potency of an RNAi construct of the invention for inhibiting ASGR1 expression in liver cells. An "IC50 value" is the dose/concentration required to achieve 50% inhibition of a biological or biochemical function. The IC50 value of any particular substance or antagonist can be determined by constructing a dose-response curve and examining the effect of different concentrations of the substance or antagonist on expression levels or functional activity in any assay. IC50 values can be calculated for a given antagonist or substance by determining the concentration needed to inhibit half of the maximum biological response or native expression levels. Thus, the IC50 value for any RNAi construct can be calculated by determining the concentration of the RNAi construct needed to inhibit half of the native ASGR1 expression level in liver cells (e.g. ASGR1 expression level in control liver cells) in any assay, such as the immunoassay, RNA FISH assay, qPCR or droplet digital PCR assays described in the Examples. The RNAi constructs of the invention may inhibit ASGR1 expression in liver cells (e.g. Hep3B cells) with an IC50 of less than about 10 nM, less

than about 5 nM, or less than about 1 nM. For example, the RNAi constructs inhibit ASGR1 expression in liver cells with an IC50 of about 0.5 nM to about 10 nM, about 0.8 nM to about 8 nM, about 1 nM to about 5 nM, about 0.8 nM to about 3 nM, about 0.001 nM to about 1 nM, about 0.001 nM to about 0.50 nM, about 0.001 nM to about 0.1 nM, about 0.001 nM to about 0.01 nM, about 0.01 nM to about 0.50 nM, about 0.02 nM to about 0.80 nM, about 0.01 nM to about 1.0 nM, about 0.1 nM to about 0.9 nM, or about 0.05 nM to about 0.5 nM. In certain embodiments, the RNAi construct inhibits ASGR1 expression in liver cells (e.g. Hep3B cells) with an IC50 of about 0.5 nM to about 5 nM. In other embodiments, the RNAi construct inhibits ASGR1 expression in liver cells (e.g. Hep3B cells) with an IC50 of about 0.01 nM to about 0.9 nM.

[0076] The RNAi constructs of the invention can readily be made using techniques known in the art, for example, using conventional nucleic acid solid phase synthesis. The polynucleotides of the RNAi constructs can be assembled on a suitable nucleic acid synthesizer utilizing standard nucleotide or nucleoside precursors (e.g. phosphoramidites). Automated nucleic acid synthesizers are sold commercially by several vendors, including DNA/RNA synthesizers from Applied Biosystems (Foster City, CA), MerMade synthesizers from BioAutomation (Irving, TX), and OligoPilot synthesizers from GE Healthcare Life Sciences (Pittsburgh, PA).

[0077] The 2′ silyl protecting group can be used in conjunction with acid labile dimethoxytrityl (DMT) at the 5′ position of ribonucleosides to synthesize oligonucleotides via phosphoramidite chemistry. Final deprotection conditions are known not to significantly degrade RNA products. All syntheses can be conducted in any automated or manual synthesizer on large, medium, or small scale. The syntheses may also be carried out in multiple well plates, columns, or glass slides.

[0078] The 2′-O-silyl group can be removed via exposure to fluoride ions, which can include any source of fluoride ion, e.g., those salts containing fluoride ion paired with inorganic counterions e.g., cesium fluoride and potassium fluoride or those salts containing fluoride ion paired with an organic counterion, e.g., a tetraalkylammonium fluoride. A crown ether catalyst can be utilized in combination with the inorganic fluoride in the deprotection reaction. Preferred fluoride ion source are tetrabutylammonium fluoride or aminohydrofluorides (e.g., combining aqueous HF with triethylamine in a dipolar aprotic solvent, e.g., dimethylformamide).

[0079] The choice of protecting groups for use on the phosphite triesters and phosphotriesters can alter the stability of the triesters towards fluoride. Methyl protection of the phosphotriester or phosphitetriester can stabilize the linkage against fluoride ions and improve process yields.

[0080] Since ribonucleosides have a reactive 2′ hydroxyl substituent, it can be desirable to protect the reactive 2′ position in RNA with a protecting group that is orthogonal to a 5′-O-dimethoxytrityl protecting group, e.g., one stable to treatment with acid. Silyl protecting groups meet this criterion and can be readily removed in a final fluoride deprotection step that can result in minimal RNA degradation.

[0081] Tetrazole catalysts can be used in the standard phosphoramidite coupling reaction. Preferred catalysts include, e.g., tetrazole, S-ethyl-tetrazole, benzylthiotetrazole, p-nitrophenyltetrazole.

[0082] As can be appreciated by the skilled artisan, further methods of synthesizing the RNAi constructs described herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Other synthetic chemistry transformations, protecting groups (e.g., for hydroxyl, amino, etc. present on the bases) and protecting group methodologies (protection and deprotection) useful in synthesizing the RNAi constructs described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof. Custom synthesis of RNAi agents is also available from several commercial vendors, including Dharmacon, Inc. (Lafayette, CO), AxoLabs GmbH (Kulmbach, Germany), and Ambion, Inc. (Foster City, CA).

[0083] The RNAi constructs of the invention may comprise a ligand. As used herein, a “ligand” refers to any compound or molecule that is capable of interacting with another compound or molecule, directly or indirectly. The interaction of a ligand with another compound or molecule may elicit a biological response (e.g. initiate a signal transduction cascade, induce receptor-mediated endocytosis) or may just be a physical association. The ligand can modify one or more properties of the double-stranded RNA molecule to which is attached, such as the

pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and/or clearance properties of the RNA molecule.

[0084] The ligand may comprise a serum protein (e.g., human serum albumin, low-density lipoprotein, globulin), a cholesterol moiety, a vitamin (biotin, vitamin E, vitamin B_{12}), a folate moiety, a steroid, a bile acid (e.g. cholic acid), a fatty acid (e.g., palmitic acid, myristic acid), a carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid), a glycoside, a phospholipid, or antibody or binding fragment thereof (e.g. antibody or binding fragment that targets the RNAi construct to a specific cell type, such as liver). Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, 03-(oleoyl)lithocholic acid, 03-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine), peptides (e.g., antennapedia peptide, Tat peptide, RGD peptides), alkylating agents, polymers, such as polyethylene glycol (PEG)(e.g., PEG-40K), polyamino acids, and polyamines (e.g. spermine, spermidine).

[0085] In certain embodiments, the ligands have endosomolytic properties. The endosomolytic ligands promote the lysis of the endosome and/or transport of the RNAi construct of the invention, or its components, from the endosome to the cytoplasm of the cell. The endosomolytic ligand may be a polycationic peptide or peptidomimetic, which shows pH-dependent membrane activity and fusogenicity. In one embodiment, the endosomolytic ligand assumes its active conformation at endosomal pH. The "active" conformation is that conformation in which the endosomolytic ligand promotes lysis of the endosome and/or transport of the RNAi construct of the invention, or its components, from the endosome to the cytoplasm of the cell. Exemplary endosomolytic ligands include the GALA peptide (Subbarao *et al.*, Biochemistry, Vol. 26: 2964-2972, 1987), the EALA peptide (Vogel *et al.*, J. Am. Chem. Soc., Vol. 118: 1581-1586, 1996), and their derivatives (Turk *et al.*, Biochem. Biophys. Acta, Vol. 1559: 56-68, 2002). In one embodiment, the endosomolytic component may contain a chemical group (e.g., an amino acid) which will undergo a change in charge or protonation in response to a change in pH. The endosomolytic component may be linear or branched.

[0086] In some embodiments, the ligand comprises a lipid or other hydrophobic molecule. In one embodiment, the ligand comprises a cholesterol moiety or other steroid. Cholesterol-conjugated oligonucleotides have been reported to be more active than their unconjugated counterparts (Manoharan, Antisense Nucleic Acid Drug Development, Vol. 12: 103-228, 2002). Ligands comprising cholesterol moieties and other lipids for conjugation to nucleic acid molecules have also been described in U.S. Patent Nos. 7,851,615; 7,745,608; and 7,833,992 , all of which are hereby incorporated by reference in their entireties. In another embodiment, the ligand comprises a folate moiety. Polynucleotides conjugated to folate moieties can be taken up by cells via a receptor-mediated endocytosis pathway. Such folate-polynucleotide conjugates are described in U.S. Patent No. 8,188,247, which is hereby incorporated by reference in its entirety.

[0087] Given that ASGR1 is expressed on the surface of liver cells (e.g. hepatocytes) as a component of the asialoglycoprotein receptor (ASGR), in certain embodiments, it is desirable to specifically deliver the RNAi construct to those liver cells. Accordingly, in certain embodiments, the ligand targets delivery of the RNAi constructs specifically to liver cells (e.g. hepatocytes) using various approaches as described in more detail below. In certain embodiments, the RNAi constructs are targeted to liver cells with a ligand that binds to the surface-expressed ASGR, ASGR1 and/or ASGR2. In these embodiments, it is envisioned that this targeting approach can result in a self-regulating system that reduces the amount of RNAi construct delivered to the liver cells as expression of ASGR1 is reduced due to the effect of the previously delivered RNAi construct.

[0088] In some embodiments, RNAi constructs can be specifically targeted to the liver by employing ligands that bind to or interact with proteins expressed on the surface of liver cells. For example, in certain embodiments, the ligands may comprise antigen binding proteins (e.g. antibodies or binding fragments thereof (e.g. Fab, scFv)) that specifically bind to a receptor expressed on hepatocytes, such as the asialoglycoprotein receptor and the LDL receptor. In one particular embodiment, the ligand comprises an antibody or binding fragment thereof that specifically binds to ASGR1 and/or ASGR2. In another embodiment, the ligand comprises a Fab fragment of an antibody that specifically binds to ASGR1 and/or ASGR2. A "Fab fragment" is comprised of one immunoglobulin light chain (i.e. light chain variable region (VL) and constant region (CL)) and the CH1 region and variable region (VH) of one immunoglobulin heavy chain. In another embodiment, the ligand comprises a single-chain variable antibody fragment (scFv

fragment) of an antibody that specifically binds to ASGR1 and/or ASGR2. An "scFv fragment" comprises the VH and VL regions of an antibody, wherein these regions are present in a single polypeptide chain, and optionally comprising a peptide linker between the VH and VL regions that enables the Fv to form the desired structure for antigen binding. Exemplary antibodies and binding fragments thereof that specifically bind to ASGR1 that can be used as ligands for targeting the RNAi constructs of the invention to the liver are described in U.S. Patent Application No. 62/234,546 and WIPO Publication No. WO 2017/058944, both of which are hereby incorporated by reference in their entireties. Other antibodies or binding fragments thereof that specifically bind to ASGR1, LDL receptor, or other liver surface-expressed proteins suitable for use as ligands in the RNAi constructs of the invention are commercially available.

[0089] In some embodiments, the ligand comprises a cys monoclonal antibody (mAb) or antigen-binding fragment thereof. A "cys mAb" is a monoclonal antibody or antigen-binding fragment thereof in which at least one amino acid in the light chain or heavy chain has been substituted with a cysteine amino acid or at least one cysteine amino acid has been inserted into the primary sequence of the light chain or heavy chain. The free thiol group in the side chain of the cysteine amino acid provides a conjugation site to which the sense strand of the RNAi constructs of the invention can be covalently linked. The cysteine substitutions/additions can be at the amino-terminus or carboxy-terminus of the light chain or heavy chain of the antibody or antigen-binding fragment. Alternatively or additionally, the cysteine substitutions/additions can be located at an internal site within the light chain or heavy chain so long as the cysteine substitution/addition does not affect the binding affinity of the antibody or antigen-binding fragment to its target antigen (e.g. ASGR1). Exemplary amino acids within the heavy and light chains of antibodies that may be substituted with cysteine residues are described in WIPO Publication Nos. WO 2006/034488 and WO 2007/022070, both of which are hereby incorporated by reference in their entireties. In certain embodiments, the ligand comprises a cys mAb or antigen-binding fragment thereof that specifically binds to human ASGR1. An exemplary anti-ASGR1 cys mAb is described in Example 10. In one embodiment, the ligand comprises an anti-ASGR1 antibody having a heavy chain and a light chain, wherein the heavy chain comprises the sequence of SEQ ID NO: 4696 and the light chain comprises the sequence of SEQ ID NO: 4697. Anti-ASGR1 cys mAbs or antigen-binding fragments thereof may be covalently attached to the 5′ end or 3′ end of the sense strand of an RNAi construct of the

invention, optionally through any of the linkers described herein. In some embodiments, the anti-ASGR1 antibody-RNA molecule conjugate comprises one copy of the interfering RNA molecule (e.g. siRNA or shRNA)(i.e. an RNAi-to-antibody ratio of 1). In other embodiments, the anti-ASGR1 antibody-RNA molecule conjugate comprises two copies of the interfering RNA molecule (e.g. siRNA or shRNA)(i.e. an RNAi-to-antibody ratio of 2).

[0090] In certain embodiments, the ligand comprises a carbohydrate. A "carbohydrate" refers to a compound made up of one or more monosaccharide units having at least 6 carbon atoms (which can be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Carbohydrates include, but are not limited to, the sugars (e.g., monosaccharides, disaccharides, trisaccharides, tetrasaccharides, and oligosaccharides containing from about 4, 5, 6, 7, 8, or 9 monosaccharide units), and polysaccharides, such as starches, glycogen, cellulose and polysaccharide gums. In some embodiments, the carbohydrate incorporated into the ligand is a monosaccharide selected from a pentose, hexose, or heptose and di- and tri-saccharides including such monosaccharide units. In other embodiments, the carbohydrate incorporated into the ligand is an amino sugar, such as galactosamine, glucosamine, N-acetylgalactosamine, and N-acetylglucosamine.

[0091] In some embodiments, the ligand comprises a hexose or hexosamine. The hexose may be selected from glucose, galactose, mannose, fucose, or fructose. The hexosamine may be selected from fructosamine, galactosamine, glucosamine, or mannosamine. In certain embodiments, the ligand comprises glucose, galactose, galactosamine, or glucosamine. In one embodiment, the ligand comprises glucose, glucosamine, or N-acetylglucosamine. In another embodiment, the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine. In particular embodiments, the ligand comprises N-acetyl-galactosamine. Ligands comprising glucose, galactose, and N-acetyl-galactosamine (GalNAc) are particularly effective in targeting compounds to liver cells because such ligands bind to the ASGR expressed on the surface of hepatocytes. *See, e.g.*, D'Souza and Devarajan, J. Control Release, Vol. 203: 126-139, 2015. Examples of GalNAc- or galactose-containing ligands that can be incorporated into the RNAi constructs of the invention are described in U.S. Patent Nos. 7,491,805; 8,106,022; and 8,877,917; U.S. Patent Publication No. 20030130186; and WIPO Publication No. WO 2013166155, all of which are hereby incorporated by reference in their entireties.

[0092] In certain embodiments, the ligand comprises a multivalent carbohydrate moiety. As used herein, a "multivalent carbohydrate moiety" refers to a moiety comprising two or more carbohydrate units capable of independently binding or interacting with other molecules. For example, a multivalent carbohydrate moiety comprises two or more binding domains comprised of carbohydrates that can bind to two or more different molecules or two or more different sites on the same molecule. The valency of the carbohydrate moiety denotes the number of individual binding domains within the carbohydrate moiety. For instance, the terms "monovalent," "bivalent," "trivalent," and "tetravalent" with reference to the carbohydrate moiety refer to carbohydrate moieties with one, two, three, and four binding domains, respectively. The multivalent carbohydrate moiety may comprise a multivalent lactose moiety, a multivalent galactose moiety, a multivalent glucose moiety, a multivalent N-acetyl-galactosamine moiety, a multivalent N-acetyl-glucosamine moiety, a multivalent mannose moiety, or a multivalent fucose moiety. In some embodiments, the ligand comprises a multivalent galactose moiety. In other embodiments, the ligand comprises a multivalent N-acetyl-galactosamine moiety. In these and other embodiments, the multivalent carbohydrate moiety is bivalent, trivalent, or tetravalent. In such embodiments, the multivalent carbohydrate moiety can be bi-antennary or tri-antennary. In one particular embodiment, the multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent. In another particular embodiment, the multivalent galactose moiety is trivalent or tetravalent. Exemplary trivalent and tetravalent GalNAc-containing ligands for incorporation into the RNAi constructs of the invention are described in detail below.

[0093] The ligand can be attached or conjugated to the RNA molecule of the RNAi construct directly or indirectly. For instance, in some embodiments, the ligand is covalently attached directly to the sense or antisense strand of the RNAi construct. In other embodiments, the ligand is covalently attached via a linker to the sense or antisense strand of the RNAi construct. The ligand can be attached to nucleobases, sugar moieties, or internucleotide linkages of polynucleotides (e.g. sense strand or antisense strand) of the RNAi constructs of the invention. Conjugation or attachment to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In certain embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached to a ligand. Conjugation or attachment to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine nucleobase can be attached to a ligand. Conjugation or

attachment to sugar moieties of nucleotides can occur at any carbon atom. Example carbon atoms of a sugar moiety that can be attached to a ligand include the 2′, 3′, and 5′ carbon atoms. The 1′ position can also be attached to a ligand, such as in an abasic residue. Internucleotide linkages can also support ligand attachments. For phosphorus-containing linkages (e.g., phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the ligand can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleoside linkages (e.g., PNA), the ligand can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

[0094] In certain embodiments, the ligand may be attached to the 3′ or 5′ end of either the sense or antisense strand. In certain embodiments, the ligand is covalently attached to the 5′ end of the sense strand. In other embodiments, the ligand is covalently attached to the 3′ end of the sense strand. For example, in some embodiments, the ligand is attached to the 3′-terminal nucleotide of the sense strand. In certain such embodiments, the ligand is attached at the 3′-position of the 3′-terminal nucleotide of the sense strand. In alternative embodiments, the ligand is attached near the 3′ end of the sense strand, but before one or more terminal nucleotides (i.e. before 1, 2, 3, or 4 terminal nucleotides). In some embodiments, the ligand is attached at the 2′-position of the sugar of the 3′-terminal nucleotide of the sense strand.

[0095] In certain embodiments, the ligand is attached to the sense or antisense strand via a linker. A “linker” is an atom or group of atoms that covalently joins a ligand to a polynucleotide component of the RNAi construct. The linker may be from about 1 to about 30 atoms in length, from about 2 to about 28 atoms in length, from about 3 to about 26 atoms in length, from about 4 to about 24 atoms in length, from about 6 to about 20 atoms in length, from about 7 to about 20 atoms in length, from about 8 to about 20 atoms in length, from about 8 to about 18 atoms in length, from about 10 to about 18 atoms in length, and from about 12 to about 18 atoms in length. In some embodiments, the linker may comprise a bifunctional linking moiety, which generally comprises an alkyl moiety with two functional groups. One of the functional groups is selected to bind to the compound of interest (e.g. sense or antisense strand of the RNAi construct) and the other is selected to bind essentially any selected group, such as a ligand as described herein. In certain embodiments, the linker comprises a chain structure or an oligomer of repeating units, such as ethylene glycol or amino acid units. Examples of functional groups that are typically employed in a bifunctional linking moiety include, but are not limited to,

electrophiles for reacting with nucleophilic groups and nucleophiles for reacting with electrophilic groups. In some embodiments, bifunctional linking moieties include amino, hydroxyl, carboxylic acid, thiol, unsaturations (e.g., double or triple bonds), and the like.

[0096] Linkers that may be used to attach a ligand to the sense or antisense strand in the RNAi constructs of the invention include, but are not limited to, pyrrolidine, 8-amino-3,6-dioxaoctanoic acid, succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, 6-aminohexanoic acid, substituted C_1-C_{10} alkyl, substituted or unsubstituted C_2-C_{10} alkenyl or substituted or unsubstituted C_2-C_{10} alkynyl. Preferred substituent groups for such linkers include, but are not limited to, hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

[0097] In certain embodiments, the linkers are cleavable. A cleavable linker is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In some embodiments, the cleavable linker is cleaved at least 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, or more, or at least 100 times faster in the target cell or under a first reference condition (which can, e.g., be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, e.g., be selected to mimic or represent conditions found in the blood or serum).

[0098] Cleavable linkers are susceptible to cleavage agents, e.g., pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, e.g., oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linker by reduction; esterases; endosomes or agents that can create an acidic environment, e.g., those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linker by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

[0099] A cleavable linker may comprise a moiety that is susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable group that is cleaved at a preferred

pH, thereby releasing the RNA molecule from the ligand inside the cell, or into the desired compartment of the cell.

[0100] A linker can include a cleavable group that is cleavable by a particular enzyme. The type of cleavable group incorporated into a linker can depend on the cell to be targeted. For example, liver-targeting ligands can be linked to RNA molecules through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other types of cells rich in esterases include cells of the lung, renal cortex, and testis. Linkers that contain peptide bonds can be used when targeting cells rich in peptidases, such as liver cells and synoviocytes.

[0101] In general, the suitability of a candidate cleavable linker can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linker. It will also be desirable to also test the candidate cleavable linker for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus, one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, e.g., blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. It may be useful to make initial evaluations in cell-free or culture conditions and to confirm by further evaluations in whole animals. In some embodiments, useful candidate linkers are cleaved at least 2, 4, 10, 20, 50, 70, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood or serum (or under *in vitro* conditions selected to mimic extracellular conditions).

[0102] In other embodiments, redox cleavable linkers are utilized. Redox cleavable linkers are cleaved upon reduction or oxidation. An example of reductively cleavable group is a disulfide linking group (-S–S-). To determine if a candidate cleavable linker is a suitable "reductively cleavable linker," or for example is suitable for use with a particular RNAi construct and particular ligand, one can use one or more methods described herein. For example, a candidate linker can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent known in the art, which mimics the rate of cleavage that would be observed in a cell, e.g., a target cell. The candidate linkers can also be evaluated under conditions which are selected to mimic blood or serum conditions. In a specific embodiment, candidate linkers are cleaved by at most 10% in

the blood. In other embodiments, useful candidate linkers are degraded at least 2, 4, 10, 20, 50, 70, or 100 times faster in the cell (or under *in vitro* conditions selected to mimic intracellular conditions) as compared to blood (or under *in vitro* conditions selected to mimic extracellular conditions).

[0103] In yet other embodiments, phosphate-based cleavable linkers are cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that hydrolyzes phosphate groups in cells are enzymes, such as phosphatases in cells. Examples of phosphate-based cleavable groups are –O–P(O)(ORk)-O–, –O–P(S)(ORk)-O–, –O–P(S)(SRk)-O–, –S–P(O)(ORk)-O–, –O–P(O)(ORk)-S–, –S–P(O)(ORk)-S–, –O–P(S)(ORk)-S–, –S–P(S)(ORk)-O–, –O–P(O)(Rk)-O–, –O–P(S)(Rk)-O–, –S–P(O)(Rk)-O–, –S–P(S)(Rk)-O–, –S–P(O)(Rk)-S–, and –O–P(S)(Rk)-S–, where Rk can be hydrogen or alkyl. Specific embodiments include –O–P(O)(OH)–O–, –O–P(S)(OH)–O–, –O–P(S)(SH)–O–, –S–P(O)(OH)–O–, –O–P(O)(OH)–S–, –S–P(O)(OH)–S–, –O–P(S)(OH)–S–, –S–P(S)(OH)–O–, –O–P(O)(H)–O–, –O–P(S)(H)–O–, –S–P(O)(H)–O–, –S–P(S)(H)–O–, –S–P(O)(H)–S–, and –O–P(S)(H)–S–. Another specific embodiment is –O–P(O)(OH)–O–. These candidate linkers can be evaluated using methods analogous to those described above.

[0104] In other embodiments, the linkers may comprise acid cleavable groups, which are groups that are cleaved under acidic conditions. In some embodiments, acid cleavable groups are cleaved in an acidic environment with a pH of about 6.5 or lower (e.g., about 6.0, 5.5, 5.0, or lower), or by agents, such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes, can provide a cleaving environment for acid cleavable groups. Examples of acid cleavable linking groups include, but are not limited to, hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula –C=NN–, C(O)O, or –OC(O). A specific embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted alkyl group, or tertiary alkyl group such as dimethyl, pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

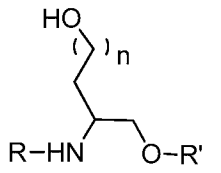
[0105] In other embodiments, the linkers may comprise ester-based cleavable groups, which are cleaved by enzymes, such as esterases and amidases in cells. Examples of ester-based cleavable groups include, but are not limited to, esters of alkylene, alkenylene and alkynylene groups.

Ester cleavable groups have the general formula –C(O)O–, or –OC(O) –. These candidate linkers can be evaluated using methods analogous to those described above.

[0106] In further embodiments, the linkers may comprise peptide-based cleavable groups, which are cleaved by enzymes, such as peptidases and proteases in cells. Peptide-based cleavable groups are peptide bonds formed between amino acids to yield oligopeptides (e.g., dipeptides, tripeptides etc.) and polypeptides. Peptide-based cleavable groups do not include the amide group (–C(O)NH–). The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (i.e., the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula –NHCHR^{A}C(O)NHCHR^{B}C(O) –, where R^A and R^B are the side chains of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

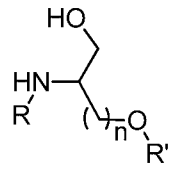
[0107] Exemplary linkers that can be employed for attaching ligands, particularly ligands comprising a GalNAc moiety, to the sense strand in the RNAi constructs of the invention, are shown in Formulas A-K below.

[0108] In one embodiment, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula A, wherein n is 1 or 2, R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



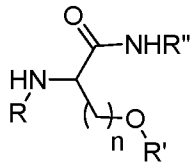
FORMULA A

[0109] In another embodiment, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula B, wherein n is 1, 2, or 3, R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



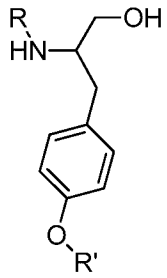
FORMULA B

[0110] In yet another embodiment, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula C, wherein n is 1 or 2, R = ligand (e.g., moiety containing 3 to 4 GalNAc units), R′ = 3′ end of sense strand of a double stranded RNA molecule, and R″ = H, alkyl, functionalized alkyl:



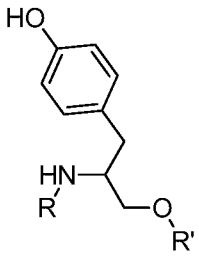
FORMULA C

[0111] In certain embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula D, wherein R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



FORMULA D

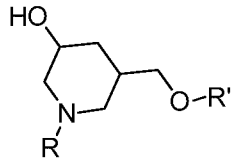
[0112] In certain other embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula E, wherein R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



FORMULA E

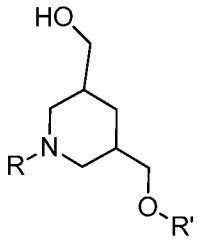
[0113] In some embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula F, wherein R = ligand

(e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



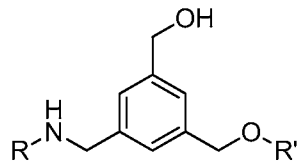
FORMULA F

[0114] In other embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula G, wherein R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



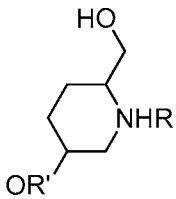
FORMULA G

[0115] In certain other embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula H, wherein R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



FORMULA H

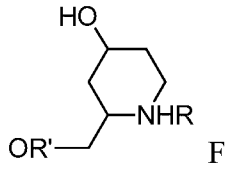
[0116] In some embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula J, wherein R = ligand (e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:



FORMULA J

[0117] In other embodiments, the linker for attaching a ligand to the 3′ end of the sense strand of an RNAi construct of the invention has the following structure of Formula K, wherein R = ligand

(e.g., moiety containing 3 to 4 GalNAc units) and R′ = 3′ end of sense strand of a double stranded RNA molecule:

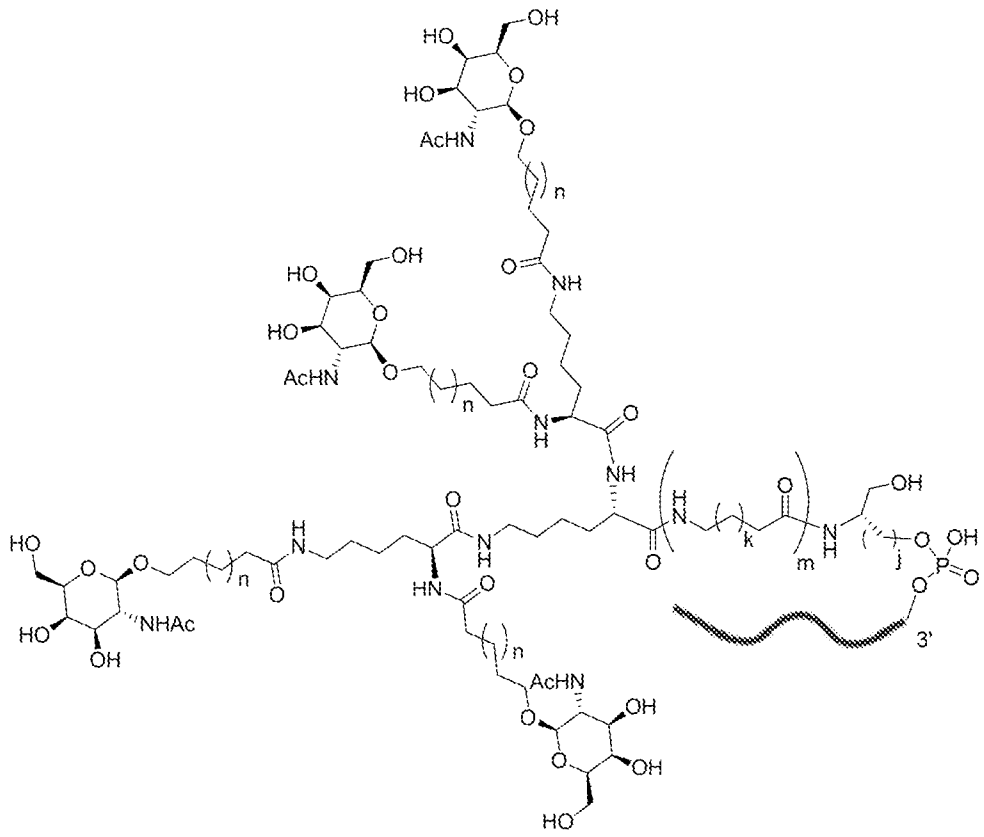


FORMULA K

[0118] Other types of linkers suitable for attaching ligands to the sense or antisense strands in the RNAi constructs of the invention are known in the art and can include the linkers described in U.S. Patent Nos. 7,723,509; 8,017,762; 8,828,956 ; 8,877,917; and 9,181,551, all of which are hereby incorporated by reference in their entireties.

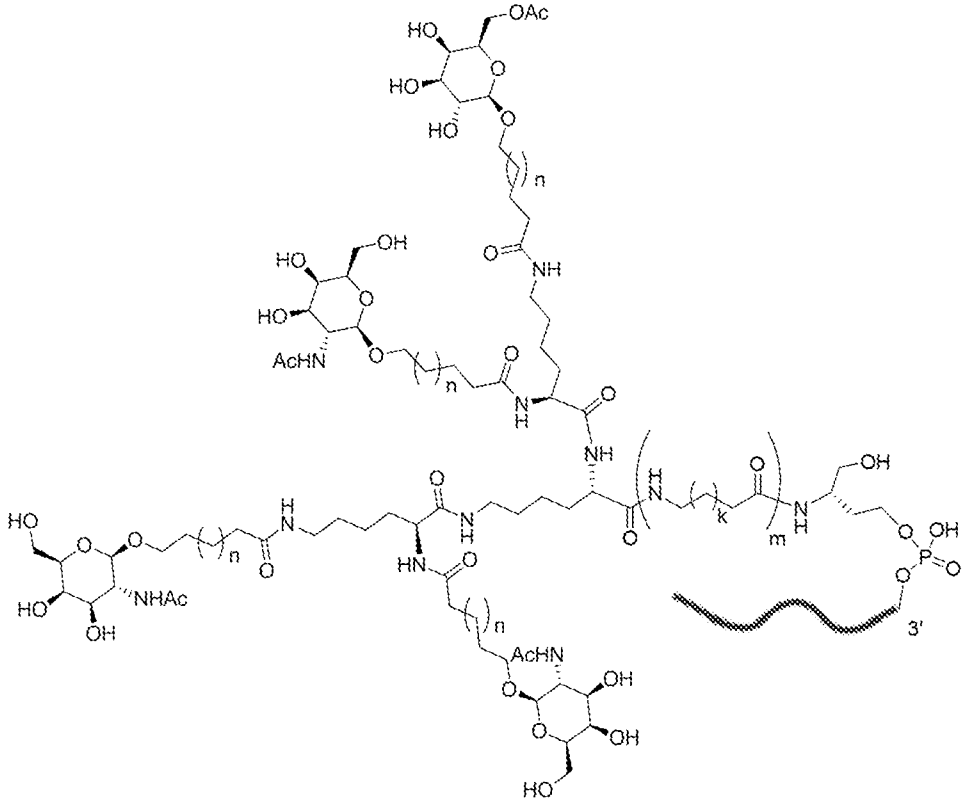
[0119] In certain embodiments, the ligand covalently attached to the sense or antisense strand of the RNAi constructs of the invention comprises a GalNAc moiety, e.g, a multivalent GalNAc moiety. In some embodiments, the multivalent GalNAc moiety is a trivalent GalNAc moiety and is attached to the 3′ end of the sense strand. In other embodiments, the multivalent GalNAc moiety is a trivalent GalNAc moiety and is attached to the 5′ end of the sense strand. In yet other embodiments, the multivalent GalNAc moiety is a tetravalent GalNAc moiety and is attached to the 3′ end of the sense strand. In still other embodiments, the multivalent GalNAc moiety is a tetravalent GalNAc moiety and is attached to the 5′ end of the sense strand. Exemplary trivalent and tetravalent GalNAc moieties and linkers that can be attached to the double-stranded RNA molecules in the RNAi constructs of the invention are provided in the structural formulas I-XXIX below.

[0120] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula I, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



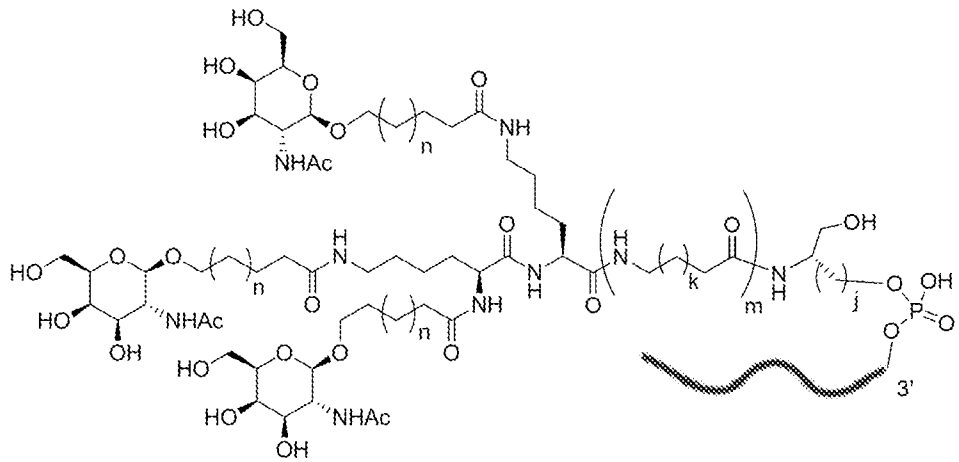
FORMULA I

[0121] In another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula II, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



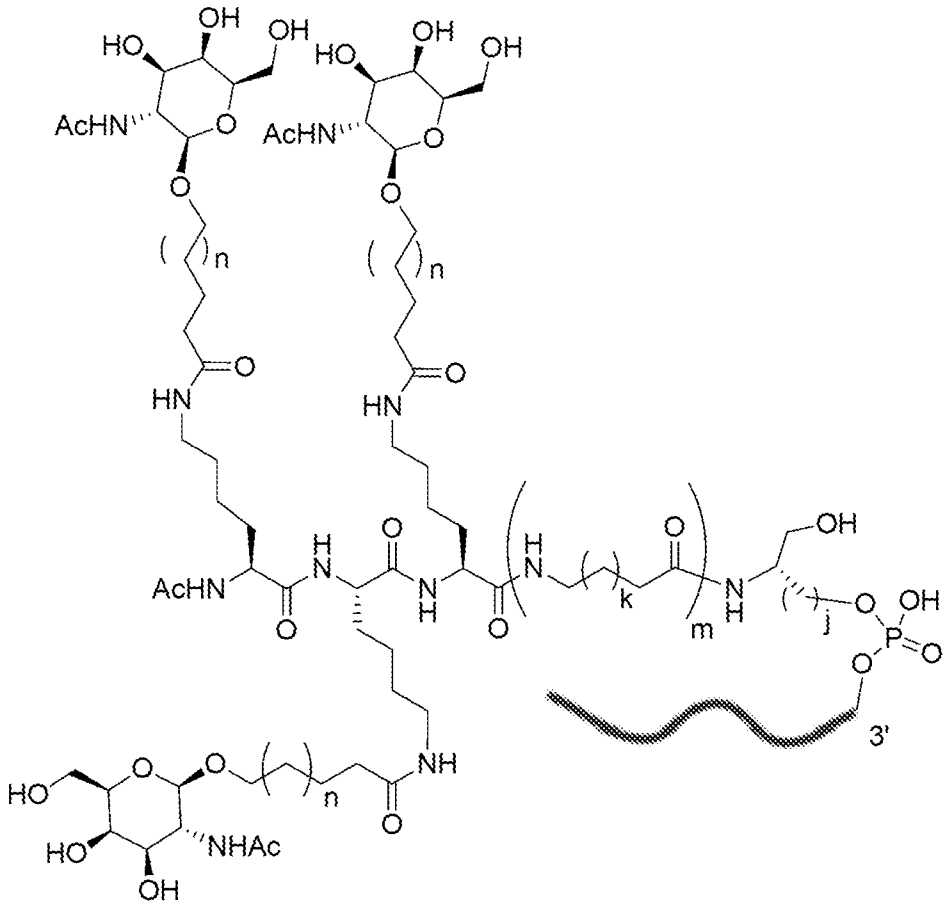
FORMULA II

[0122] In yet another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula III, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



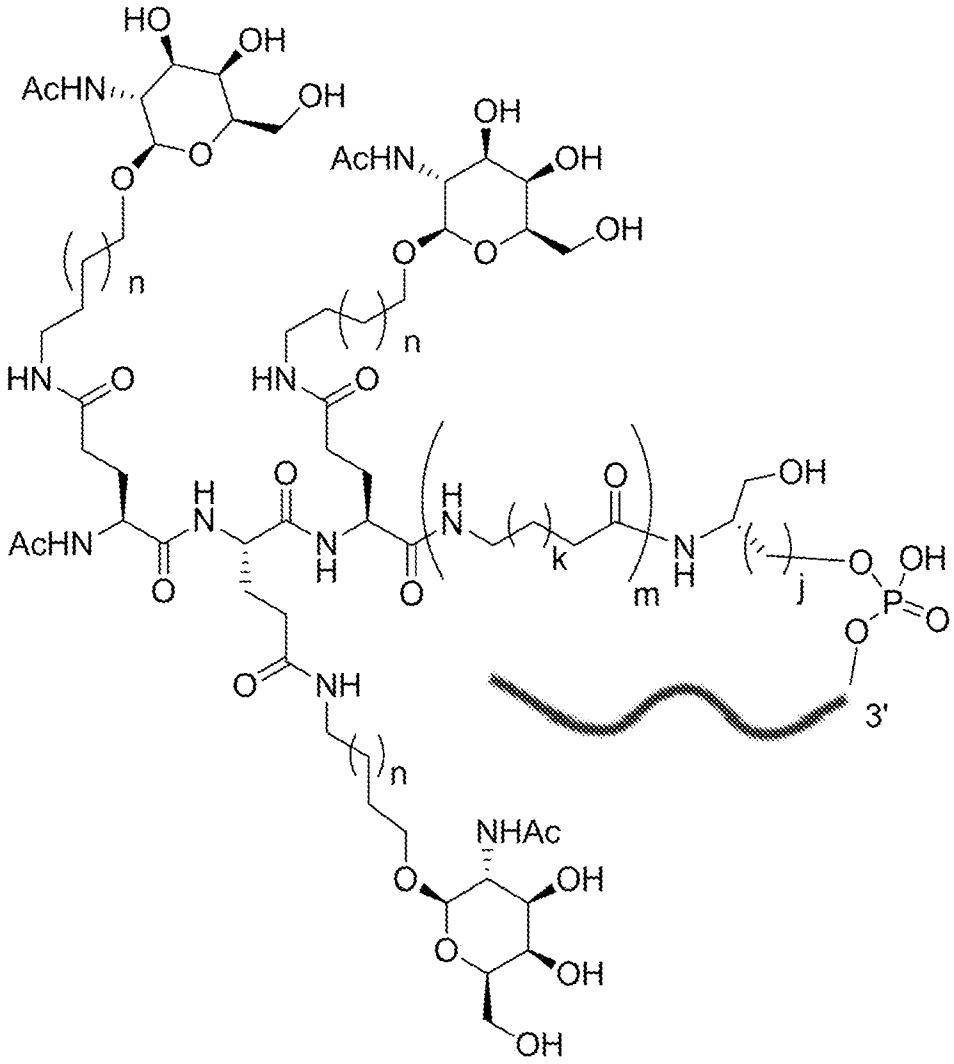
FORMULA III

[0123] In still another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula IV, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



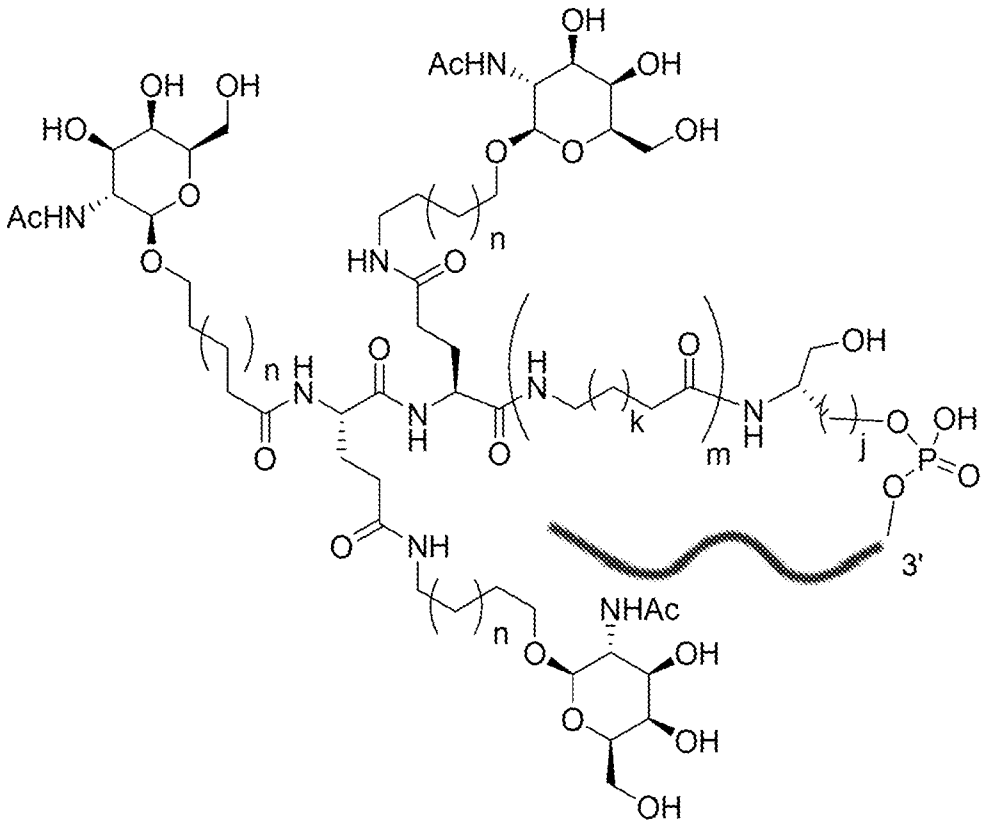
FORMULA IV

[0124] In still another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula V, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



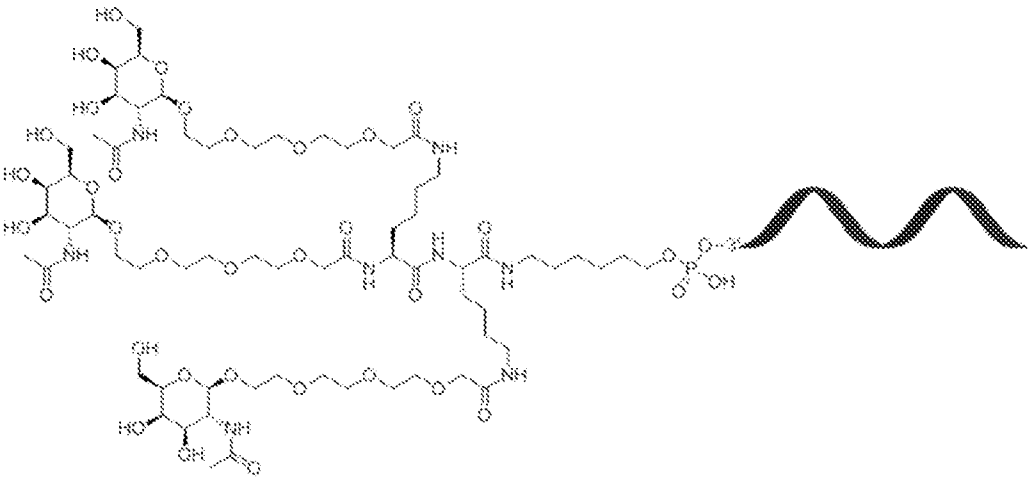
FORMULA V

[0125] In another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula VI, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, j is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



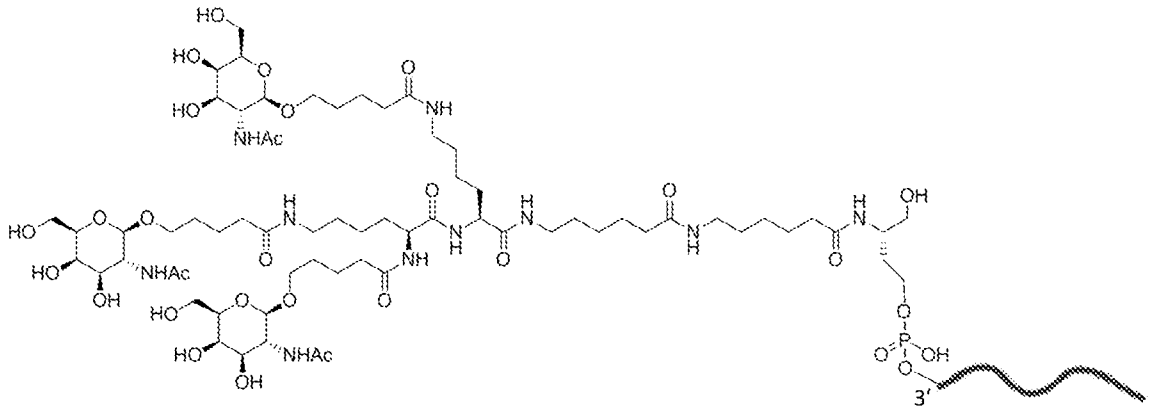
FORMULA VI

[0126] In one particular embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula VII, wherein the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



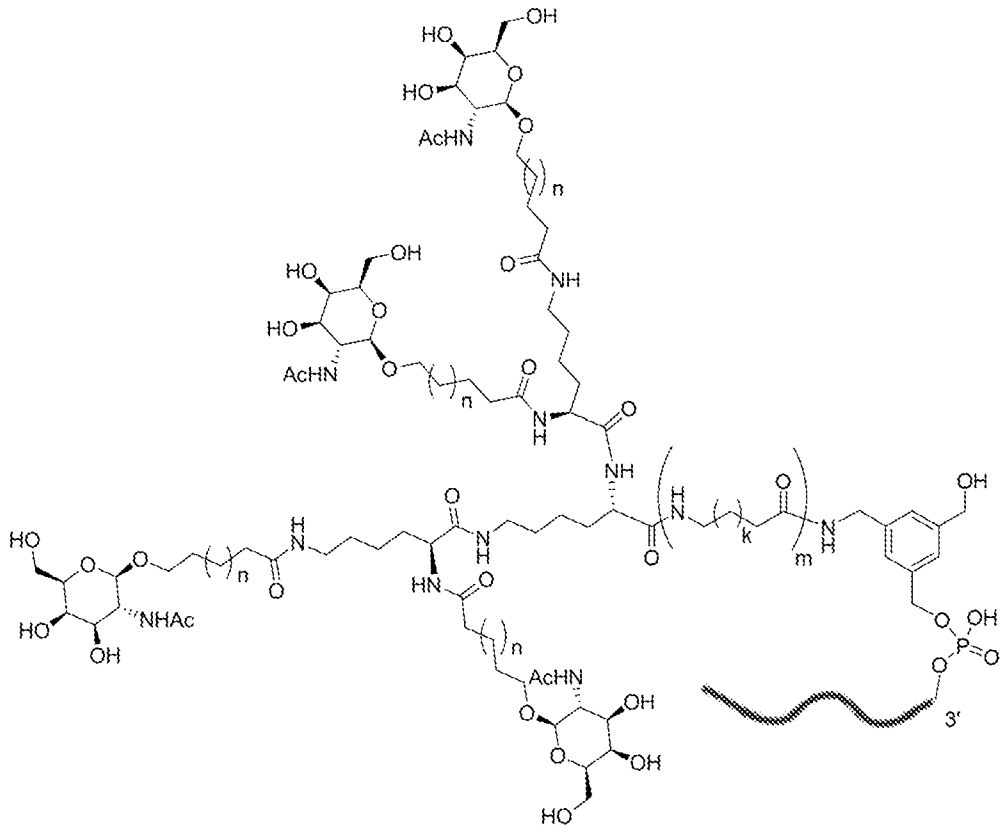
FORMULA VII

[0127] In another particular embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula VIII, wherein the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA VIII

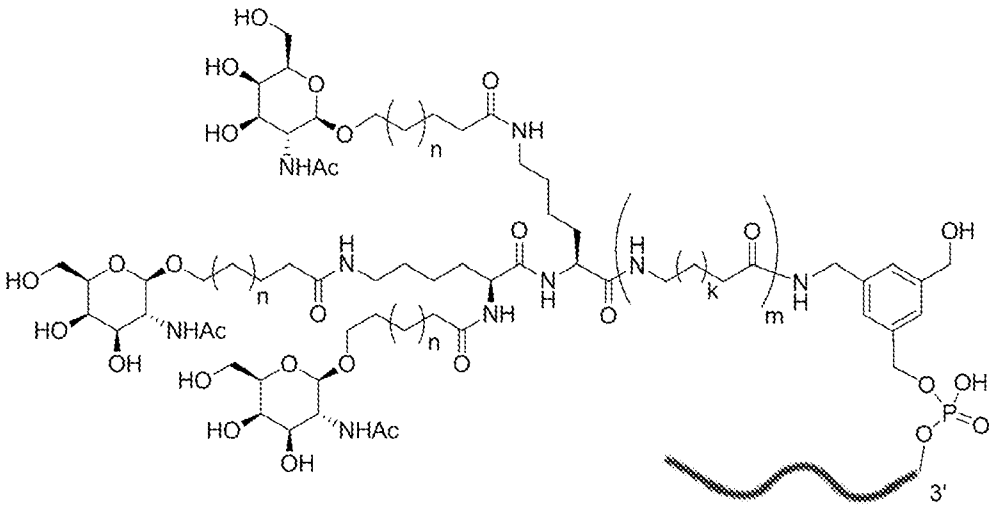
[0128] In certain embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula IX, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA IX

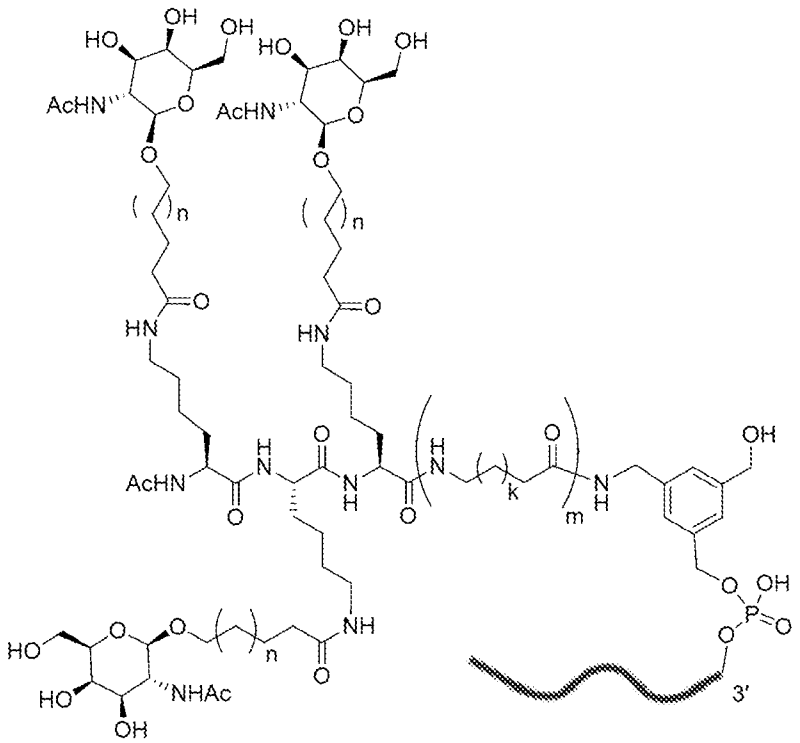
[0129] In other embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula X, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2,

and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



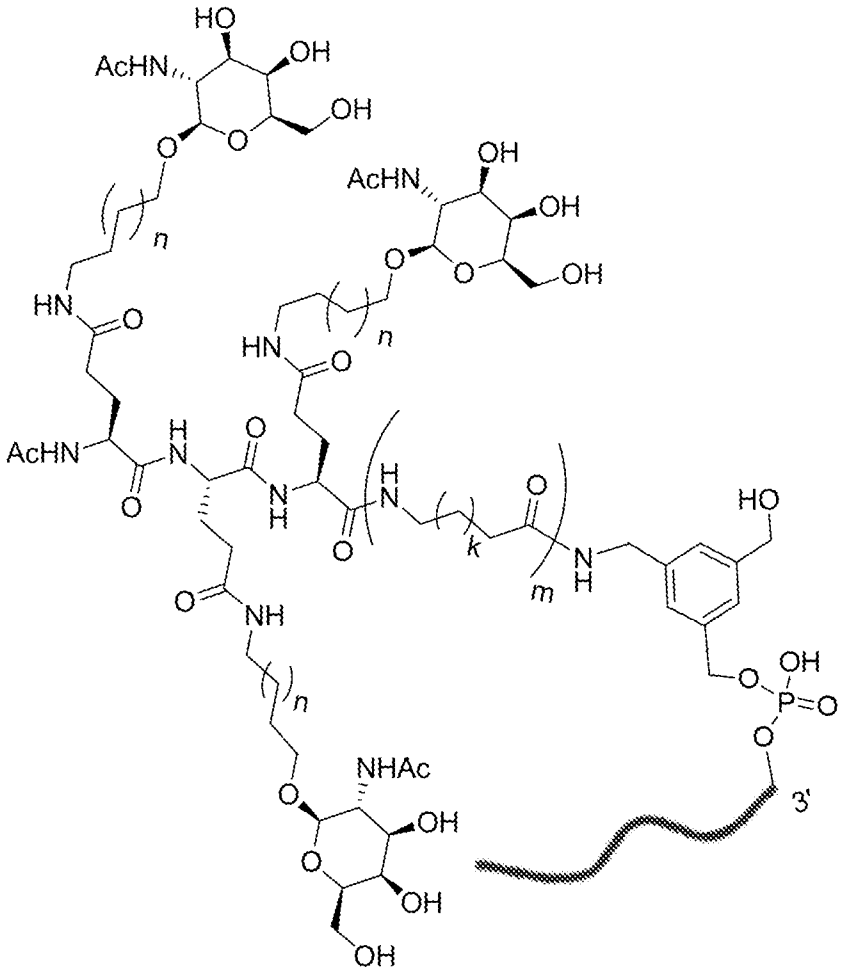
FORMULA X

[0130] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XI, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



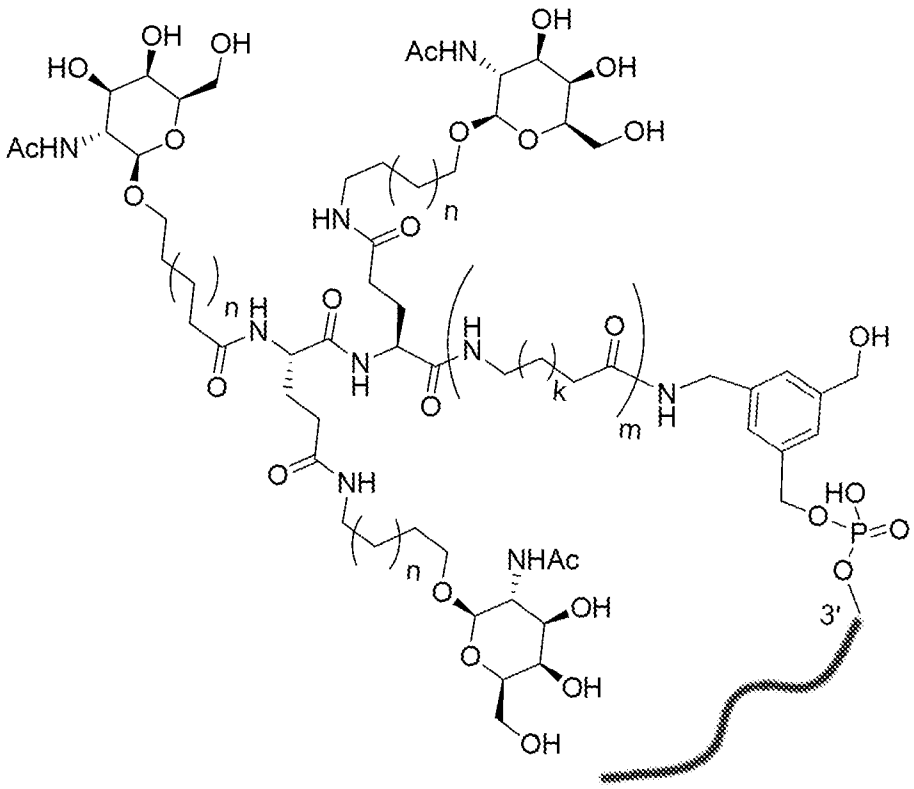
FORMULA XI

[0131] In another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XII, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



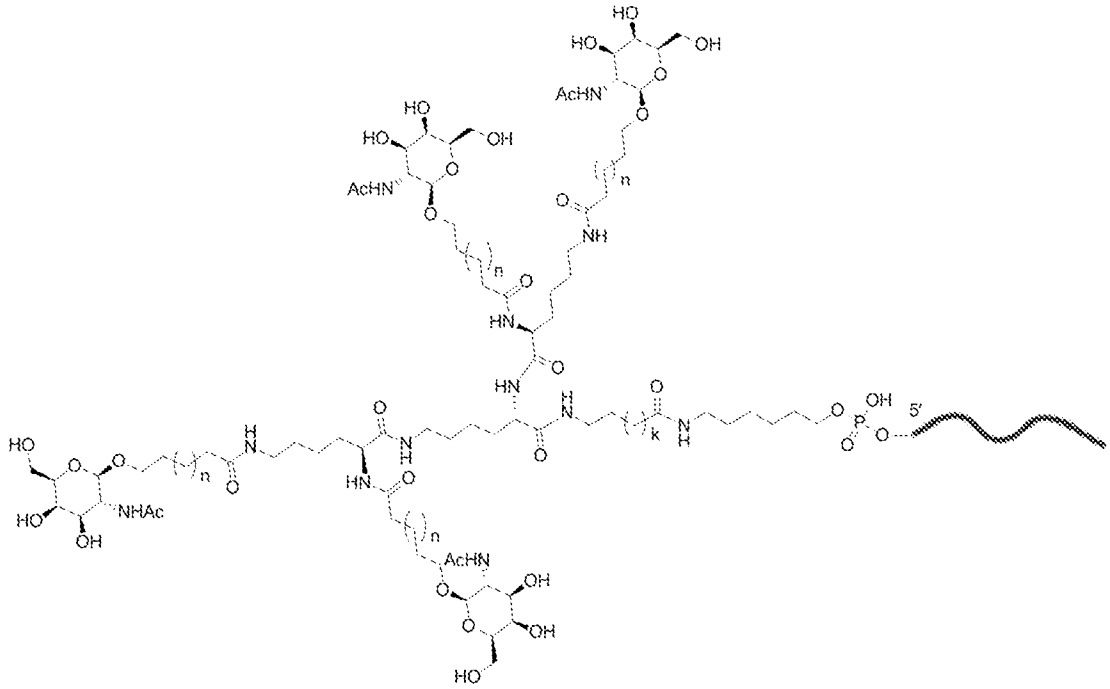
FORMULA XII

[0132] In yet another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XIII, wherein each n is independently 1 to 3, k is 1 to 3, m is 1 or 2, and the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



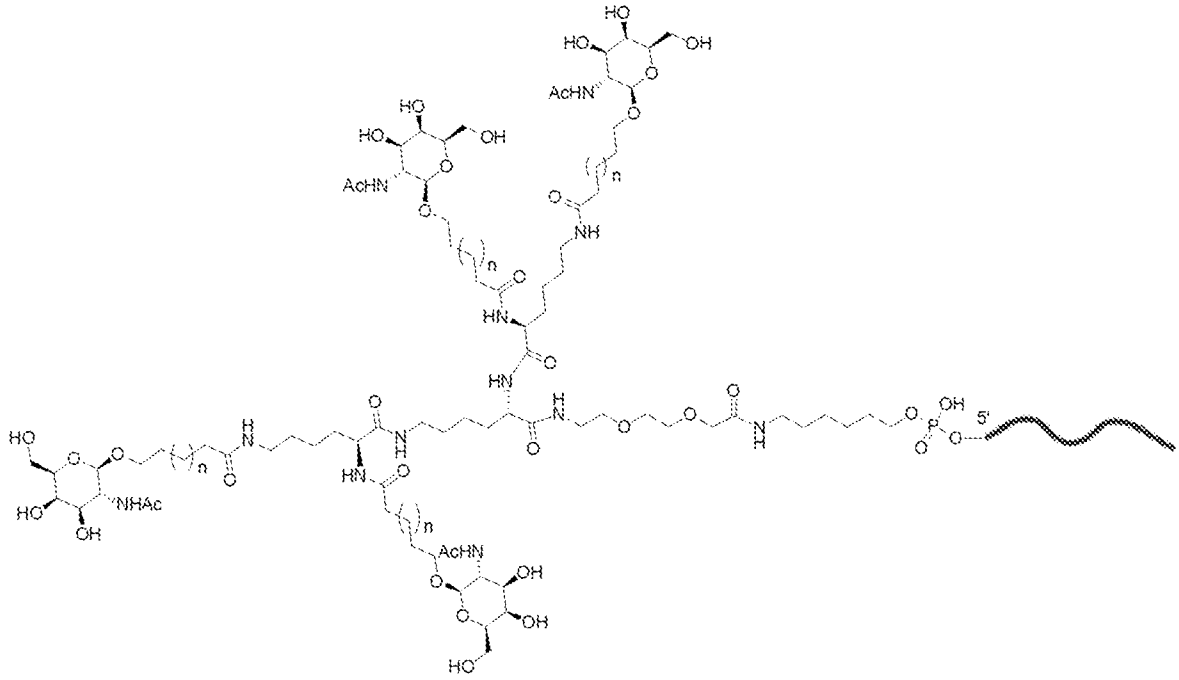
FORMULA XIII

[0133] In certain embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XIV, wherein each n is independently 1 to 3, k is 1 to 3, and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



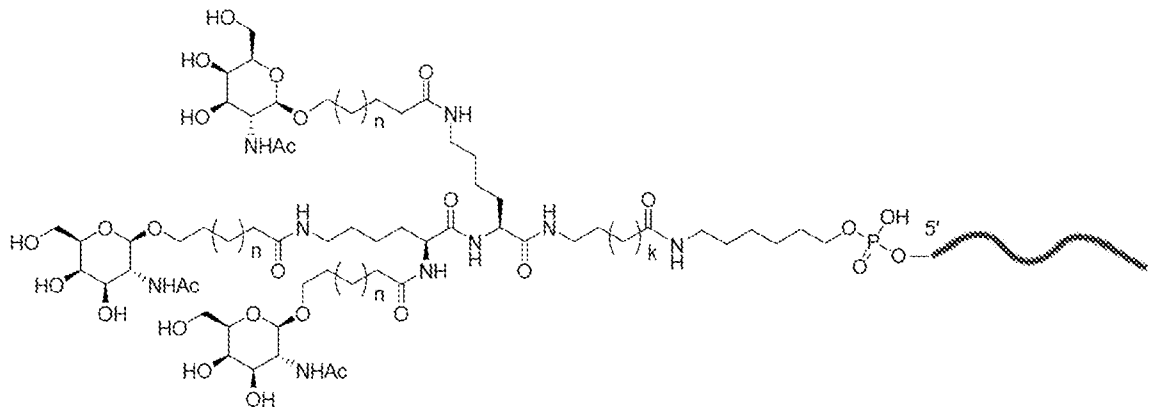
FORMULA XIV

[0134] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XV, wherein each n is independently 1 to 3 and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



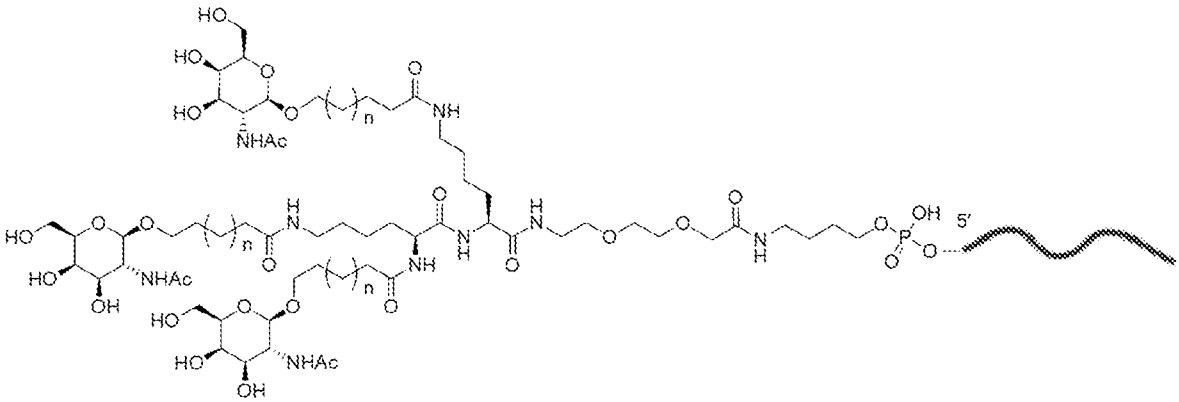
FORMULA XV

[0135] In other embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XVI, wherein each n is independently 1 to 3, k is 1 to 3, and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



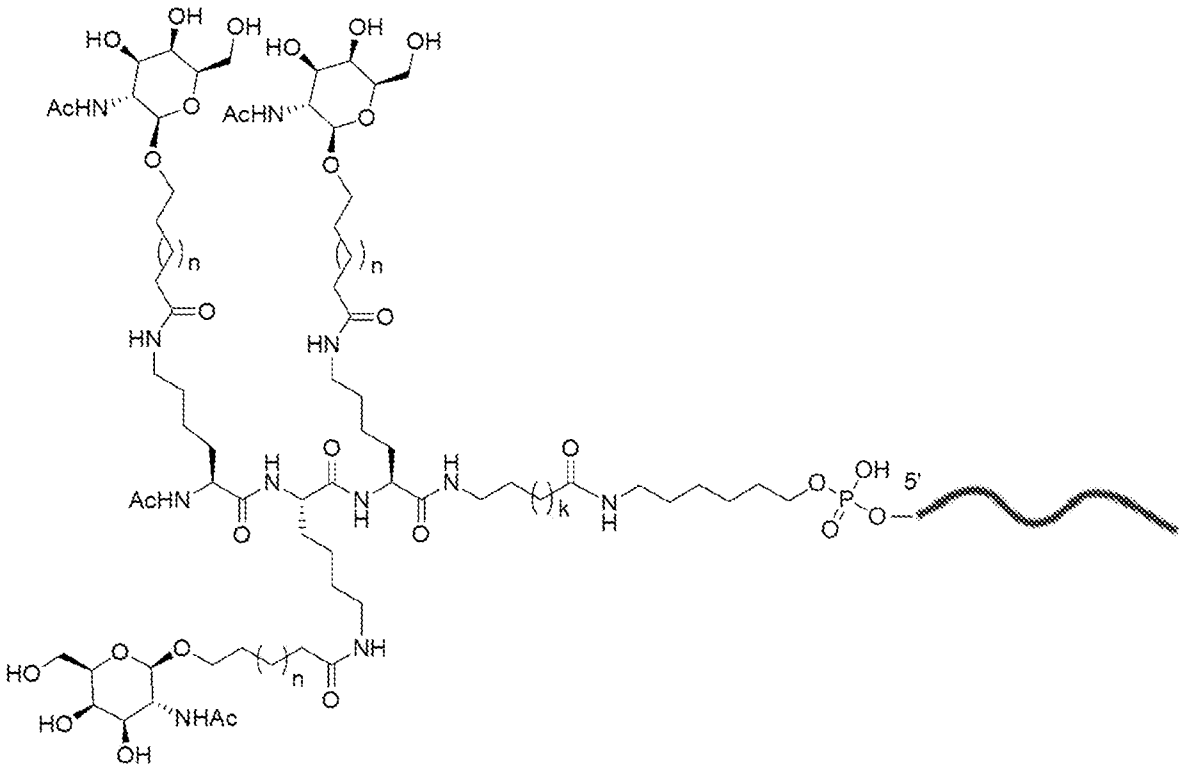
FORMULA XVI

[0136] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XVII, wherein each n is independently 1 to 3 and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



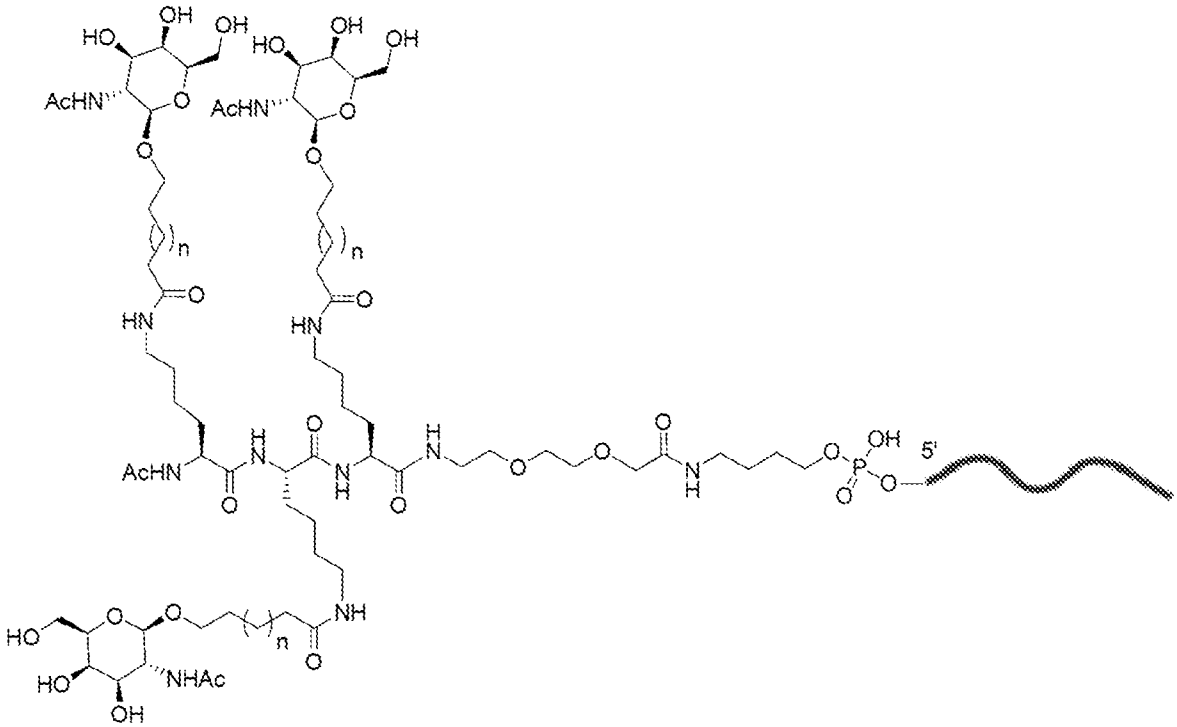
FORMULA XVII

[0137] In certain other embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XVIII, wherein each n is independently 1 to 3, k is 1 to 3, and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



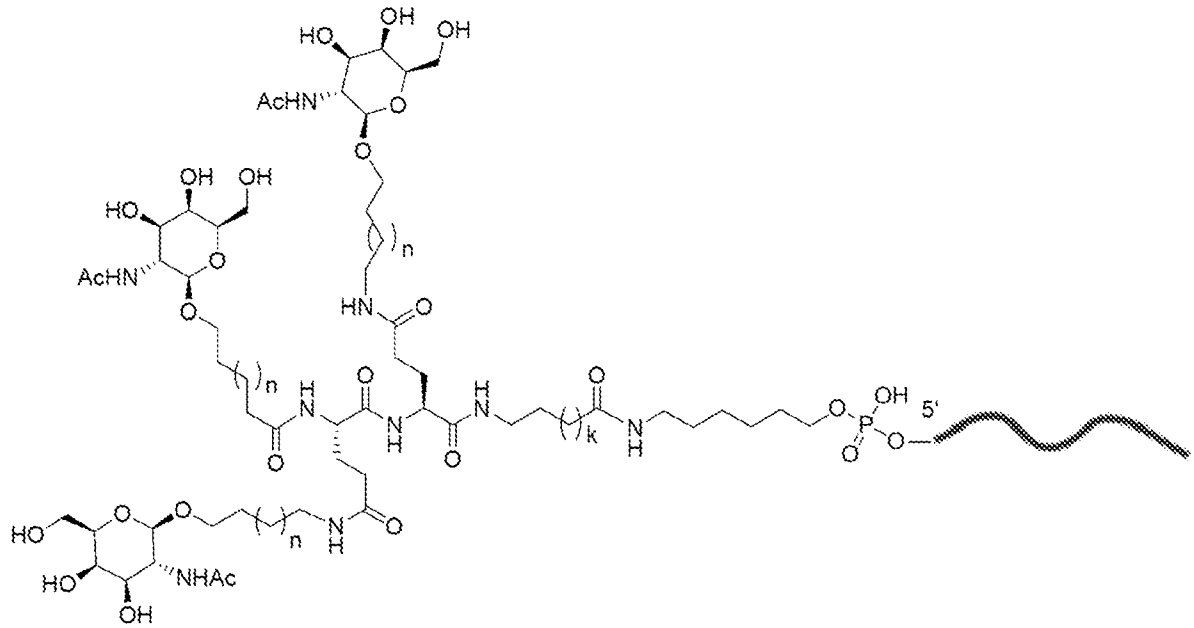
FORMULA XVIII

[0138] In one particular embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XIX, wherein each n is independently 1 to 3 and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



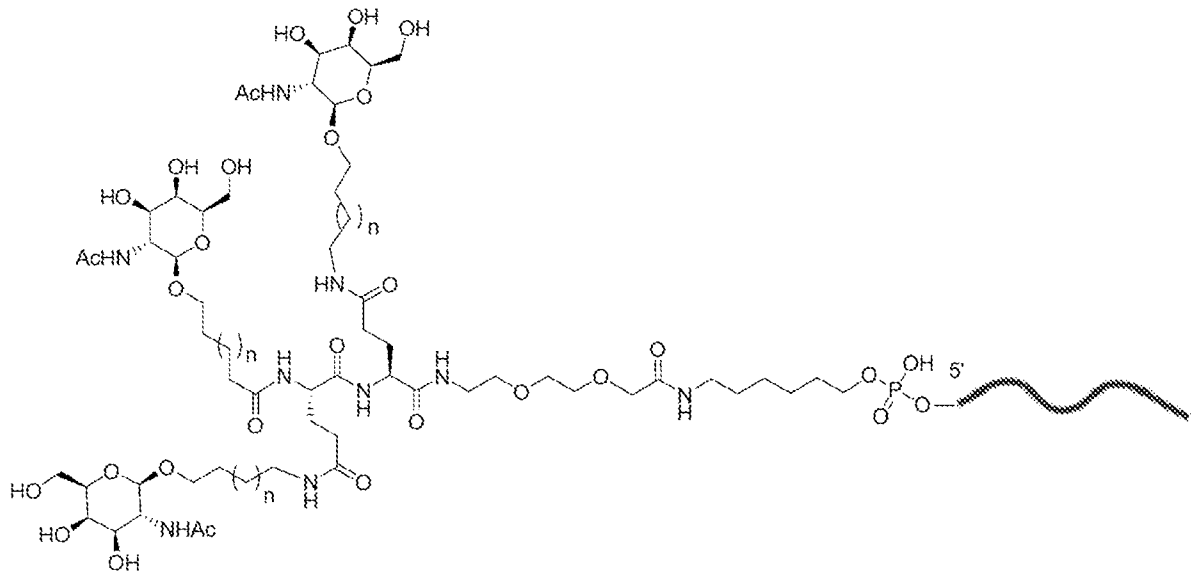
FORMULA XIX

[0139] In some embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XX, wherein each n is independently 1 to 3, k is 1 to 3, and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA XX

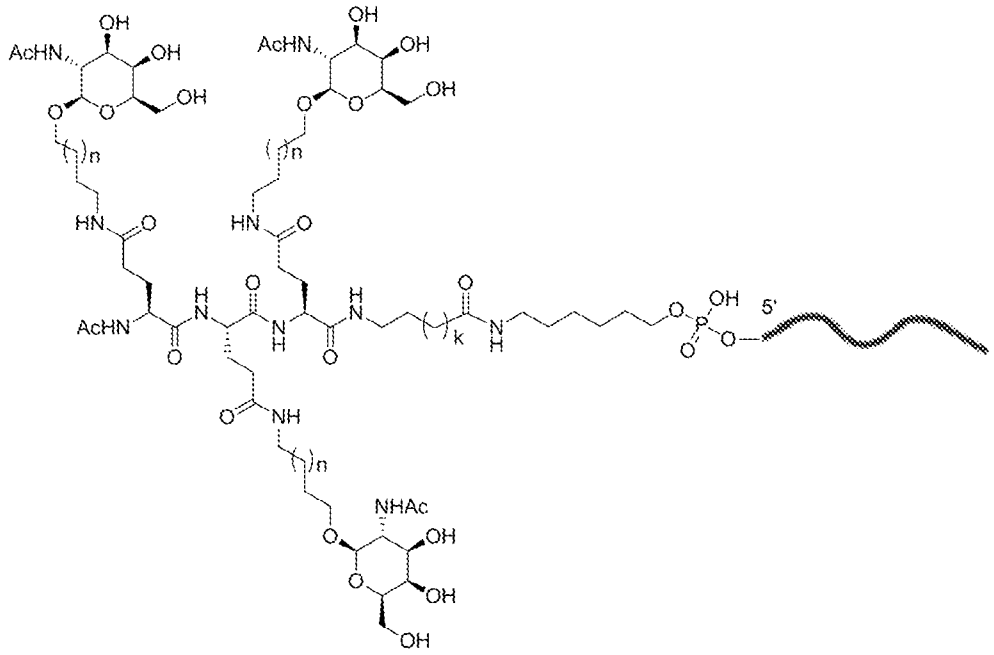
[0140] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XXI, wherein each n is independently 1 to 3, and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA XXI

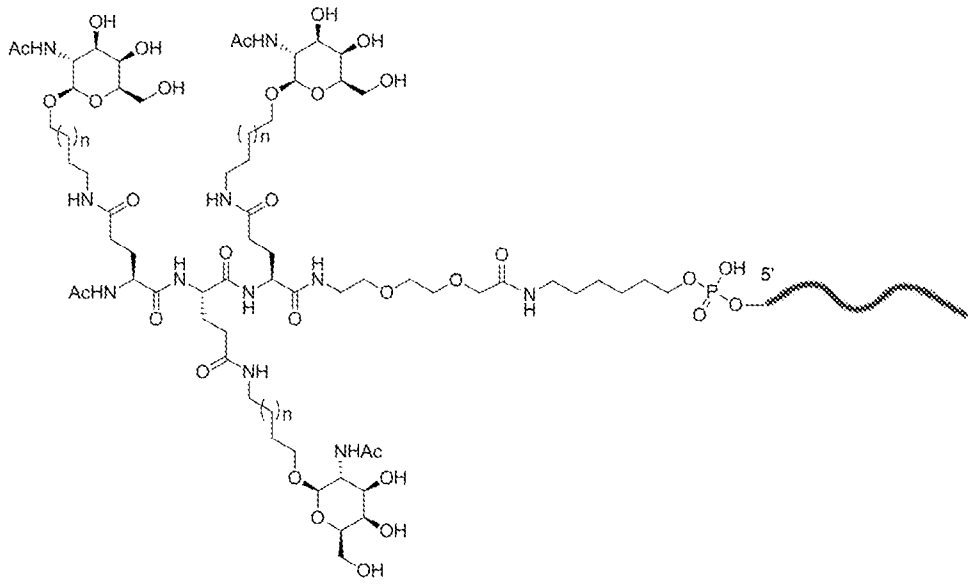
[0141] In certain embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XXII, wherein each n is independently 1 to 3, k is 1 to 3, and the

ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



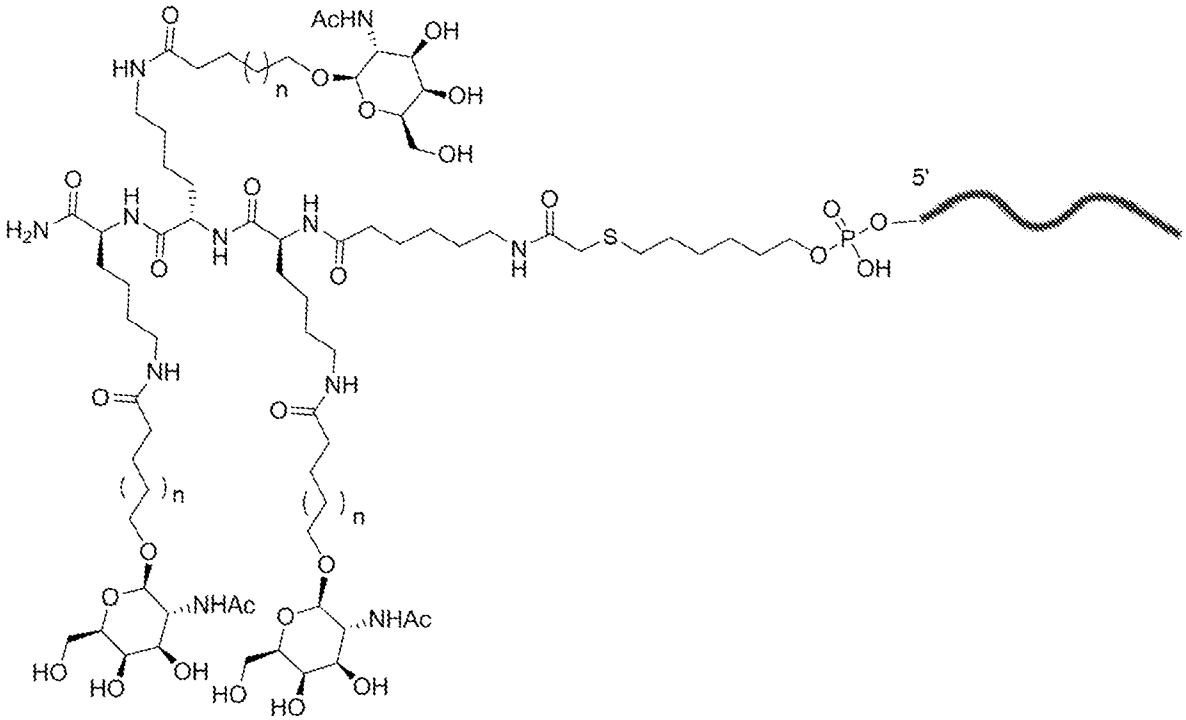
FORMULA XXII

[0142] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XXIII, wherein each n is independently 1 to 3 and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



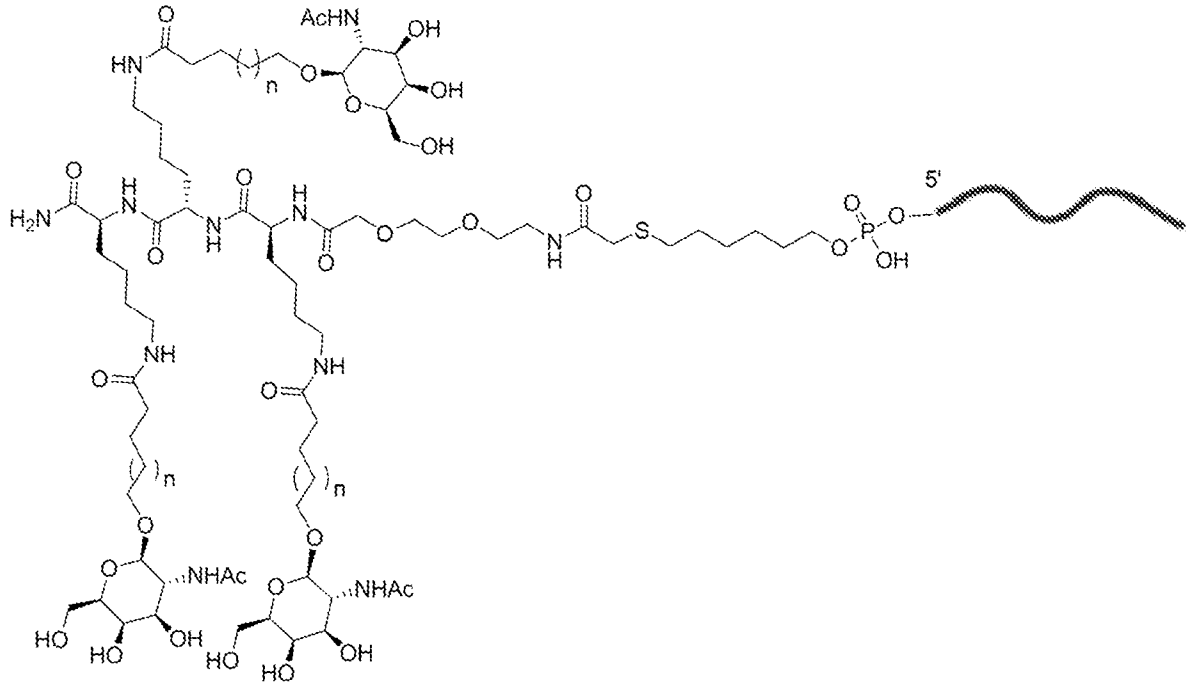
FORMULA XXIII

[0143] In certain other embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XXIV, wherein each n is independently 1 to 3 and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



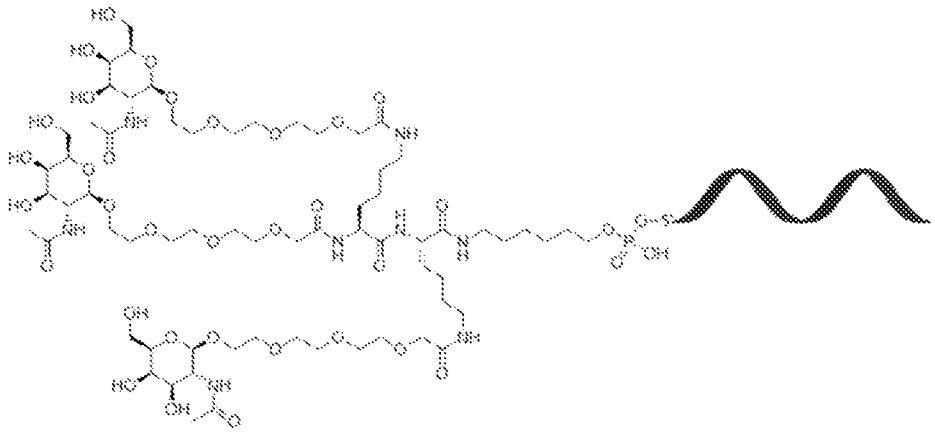
FORMULA XXIV

[0144] In another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XXV, wherein each n is independently 1 to 3 and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



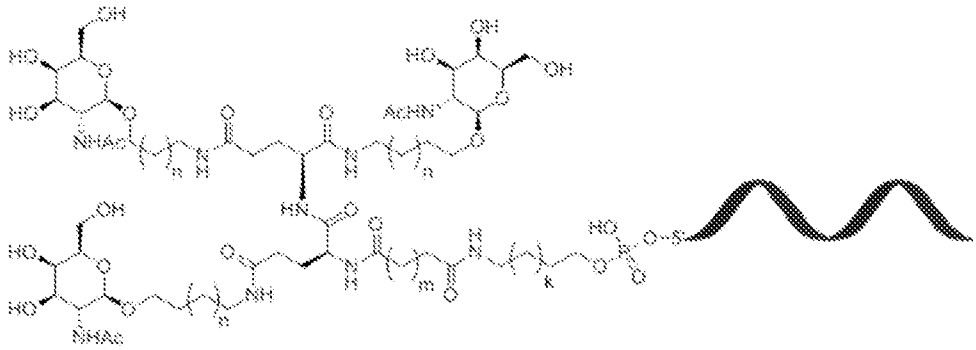
FORMULA XXV

[0145] In certain embodiments, the RNAi construct comprises a ligand and linker having the following structure of Formula XXVI, wherein the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



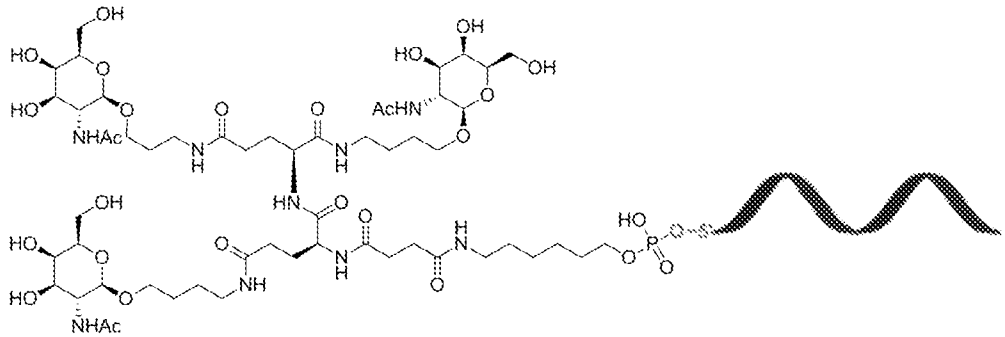
FORMULA XXVI

[0146] In one embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XXVII, wherein each n is independently 1 to 3, k is 1 to 9, m is 1 or 2, and the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



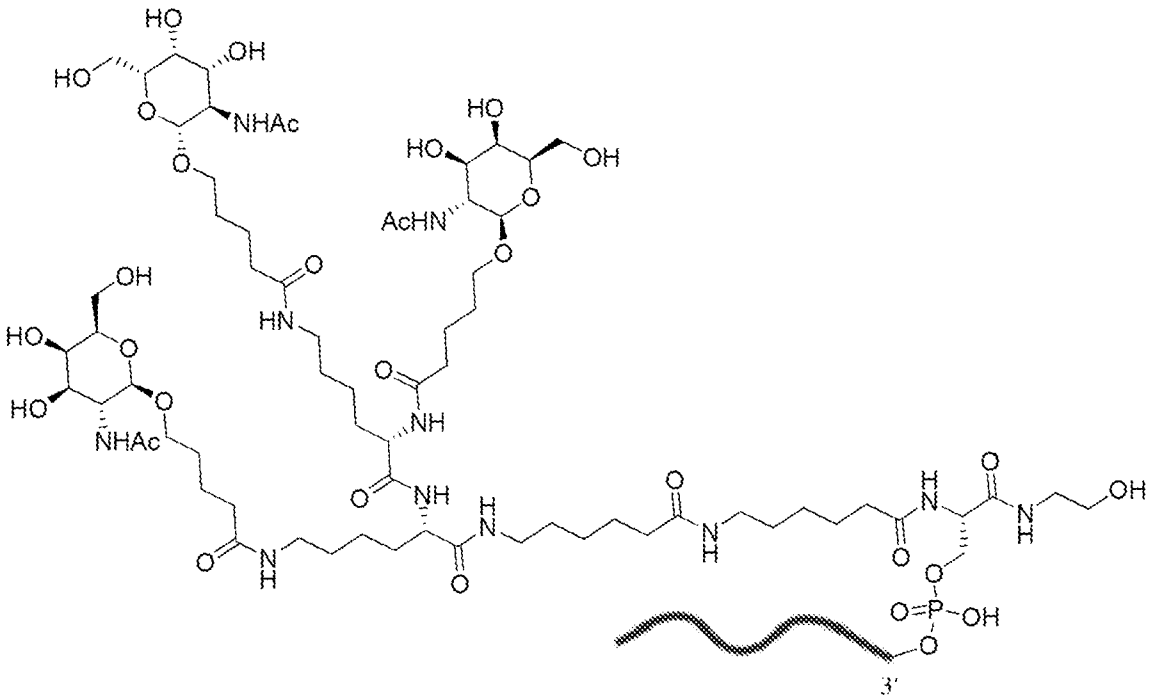
FORMULA XXVII

[0147] In another embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XXVIII, wherein the ligand is attached to the 5′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA XXVIII

[0148] In one particular embodiment, the RNAi construct comprises a ligand and linker having the following structure of Formula XXIX, wherein the ligand is attached to the 3′ end of the sense strand of the double-stranded RNA molecule (represented by the solid wavy line):



FORMULA XXIX

[0149] In some embodiments, the RNAi constructs of the invention may be delivered to a cell or tissue of interest by administering a vector that encodes and controls the intracellular expression of the RNAi construct. A "vector" (also referred to herein as an "expression vector) is a composition of matter which can be used to deliver a nucleic acid of interest to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated viral vectors, retroviral vectors, and the like. A vector can be replicated in a living cell, or it can be made synthetically.

[0150] Generally, a vector for expressing an RNAi construct of the invention will comprise one or more promoters operably linked to sequences encoding the RNAi construct. The phrase "operably linked" or "under transcriptional control" as used herein means that the promoter is in the correct location and orientation in relation to a polynucleotide sequence to control the initiation of transcription by RNA polymerase and expression of the polynucleotide sequence. A "promoter" refers to a sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a gene sequence. Suitable

promoters include, but are not limited to, RNA pol I, pol II, H1 or U6 RNA pol III, and viral promoters (e.g. human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter, and the Rous sarcoma virus long terminal repeat). In some embodiments, a H1 or U6 RNA pol III promoter is preferred. The promoter can be a tissue-specific or inducible promoter. Of particular interest are liver-specific promoters, such as promoter sequences from human alpha 1-antitrypsin gene, albumin gene, hemopexin gene, and hepatic lipase gene. Inducible promoters include promoters regulated by ecdysone, estrogen, progesterone, tetracycline, and isopropyl-P-D1-thiogalactopyranoside (IPTG).

[0151] In some embodiments in which the RNAi construct comprises a siRNA, the two separate strands (sense and antisense strand) can be expressed from a single vector or two separate vectors. For example, in one embodiment, the sequence encoding the sense strand is operably linked to a promoter on a first vector and the sequence encoding the antisense strand is operably linked to a promoter on a second vector. In such an embodiment, the first and second vectors are co-introduced, e.g., by infection or transfection, into a target cell, such that the sense and antisense strands, once transcribed, will hybridize intracellularly to form the siRNA molecule. In another embodiment, the sense and antisense strands are transcribed from two separate promoters located in a single vector. In some such embodiments, the sequence encoding the sense strand is operably linked to a first promoter and the sequence encoding the antisense strand is operably linked to a second promoter, wherein the first and second promoters are located in a single vector. In one embodiment, the vector comprises a first promoter operably linked to a sequence encoding the siRNA molecule, and a second promoter operably linked to the same sequence in the opposite direction, such that transcription of the sequence from the first promoter results in the synthesis of the sense strand of the siRNA molecule and transcription of the sequence from the second promoter results in synthesis of the antisense strand of the siRNA molecule.

[0152] In other embodiments in which the RNAi construct comprises a shRNA, a sequence encoding the single, at least partially self-complementary RNA molecule is operably linked to a promoter to produce a single transcript. In some embodiments, the sequence encoding the shRNA comprises an inverted repeat joined by a linker polynucleotide sequence to produce the the stem and loop structure of the shRNA following transcription.

[0153] In some embodiments, the vector encoding an RNAi construct of the invention is a viral vector. Various viral vector systems that are suitable to express the RNAi constructs described herein include, but are not limited to, adenoviral vectors, retroviral vectors (e.g., lentiviral vectors, moloney murine leukemia virus), adeno- associated viral vectors; herpes simplex viral vectors; SV40 vectors; polyoma viral vectors; papilloma viral vectors; picornaviral vectors; and pox viral vectors (e.g. vaccinia virus). In certain embodiments, the viral vector is a retroviral vector (e.g. lentiviral vector).

[0154] Various vectors suitable for use in the invention, methods for inserting nucleic acid sequences encoding siRNA or shRNA molecules into vectors, and methods of delivering the vectors to the cells of interest are within the skill of those in the art. *See, e.g.*, Dornburg , Gene Therap., Vol. 2: 301-310, 1995; Eglitis, Biotechniques, Vol. 6: 608-614, 1988; Miller, Hum Gene Therap., Vol. 1: 5-14, 1990; Anderson, Nature, Vol. 392: 25-30, 1998; Rubinson D A *et al.*, Nat. Genet., Vol. 33: 401-406, 2003; Brummelkamp *et al.*, Science, Vol. 296: 550-553, 2002; Brummelkamp *et al.*, Cancer Cell, Vol. 2: 243-247, 2002; Lee *et al.*, Nat Biotechnol, Vol. 20: 500-505, 2002; Miyagishi *et al.*, Nat Biotechnol, Vol. 20: 497-500, 2002; Paddison *et al.*, Genes Dev, Vol. 16: 948-958, 2002; Paul *et al.*, Nat Biotechnol, Vol. 20: 505-508, 2002; Sui *et al.*, Proc Natl Acad Sci USA, Vol. 99: 5515-5520, 2002; and Yu *et al.*, Proc Natl Acad Sci USA, Vol. 99: 6047-6052, 2002, all of which are hereby incorporated by reference in their entireties.

[0155] The present invention also includes pharmaceutical compositions and formulations comprising the RNAi constructs described herein and pharmaceutically acceptable carriers, excipients, or diluents. Such compositions and formulations are useful for reducing expression of ASGR1 in a subject in need thereof. Where clinical applications are contemplated, pharmaceutical compositions and formulations will be prepared in a form appropriate for the intended application. Generally, this will entail preparing compositions that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

[0156] The phrases "pharmaceutically acceptable" or "pharmacologically acceptable" refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable carrier, excipient, or diluent" includes solvents, buffers, solutions, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like acceptable for use in formulating pharmaceuticals, such as pharmaceuticals suitable for

administration to humans. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the RNAi constructs of the present invention, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions, provided they do not inactivate the vectors or RNAi constructs of the compositions.

[0157] Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, type and extent of disease or disorder to be treated, or dose to be administered. In some embodiments, the pharmaceutical compositions are formulated based on the intended route of delivery. For instance, in certain embodiments, the pharmaceutical compositions are formulated for parenteral delivery. Parenteral forms of delivery include intravenous, intraarterial, subcutaneous, intrathecal, intraperitoneal or intramuscular injection or infusion. In one embodiment, the pharmaceutical composition is formulated for intravenous delivery. In such an embodiment, the pharmaceutical composition may include a lipid-based delivery vehicle. In another embodiment, the pharmaceutical composition is formulated for subcutaneous delivery. In such an embodiment, the pharmaceutical composition may include a targeting ligand (e.g. GalNAc-containing or antibody-containing ligands described herein).

[0158] In some embodiments, the pharmaceutical compositions comprise an effective amount of an RNAi construct described herein. An "effective amount" is an amount sufficient to produce a beneficial or desired clinical result. In some embodiments, an effective amount is an amount sufficient to reduce ASGR1 expression in hepatocytes of a subject. In some embodiments, an effective amount may be an amount sufficient to only partially reduce ASGR1 expression, for example, to a level comparable to expression of the wild-type ASGR1 allele in human heterozygotes. Human heterozygous carriers of loss of function ASGR1 variant alleles were reported to have lower serum levels of non- HDL cholesterol and a lower risk of coronary artery disease and myocardial infarction as compared to non-carriers (Nioi *et al.*, New England Journal of Medicine, Vol. 374(22):2131-2141, 2016). Thus, without being bound by theory, it is believed that partial reduction of ASGR1 expression may be sufficient to achieve the benefical reduction of serum non-HDL cholesterol and reduction of risk of coronary artery disease and myocardial infarction.

[0159] An effective amount of an RNAi construct of the invention may be from about 0.01 mg/kg body weight to about 100 mg/kg body weight, about 0.05 mg/kg body weight to about 75 mg/kg body weight, about 0.1 mg/kg body weight to about 50 mg/kg body weight, about 1 mg/kg to about 30 mg/kg body weight, about 2.5 mg/kg of body weight to about 20 mg/kg body weight, or about 5 mg/kg body weight to about 15 mg/kg body weight. In certain embodiments, a single effective dose of an RNAi construct of the invention may be about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, or about 10 mg/kg. The pharmaceutical composition comprising an effective amount of RNAi construct can be administered weekly, biweekly, monthly, quarterly, or biannually. The precise determination of what would be considered an effective amount and frequency of administration may be based on several factors, including a patient's size, age, and general condition, type of disorder to be treated (e.g. myocardial infarction, heart failure, coronary artery disease, hypercholesterolemia), particular RNAi construct employed, and route of administration. Estimates of effective dosages and *in vivo* half-lives for any particular RNAi construct of the invention can be ascertained using conventional methods and/or testing in appropriate animal models.

[0160] Administration of the pharmaceutical compositions of the present invention may be via any common route so long as the target tissue is available via that route. Such routes include, but are not limited to, parenteral (e.g., subcutaneous, intramuscular, intraperitoneal or intravenous), oral, nasal, buccal, intradermal, transdermal, and sublingual routes, or by direct injection into liver tissue or delivery through the hepatic portal vein. In some embodiments, the pharmaceutical composition is administered parenterally. For instance, in certain embodiments, the pharmaceutical composition is administered intravenously. In other embodiments, the pharmaceutical composition is administered subcutaneously.

[0161] Colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes, may be used as delivery vehicles for the RNAi constructs of the invention or vectors encoding such constructs. Commercially available fat emulsions that are suitable for delivering the nucleic acids of the invention include Intralipid® (Baxter International Inc.), Liposyn® (Abbott Pharmaceuticals), Liposyn®II (Hospira), Liposyn®III (Hospira), Nutrilipid (B. Braun Medical Inc.), and other similar lipid emulsions. A preferred colloidal

system for use as a delivery vehicle *in vivo* is a liposome (i.e., an artificial membrane vesicle). The RNAi constructs of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi constructs of the invention may be complexed to lipids, in particular to cationic lipids. Suitable lipids and liposomes include neutral (e.g., dioleoylphosphatidyl ethanolamine (DOPE), dimyristoylphosphatidyl choline (DMPC), and dipalmitoyl phosphatidylcholine (DPPC)), distearolyphosphatidyl choline), negative (e.g., dimyristoylphosphatidyl glycerol (DMPG)), and cationic (e.g., dioleoyltetramethylaminopropyl (DOTAP) and dioleoylphosphatidyl ethanolamine (DOTMA)). The preparation and use of such colloidal disperson systems is well known in the art. Exemplary formulations are also disclosed in U.S. Pat. No. 5,981,505; U.S. Pat. No. 6,217,900; U.S. Pat. No. 6,383,512; U.S. Pat. No. 5,783,565; U.S. Pat. No. 7,202,227; U.S. Pat. No. 6,379,965; U.S. Pat. No. 6,127,170; U.S. Pat. No. 5,837,533; U.S. Pat. No. 6,747,014; and WO03/093449.

[0162] In some embodiments, the RNAi constructs of the invention are fully encapsulated in a lipid formulation, e.g., to form a SPLP, pSPLP, SNALP, or other nucleic acid-lipid particle. As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle, including SPLP. As used herein, the term "SPLP" refers to a nucleic acid-lipid particle comprising plasmid DNA encapsulated within a lipid vesicle. SNALPs and SPLPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (e.g., a PEG-lipid conjugate). SNALPs and SPLPs are exceptionally useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous injection and accumulate at distal sites (e.g., sites physically separated from the administration site). SPLPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The nucleic acid-lipid particles typically have a mean diameter of about 50 nm to about 150 nm, about 60 nm to about 130 nm, about 70 nm to about 110 nm, or about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid-lipid particles are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Patent Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; and PCT Publication No. WO 96/40964.

[0163] The pharmaceutical compositions suitable for injectable use include, for example, sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Generally, these preparations are sterile and fluid to the extent that easy injectability exists. Preparations should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. Appropriate solvents or dispersion media may contain, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial an antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0164] Sterile injectable solutions may be prepared by incorporating the active compounds in an appropriate amount into a solvent along with any other ingredients (for example as enumerated above) as desired, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the desired other ingredients, e.g., as enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation include vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient(s) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0165] The compositions of the present invention generally may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include, for example, acid addition salts (formed with free amino groups) derived from inorganic acids (e.g., hydrochloric or phosphoric acids), or from organic acids (e.g., acetic, oxalic, tartaric, mandelic, and the like). Salts formed with the free carboxyl groups can also be derived from inorganic bases (e.g., sodium, potassium,

ammonium, calcium, or ferric hydroxides) or from organic bases (e.g., isopropylamine, trimethylamine, histidine, procaine and the like).

[0166] For parenteral administration in an aqueous solution, for example, the solution generally is suitably buffered and the liquid diluent first rendered isotonic for example with sufficient saline or glucose. Such aqueous solutions may be used, for example, for intravenous, intramuscular, subcutaneous and intraperitoneal administration. Preferably, sterile aqueous media are employed as is known to those of skill in the art, particularly in light of the present disclosure. By way of illustration, a single dose may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA standards. In certain embodiments, a pharmaceutical composition of the invention comprises or consists of a sterile saline solution and an RNAi construct described herein. In other embodiments, a pharmaceutical composition of the invention comprises or consists of an RNAi construct described herein and sterile water (e.g. water for injection, WFI). In still other embodiments, a pharmaceutical composition of the invention comprises or consists of an RNAi construct described herein and phosphate-buffered saline (PBS).

[0167] In some embodiments, the pharmaceutical compositions of the invention are packaged with or stored within a device for administration. Devices for injectable formulations include, but are not limited to, injection ports, pre-filled syringes, autoinjectors, injection pumps, on-body injectors, and injection pens. Devices for aerosolized or powder formulations include, but are not limited to, inhalers, insufflators, aspirators, and the like. Thus, the present invention includes administration devices comprising a pharmaceutical composition of the invention for treating or preventing one or more of the disorders described herein.

[0168] The present invention provides methods for reducing or inhibiting expression of ASGR1 in a subject in need thereof as well as methods of treating or preventing conditions, diseases, or disorders associated with ASGR1 expression or activity. A “condition, disease, or disorder associated with ASGR1 expression” refers to conditions, diseases, or disorders in which ASGR1 expression levels are altered or where elevated expression levels of ASGR1 are associated with an increased risk of developing the condition, disease or disorder. A condition, disease, or

disorder associated with ASGR1 expression can also include conditions, diseases, or disorders resulting from aberrant changes in lipoprotein metabolism, such as changes resulting in abnormal levels of cholesterol, lipids, triglycerides, etc. or impaired clearance of these molecules. Recently, human carriers of loss of function variant alleles of the ASGR1 subunit of the asialoglycoprotein receptor were reported to have lower serum levels of non- HDL cholesterol and a lower risk of coronary artery disease and myocardial infarction as compared to non-carriers (Nioi *et al.*, New England Journal of Medicine, Vol. 374(22):2131-2141, 2016, which is hereby incorporated by reference in its entirety). Thus, in certain embodiments, the RNAi constructs of the invention are particularly useful for treating or preventing cardiovascular disease (e.g. coronary artery disease and myocardial infarction) and cholesterol-related disorders (e.g. hypercholesterolemia).

[0169] Conditions, diseases, and disorders associated with ASGR1 expression that can be treated or prevented according to the methods of the invention include, but are not limited to, cardiovascular disease, such as myocardial infarction, heart failure, stroke (ischemic and hemorrhagic), atherosclerosis, coronary artery disease, peripheral vascular disease (e.g. peripheral artery disease), vulnerable plaque, hypercholesterolemia, and dyslipidemia (manifesting, e.g., as elevated total cholesterol, elevated low-density lipoprotein (LDL), elevated very low-density lipoprotein (VLDL), elevated triglycerides, and/or low levels of high-density lipoprotein (HDL)).

[0170] In certain embodiments, the present invention provides a method for reducing the expression of ASGR1 in a patient in need thereof comprising administering to the patient any of the RNAi constructs described herein. The term "patient," as used herein, refers to a mammal, including humans, and can be used interchangeably with the term "subject." Preferably, the expression level of ASGR1 in hepatocytes in the patient is reduced following administration of the RNAi construct as compared to the ASGR1 expression level in a patient not receiving the RNAi construct.

[0171] In some embodiments, a patient in need of reduction of ASGR1 expression is a patient who is at risk of having a myocardial infarction. A patient who is at risk of having a myocardial infarction may be a patient who has a history of myocardial infarction (e.g. has had a previous myocardial infarction). A patient at risk of having a myocardial infarction may also be a patient who has a familial history of myocardial infarction or who has one or more risk factors of

myocardial infarction. Such risk factors include, but are not limited to, hypertension, elevated levels of non-HDL cholesterol, elevated levels of triglycerides, diabetes, obesity, or history of autoimmune diseases (e.g. rheumatoid arthritis, lupus). In one embodiment, a patient who is at risk of having a myocardial infarction is a patient who has or is diagnosed with coronary artery disease. The risk of myocardial infarction in these and other patients can be reduced by administering to the patients any of the RNAi constructs described herein. Accordingly, the present invention provides a method for reducing the risk of myocardial infarction in a patient in need thereof comprising administering to the patient an RNAi construct described herein. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for reducing the risk of myocardial infarction in a patient in need thereof. In other embodiments, the present invention provides an ASGR1-targeting RNAi construct for use in a method for reducing the risk of myocardial infarction in a patient in need thereof.

[0172] In certain embodiments, a patient in need of reduction of ASGR1 expression is a patient who is diagnosed with or at risk of cardiovascular disease. Thus, the present invention includes a method for treating or preventing cardiovascular disease in a patient in need thereof by administering any of the RNAi constructs of the invention. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for treating or preventing cardiovascular disease in a patient in need thereof. In other embodiments, the present invention provides an ASGR1-targeting RNAi construct for use in a method for treating or preventing cardiovascular disease in a patient in need thereof. Cardiovascular disease includes myocardial infarction, heart failure, stroke (ischemic and hemorrhagic), atherosclerosis, coronary artery disease, peripheral vascular disease (e.g. peripheral artery disease), and vulnerable plaque. In some embodiments, the cardiovascular disease to be treated or prevented according to the methods of the invention is coronary artery disease. In other embodiments, the cardiovascular disease to be treated or prevented according to the methods of the invention is myocardial infarction. In certain embodiments, administration of the RNAi constructs described herein reduces the risk of non-fatal myocardial infarctions, fatal and non-fatal strokes, certain types of heart surgery (e.g. angioplasty, bypass), hospitalization for heart failure, chest pain in patients with heart disease, and/or cardiovascular events in patients with established heart disease (e.g. prior myocardial infarction, prior heart

surgery, and/or chest pain with evidence of blocked arteries). In some embodiments, administration of the RNAi constructs described herein according to the methods of the invention can be used to reduce the risk of recurrent cardiovascular events.

[0173] In certain other embodiments, a patient in need of reduction of ASGR1 expression is a patient who has elevated levels of non-HDL cholesterol. Accordingly, in some embodiments, the present invention provides a method for reducing non-HDL cholesterol in a patient in need thereof by administering to the patient any of the RNAi constructs described herein. In some embodiments, the present invention includes use of any of the RNAi constructs described herein in the preparation of a medicament for reducing non-HDL cholesterol in a patient in need thereof. In other embodiments, the present invention provides an ASGR1-targeting RNAi construct for use in a method for reducing non-HDL cholesterol in a patient in need thereof. Non-HDL cholesterol is a measure of all cholesterol-containing proatherogenic lipoproteins, including LDL cholesterol, very low-density lipoprotein, intermediate-density lipoprotein, lipoprotein(a), chylomicron, and chylomicron remnants. Non-HDL cholesterol has been reported to be a good predictor of cardiovascular risk (Rana *et al.*, Curr. Atheroscler. Rep., Vol. 14:130-134, 2012). Non-HDL cholesterol levels can be calculated by subtracting HDL cholesterol levels from total cholesterol levels. In one embodiment, a patient's LDL cholesterol levels are reduced following administration of the RNAi construct. In another embodiment, a patient's lipoprotein (a) levels are reduced following administration of the RNAi construct.

[0174] In some embodiments, a patient to be treated according to the methods of the invention is a patient who has elevated levels of non-HDL cholesterol (e.g. elevated serum levels of non-HDL cholesterol). Ideally, levels of non-HDL cholesterol should be about 30 mg/dL above the target for LDL cholesterol levels for any given patient. In particular embodiments, a patient is administered an RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 130 mg/dL or greater. In one embodiment, a patient is administered an RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 160 mg/dL or greater. In another embodiment, a patient is administered an RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 190 mg/dL or greater. In still another embodiment, a patient is administered an RNAi construct of the invention if the patient has a non-HDL cholesterol level of about 220 mg/dL or greater. In certain embodiments, a patient is administered an RNAi construct of the invention if the patient is at a high or very high risk of

cardiovascular disease according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff *et al.*, ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;00:000–000) and has a non-HDL cholesterol level of about 100 mg/dL or greater.

[0175] In some embodiments of the methods of the invention, a patient is administered an RNAi construct described herein if they are at a moderate risk or higher for cardiovascular disease according to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (referred to herein as the "2013 Guidelines"). In certain embodiments, an RNAi construct of the invention is administered to a patient if the patient's LDL cholesterol level is greater than about 160 mg/dL. In other embodiments, an RNAi construct of the invention is administered to a patient if the patient's LDL cholesterol level is greater than about 130 mg/dL and the patient has a moderate risk of cardiovascular disease according to the 2013 Guidelines. In still other embodiments, an RNAi construct of the invention is administered to a patient if the patient's LDL cholesterol level is greater than 100 mg/dL and the patient has a high or very high risk of cardiovascular disease according to the 2013 Guidelines.

[0176] In certain embodiments, a patient to be treated according to the methods of the invention is a patient who has a vulnerable plaque (also referred to as unstable plaque). Vulnerable plaques are a build-up of macrophages and lipids containing predominantly cholesterol that lie underneath the endothelial lining of the arterial wall. These vulnerable plaques can rupture resulting in the formation of a blood clot, which can potentially block blood flow through the artery and cause a myocardial infarction or stroke. Vulnerable plaques can be identified by methods known in the art, including, but not limited to, intravascular ultrasound and computed tomography (Sahara *et al.*, European Heart Journal, Vol. 25: 2026-2033, 2004; Budhoff, J. Am. Coll. Cardiol., Vol. 48: 319-321, 2006; Hausleiter *et al.*, J. Am. Coll. Cardiol., Vol. 48: 312-318, 2006).

[0177] In some embodiments of the methods of the invention, the RNAi construct is administered in combination with another therapeutic agent, such as a therapeutic agent for treating or preventing cardiovascular disease. In one embodiment, an RNAi construct of the invention is administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Examples of such agents include both

proteinaceous and non-proteinaceous drugs. When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art. "Co-administration" and combination therapy are not limited to simultaneous administration, but also include treatment regimens in which an RNAi construct of the invention is administered at least once during a course of treatment that involves administering at least one other therapeutic agent to the patient. In certain embodiments, an RNAi construct of the invention is administered prior to the administration of at least one other therapeutic agent. In other embodiments, an RNAi construct of the invention is administered concurrent with the administration of at least one other therapeutic agent. In some embodiments, an RNAi construct of the invention is administered subsequent to the administration of at least one other therapeutic agent.

[0178] In certain embodiments of the methods of the invention, the RNAi construct is administered to a patient in combination with a PCSK9 antagonist, such as an anti-hPCSK9 antibody (e.g., Repatha® (evolocumab)). In another embodiment, the RNAi construct of the invention is administered to a patient in combination with at least one other cholesterol-lowering (serum and/or total body cholesterol) agent. In some embodiments, the agent increases the expression of LDLR, has been observed to increase serum HDL levels, lower LDL levels, or lower triglyceride levels. Exemplary agents include, but are not limited to, statins (e.g., atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin); nicotinic acid (Niacin) (NIACOR, NIASPAN (slow release niacin), SLO-NIACIN (slow release niacin)); fibric acid (LOPID (Gemfibrozil), TRICOR (fenofibrate)); bile acid sequestrants (QUESTRAN (cholestyramine), colesevelam (WELCHOL), COLESTID (colestipol)); cholesterol absorption inhibitors (ZETIA (ezetimibe)), combining nicotinic acid with statin (ADVICOR (LOVASTATIN and NIASPAN), combinations of a statin with an absorption inhibitor (VYTORIN (ZOCOR and ZETIA); and/or lipid modifying agents.

[0179] In some embodiments, the RNAi construct of the invention is combined with PPAR gamma agonists, PPAR alpha/gamma agonists, squalene synthase inhibitors, CETP inhibitors, anti-hypertensives, anti-diabetic agents (such as sulphonyl ureas, insulin, GLP-1 analogs, DDPIV inhibitors), ApoB modulators, MTP inhibitors and/or arteriosclerosis obliterans treatments. In certain embodiments, the RNAi construct of the invention is combined with an agent that increases the level of LDL receptor (LDLR) protein in a patient, such as statins, certain cytokines, like oncostatin M, estrogen, and/or certain herbal ingredients, such as berberine.

[0180] In some embodiments, the RNAi construct of the invention is combined with an agent that increases serum cholesterol levels in a patient (such as certain anti-psycotic agents, certain HIV protease inhibitors, dietary factors such as high fructose, sucrose, cholesterol or certain fatty acids and certain nuclear receptor agonists and antagonists for RXR, RAR, LXR, FXR). In certain embodiments, the RNAi construct of the invention is combined with an agent that increases the level of PCSK9 protein in a subject, such as statins and/or insulin. The administration of RNAi constructs in such embodiments can allow for the RNAi construct to mitigate the undesirable side-effects of these other agents, such as increases in serum non-HDL cholesterol.

[0181] It is understood that all ribonucleic acid sequences disclosed herein can be converted to deoxyribonucleic acid sequences by substituting a thymine base for a uracil base in the sequence. Likewise, all deoxyribonucleic acid sequences disclosed herein can be converted to ribonucleic acid sequences by substituting a uracil base for a thymine base in the sequence. Deoxyribonucleic acid sequences, ribonucleic acid sequences, and sequences containing mixtures of deoxyribonucleotides and ribonucleotides of all sequences disclosed herein are included in the invention.

[0182] Additionally, any nucleic acid sequences disclosed herein may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified polynucleotides is, in certain instances, arbitrary. For example, a polynucleotide comprising a nucleotide having a 2′-OH substituent on the ribose sugar and a thymine base could be described as a DNA molecule having a modified sugar (2′-OH for the natural 2′-H of DNA) or as an RNA molecule having a modified base (thymine (methylated uracil) for natural uracil of RNA).

[0183] Accordingly, nucleic acid sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of a further example and without limitation, a polynucleotide having the sequence "ATCGATCG" encompasses any polynucleotides having such a sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and polynucleotides having other modified bases,

such as "ATmeCGAUCG," wherein meC indicates a cytosine base comprising a methyl group at the 5-position.

[0184] The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the scope of the appended claims.

EXAMPLES

Example 1. Selection and Design of ASGR1 siRNA Sequences

[0185] The identification and selection of optimal sequences for therapeutic siRNA molecules targeting the human asialoglycoprotein receptor 1 (ASGR1) proceeded in two phases. Candidate sequences for inclusion in an initial Tier 1 screening set were identified using a bioinformatics analysis of two alternatively spliced transcripts for human ASGR1: transcript variant 1 encoding the longer isoform A (NCBI Reference Sequence No. NM_001671.4; see Figure 1A) and transcript variant 2 encoding the shorter isoform B (NCBI Reference Sequence No. NM_001197216.2; see Figure 1B). The two human ASGR1 transcript sequences were analyzed using an in-house siRNA design algorithm, which identifies 19mer sequences having a particular base content at certain positions or regions within the 19mer sequences. Sequences were also evaluated for identity to ASGR1 sequences in the mouse (NCBI Reference No. NM_009714.2; see Figure 2), rat (Figure 3), and cynomolgus monkey (NCBI Reference No. XM_005582698.1; see Figure 4). 19mer sequences were also evaluated for sequence identity to other human gene sequences to predict off-target effects and for overlap with known single nucleotide polymorphisms. Based on the results of the bioinformatics analysis, 211 sequences were included in the Tier 1 screening set. A UU dinucleotide was added to the 3′ end of the selected 19mer sense and antisense sequences to produce siRNA molecules with 19 base pair duplex regions and a 2 nucleotide overhang at the 3′ ends of both strands.

[0186] The second phase of siRNA sequence selection was directed to identifying additional active siRNAs targeting the human ASGR1 mRNA that may have been excluded as a result of the bioinformatics analysis. All overlapping 19mer sequences from the human ASGR1 transcript variants 1 and 2 (NCBI Reference Sequence Nos. NM_001671.4 and NM_001197216.2; see Figures 1A and 1B) were extracted and reverse complement antisense sequences designed. 1284 sequences that were not included in Tier 1 were included as part of the Tier 2 sequences. Like

the Tier 1 sequences, the Tier 2 sequences were converted to 21mers by adding a UU dinucleotide to the 3′ ends of the sense and antisense strand to produce siRNA molecules with 19 base pair duplex regions and 2 nucleotide overhangs at each 3′ end. Tier 2 also included 55 sequences identified in Tier 1 for resynthesis and testing. The combined Tier 1 and Tier 2 screening sets included 1495 19mer sequences across the human ASGR1 mRNA transcripts. The sense and antisense sequences of the siRNA molecules included in both Tier 1 and Tier 2 screening sets, as well as the sequences for 8 additional siRNA molecules that target the terminal regions of the transcripts, are shown in Table 1 below. The site within each of the human ASGR1 transcripts that is targeted by each of the siRNA molecules is also listed in Table 1.

Table 1. ASGR1 siRNA Sequences

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1000	1000-1018	883-901	UGUCCAGCACCACAUAGGCUU	5	GCCUAUGUGGUGCUGGACAUU	1508
D-1001	1001-1019	884-902	GUCCAGCACCACAUAGGCCUU	6	GGCCUAUGUGGUGCUGGACUU	1509
D-1002	100-118	100-118	CACCCCCACACUCCCCUAAUU	7	UUAGGGGAGUGUGGGGGUGUU	1510
D-1003	1002-1020	885-903	UCCAGCACCACAUAGGCCCUU	8	GGGCCUAUGUGGUGCUGGAUU	1511
D-1004	1003-1021	886-904	CCAGCACCACAUAGGCCCUUU	9	AGGGCCUAUGUGGUGCUGGUU	1512
D-1005	1004-1022	887-905	CAGCACCACAUAGGCCCUGUU	10	CAGGGCCUAUGUGGUGCUGUU	1513
D-1006	1005-1023	888-906	AGCACCACAUAGGCCCUGUUU	11	ACAGGGCCUAUGUGGUGCUUU	1514
D-1007	1006-1024	889-907	GCACCACAUAGGCCCUGUGUU	12	CACAGGGCCUAUGUGGUGCUU	1515
D-1008	1007-1025	890-908	CACCACAUAGGCCCUGUGAUU	13	UCACAGGGCCUAUGUGGUGUU	1516
D-1009	1008-1026	891-909	ACCACAUAGGCCCUGUGAAUU	14	UUCACAGGGCCUAUGUGGUUU	1517
D-1010	1009-1027	892-910	CCACAUAGGCCCUGUGAACUU	15	GUUCACAGGGCCUAUGUGGUU	1518
D-1011	1010-1028	893-911	CACAUAGGCCCUGUGAACAUU	16	UGUUCACAGGGCCUAUGUGUU	1519
D-1012	1011-1029	894-912	ACAUAGGCCCUGUGAACACUU	17	GUGUUCACAGGGCCUAUGUUU	1520
D-1013	101-119	101-119	ACCCCCACACUCCCCUAAGUU	18	CUUAGGGGAGUGUGGGGGUUU	1521
D-1014	1012-1030	895-913	CAUAGGCCCUGUGAACACCUU	19	GGUGUUCACAGGGCCUAUGUU	1522

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1015	1013-1031	896-914	AUAGGCCCUGUGAACACCUUU	20	AGGUGUUCACAGGGCCUAUUU	1523
D-1016	1014-1032	897-915	UAGGCCCUGUGAACACCUGUU	21	CAGGUGUUCACAGGGCCUAUU	1524
D-1017	1015-1033	898-916	AGGCCCUGUGAACACCUGGUU	22	CCAGGUGUUCACAGGGCCUUU	1525
D-1018	1016-1034	899-917	GGCCCUGUGAACACCUGGAUU	23	UCCAGGUGUUCACAGGGCCUU	1526
D-1019	1017-1035	900-918	GCCCUGUGAACACCUGGAUUU	24	AUCCAGGUGUUCACAGGGCUU	1527
D-1020	1018-1036	901-919	CCCUGUGAACACCUGGAUGUU	25	CAUCCAGGUGUUCACAGGGUU	1528
D-1021	1019-1037	902-920	CCUGUGAACACCUGGAUGGUU	26	CCAUCCAGGUGUUCACAGGUU	1529
D-1022	1020-1038	903-921	CUGUGAACACCUGGAUGGGUU	27	CCCAUCCAGGUGUUCACAGUU	1530
D-1023	1021-1039	904-922	UGUGAACACCUGGAUGGGCUU	28	GCCCAUCCAGGUGUUCACAUU	1531
D-1024	102-120	102-120	CCCCCACACUCCCCUAAGUUU	29	ACUUAGGGGAGUGUGGGGGUU	1532
D-1025	1022-1040	905-923	GUGAACACCUGGAUGGGCCUU	30	GGCCCAUCCAGGUGUUCACUU	1533
D-1026	1023-1041	906-924	UGAACACCUGGAUGGGCCUUU	31	AGGCCCAUCCAGGUGUUCAUU	1534
D-1027	1024-1042	907-925	GAACACCUGGAUGGGCCUCUU	32	GAGGCCCAUCCAGGUGUUCUU	1535
D-1028	1025-1043	908-926	AACACCUGGAUGGGCCUCCUU	33	GGAGGCCCAUCCAGGUGUUUU	1536
D-1029	1026-1044	909-927	ACACCUGGAUGGGCCUCCAUU	34	UGGAGGCCCAUCCAGGUGUUU	1537
D-1030	1027-1045	910-928	CACCUGGAUGGGCCUCCACUU	35	GUGGAGGCCCAUCCAGGUGUU	1538
D-1031	10-28	10-28	UGCACGGAAGAGUGAGGUGUU	36	CACCUCACUCUUCCGUGCAUU	1539
D-1032	1028-1046	911-929	ACCUGGAUGGGCCUCCACGUU	37	CGUGGAGGCCCAUCCAGGUUU	1540
D-1033	1029-1047	912-930	CCUGGAUGGGCCUCCACGAUU	38	UCGUGGAGGCCCAUCCAGGUU	1541
D-1034	1030-1048	913-931	CUGGAUGGGCCUCCACGACUU	39	GUCGUGGAGGCCCAUCCAGUU	1542
D-1035	1031-1049	914-932	UGGAUGGGCCUCCACGACCUU	40	GGUCGUGGAGGCCCAUCCAUU	1543
D-1036	103-121	103-121	CCCCACACUCCCCUAAGUUUU	41	AACUUAGGGGAGUGUGGGGUU	1544
D-1037	1032-1050	915-933	GGAUGGGCCUCCACGACCAUU	42	UGGUCGUGGAGGCCCAUCCUU	1545
D-1038	1033-1051	916-934	GAUGGGCCUCCACGACCAAUU	43	UUGGUCGUGGAGGCCCAUCUU	1546
D-1039	1034-1052	917-935	AUGGGCCUCCACGACCAAAUU	44	UUUGGUCGUGGAGGCCCAUUU	1547
D-1040	1035-1053	918-936	UGGGCCUCCACGACCAAAAUU	45	UUUUGGUCGUGGAGGCCCAUU	1548

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1041	1036-1054	919-937	GGGCCUCCACGACCAAAACUU	46	GUUUUGGUCGUGGAGGCCCUU	1549
D-1042	1037-1055	920-938	GGCCUCCACGACCAAAACGUU	47	CGUUUUGGUCGUGGAGGCCUU	1550
D-1043	1038-1056	921-939	GCCUCCACGACCAAAACGGUU	48	CCGUUUUGGUCGUGGAGGCUU	1551
D-1044	1039-1057	922-940	CCUCCACGACCAAAACGGGUU	49	CCCGUUUUGGUCGUGGAGGUU	1552
D-1045	1040-1058	923-941	CUCCACGACCAAAACGGGCUU	50	GCCCGUUUUGGUCGUGGAGUU	1553
D-1046	1041-1059	924-942	UCCACGACCAAAACGGGCCUU	51	GGCCCGUUUUGGUCGUGGAUU	1554
D-1047	104-122	104-122	CCCACACUCCCCUAAGUUCUU	52	GAACUUAGGGGAGUGUGGGUU	1555
D-1048	1042-1060	925-943	CCACGACCAAAACGGGCCCUU	53	GGGCCCGUUUUGGUCGUGGUU	1556
D-1049	1043-1061	926-944	CACGACCAAAACGGGCCCUUU	54	AGGGCCCGUUUUGGUCGUGUU	1557
D-1050	1044-1062	927-945	ACGACCAAAACGGGCCCUGUU	55	CAGGGCCCGUUUUGGUCGUUU	1558
D-1051	1045-1063	928-946	CGACCAAAACGGGCCCUGGUU	56	CCAGGGCCCGUUUUGGUCGUU	1559
D-1052	1046-1064	929-947	GACCAAAACGGGCCCUGGAUU	57	UCCAGGGCCCGUUUUGGUCUU	1560
D-1053	1047-1065	930-948	ACCAAAACGGGCCCUGGAAUU	58	UUCCAGGGCCCGUUUUGGUUU	1561
D-1054	1048-1066	931-949	CCAAAACGGGCCCUGGAAGUU	59	CUUCCAGGGCCCGUUUUGGUU	1562
D-1055	1049-1067	932-950	CAAAACGGGCCCUGGAAGUUU	60	ACUUCCAGGGCCCGUUUUGUU	1563
D-1056	1050-1068	933-951	AAAACGGGCCCUGGAAGUGUU	61	CACUUCCAGGGCCCGUUUUUU	1564
D-1057	1051-1069	934-952	AAACGGGCCCUGGAAGUGGUU	62	CCACUUCCAGGGCCCGUUUUU	1565
D-1058	105-123	105-123	CCACACUCCCCUAAGUUCCUU	63	GGAACUUAGGGGAGUGUGGGUU	1566
D-1059	1052-1070	935-953	AACGGGCCCUGGAAGUGGGUU	64	CCCACUUCCAGGGCCCGUUUU	1567
D-1060	1053-1071	936-954	ACGGGCCCUGGAAGUGGGUUU	65	ACCCACUUCCAGGGCCCGUUU	1568
D-1061	1054-1072	937-955	CGGGCCCUGGAAGUGGGUGUU	66	CACCCACUUCCAGGGCCCGUU	1569
D-1062	1055-1073	938-956	GGGCCCUGGAAGUGGGUGGUU	67	CCACCCACUUCCAGGGCCCUU	1570
D-1063	1056-1074	939-957	GGCCCUGGAAGUGGGUGGAUU	68	UCCACCCACUUCCAGGGCCUU	1571
D-1064	1057-1075	940-958	GCCCUGGAAGUGGGUGGACUU	69	GUCCACCCACUUCCAGGGCUU	1572
D-1065	1058-1076	941-959	CCCUGGAAGUGGGUGGACGUU	70	CGUCCACCCACUUCCAGGGUU	1573

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1066	1059-1077	942-960	CCUGGAAGUGGGUGGACGGUU	71	CCGUCCACCCACUUCCAGGUU	1574
D-1067	1060-1078	943-961	CUGGAAGUGGGUGGACGGGUU	72	CCCGUCCACCCACUUCCAGUU	1575
D-1068	1061-1079	944-962	UGGAAGUGGGUGGACGGGAUU	73	UCCCGUCCACCCACUUCCAUU	1576
D-1069	106-124	106-124	CACACUCCCCUAAGUUCCAUU	74	UGGAACUUAGGGGAGUGUGUU	1577
D-1070	1062-1080	945-963	GGAAGUGGGUGGACGGGACUU	75	GUCCCGUCCACCCACUUCCUU	1578
D-1071	1063-1081	946-964	GAAGUGGGUGGACGGGACGUU	76	CGUCCCGUCCACCCACUUCUU	1579
D-1072	1064-1082	947-965	AAGUGGGUGGACGGGACGGUU	77	CCGUCCCGUCCACCCACUUUU	1580
D-1073	1065-1083	948-966	AGUGGGUGGACGGGACGGAUU	78	UCCGUCCCGUCCACCCACUUU	1581
D-1074	1066-1084	949-967	GUGGGUGGACGGGACGGACUU	79	GUCCGUCCCGUCCACCCACUU	1582
D-1075	1067-1085	950-968	UGGGUGGACGGGACGGACUUU	80	AGUCCGUCCCGUCCACCCAUU	1583
D-1076	1068-1086	951-969	GGGUGGACGGGACGGACUAUU	81	UAGUCCGUCCCGUCCACCCUU	1584
D-1077	1069-1087	952-970	GGUGGACGGGACGGACUACUU	82	GUAGUCCGUCCCGUCCACCUU	1585
D-1078	1070-1088	953-971	GUGGACGGGACGGACUACGUU	83	CGUAGUCCGUCCCGUCCACUU	1586
D-1079	1071-1089	954-972	UGGACGGGACGGACUACGAUU	84	UCGUAGUCCGUCCCGUCCAUU	1587
D-1080	107-125	107-125	ACACUCCCCUAAGUUCCAAUU	85	UUGGAACUUAGGGGAGUGUUU	1588
D-1081	1072-1090	955-973	GGACGGGACGGACUACGAGUU	86	CUCGUAGUCCGUCCCGUCCUU	1589
D-1082	1073-1091	956-974	GACGGGACGGACUACGAGAUU	87	UCUCGUAGUCCGUCCCGUCUU	1590
D-1083	1074-1092	957-975	ACGGGACGGACUACGAGACUU	88	GUCUCGUAGUCCGUCCCGUUU	1591
D-1084	1075-1093	958-976	CGGGACGGACUACGAGACGUU	89	CGUCUCGUAGUCCGUCCCGUU	1592
D-1085	1076-1094	959-977	GGGACGGACUACGAGACGGUU	90	CCGUCUCGUAGUCCGUCCCUU	1593
D-1086	1077-1095	960-978	GGACGGACUACGAGACGGGUU	91	CCCGUCUCGUAGUCCGUCCUU	1594
D-1087	1078-1096	961-979	GACGGACUACGAGACGGGCUU	92	GCCCGUCUCGUAGUCCGUCUU	1595
D-1088	1079-1097	962-980	ACGGACUACGAGACGGGCUUU	93	AGCCCGUCUCGUAGUCCGUUU	1596
D-1089	1080-1098	963-981	CGGACUACGAGACGGGCUUUU	94	AAGCCCGUCUCGUAGUCCGUU	1597
D-1090	1081-1099	964-982	GGACUACGAGACGGGCUUCUU	95	GAAGCCCGUCUCGUAGUCCUU	1598
D-1091	108-126	108-126	CACUCCCCUAAGUUCCAAUUU	96	AUUGGAACUUAGGGGAGUGUU	1599

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1092	1082-1100	965-983	GACUACGAGACGGGCUUCAUU	97	UGAAGCCCGUCUCGUAGUCUU	1600
D-1093	1083-1101	966-984	ACUACGAGACGGGCUUCAAUU	98	UUGAAGCCCGUCUCGUAGUUU	1601
D-1094	1084-1102	967-985	CUACGAGACGGGCUUCAAGUU	99	CUUGAAGCCCGUCUCGUAGUU	1602
D-1095	1085-1103	968-986	UACGAGACGGGCUUCAAGAUU	100	UCUUGAAGCCCGUCUCGUAUU	1603
D-1096	1086-1104	969-987	ACGAGACGGGCUUCAAGAAUU	101	UUCUUGAAGCCCGUCUCGUUU	1604
D-1097	1087-1105	970-988	CGAGACGGGCUUCAAGAACUU	102	GUUCUUGAAGCCCGUCUCGUU	1605
D-1098	1088-1106	971-989	GAGACGGGCUUCAAGAACUUU	103	AGUUCUUGAAGCCCGUCUCUU	1606
D-1099	1089-1107	972-990	AGACGGGCUUCAAGAACUGUU	104	CAGUUCUUGAAGCCCGUCUUU	1607
D-1100	1090-1108	973-991	GACGGGCUUCAAGAACUGGUU	105	CCAGUUCUUGAAGCCCGUCUU	1608
D-1101	1091-1109	974-992	ACGGGCUUCAAGAACUGGAUU	106	UCCAGUUCUUGAAGCCCGUUU	1609
D-1102	109-127	109-127	ACUCCCCUAAGUUCCAAUCUU	107	GAUUGGAACUUAGGGGAGUUU	1610
D-1103	1092-1110	975-993	CGGGCUUCAAGAACUGGAGUU	108	CUCCAGUUCUUGAAGCCCGUU	1611
D-1104	1093-1111	976-994	GGGCUUCAAGAACUGGAGGUU	109	CCUCCAGUUCUUGAAGCCCUU	1612
D-1105	1094-1112	977-995	GGCUUCAAGAACUGGAGGCUU	110	GCCUCCAGUUCUUGAAGCCUU	1613
D-1106	1095-1113	978-996	GCUUCAAGAACUGGAGGCCUU	111	GGCCUCCAGUUCUUGAAGCUU	1614
D-1107	1096-1114	979-997	CUUCAAGAACUGGAGGCCGUU	112	CGGCCUCCAGUUCUUGAAGUU	1615
D-1108	1097-1115	980-998	UUCAAGAACUGGAGGCCGGUU	113	CCGGCCUCCAGUUCUUGAAUU	1616
D-1109	1098-1116	981-999	UCAAGAACUGGAGGCCGGAUU	114	UCCGGCCUCCAGUUCUUGAUU	1617
D-1110	1099-1117	982-1000	CAAGAACUGGAGGCCGGAGUU	115	CUCCGGCCUCCAGUUCUUGUU	1618
D-1111	1100-1118	983-1001	AAGAACUGGAGGCCGGAGCUU	116	GCUCCGGCCUCCAGUUCUUUU	1619
D-1112	1101-1119	984-1002	AGAACUGGAGGCCGGAGCAUU	117	UGCUCCGGCCUCCAGUUCUUU	1620
D-1113	110-128	110-128	CUCCCCUAAGUUCCAAUCCUU	118	GGAUUGGAACUUAGGGGAGUU	1621
D-1114	1102-1120	985-1003	GAACUGGAGGCCGGAGCAGUU	119	CUGCUCCGGCCUCCAGUUCUU	1622
D-1115	1103-1121	986-1004	AACUGGAGGCCGGAGCAGCUU	120	GCUGCUCCGGCCUCCAGUUUU	1623
D-1116	1104-1122	987-1005	ACUGGAGGCCGGAGCAGCCUU	121	GGCUGCUCCGGCCUCCAGUUU	1624

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1117	1105-1123	988-1006	CUGGAGGCCGGAGCAGCCGUU	122	CGGCUGCUCCGGCCUCCAGUU	1625
D-1118	1106-1124	989-1007	UGGAGGCCGGAGCAGCCGGUU	123	CCGGCUGCUCCGGCCUCCAUU	1626
D-1119	1107-1125	990-1008	GGAGGCCGGAGCAGCCGGAUU	124	UCCGGCUGCUCCGGCCUCCUU	1627
D-1120	1108-1126	991-1009	GAGGCCGGAGCAGCCGGACUU	125	GUCCGGCUGCUCCGGCCUCUU	1628
D-1121	1109-1127	992-1010	AGGCCGGAGCAGCCGGACGUU	126	CGUCCGGCUGCUCCGGCCUUU	1629
D-1122	1110-1128	993-1011	GGCCGGAGCAGCCGGACGAUU	127	UCGUCCGGCUGCUCCGGCCUU	1630
D-1123	1111-1129	994-1012	GCCGGAGCAGCCGGACGACUU	128	GUCGUCCGGCUGCUCCGGCUU	1631
D-1124	111-129	111-129	UCCCCUAAGUUCCAAUCCAUU	129	UGGAUUGGAACUUAGGGGAUU	1632
D-1125	1112-1130	995-1013	CCGGAGCAGCCGGACGACUUU	130	AGUCGUCCGGCUGCUCCGGUU	1633
D-1126	1113-1131	996-1014	CGGAGCAGCCGGACGACUGUU	131	CAGUCGUCCGGCUGCUCCGUU	1634
D-1127	1114-1132	997-1015	GGAGCAGCCGGACGACUGGUU	132	CCAGUCGUCCGGCUGCUCCUU	1635
D-1128	1115-1133	998-1016	GAGCAGCCGGACGACUGGUUU	133	ACCAGUCGUCCGGCUGCUCUU	1636
D-1129	1116-1134	999-1017	AGCAGCCGGACGACUGGUAUU	134	UACCAGUCGUCCGGCUGCUUU	1637
D-1130	1117-1135	1000-1018	GCAGCCGGACGACUGGUACUU	135	GUACCAGUCGUCCGGCUGCUU	1638
D-1131	1118-1136	1001-1019	CAGCCGGACGACUGGUACGUU	136	CGUACCAGUCGUCCGGCUGUU	1639
D-1132	1119-1137	1002-1020	AGCCGGACGACUGGUACGGUU	137	CCGUACCAGUCGUCCGGCUUU	1640
D-1133	1120-1138	1003-1021	GCCGGACGACUGGUACGGCUU	138	GCCGUACCAGUCGUCCGGCUU	1641
D-1134	1121-1139	1004-1022	CCGGACGACUGGUACGGCCUU	139	GGCCGUACCAGUCGUCCGGUU	1642
D-1135	112-130	112-130	CCCCUAAGUUCCAAUCCAUUU	140	AUGGAUUGGAACUUAGGGGUU	1643
D-1136	1122-1140	1005-1023	CGGACGACUGGUACGGCCAUU	141	UGGCCGUACCAGUCGUCCGUU	1644
D-1137	1123-1141	1006-1024	GGACGACUGGUACGGCCACUU	142	GUGGCCGUACCAGUCGUCCUU	1645
D-1138	1124-1142	1007-1025	GACGACUGGUACGGCCACGUU	143	CGUGGCCGUACCAGUCGUCUU	1646
D-1139	1125-1143	1008-1026	ACGACUGGUACGGCCACGGUU	144	CCGUGGCCGUACCAGUCGUUU	1647
D-1140	1126-1144	1009-1027	CGACUGGUACGGCCACGGGUU	145	CCCGUGGCCGUACCAGUCGUU	1648
D-1141	1127-1145	1010-1028	GACUGGUACGGCCACGGGCUU	146	GCCCGUGGCCGUACCAGUCUU	1649

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1142	1128-1146	1011-1029	ACUGGUACGGCCACGGGCUUU	147	AGCCCGUGGCCGUACCAGUUU	1650
D-1143	11-29	11-29	GCACGGAAGAGUGAGGUGAUU	148	UCACCUCACUCUUCCGUGCUU	1651
D-1144	1129-1147	1012-1030	CUGGUACGGCCACGGGCUCUU	149	GAGCCCGUGGCCGUACCAGUU	1652
D-1145	1130-1148	1013-1031	UGGUACGGCCACGGGCUCGUU	150	CGAGCCCGUGGCCGUACCAUU	1653
D-1146	1131-1149	1014-1032	GGUACGGCCACGGGCUCGGUU	151	CCGAGCCCGUGGCCGUACCUU	1654
D-1147	113-131	113-131	CCCUAAGUUCCAAUCCAUUUU	152	AAUGGAUUGGAACUUAGGGUU	1655
D-1148	1132-1150	1015-1033	GUACGGCCACGGGCUCGGAUU	153	UCCGAGCCCGUGGCCGUACUU	1656
D-1149	1133-1151	1016-1034	UACGGCCACGGGCUCGGAGUU	154	CUCCGAGCCCGUGGCCGUAUU	1657
D-1150	1134-1152	1017-1035	ACGGCCACGGGCUCGGAGGUU	155	CCUCCGAGCCCGUGGCCGUUU	1658
D-1151	1135-1153	1018-1036	CGGCCACGGGCUCGGAGGAUU	156	UCCUCCGAGCCCGUGGCCGUU	1659
D-1152	1136-1154	1019-1037	GGCCACGGGCUCGGAGGAGUU	157	CUCCUCCGAGCCCGUGGCCUU	1660
D-1153	1137-1155	1020-1038	GCCACGGGCUCGGAGGAGGUU	158	CCUCCUCCGAGCCCGUGGCUU	1661
D-1154	1138-1156	1021-1039	CCACGGGCUCGGAGGAGGCUU	159	GCCUCCUCCGAGCCCGUGGUU	1662
D-1155	1139-1157	1022-1040	CACGGGCUCGGAGGAGGCGUU	160	CGCCUCCUCCGAGCCCGUGUU	1663
D-1156	1140-1158	1023-1041	ACGGGCUCGGAGGAGGCGAUU	161	UCGCCUCCUCCGAGCCCGUUU	1664
D-1157	1141-1159	1024-1042	CGGGCUCGGAGGAGGCGAGUU	162	CUCGCCUCCUCCGAGCCCGUU	1665
D-1158	114-132	114-132	CCUAAGUUCCAAUCCAUUUUU	163	AAAUGGAUUGGAACUUAGGUU	1666
D-1159	1142-1160	1025-1043	GGGCUCGGAGGAGGCGAGGUU	164	CCUCGCCUCCUCCGAGCCCUU	1667
D-1160	1143-1161	1026-1044	GGCUCGGAGGAGGCGAGGAUU	165	UCCUCGCCUCCUCCGAGCCUU	1668
D-1161	1144-1162	1027-1045	GCUCGGAGGAGGCGAGGACUU	166	GUCCUCGCCUCCUCCGAGCUU	1669
D-1162	1145-1163	1028-1046	CUCGGAGGAGGCGAGGACUUU	167	AGUCCUCGCCUCCUCCGAGUU	1670
D-1163	1146-1164	1029-1047	UCGGAGGAGGCGAGGACUGUU	168	CAGUCCUCGCCUCCUCCGAUU	1671
D-1164	1147-1165	1030-1048	CGGAGGAGGCGAGGACUGUUU	169	ACAGUCCUCGCCUCCUCCGUU	1672
D-1165	1148-1166	1031-1049	GGAGGAGGCGAGGACUGUGUU	170	CACAGUCCUCGCCUCCUCCUU	1673
D-1166	1149-1167	1032-1050	GAGGAGGCGAGGACUGUGCUU	171	GCACAGUCCUCGCCUCCUCUU	1674
D-1167	1150-1168	1033-1051	AGGAGGCGAGGACUGUGCCUU	172	GGCACAGUCCUCGCCUCCUUU	1675

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1168	1151-1169	1034-1052	GGAGGCGAGGACUGUGCCCUU	173	GGGCACAGUCCUCGCCUCCUU	1676
D-1169	115-133	115-133	CUAAGUUCCAAUCCAUUUCUU	174	GAAAUGGAUUGGAACUUAGUU	1677
D-1170	1152-1170	1035-1053	GAGGCGAGGACUGUGCCCAUU	175	UGGGCACAGUCCUCGCCUCUU	1678
D-1171	1153-1171	1036-1054	AGGCGAGGACUGUGCCCACUU	176	GUGGGCACAGUCCUCGCCUUU	1679
D-1172	1154-1172	1037-1055	GGCGAGGACUGUGCCCACUUU	177	AGUGGGCACAGUCCUCGCCUU	1680
D-1173	1155-1173	1038-1056	GCGAGGACUGUGCCCACUUUU	178	AAGUGGGCACAGUCCUCGCUU	1681
D-1174	1156-1174	1039-1057	CGAGGACUGUGCCCACUUCUU	179	GAAGUGGGCACAGUCCUCGUU	1682
D-1175	1157-1175	1040-1058	GAGGACUGUGCCCACUUCAUU	180	UGAAGUGGGCACAGUCCUCUU	1683
D-1176	1158-1176	1041-1059	AGGACUGUGCCCACUUCACUU	181	GUGAAGUGGGCACAGUCCUUU	1684
D-1177	1159-1177	1042-1060	GGACUGUGCCCACUUCACCUU	182	GGUGAAGUGGGCACAGUCCUU	1685
D-1178	1160-1178	1043-1061	GACUGUGCCCACUUCACCGUU	183	CGGUGAAGUGGGCACAGUCUU	1686
D-1179	1161-1179	1044-1062	ACUGUGCCCACUUCACCGAUU	184	UCGGUGAAGUGGGCACAGUUU	1687
D-1180	116-134	116-134	UAAGUUCCAAUCCAUUUCCUU	185	GGAAAUGGAUUGGAACUUAUU	1688
D-1181	1162-1180	1045-1063	CUGUGCCCACUUCACCGACUU	186	GUCGGUGAAGUGGGCACAGUU	1689
D-1182	1163-1181	1046-1064	UGUGCCCACUUCACCGACGUU	187	CGUCGGUGAAGUGGGCACAUU	1690
D-1183	1164-1182	1047-1065	GUGCCCACUUCACCGACGAUU	188	UCGUCGGUGAAGUGGGCACUU	1691
D-1184	1165-1183	1048-1066	UGCCCACUUCACCGACGACUU	189	GUCGUCGGUGAAGUGGGCAUU	1692
D-1185	1166-1184	1049-1067	GCCCACUUCACCGACGACGUU	190	CGUCGUCGGUGAAGUGGGCUU	1693
D-1186	1167-1185	1050-1068	CCCACUUCACCGACGACGGUU	191	CCGUCGUCGGUGAAGUGGGUU	1694
D-1187	1168-1186	1051-1069	CCACUUCACCGACGACGGCUU	192	GCCGUCGUCGGUGAAGUGGUU	1695
D-1188	1169-1187	1052-1070	CACUUCACCGACGACGGCCUU	193	GGCCGUCGUCGGUGAAGUGUU	1696
D-1189	1170-1188	1053-1071	ACUUCACCGACGACGGCCGUU	194	CGGCCGUCGUCGGUGAAGUUU	1697
D-1190	1171-1189	1054-1072	CUUCACCGACGACGGCCGCUU	195	GCGGCCGUCGUCGGUGAAGUU	1698
D-1191	117-135	117-135	AAGUUCCAAUCCAUUUCCAUU	196	UGGAAAUGGAUUGGAACUUUU	1699
D-1192	1172-1190	1055-1073	UUCACCGACGACGGCCGCUUU	197	AGCGGCCGUCGUCGGUGAAUU	1700
D-1193	1173-1191	1056-1074	UCACCGACGACGGCCGCUGUU	198	CAGCGGCCGUCGUCGGUGAUU	1701

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1194	1174-1192	1057-1075	CACCGACGACGGCCGCUGGUU	199	CCAGCGGCCGUCGUCGGUGUU	1702
D-1195	1175-1193	1058-1076	ACCGACGACGGCCGCUGGAUU	200	UCCAGCGGCCGUCGUCGGUUU	1703
D-1196	1176-1194	1059-1077	CCGACGACGGCCGCUGGAAUU	201	UUCCAGCGGCCGUCGUCGGUU	1704
D-1197	1177-1195	1060-1078	CGACGACGGCCGCUGGAACUU	202	GUUCCAGCGGCCGUCGUCGUU	1705
D-1198	1178-1196	1061-1079	GACGACGGCCGCUGGAACGUU	203	CGUUCCAGCGGCCGUCGUCUU	1706
D-1199	1179-1197	1062-1080	ACGACGGCCGCUGGAACGAUU	204	UCGUUCCAGCGGCCGUCGUUU	1707
D-1200	1180-1198	1063-1081	CGACGGCCGCUGGAACGACUU	205	GUCGUUCCAGCGGCCGUCGUU	1708
D-1201	1181-1199	1064-1082	GACGGCCGCUGGAACGACGUU	206	CGUCGUUCCAGCGGCCGUCUU	1709
D-1202	118-136	118-136	AGUUCCAAUCCAUUUCCACUU	207	GUGGAAAUGGAUUGGAACUUU	1710
D-1203	1182-1200	1065-1083	ACGGCCGCUGGAACGACGAUU	208	UCGUCGUUCCAGCGGCCGUUU	1711
D-1204	1183-1201	1066-1084	CGGCCGCUGGAACGACGACUU	209	GUCGUCGUUCCAGCGGCCGUU	1712
D-1205	1184-1202	1067-1085	GGCCGCUGGAACGACGACGUU	210	CGUCGUCGUUCCAGCGGCCUU	1713
D-1206	1185-1203	1068-1086	GCCGCUGGAACGACGACGUUU	211	ACGUCGUCGUUCCAGCGGCUU	1714
D-1207	1186-1204	1069-1087	CCGCUGGAACGACGACGUCUU	212	GACGUCGUCGUUCCAGCGGUU	1715
D-1208	1187-1205	1070-1088	CGCUGGAACGACGACGUCUUU	213	AGACGUCGUCGUUCCAGCGUU	1716
D-1209	1188-1206	1071-1089	GCUGGAACGACGACGUCUGUU	214	CAGACGUCGUCGUUCCAGCUU	1717
D-1210	1189-1207	1072-1090	CUGGAACGACGACGUCUGCUU	215	GCAGACGUCGUCGUUCCAGUU	1718
D-1211	1-19	1-19	CCCAAACGGUGCACGGAAGUU	216	CUUCCGUGCACCGUUUGGGUU	1719
D-1212	1190-1208	1073-1091	UGGAACGACGACGUCUGCCUU	217	GGCAGACGUCGUCGUUCCAUU	1720
D-1213	1191-1209	1074-1092	GGAACGACGACGUCUGCCAUU	218	UGGCAGACGUCGUCGUUCCUU	1721
D-1214	119-137	119-137	GUUCCAAUCCAUUUCCACCUU	219	GGUGGAAAUGGAUUGGAACUU	1722
D-1215	1192-1210	1075-1093	GAACGACGACGUCUGCCAGUU	220	CUGGCAGACGUCGUCGUUCUU	1723
D-1216	1193-1211	1076-1094	AACGACGACGUCUGCCAGAUU	221	UCUGGCAGACGUCGUCGUUUU	1724
D-1217	1194-1212	1077-1095	ACGACGACGUCUGCCAGAGUU	222	CUCUGGCAGACGUCGUCGUUU	1725
D-1218	1195-1213	1078-1096	CGACGACGUCUGCCAGAGGUU	223	CCUCUGGCAGACGUCGUCGUU	1726
D-1219	1196-1214	1079-1097	GACGACGUCUGCCAGAGGCUU	224	GCCUCUGGCAGACGUCGUCUU	1727

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1220	1197-1215	1080-1098	ACGACGUCUGCCAGAGGCCUU	225	GGCCUCUGGCAGACGUCGUUU	1728
D-1221	1198-1216	1081-1099	CGACGUCUGCCAGAGGCCCUU	226	GGGCCUCUGGCAGACGUCGUU	1729
D-1222	1199-1217	1082-1100	GACGUCUGCCAGAGGCCCUUU	227	AGGGCCUCUGGCAGACGUCUU	1730
D-1223	1200-1218	1083-1101	ACGUCUGCCAGAGGCCCUAUU	228	UAGGGCCUCUGGCAGACGUUU	1731
D-1224	1201-1219	1084-1102	CGUCUGCCAGAGGCCCUACUU	229	GUAGGGCCUCUGGCAGACGUU	1732
D-1225	120-138	120-138	UUCCAAUCCAUUUCCACCUUU	230	AGGUGGAAAUGGAUUGGAAUU	1733
D-1226	1202-1220	1085-1103	GUCUGCCAGAGGCCCUACCUU	231	GGUAGGGCCUCUGGCAGACUU	1734
D-1227	1203-1221	1086-1104	UCUGCCAGAGGCCCUACCGUU	232	CGGUAGGGCCUCUGGCAGAUU	1735
D-1228	1204-1222	1087-1105	CUGCCAGAGGCCCUACCGCUU	233	GCGGUAGGGCCUCUGGCAGUU	1736
D-1229	1205-1223	1088-1106	UGCCAGAGGCCCUACCGCUUU	234	AGCGGUAGGGCCUCUGGCAUU	1737
D-1230	1206-1224	1089-1107	GCCAGAGGCCCUACCGCUGUU	235	CAGCGGUAGGGCCUCUGGCUU	1738
D-1231	1207-1225	1090-1108	CCAGAGGCCCUACCGCUGGUU	236	CCAGCGGUAGGGCCUCUGGUU	1739
D-1232	1208-1226	1091-1109	CAGAGGCCCUACCGCUGGGUU	237	CCCAGCGGUAGGGCCUCUGUU	1740
D-1233	1209-1227	1092-1110	AGAGGCCCUACCGCUGGGUUU	238	ACCCAGCGGUAGGGCCUCUUU	1741
D-1234	1210-1228	1093-1111	GAGGCCCUACCGCUGGGUCUU	239	GACCCAGCGGUAGGGCCUCUU	1742
D-1235	1211-1229	1094-1112	AGGCCCUACCGCUGGGUCUUU	240	AGACCCAGCGGUAGGGCCUUU	1743
D-1236	121-139	121-139	UCCAAUCCAUUUCCACCUCUU	241	GAGGUGGAAAUGGAUUGGAUU	1744
D-1237	1212-1230	1095-1113	GGCCCUACCGCUGGGUCUGUU	242	CAGACCCAGCGGUAGGGCCUU	1745
D-1238	1213-1231	1096-1114	GCCCUACCGCUGGGUCUGCUU	243	GCAGACCCAGCGGUAGGGCUU	1746
D-1239	1214-1232	1097-1115	CCCUACCGCUGGGUCUGCGUU	244	CGCAGACCCAGCGGUAGGGUU	1747
D-1240	1215-1233	1098-1116	CCUACCGCUGGGUCUGCGAUU	245	UCGCAGACCCAGCGGUAGGUU	1748
D-1241	1216-1234	1099-1117	CUACCGCUGGGUCUGCGAGUU	246	CUCGCAGACCCAGCGGUAGUU	1749
D-1242	1217-1235	1100-1118	UACCGCUGGGUCUGCGAGAUU	247	UCUCGCAGACCCAGCGGUAUU	1750
D-1243	1218-1236	1101-1119	ACCGCUGGGUCUGCGAGACUU	248	GUCUCGCAGACCCAGCGGUUU	1751
D-1244	1219-1237	1102-1120	CCGCUGGGUCUGCGAGACAUU	249	UGUCUCGCAGACCCAGCGGUU	1752

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1245	1220-1238	1103-1121	CGCUGGGUCUGCGAGACAGUU	250	CUGUCUCGCAGACCCAGCGUU	1753
D-1246	1221-1239	1104-1122	GCUGGGUCUGCGAGACAGAUU	251	UCUGUCUCGCAGACCCAGCUU	1754
D-1247	122-140	122-140	CCAAUCCAUUUCCACCUCUUU	252	AGAGGUGGAAAUGGAUUGGUU	1755
D-1248	1222-1240	1105-1123	CUGGGUCUGCGAGACAGAGUU	253	CUCUGUCUCGCAGACCCAGUU	1756
D-1249	1223-1241	1106-1124	UGGGUCUGCGAGACAGAGCUU	254	GCUCUGUCUCGCAGACCCAUU	1757
D-1250	1224-1242	1107-1125	GGGUCUGCGAGACAGAGCUUU	255	AGCUCUGUCUCGCAGACCCUU	1758
D-1251	1225-1243	1108-1126	GGUCUGCGAGACAGAGCUGUU	256	CAGCUCUGUCUCGCAGACCUU	1759
D-1252	1226-1244	1109-1127	GUCUGCGAGACAGAGCUGGUU	257	CCAGCUCUGUCUCGCAGACUU	1760
D-1253	1227-1245	1110-1128	UCUGCGAGACAGAGCUGGAUU	258	UCCAGCUCUGUCUCGCAGAUU	1761
D-1254	1228-1246	1111-1129	CUGCGAGACAGAGCUGGACUU	259	GUCCAGCUCUGUCUCGCAGUU	1762
D-1255	1229-1247	1112-1130	UGCGAGACAGAGCUGGACAUU	260	UGUCCAGCUCUGUCUCGCAUU	1763
D-1256	12-30	12-30	CACGGAAGAGUGAGGUGACUU	261	GUCACCUCACUCUUCCGUGUU	1764
D-1257	1230-1248	1113-1131	GCGAGACAGAGCUGGACAAUU	262	UUGUCCAGCUCUGUCUCGCUU	1765
D-1258	1231-1249	1114-1132	CGAGACAGAGCUGGACAAGUU	263	CUUGUCCAGCUCUGUCUCGUU	1766
D-1259	123-141	123-141	CAAUCCAUUUCCACCUCUGUU	264	CAGAGGUGGAAAUGGAUUGUU	1767
D-1260	1232-1250	1115-1133	GAGACAGAGCUGGACAAGGUU	265	CCUUGUCCAGCUCUGUCUCUU	1768
D-1261	1233-1251	1116-1134	AGACAGAGCUGGACAAGGCUU	266	GCCUUGUCCAGCUCUGUCUUU	1769
D-1262	1234-1252	1117-1135	GACAGAGCUGGACAAGGCCUU	267	GGCCUUGUCCAGCUCUGUCUU	1770
D-1263	1235-1253	1118-1136	ACAGAGCUGGACAAGGCCAUU	268	UGGCCUUGUCCAGCUCUGUUU	1771
D-1264	1236-1254	1119-1137	CAGAGCUGGACAAGGCCAGUU	269	CUGGCCUUGUCCAGCUCUGUU	1772
D-1265	1237-1255	1120-1138	AGAGCUGGACAAGGCCAGCUU	270	GCUGGCCUUGUCCAGCUCUUU	1773
D-1266	1238-1256	1121-1139	GAGCUGGACAAGGCCAGCCUU	271	GGCUGGCCUUGUCCAGCUCUU	1774
D-1267	1239-1257	1122-1140	AGCUGGACAAGGCCAGCCAUU	272	UGGCUGGCCUUGUCCAGCUUU	1775
D-1268	1240-1258	1123-1141	GCUGGACAAGGCCAGCCAGUU	273	CUGGCUGGCCUUGUCCAGCUU	1776
D-1269	1241-1259	1124-1142	CUGGACAAGGCCAGCCAGGUU	274	CCUGGCUGGCCUUGUCCAGUU	1777
D-1270	124-142	124-142	AAUCCAUUUCCACCUCUGUUU	275	ACAGAGGUGGAAAUGGAUUUU	1778

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1271	1242-1260	1125-1143	UGGACAAGGCCAGCCAGGAUU	276	UCCUGGCUGGCCUUGUCCAUU	1779
D-1272	1243-1261	1126-1144	GGACAAGGCCAGCCAGGAGUU	277	CUCCUGGCUGGCCUUGUCCUU	1780
D-1273	1244-1262	1127-1145	GACAAGGCCAGCCAGGAGCUU	278	GCUCCUGGCUGGCCUUGUCUU	1781
D-1274	1245-1263	1128-1146	ACAAGGCCAGCCAGGAGCCUU	279	GGCUCCUGGCUGGCCUUGUUU	1782
D-1275	1246-1264	1129-1147	CAAGGCCAGCCAGGAGCCAUU	280	UGGCUCCUGGCUGGCCUUGUU	1783
D-1276	1247-1265	1130-1148	AAGGCCAGCCAGGAGCCACUU	281	GUGGCUCCUGGCUGGCCUUUU	1784
D-1277	1248-1266	1131-1149	AGGCCAGCCAGGAGCCACCUU	282	GGUGGCUCCUGGCUGGCCUUU	1785
D-1278	1249-1267	1132-1150	GGCCAGCCAGGAGCCACCUUU	283	AGGUGGCUCCUGGCUGGCCUU	1786
D-1279	1250-1268	1133-1151	GCCAGCCAGGAGCCACCUCUU	284	GAGGUGGCUCCUGGCUGGCUU	1787
D-1280	1251-1269	1134-1152	CCAGCCAGGAGCCACCUCUUU	285	AGAGGUGGCUCCUGGCUGGUU	1788
D-1281	125-143	125-143	AUCCAUUUCCACCUCUGUUUU	286	AACAGAGGUGGAAAUGGAUUU	1789
D-1282	1252-1270	1135-1153	CAGCCAGGAGCCACCUCUCUU	287	GAGAGGUGGCUCCUGGCUGUU	1790
D-1283	1253-1271	1136-1154	AGCCAGGAGCCACCUCUCCUU	288	GGAGAGGUGGCUCCUGGCUUU	1791
D-1284	1254-1272	1137-1155	GCCAGGAGCCACCUCUCCUUU	289	AGGAGAGGUGGCUCCUGGCUU	1792
D-1285	1255-1273	1138-1156	CCAGGAGCCACCUCUCCUUUU	290	AAGGAGAGGUGGCUCCUGGUU	1793
D-1286	1256-1274	1139-1157	CAGGAGCCACCUCUCCUUUUU	291	AAAGGAGAGGUGGCUCCUGUU	1794
D-1287	1257-1275	1140-1158	AGGAGCCACCUCUCCUUUAUU	292	UAAAGGAGAGGUGGCUCCUUU	1795
D-1288	1258-1276	1141-1159	GGAGCCACCUCUCCUUUAAUU	293	UUAAAGGAGAGGUGGCUCCUU	1796
D-1289	1259-1277	1142-1160	GAGCCACCUCUCCUUUAAUUU	294	AUUAAAGGAGAGGUGGCUCUU	1797
D-1290	1260-1278	1143-1161	AGCCACCUCUCCUUUAAUUUU	295	AAUUAAAGGAGAGGUGGCUUU	1798
D-1291	1261-1279	1144-1162	GCCACCUCUCCUUUAAUUUUU	296	AAAUUAAAGGAGAGGUGGCUU	1799
D-1292	126-144	126-144	UCCAUUUCCACCUCUGUUUUU	297	AAACAGAGGUGGAAAUGGAUU	1800
D-1293	1262-1280	1145-1163	CCACCUCUCCUUUAAUUUAUU	298	UAAAUUAAAGGAGAGGUGGUU	1801
D-1294	1263-1281	1146-1164	CACCUCUCCUUUAAUUUAUUU	299	AUAAAUUAAAGGAGAGGUGUU	1802
D-1295	1264-1282	1147-1165	ACCUCUCCUUUAAUUUAUUUU	300	AAUAAAUUAAAGGAGAGGUUU	1803

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1296	1265-1283	1148-1166	CCUCUCCUUUAAUUUAUUUUU	301	AAAUAAAUUAAAGGAGAGGUU	1804
D-1297	1266-1284	1149-1167	CUCUCCUUUAAUUUAUUUCUU	302	GAAAUAAAUUAAAGGAGAGUU	1805
D-1298	1267-1285	1150-1168	UCUCCUUUAAUUUAUUUCUUU	303	AGAAAUAAAUUAAAGGAGAUU	1806
D-1299	1268-1286	1151-1169	CUCCUUUAAUUUAUUUCUUUU	304	AAGAAAUAAAUUAAAGGAGUU	1807
D-1300	1269-1287	1152-1170	UCCUUUAAUUUAUUUCUUCUU	305	GAAGAAAUAAAUUAAAGGAUU	1808
D-1301	1270-1288	1153-1171	CCUUUAAUUUAUUUCUUCAUU	306	UGAAGAAAUAAAUUAAAGGUU	1809
D-1302	1271-1289	1154-1172	CUUUAAUUUAUUUCUUCAAUU	307	UUGAAGAAAUAAAUUAAAGUU	1810
D-1303	127-145	127-145	CCAUUUCCACCUCUGUUUAUU	308	UAAACAGAGGUGGAAAUGGUU	1811
D-1304	1272-1290	1155-1173	UUUAAUUUAUUUCUUCAAUUU	309	AUUGAAGAAAUAAAUUAAAUU	1812
D-1305	1273-1291	1156-1174	UUAAUUUAUUUCUUCAAUGUU	310	CAUUGAAGAAAUAAAUUAAUU	1813
D-1306	1274-1292	1157-1175	UAAUUUAUUUCUUCAAUGCUU	311	GCAUUGAAGAAAUAAAUUAUU	1814
D-1307	1275-1293	1158-1176	AAUUUAUUUCUUCAAUGCCUU	312	GGCAUUGAAGAAAUAAAUUUU	1815
D-1308	1276-1294	1159-1177	AUUUAUUUCUUCAAUGCCUUU	313	AGGCAUUGAAGAAAUAAAUUU	1816
D-1309	1277-1295	1160-1178	UUUAUUUCUUCAAUGCCUCUU	314	GAGGCAUUGAAGAAAUAAAUU	1817
D-1310	1278-1296	1161-1179	UUAUUUCUUCAAUGCCUCGUU	315	CGAGGCAUUGAAGAAAUAAUU	1818
D-1311	1279-1297	1162-1180	UAUUUCUUCAAUGCCUCGAUU	316	UCGAGGCAUUGAAGAAAUAUU	1819
D-1312	1280-1298	1163-1181	AUUUCUUCAAUGCCUCGACUU	317	GUCGAGGCAUUGAAGAAAUUU	1820
D-1313	1281-1299	1164-1182	UUUCUUCAAUGCCUCGACCUU	318	GGUCGAGGCAUUGAAGAAAUU	1821
D-1314	128-146	128-146	CAUUUCCACCUCUGUUUACUU	319	GUAAACAGAGGUGGAAAUGUU	1822
D-1315	1282-1300	1165-1183	UUCUUCAAUGCCUCGACCUUU	320	AGGUCGAGGCAUUGAAGAAUU	1823
D-1316	1283-1301	1166-1184	UCUUCAAUGCCUCGACCUGUU	321	CAGGUCGAGGCAUUGAAGAUU	1824
D-1317	1284-1302	1167-1185	CUUCAAUGCCUCGACCUGCUU	322	GCAGGUCGAGGCAUUGAAGUU	1825
D-1318	1285-1303	1168-1186	UUCAAUGCCUCGACCUGCCUU	323	GGCAGGUCGAGGCAUUGAAUU	1826
D-1319	1286-1304	1169-1187	UCAAUGCCUCGACCUGCCGUU	324	CGGCAGGUCGAGGCAUUGAUU	1827
D-1320	1287-1305	1170-1188	CAAUGCCUCGACCUGCCGCUU	325	GCGGCAGGUCGAGGCAUUGUU	1828

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1321	1288-1306	1171-1189	AAUGCCUCGACCUGCCGCAUU	326	UGCGGCAGGUCGAGGCAUUUU	1829
D-1322	1289-1307	1172-1190	AUGCCUCGACCUGCCGCAGUU	327	CUGCGGCAGGUCGAGGCAUUU	1830
D-1323	1290-1308	1173-1191	UGCCUCGACCUGCCGCAGGUU	328	CCUGCGGCAGGUCGAGGCAUU	1831
D-1324	1291-1309	1174-1192	GCCUCGACCUGCCGCAGGGUU	329	CCCUGCGGCAGGUCGAGGCUU	1832
D-1325	129-147	129-147	AUUUCCACCUCUGUUUACUUU	330	AGUAAACAGAGGUGGAAAUUU	1833
D-1326	1292-1310	1175-1193	CCUCGACCUGCCGCAGGGGUU	331	CCCCUGCGGCAGGUCGAGGUU	1834
D-1327	1293-1311	1176-1194	CUCGACCUGCCGCAGGGGUUU	332	ACCCCUGCGGCAGGUCGAGUU	1835
D-1328	1294-1312	1177-1195	UCGACCUGCCGCAGGGGUCUU	333	GACCCCUGCGGCAGGUCGAUU	1836
D-1329	1295-1313	1178-1196	CGACCUGCCGCAGGGGUCCUU	334	GGACCCCUGCGGCAGGUCGUU	1837
D-1330	1296-1314	1179-1197	GACCUGCCGCAGGGGUCCGUU	335	CGGACCCCUGCGGCAGGUCUU	1838
D-1331	1297-1315	1180-1198	ACCUGCCGCAGGGGUCCGGUU	336	CCGGACCCCUGCGGCAGGUUU	1839
D-1332	1298-1316	1181-1199	CCUGCCGCAGGGGUCCGGGUU	337	CCCGGACCCCUGCGGCAGGUU	1840
D-1333	1299-1317	1182-1200	CUGCCGCAGGGGUCCGGGAUU	338	UCCCGGACCCCUGCGGCAGUU	1841
D-1334	1300-1318	1183-1201	UGCCGCAGGGGUCCGGGAUUU	339	AUCCCGGACCCCUGCGGCAUU	1842
D-1335	1301-1319	1184-1202	GCCGCAGGGGUCCGGGAUUUU	340	AAUCCCGGACCCCUGCGGCUU	1843
D-1336	130-148	130-148	UUUCCACCUCUGUUUACUGUU	341	CAGUAAACAGAGGUGGAAAUU	1844
D-1337	1302-1320	1185-1203	CCGCAGGGGUCCGGGAUUGUU	342	CAAUCCCGGACCCCUGCGGUU	1845
D-1338	1303-1321	1186-1204	CGCAGGGGUCCGGGAUUGGUU	343	CCAAUCCCGGACCCCUGCGUU	1846
D-1339	1304-1322	1187-1205	GCAGGGGUCCGGGAUUGGGUU	344	CCCAAUCCCGGACCCCUGCUU	1847
D-1340	1305-1323	1188-1206	CAGGGGUCCGGGAUUGGGAUU	345	UCCCAAUCCCGGACCCCUGUU	1848
D-1341	1306-1324	1189-1207	AGGGGUCCGGGAUUGGGAAUU	346	UUCCCAAUCCCGGACCCCUUU	1849
D-1342	1307-1325	1190-1208	GGGGUCCGGGAUUGGGAAUUU	347	AUUCCCAAUCCCGGACCCCUU	1850
D-1343	1308-1326	1191-1209	GGGUCCGGGAUUGGGAAUCUU	348	GAUUCCCAAUCCCGGACCCUU	1851
D-1344	1309-1327	1192-1210	GGUCCGGGAUUGGGAAUCCUU	349	GGAUUCCCAAUCCCGGACCUU	1852
D-1345	1310-1328	1193-1211	GUCCGGGAUUGGGAAUCCGUU	350	CGGAUUCCCAAUCCCGGACUU	1853

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1346	1311-1329	1194-1212	UCCGGGAUUGGGAAUCCGCUU	351	GCGGAUUCCCAAUCCCGGAUU	1854
D-1347	131-149	131-149	UUCCACCUCUGUUUACUGUUU	352	ACAGUAAACAGAGGUGGAAUU	1855
D-1348	1312-1330	1195-1213	CCGGGAUUGGGAAUCCGCCUU	353	GGCGGAUUCCCAAUCCCGGUU	1856
D-1349	1313-1331	1196-1214	CGGGAUUGGGAAUCCGCCCUU	354	GGGCGGAUUCCCAAUCCCGUU	1857
D-1350	1314-1332	1197-1215	GGGAUUGGGAAUCCGCCCAUU	355	UGGGCGGAUUCCCAAUCCCUU	1858
D-1351	1315-1333	1198-1216	GGAUUGGGAAUCCGCCCAUUU	356	AUGGGCGGAUUCCCAAUCCUU	1859
D-1352	1316-1334	1199-1217	GAUUGGGAAUCCGCCCAUCUU	357	GAUGGGCGGAUUCCCAAUCUU	1860
D-1353	1317-1335	1200-1218	AUUGGGAAUCCGCCCAUCUUU	358	AGAUGGGCGGAUUCCCAAUUU	1861
D-1354	1318-1336	1201-1219	UUGGGAAUCCGCCCAUCUGUU	359	CAGAUGGGCGGAUUCCCAAUU	1862
D-1355	1319-1337	1202-1220	UGGGAAUCCGCCCAUCUGGUU	360	CCAGAUGGGCGGAUUCCCAUU	1863
D-1356	1320-1338	1203-1221	GGGAAUCCGCCCAUCUGGGUU	361	CCCAGAUGGGCGGAUUCCCUU	1864
D-1357	1321-1339	1204-1222	GGAAUCCGCCCAUCUGGGGUU	362	CCCCAGAUGGGCGGAUUCCUU	1865
D-1358	132-150	132-150	UCCACCUCUGUUUACUGUCUU	363	GACAGUAAACAGAGGUGGAUU	1866
D-1359	1322-1340	1205-1223	GAAUCCGCCCAUCUGGGGGUU	364	CCCCCAGAUGGGCGGAUUCUU	1867
D-1360	1323-1341	1206-1224	AAUCCGCCCAUCUGGGGGCUU	365	GCCCCCAGAUGGGCGGAUUUU	1868
D-1361	1324-1342	1207-1225	AUCCGCCCAUCUGGGGGCCUU	366	GGCCCCCAGAUGGGCGGAUUU	1869
D-1362	1325-1343	1208-1226	UCCGCCCAUCUGGGGGCCUUU	367	AGGCCCCCAGAUGGGCGGAUU	1870
D-1363	1326-1344	1209-1227	CCGCCCAUCUGGGGGCCUCUU	368	GAGGCCCCCAGAUGGGCGGUU	1871
D-1364	1327-1345	1210-1228	CGCCCAUCUGGGGGCCUCUUU	369	AGAGGCCCCCAGAUGGGCGUU	1872
D-1365	1328-1346	1211-1229	GCCCAUCUGGGGGCCUCUUUU	370	AAGAGGCCCCCAGAUGGGCUU	1873
D-1366	1329-1347	1212-1230	CCCAUCUGGGGGCCUCUUCUU	371	GAAGAGGCCCCCAGAUGGGUU	1874
D-1367	1330-1348	1213-1231	CCAUCUGGGGGCCUCUUCUUU	372	AGAAGAGGCCCCCAGAUGGUU	1875
D-1368	13-31	13-31	ACGGAAGAGUGAGGUGACUUU	373	AGUCACCUCACUCUUCCGUUU	1876
D-1369	1331-1349	1214-1232	CAUCUGGGGGCCUCUUCUGUU	374	CAGAAGAGGCCCCCAGAUGUU	1877
D-1370	133-151	133-151	CCACCUCUGUUUACUGUCCUU	375	GGACAGUAAACAGAGGUGGUU	1878
D-1371	1332-1350	1215-1233	AUCUGGGGGCCUCUUCUGCUU	376	GCAGAAGAGGCCCCCAGAUUU	1879

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1372	1333-1351	1216-1234	UCUGGGGGCCUCUUCUGCUUU	377	AGCAGAAGAGGCCCCCAGAUU	1880
D-1373	1334-1352	1217-1235	CUGGGGGCCUCUUCUGCUUUU	378	AAGCAGAAGAGGCCCCCAGUU	1881
D-1374	1335-1353	1218-1236	UGGGGGCCUCUUCUGCUUUUU	379	AAAGCAGAAGAGGCCCCCAUU	1882
D-1375	1336-1354	1219-1237	GGGGGCCUCUUCUGCUUUCUU	380	GAAAGCAGAAGAGGCCCCCUU	1883
D-1376	1337-1355	1220-1238	GGGGCCUCUUCUGCUUUCUUU	381	AGAAAGCAGAAGAGGCCCCUU	1884
D-1377	1338-1356	1221-1239	GGGCCUCUUCUGCUUUCUCUU	382	GAGAAAGCAGAAGAGGCCCUU	1885
D-1378	1339-1357	1222-1240	GGCCUCUUCUGCUUUCUCGUU	383	CGAGAAAGCAGAAGAGGCCUU	1886
D-1379	1340-1358	1223-1241	GCCUCUUCUGCUUUCUCGGUU	384	CCGAGAAAGCAGAAGAGGCUU	1887
D-1380	1341-1359	1224-1242	CCUCUUCUGCUUUCUCGGGUU	385	CCCGAGAAAGCAGAAGAGGUU	1888
D-1381	134-152	134-152	CACCUCUGUUUACUGUCCAUU	386	UGGACAGUAAACAGAGGUGUU	1889
D-1382	1342-1360	1225-1243	CUCUUCUGCUUUCUCGGGAUU	387	UCCCGAGAAAGCAGAAGAGUU	1890
D-1383	1343-1361	1226-1244	UCUUCUGCUUUCUCGGGAAUU	388	UUCCCGAGAAAGCAGAAGAUU	1891
D-1384	1344-1362	1227-1245	CUUCUGCUUUCUCGGGAAUUU	389	AUUCCCGAGAAAGCAGAAGUU	1892
D-1385	1345-1363	1228-1246	UUCUGCUUUCUCGGGAAUUUU	390	AAUUCCCGAGAAAGCAGAAUU	1893
D-1386	1346-1364	1229-1247	UCUGCUUUCUCGGGAAUUUUU	391	AAAUUCCCGAGAAAGCAGAUU	1894
D-1387	1347-1365	1230-1248	CUGCUUUCUCGGGAAUUUUUU	392	AAAAUUCCCGAGAAAGCAGUU	1895
D-1388	1348-1366	1231-1249	UGCUUUCUCGGGAAUUUUCUU	393	GAAAAUUCCCGAGAAAGCAUU	1896
D-1389	1349-1367	1232-1250	GCUUUCUCGGGAAUUUUCAUU	394	UGAAAAUUCCCGAGAAAGCUU	1897
D-1390	1350-1368	1233-1251	CUUUCUCGGGAAUUUUCAUUU	395	AUGAAAAUUCCCGAGAAAGUU	1898
D-1391	1351-1369	1234-1252	UUUCUCGGGAAUUUUCAUCUU	396	GAUGAAAAUUCCCGAGAAAUU	1899
D-1392	135-153	135-153	ACCUCUGUUUACUGUCCAAUU	397	UUGGACAGUAAACAGAGGUUU	1900
D-1393	1352-1370	1235-1253	UUCUCGGGAAUUUUCAUCUUU	398	AGAUGAAAAUUCCCGAGAAUU	1901
D-1394	1353-1371	1236-1254	UCUCGGGAAUUUUCAUCUAUU	399	UAGAUGAAAAUUCCCGAGAUU	1902
D-1395	1354-1372	1237-1255	CUCGGGAAUUUUCAUCUAGUU	400	CUAGAUGAAAAUUCCCGAGUU	1903
D-1396	1355-1373	1238-1256	UCGGGAAUUUUCAUCUAGGUU	401	CCUAGAUGAAAAUUCCCGAUU	1904

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1397	1356-1374	1239-1257	CGGGAAUUUUCAUCUAGGAUU	402	UCCUAGAUGAAAAUUCCCGUU	1905
D-1398	1357-1375	1240-1258	GGGAAUUUUCAUCUAGGAUUU	403	AUCCUAGAUGAAAAUUCCCUU	1906
D-1399	1358-1376	1241-1259	GGAAUUUUCAUCUAGGAUUUU	404	AAUCCUAGAUGAAAAUUCCUU	1907
D-1400	1359-1377	1242-1260	GAAUUUUCAUCUAGGAUUUUU	405	AAAUCCUAGAUGAAAAUUCUU	1908
D-1401	1360-1378	1243-1261	AAUUUUCAUCUAGGAUUUUUU	406	AAAAUCCUAGAUGAAAAUUUU	1909
D-1402	1361-1379	1244-1262	AUUUUCAUCUAGGAUUUUAUU	407	UAAAAUCCUAGAUGAAAAUUU	1910
D-1403	136-154	136-154	CCUCUGUUUACUGUCCAAAUU	408	UUUGGACAGUAAACAGAGGUU	1911
D-1404	1362-1380	1245-1263	UUUUCAUCUAGGAUUUUAAUU	409	UUAAAAUCCUAGAUGAAAAUU	1912
D-1405	1363-1381	1246-1264	UUUCAUCUAGGAUUUUAAGUU	410	CUUAAAAUCCUAGAUGAAAUU	1913
D-1406	1364-1382	1247-1265	UUCAUCUAGGAUUUUAAGGUU	411	CCUUAAAAUCCUAGAUGAAUU	1914
D-1407	1365-1383	1248-1266	UCAUCUAGGAUUUUAAGGGUU	412	CCCUUAAAAUCCUAGAUGAUU	1915
D-1408	1366-1384	1249-1267	CAUCUAGGAUUUUAAGGGAUU	413	UCCCUUAAAAUCCUAGAUGUU	1916
D-1409	1367-1385	1250-1268	AUCUAGGAUUUUAAGGGAAUU	414	UUCCCUUAAAAUCCUAGAUUU	1917
D-1410	1368-1386	1251-1269	UCUAGGAUUUUAAGGGAAGUU	415	CUUCCCUUAAAAUCCUAGAUU	1918
D-1411	1369-1387	1252-1270	CUAGGAUUUUAAGGGAAGGUU	416	CCUUCCCUUAAAAUCCUAGUU	1919
D-1412	1370-1388	1253-1271	UAGGAUUUUAAGGGAAGGGUU	417	CCCUUCCCUUAAAAUCCUAUU	1920
D-1413	1371-1389	1254-1272	AGGAUUUUAAGGGAAGGGGUU	418	CCCCUUCCCUUAAAAUCCUUU	1921
D-1414	137-155	137-155	CUCUGUUUACUGUCCAAAGUU	419	CUUUGGACAGUAAACAGAGUU	1922
D-1415	1372-1390	1255-1273	GGAUUUUAAGGGAAGGGGAUU	420	UCCCCUUCCCUUAAAAUCCUU	1923
D-1416	1373-1391	1256-1274	GAUUUUAAGGGAAGGGGAAUU	421	UUCCCCUUCCCUUAAAAUCUU	1924
D-1417	1374-1392	1257-1275	AUUUUAAGGGAAGGGGAAGUU	422	CUUCCCCUUCCCUUAAAAUUU	1925
D-1418	1375-1393	1258-1276	UUUUAAGGGAAGGGGAAGGUU	423	CCUUCCCCUUCCCUUAAAAUU	1926
D-1419	1376-1394	1259-1277	UUUAAGGGAAGGGGAAGGAUU	424	UCCUUCCCCUUCCCUUAAAUU	1927
D-1420	1377-1395	1260-1278	UUAAGGGAAGGGGAAGGAUUU	425	AUCCUUCCCCUUCCCUUAAUU	1928
D-1421	1378-1396	1261-1279	UAAGGGAAGGGGAAGGAUAUU	426	UAUCCUUCCCCUUCCCUUAUU	1929

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1422	1379-1397	1262-1280	AAGGGAAGGGGAAGGAUAGUU	427	CUAUCCUUCCCCUUCCCUUUU	1930
D-1423	1380-1398	1263-1281	AGGGAAGGGGAAGGAUAGGUU	428	CCUAUCCUUCCCCUUCCCUUU	1931
D-1424	1381-1399	1264-1282	GGGAAGGGGAAGGAUAGGGUU	429	CCCUAUCCUUCCCCUUCCCUU	1932
D-1425	138-156	138-156	UCUGUUUACUGUCCAAAGUUU	430	ACUUUGGACAGUAAACAGAUU	1933
D-1426	1382-1400	1265-1283	GGAAGGGGAAGGAUAGGGUUU	431	ACCCUAUCCUUCCCCUUCCUU	1934
D-1427	1383-1401	1266-1284	GAAGGGGAAGGAUAGGGUGUU	432	CACCCUAUCCUUCCCCUUCUU	1935
D-1428	1384-1402	1267-1285	AAGGGGAAGGAUAGGGUGAUU	433	UCACCCUAUCCUUCCCCUUUU	1936
D-1429	1385-1403	1268-1286	AGGGGAAGGAUAGGGUGAUUU	434	AUCACCCUAUCCUUCCCCUUU	1937
D-1430	1386-1404	1269-1287	GGGGAAGGAUAGGGUGAUGUU	435	CAUCACCCUAUCCUUCCCCUU	1938
D-1431	1387-1405	1270-1288	GGGAAGGAUAGGGUGAUGUUU	436	ACAUCACCCUAUCCUUCCCUU	1939
D-1432	1388-1406	1271-1289	GGAAGGAUAGGGUGAUGUUUU	437	AACAUCACCCUAUCCUUCCUU	1940
D-1433	1389-1407	1272-1290	GAAGGAUAGGGUGAUGUUCUU	438	GAACAUCACCCUAUCCUUCUU	1941
D-1434	1390-1408	1273-1291	AAGGAUAGGGUGAUGUUCCUU	439	GGAACAUCACCCUAUCCUUUU	1942
D-1435	1391-1409	1274-1292	AGGAUAGGGUGAUGUUCCGUU	440	CGGAACAUCACCCUAUCCUUU	1943
D-1436	139-157	139-157	CUGUUUACUGUCCAAAGUCUU	441	GACUUUGGACAGUAAACAGUU	1944
D-1437	1392-1410	1275-1293	GGAUAGGGUGAUGUUCCGAUU	442	UCGGAACAUCACCCUAUCCUU	1945
D-1438	1393-1411	1276-1294	GAUAGGGUGAUGUUCCGAAUU	443	UUCGGAACAUCACCCUAUCUU	1946
D-1439	1394-1412	1277-1295	AUAGGGUGAUGUUCCGAAGUU	444	CUUCGGAACAUCACCCUAUUU	1947
D-1440	1395-1413	1278-1296	UAGGGUGAUGUUCCGAAGGUU	445	CCUUCGGAACAUCACCCUAUU	1948
D-1441	1396-1414	1279-1297	AGGGUGAUGUUCCGAAGGUUU	446	ACCUUCGGAACAUCACCCUUU	1949
D-1442	1397-1415	1280-1298	GGGUGAUGUUCCGAAGGUGUU	447	CACCUUCGGAACAUCACCCUU	1950
D-1443	1398-1416	1281-1299	GGUGAUGUUCCGAAGGUGAUU	448	UCACCUUCGGAACAUCACCUU	1951
D-1444	1399-1417	1282-1300	GUGAUGUUCCGAAGGUGAGUU	449	CUCACCUUCGGAACAUCACUU	1952
D-1445	1400-1418	1283-1301	UGAUGUUCCGAAGGUGAGGUU	450	CCUCACCUUCGGAACAUCAUU	1953
D-1446	1401-1419	1284-1302	GAUGUUCCGAAGGUGAGGAUU	451	UCCUCACCUUCGGAACAUCUU	1954
D-1447	140-158	140-158	UGUUUACUGUCCAAAGUCCUU	452	GGACUUUGGACAGUAAACAUU	1955

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1448	1402-1420	1285-1303	AUGUUCCGAAGGUGAGGAGUU	453	CUCCUCACCUUCGGAACAUUU	1956
D-1449	1403-1421	1286-1304	UGUUCCGAAGGUGAGGAGCUU	454	GCUCCUCACCUUCGGAACAUU	1957
D-1450	1404-1422	1287-1305	GUUCCGAAGGUGAGGAGCUUU	455	AGCUCCUCACCUUCGGAACUU	1958
D-1451	1405-1423	1288-1306	UUCCGAAGGUGAGGAGCUUUU	456	AAGCUCCUCACCUUCGGAAUU	1959
D-1452	1406-1424	1289-1307	UCCGAAGGUGAGGAGCUUGUU	457	CAAGCUCCUCACCUUCGGAUU	1960
D-1453	1407-1425	1290-1308	CCGAAGGUGAGGAGCUUGAUU	458	UCAAGCUCCUCACCUUCGGUU	1961
D-1454	1408-1426	1291-1309	CGAAGGUGAGGAGCUUGAAUU	459	UUCAAGCUCCUCACCUUCGUU	1962
D-1455	1409-1427	1292-1310	GAAGGUGAGGAGCUUGAAAUU	460	UUUCAAGCUCCUCACCUUCUU	1963
D-1456	1410-1428	1293-1311	AAGGUGAGGAGCUUGAAACUU	461	GUUUCAAGCUCCUCACCUUUU	1964
D-1457	1411-1429	1294-1312	AGGUGAGGAGCUUGAAACCUU	462	GGUUUCAAGCUCCUCACCUUU	1965
D-1458	141-159	141-159	GUUUACUGUCCAAAGUCCCUU	463	GGGACUUUGGACAGUAAACUU	1966
D-1459	1412-1430	1295-1313	GGUGAGGAGCUUGAAACCCUU	464	GGGUUUCAAGCUCCUCACCUU	1967
D-1460	1413-1431	1296-1314	GUGAGGAGCUUGAAACCCGUU	465	CGGGUUUCAAGCUCCUCACUU	1968
D-1461	1414-1432	1297-1315	UGAGGAGCUUGAAACCCGUUU	466	ACGGGUUUCAAGCUCCUCAUU	1969
D-1462	1415-1433	1298-1316	GAGGAGCUUGAAACCCGUGUU	467	CACGGGUUUCAAGCUCCUCUU	1970
D-1463	1416-1434	1299-1317	AGGAGCUUGAAACCCGUGGUU	468	CCACGGGUUUCAAGCUCCUUU	1971
D-1464	1417-1435	1300-1318	GGAGCUUGAAACCCGUGGCUU	469	GCCACGGGUUUCAAGCUCCUU	1972
D-1465	1418-1436	1301-1319	GAGCUUGAAACCCGUGGCGUU	470	CGCCACGGGUUUCAAGCUCUU	1973
D-1466	1419-1437	1302-1320	AGCUUGAAACCCGUGGCGCUU	471	GCGCCACGGGUUUCAAGCUUU	1974
D-1467	1420-1438	1303-1321	GCUUGAAACCCGUGGCGCUUU	472	AGCGCCACGGGUUUCAAGCUU	1975
D-1468	1421-1439	1304-1322	CUUGAAACCCGUGGCGCUUUU	473	AAGCGCCACGGGUUUCAAGUU	1976
D-1469	142-160	142-160	UUUACUGUCCAAAGUCCCGUU	474	CGGGACUUUGGACAGUAAAUU	1977
D-1470	1422-1440	1305-1323	UUGAAACCCGUGGCGCUUUUU	475	AAAGCGCCACGGGUUUCAAUU	1978
D-1471	1423-1441	1306-1324	UGAAACCCGUGGCGCUUUCUU	476	GAAAGCGCCACGGGUUUCAUU	1979
D-1472	1424-1442	1307-1325	GAAACCCGUGGCGCUUUCUUU	477	AGAAAGCGCCACGGGUUUCUU	1980

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1473	1425-1443	1308-1326	AAACCCGUGGCGCUUUCUGUU	478	CAGAAAGCGCCACGGGUUUUU	1981
D-1474	1426-1444	1309-1327	AACCCGUGGCGCUUUCUGCUU	479	GCAGAAAGCGCCACGGGUUUU	1982
D-1475	1427-1445	1310-1328	ACCCGUGGCGCUUUCUGCAUU	480	UGCAGAAAGCGCCACGGGUUU	1983
D-1476	1428-1446	1311-1329	CCCGUGGCGCUUUCUGCAGUU	481	CUGCAGAAAGCGCCACGGGUU	1984
D-1477	1429-1447	1312-1330	CCGUGGCGCUUUCUGCAGUUU	482	ACUGCAGAAAGCGCCACGGUU	1985
D-1478	1430-1448	1313-1331	CGUGGCGCUUUCUGCAGUUUU	483	AACUGCAGAAAGCGCCACGUU	1986
D-1479	1431-1449	1314-1332	GUGGCGCUUUCUGCAGUUUUU	484	AAACUGCAGAAAGCGCCACUU	1987
D-1480	143-161	143-161	UUACUGUCCAAAGUCCCGGUU	485	CCGGGACUUUGGACAGUAAUU	1988
D-1481	14-32	14-32	CGGAAGAGUGAGGUGACUGUU	486	CAGUCACCUCACUCUUCCGUU	1989
D-1482	1432-1450	1315-1333	UGGCGCUUUCUGCAGUUUGUU	487	CAAACUGCAGAAAGCGCCAUU	1990
D-1483	1433-1451	1316-1334	GGCGCUUUCUGCAGUUUGCUU	488	GCAAACUGCAGAAAGCGCCUU	1991
D-1484	1434-1452	1317-1335	GCGCUUUCUGCAGUUUGCAUU	489	UGCAAACUGCAGAAAGCGCUU	1992
D-1485	1435-1453	1318-1336	CGCUUUCUGCAGUUUGCAGUU	490	CUGCAAACUGCAGAAAGCGUU	1993
D-1486	1436-1454	1319-1337	GCUUUCUGCAGUUUGCAGGUU	491	CCUGCAAACUGCAGAAAGCUU	1994
D-1487	1437-1455	1320-1338	CUUUCUGCAGUUUGCAGGUUU	492	ACCUGCAAACUGCAGAAAGUU	1995
D-1488	1438-1456	1321-1339	UUUCUGCAGUUUGCAGGUUUU	493	AACCUGCAAACUGCAGAAAUU	1996
D-1489	1439-1457	1322-1340	UUCUGCAGUUUGCAGGUUAUU	494	UAACCUGCAAACUGCAGAAUU	1997
D-1490	1440-1458	1323-1341	UCUGCAGUUUGCAGGUUAUUU	495	AUAACCUGCAAACUGCAGAUU	1998
D-1491	1441-1459	1324-1342	CUGCAGUUUGCAGGUUAUCUU	496	GAUAACCUGCAAACUGCAGUU	1999
D-1492	144-162	144-162	UACUGUCCAAAGUCCCGGGUU	497	CCCGGGACUUUGGACAGUAUU	2000
D-1493	1442-1460	1325-1343	UGCAGUUUGCAGGUUAUCAUU	498	UGAUAACCUGCAAACUGCAUU	2001
D-1494	1443-1461	1326-1344	GCAGUUUGCAGGUUAUCAUUU	499	AUGAUAACCUGCAAACUGCUU	2002
D-1495	1444-1462	1327-1345	CAGUUUGCAGGUUAUCAUUUU	500	AAUGAUAACCUGCAAACUGUU	2003
D-1496	1445-1463	1328-1346	AGUUUGCAGGUUAUCAUUGUU	501	CAAUGAUAACCUGCAAACUUU	2004
D-1497	1446-1464	1329-1347	GUUUGCAGGUUAUCAUUGUUU	502	ACAAUGAUAACCUGCAAACUU	2005
D-1498	1447-1465	1330-1348	UUUGCAGGUUAUCAUUGUGUU	503	CACAAUGAUAACCUGCAAAUU	2006

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1499	1448-1466	1331-1349	UUGCAGGUUAUCAUUGUGAUU	504	UCACAAUGAUAACCUGCAAUU	2007
D-1500	1449-1467	1332-1350	UGCAGGUUAUCAUUGUGAAUU	505	UUCACAAUGAUAACCUGCAUU	2008
D-1501	1450-1468	1333-1351	GCAGGUUAUCAUUGUGAACUU	506	GUUCACAAUGAUAACCUGCUU	2009
D-1502	1451-1469	1334-1352	CAGGUUAUCAUUGUGAACUUU	507	AGUUCACAAUGAUAACCUGUU	2010
D-1503	145-163	145-163	ACUGUCCAAAGUCCCGGGCUU	508	GCCCGGGACUUUGGACAGUUU	2011
D-1504	1452-1470	1335-1353	AGGUUAUCAUUGUGAACUUUU	509	AAGUUCACAAUGAUAACCUUU	2012
D-1505	1453-1471	1336-1354	GGUUAUCAUUGUGAACUUUUU	510	AAAGUUCACAAUGAUAACCUU	2013
D-1506	1454-1472	1337-1355	GUUAUCAUUGUGAACUUUUUU	511	AAAAGUUCACAAUGAUAACUU	2014
D-1507	1455-1473	1338-1356	UUAUCAUUGUGAACUUUUUUU	512	AAAAAGUUCACAAUGAUAAUU	2015
D-1508	1456-1474	1339-1357	UAUCAUUGUGAACUUUUUUUU	513	AAAAAAGUUCACAAUGAUAUU	2016
D-1509	1457-1475	1340-1358	AUCAUUGUGAACUUUUUUUUU	514	AAAAAAAGUUCACAAUGAUUU	2017
D-1510	1458-1476	1341-1359	UCAUUGUGAACUUUUUUUUUU	515	AAAAAAAAGUUCACAAUGAUU	2018
D-1511	1459-1477	1342-1360	CAUUGUGAACUUUUUUUUUUU	516	AAAAAAAAAGUUCACAAUGUU	2019
D-1512	1460-1478	1343-1361	AUUGUGAACUUUUUUUUUUUU	517	AAAAAAAAAAGUUCACAAUUU	2020
D-1513	1461-1479	1344-1362	UUGUGAACUUUUUUUUUUUUU	518	AAAAAAAAAAAGUUCACAAUU	2021
D-1514	146-164	146-164	CUGUCCAAAGUCCCGGGCAUU	519	UGCCCGGGACUUUGGACAGUU	2022
D-1515	1462-1480	1345-1363	UGUGAACUUUUUUUUUUUAUU	520	UAAAAAAAAAAAGUUCACAUU	2023
D-1516	1463-1481	1346-1364	GUGAACUUUUUUUUUUUAAUU	521	UUAAAAAAAAAAAGUUCACUU	2024
D-1517	1464-1482	1347-1365	UGAACUUUUUUUUUUUAAGUU	522	CUUAAAAAAAAAAAGUUCAUU	2025
D-1518	1465-1483	1348-1366	GAACUUUUUUUUUUUAAGAUU	523	UCUUAAAAAAAAAAAGUUCUU	2026
D-1519	1466-1484	1349-1367	AACUUUUUUUUUUUAAGAGUU	524	CUCUUAAAAAAAAAAAGUUUU	2027
D-1520	1467-1485	1350-1368	ACUUUUUUUUUUUAAGAGUUU	525	ACUCUUAAAAAAAAAAAGUUU	2028
D-1521	1468-1486	1351-1369	CUUUUUUUUUUUAAGAGUAUU	526	UACUCUUAAAAAAAAAAAGUU	2029
D-1522	1469-1487	1352-1370	UUUUUUUUUUUAAGAGUAAUU	527	UUACUCUUAAAAAAAAAAAUU	2030
D-1523	1470-1488	1353-1371	UUUUUUUUUUAAGAGUAAAUU	528	UUUACUCUUAAAAAAAAAAUU	2031

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1524	1471-1489	1354-1372	UUUUUUUUUAAGAGUAAAAUU	529	UUUUACUCUUAAAAAAAAAUU	2032
D-1525	147-165	147-165	UGUCCAAAGUCCCGGGCACUU	530	GUGCCCGGGACUUUGGACAUU	2033
D-1526	1472-1490	1355-1373	UUUUUUUUAAGAGUAAAAAUU	531	UUUUUACUCUUAAAAAAAAUU	2034
D-1527	1473-1491	1356-1374	UUUUUUUAAGAGUAAAAAGUU	532	CUUUUUACUCUUAAAAAAAUU	2035
D-1528	1474-1492	1357-1375	UUUUUUAAGAGUAAAAAGAUU	533	UCUUUUUACUCUUAAAAAAUU	2036
D-1529	1475-1493	1358-1376	UUUUUAAGAGUAAAAAGAAUU	534	UUCUUUUUACUCUUAAAAAUU	2037
D-1530	1476-1494	1359-1377	UUUUAAGAGUAAAAAGAAAUU	535	UUUCUUUUUACUCUUAAAAUU	2038
D-1531	1477-1495	1360-1378	UUUAAGAGUAAAAAGAAAUUU	536	AUUUCUUUUUACUCUUAAAUU	2039
D-1532	1478-1496	1361-1379	UUAAGAGUAAAAAGAAAUAUU	537	UAUUUCUUUUUACUCUUAAUU	2040
D-1533	1479-1497	1362-1380	UAAGAGUAAAAAGAAAUAUUU	538	AUAUUUCUUUUUACUCUUAUU	2041
D-1534	1480-1498	1363-1381	AAGAGUAAAAAGAAAUAUAUU	539	UAUAUUUCUUUUUACUCUUUU	2042
D-1535	1481-1499	1364-1382	AGAGUAAAAAGAAAUAUACUU	540	GUAUAUUUCUUUUUACUCUUU	2043
D-1536	148-166	148-166	GUCCAAAGUCCCGGGCACUUU	541	AGUGCCCGGGACUUUGGACUU	2044
D-1537	1482-1500	1365-1383	GAGUAAAAAGAAAUAUACCUU	542	GGUAUAUUUCUUUUUACUCUU	2045
D-1538	1483-1501	—	AGUAAAAAGAAAUAUACCUUU	543	AGGUAUAUUUCUUUUUACUUU	2046
D-1539	1484-1502	—	GUAAAAAGAAAUAUACCUAUU	544	UAGGUAUAUUUCUUUUUACUU	2047
D-1540	1485-1503	—	UAAAAAGAAAUAUACCUAAUU	545	UUAGGUAUAUUUCUUUUUAUU	2048
D-1541	149-167	149-167	UCCAAAGUCCCGGGCACUGUU	546	CAGUGCCCGGGACUUUGGAUU	2049
D-1542	150-168	150-168	CCAAAGUCCCGGGCACUGGUU	547	CCAGUGCCCGGGACUUUGGUU	2050
D-1543	151-169	151-169	CAAAGUCCCGGGCACUGGAUU	548	UCCAGUGCCCGGGACUUUGUU	2051
D-1544	152-170	152-170	AAAGUCCCGGGCACUGGAGUU	549	CUCCAGUGCCCGGGACUUUUU	2052
D-1545	153-171	153-171	AAGUCCCGGGCACUGGAGAUU	550	UCUCCAGUGCCCGGGACUUUU	2053
D-1546	15-33	15-33	GGAAGAGUGAGGUGACUGGUU	551	CCAGUCACCUCACUCUUCCUU	2054
D-1547	154-172	154-172	AGUCCCGGGCACUGGAGAUUU	552	AUCUCCAGUGCCCGGGACUUU	2055
D-1548	155-173	155-173	GUCCCGGGCACUGGAGAUGUU	553	CAUCUCCAGUGCCCGGGACUU	2056
D-1549	156-174	156-174	UCCCGGGCACUGGAGAUGCUU	554	GCAUCUCCAGUGCCCGGGAUU	2057
D-1550	157-175	157-175	CCCGGGCACUGGAGAUGCCUU	555	GGCAUCUCCAGUGCCCGGGUU	2058
D-1551	158-176	158-176	CCGGGCACUGGAGAUGCCAUU	556	UGGCAUCUCCAGUGCCCGGUU	2059
D-1552	159-177	159-177	CGGGCACUGGAGAUGCCACUU	557	GUGGCAUCUCCAGUGCCCGUU	2060
D-1553	160-178	160-178	GGGCACUGGAGAUGCCACGUU	558	CGUGGCAUCUCCAGUGCCCUU	2061

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1554	161-179	161-179	GGCACUGGAGAUGCCACGUUU	559	ACGUGGCAUCUCCAGUGCCUU	2062
D-1555	162-180	162-180	GCACUGGAGAUGCCACGUUUU	560	AACGUGGCAUCUCCAGUGCUU	2063
D-1556	163-181	163-181	CACUGGAGAUGCCACGUUUUU	561	AAACGUGGCAUCUCCAGUGUU	2064
D-1557	16-34	16-34	GAAGAGUGAGGUGACUGGCUU	562	GCCAGUCACCUCACUCUUCUU	2065
D-1558	164-182	164-182	ACUGGAGAUGCCACGUUUGUU	563	CAAACGUGGCAUCUCCAGUUU	2066
D-1559	165-183	165-183	CUGGAGAUGCCACGUUUGGUU	564	CCAAACGUGGCAUCUCCAGUU	2067
D-1560	166-184	166-184	UGGAGAUGCCACGUUUGGCUU	565	GCCAAACGUGGCAUCUCCAUU	2068
D-1561	167-185	167-185	GGAGAUGCCACGUUUGGCGUU	566	CGCCAAACGUGGCAUCUCCUU	2069
D-1562	168-186	168-186	GAGAUGCCACGUUUGGCGUUU	567	ACGCCAAACGUGGCAUCUCUU	2070
D-1563	169-187	169-187	AGAUGCCACGUUUGGCGUGUU	568	CACGCCAAACGUGGCAUCUUU	2071
D-1564	170-188	170-188	GAUGCCACGUUUGGCGUGCUU	569	GCACGCCAAACGUGGCAUCUU	2072
D-1565	171-189	171-189	AUGCCACGUUUGGCGUGCUUU	570	AGCACGCCAAACGUGGCAUUU	2073
D-1566	172-190	172-190	UGCCACGUUUGGCGUGCUUUU	571	AAGCACGCCAAACGUGGCAUU	2074
D-1567	173-191	173-191	GCCACGUUUGGCGUGCUUGUU	572	CAAGCACGCCAAACGUGGCUU	2075
D-1568	17-35	17-35	AAGAGUGAGGUGACUGGCAUU	573	UGCCAGUCACCUCACUCUUUU	2076
D-1569	174-192	174-192	CCACGUUUGGCGUGCUUGGUU	574	CCAAGCACGCCAAACGUGGUU	2077
D-1570	175-193	175-193	CACGUUUGGCGUGCUUGGAUU	575	UCCAAGCACGCCAAACGUGUU	2078
D-1571	176-194	176-194	ACGUUUGGCGUGCUUGGACUU	576	GUCCAAGCACGCCAAACGUUU	2079
D-1572	177-195	177-195	CGUUUGGCGUGCUUGGACAUU	577	UGUCCAAGCACGCCAAACGUU	2080
D-1573	178-196	178-196	GUUUGGCGUGCUUGGACACUU	578	GUGUCCAAGCACGCCAAACUU	2081
D-1574	179-197	179-197	UUUGGCGUGCUUGGACACAUU	579	UGUGUCCAAGCACGCCAAAUU	2082
D-1575	180-198	180-198	UUGGCGUGCUUGGACACACUU	580	GUGUGUCCAAGCACGCCAAUU	2083
D-1576	181-199	181-199	UGGCGUGCUUGGACACACAUU	581	UGUGUGUCCAAGCACGCCAUU	2084
D-1577	182-200	182-200	GGCGUGCUUGGACACACAGUU	582	CUGUGUGUCCAAGCACGCCUU	2085
D-1578	183-201	183-201	GCGUGCUUGGACACACAGAUU	583	UCUGUGUGUCCAAGCACGCUU	2086
D-1579	18-36	18-36	AGAGUGAGGUGACUGGCAUUU	584	AUGCCAGUCACCUCACUCUUU	2087
D-1580	184-202	184-202	CGUGCUUGGACACACAGACUU	585	GUCUGUGUGUCCAAGCACGUU	2088
D-1581	185-203	185-203	GUGCUUGGACACACAGACAUU	586	UGUCUGUGUGUCCAAGCACUU	2089
D-1582	186-204	186-204	UGCUUGGACACACAGACACUU	587	GUGUCUGUGUGUCCAAGCAUU	2090
D-1583	187-205	187-205	GCUUGGACACACAGACACGUU	588	CGUGUCUGUGUGUCCAAGCUU	2091
D-1584	188-206	188-206	CUUGGACACACAGACACGCUU	589	GCGUGUCUGUGUGUCCAAGUU	2092
D-1585	189-207	189-207	UUGGACACACAGACACGCAUU	590	UGCGUGUCUGUGUGUCCAAUU	2093
D-1586	190-208	190-208	UGGACACACAGACACGCAGUU	591	CUGCGUGUCUGUGUGUCCAUU	2094
D-1587	191-209	191-209	GGACACACAGACACGCAGAUU	592	UCUGCGUGUCUGUGUGUCCUU	2095
D-1588	192-210	192-210	GACACACAGACACGCAGACUU	593	GUCUGCGUGUCUGUGUGUCUU	2096
D-1589	193-211	193-211	ACACACAGACACGCAGACAUU	594	UGUCUGCGUGUCUGUGUGUUU	2097

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1590	19-37	19-37	GAGUGAGGUGACUGGCAUGUU	595	CAUGCCAGUCACCUCACUCUU	2098
D-1591	194-212	194-212	CACACAGACACGCAGACACUU	596	GUGUCUGCGUGUCUGUGUGUU	2099
D-1592	195-213	195-213	ACACAGACACGCAGACACAUU	597	UGUGUCUGCGUGUCUGUGUUU	2100
D-1593	196-214	196-214	CACAGACACGCAGACACAGUU	598	CUGUGUCUGCGUGUCUGUGUU	2101
D-1594	197-215	197-215	ACAGACACGCAGACACAGAUU	599	UCUGUGUCUGCGUGUCUGUUU	2102
D-1595	198-216	198-216	CAGACACGCAGACACAGAGUU	600	CUCUGUGUCUGCGUGUCUGUU	2103
D-1596	199-217	199-217	AGACACGCAGACACAGAGAUU	601	UCUCUGUGUCUGCGUGUCUUU	2104
D-1597	200-218	200-218	GACACGCAGACACAGAGACUU	602	GUCUCUGUGUCUGCGUGUCUU	2105
D-1598	201-219	201-219	ACACGCAGACACAGAGACAUU	603	UGUCUCUGUGUCUGCGUGUUU	2106
D-1599	202-220	202-220	CACGCAGACACAGAGACACUU	604	GUGUCUCUGUGUCUGCGUGUU	2107
D-1600	203-221	203-221	ACGCAGACACAGAGACACCUU	605	GGUGUCUCUGUGUCUGCGUUU	2108
D-1601	20-38	20-38	AGUGAGGUGACUGGCAUGUUU	606	ACAUGCCAGUCACCUCACUUU	2109
D-1602	204-222	204-222	CGCAGACACAGAGACACCGUU	607	CGGUGUCUCUGUGUCUGCGUU	2110
D-1603	205-223	205-223	GCAGACACAGAGACACCGGUU	608	CCGGUGUCUCUGUGUCUGCUU	2111
D-1604	206-224	206-224	CAGACACAGAGACACCGGGUU	609	CCCGGUGUCUCUGUGUCUGUU	2112
D-1605	207-225	207-225	AGACACAGAGACACCGGGGUU	610	CCCCGGUGUCUCUGUGUCUUU	2113
D-1606	208-226	208-226	GACACAGAGACACCGGGGCUU	611	GCCCCGGUGUCUCUGUGUCUU	2114
D-1607	209-227	209-227	ACACAGAGACACCGGGGCCUU	612	GGCCCCGGUGUCUCUGUGUUU	2115
D-1608	210-228	210-228	CACAGAGACACCGGGGCCCUU	613	GGGCCCCGGUGUCUCUGUGUU	2116
D-1609	211-229	211-229	ACAGAGACACCGGGGCCCAUU	614	UGGGCCCCGGUGUCUCUGUUU	2117
D-1610	212-230	212-230	CAGAGACACCGGGGCCCAGUU	615	CUGGGCCCCGGUGUCUCUGUU	2118
D-1611	213-231	213-231	AGAGACACCGGGGCCCAGGUU	616	CCUGGGCCCCGGUGUCUCUUU	2119
D-1612	21-39	21-39	GUGAGGUGACUGGCAUGUGUU	617	CACAUGCCAGUCACCUCACUU	2120
D-1613	214-232	214-232	GAGACACCGGGGCCCAGGGUU	618	CCCUGGGCCCCGGUGUCUCUU	2121
D-1614	215-233	215-233	AGACACCGGGGCCCAGGGCUU	619	GCCCUGGGCCCCGGUGUCUUU	2122
D-1615	216-234	216-234	GACACCGGGGCCCAGGGCCUU	620	GGCCCUGGGCCCCGGUGUCUU	2123
D-1616	217-235	217-235	ACACCGGGGCCCAGGGCCCUU	621	GGGCCCUGGGCCCCGGUGUUU	2124
D-1617	218-236	218-236	CACCGGGGCCCAGGGCCCUUU	622	AGGGCCCUGGGCCCCGGUGUU	2125
D-1618	219-237	219-237	ACCGGGGCCCAGGGCCCUCUU	623	GAGGGCCCUGGGCCCCGGUUU	2126
D-1619	2-20	2-20	CCAAACGGUGCACGGAAGAUU	624	UCUUCCGUGCACCGUUUGGUU	2127
D-1620	220-238	220-238	CCGGGGCCCAGGGCCCUCCUU	625	GGAGGGCCCUGGGCCCCGGUU	2128
D-1621	221-239	221-239	CGGGGCCCAGGGCCCUCCUUU	626	AGGAGGGCCCUGGGCCCCGUU	2129
D-1622	222-240	222-240	GGGGCCCAGGGCCCUCCUAUU	627	UAGGAGGGCCCUGGGCCCCUU	2130
D-1623	223-241	223-241	GGGCCCAGGGCCCUCCUAUUU	628	AUAGGAGGGCCCUGGGCCCUU	2131
D-1624	22-40	22-40	UGAGGUGACUGGCAUGUGUUU	629	ACACAUGCCAGUCACCUCAUU	2132
D-1625	224-242	224-242	GGCCCAGGGCCCUCCUAUGUU	630	CAUAGGAGGGCCCUGGGCCUU	2133

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1626	225-243	225-243	GCCCAGGGCCCUCCUAUGGUU	631	CCAUAGGAGGGCCCUGGGCUU	2134
D-1627	226-244	226-244	CCCAGGGCCCUCCUAUGGAUU	632	UCCAUAGGAGGGCCCUGGGUU	2135
D-1628	227-245	227-245	CCAGGGCCCUCCUAUGGACUU	633	GUCCAUAGGAGGGCCCUGGUU	2136
D-1629	228-246	228-246	CAGGGCCCUCCUAUGGACCUU	634	GGUCCAUAGGAGGGCCCUGUU	2137
D-1630	229-247	229-247	AGGGCCCUCCUAUGGACCCUU	635	GGGUCCAUAGGAGGGCCCUUU	2138
D-1631	230-248	230-248	GGGCCCUCCUAUGGACCCUUU	636	AGGGUCCAUAGGAGGGCCCUU	2139
D-1632	231-249	231-249	GGCCCUCCUAUGGACCCUGUU	637	CAGGGUCCAUAGGAGGGCCUU	2140
D-1633	232-250	232-250	GCCCUCCUAUGGACCCUGCUU	638	GCAGGGUCCAUAGGAGGGCUU	2141
D-1634	233-251	233-251	CCCUCCUAUGGACCCUGCCUU	639	GGCAGGGUCCAUAGGAGGGUU	2142
D-1635	23-41	23-41	GAGGUGACUGGCAUGUGUGUU	640	CACACAUGCCAGUCACCUCUU	2143
D-1636	234-252	234-252	CCUCCUAUGGACCCUGCCCUU	641	GGGCAGGGUCCAUAGGAGGUU	2144
D-1637	235-253	235-253	CUCCUAUGGACCCUGCCCGUU	642	CGGGCAGGGUCCAUAGGAGUU	2145
D-1638	236-254	236-254	UCCUAUGGACCCUGCCCGCUU	643	GCGGGCAGGGUCCAUAGGAUU	2146
D-1639	237-255	237-255	CCUAUGGACCCUGCCCGCUUU	644	AGCGGGCAGGGUCCAUAGGUU	2147
D-1640	238-256	238-256	CUAUGGACCCUGCCCGCUCUU	645	GAGCGGGCAGGGUCCAUAGUU	2148
D-1641	239-257	239-257	UAUGGACCCUGCCCGCUCCUU	646	GGAGCGGGCAGGGUCCAUAUU	2149
D-1642	240-258	240-258	AUGGACCCUGCCCGCUCCCUU	647	GGGAGCGGGCAGGGUCCAUUU	2150
D-1643	241-259	241-259	UGGACCCUGCCCGCUCCCCUU	648	GGGGAGCGGGCAGGGUCCAUU	2151
D-1644	242-260	242-260	GGACCCUGCCCGCUCCCCUUU	649	AGGGGAGCGGGCAGGGUCCUU	2152
D-1645	243-261	243-261	GACCCUGCCCGCUCCCCUCUU	650	GAGGGGAGCGGGCAGGGUCUU	2153
D-1646	24-42	24-42	AGGUGACUGGCAUGUGUGGUU	651	CCACACAUGCCAGUCACCUUU	2154
D-1647	244-262	244-262	ACCCUGCCCGCUCCCCUCCUU	652	GGAGGGGAGCGGGCAGGGUUU	2155
D-1648	245-263	245-263	CCCUGCCCGCUCCCCUCCCUU	653	GGGAGGGGAGCGGGCAGGGUU	2156
D-1649	246-264	246-264	CCUGCCCGCUCCCCUCCCAUU	654	UGGGAGGGGAGCGGGCAGGUU	2157
D-1650	247-265	247-265	CUGCCCGCUCCCCUCCCAUUU	655	AUGGGAGGGGAGCGGGCAGUU	2158
D-1651	248-266	248-266	UGCCCGCUCCCCUCCCAUUUU	656	AAUGGGAGGGGAGCGGGCAUU	2159
D-1652	249-267	249-267	GCCCGCUCCCCUCCCAUUGUU	657	CAAUGGGAGGGGAGCGGGCUU	2160
D-1653	250-268	250-268	CCCGCUCCCCUCCCAUUGUUU	658	ACAAUGGGAGGGGAGCGGGUU	2161
D-1654	251-269	251-269	CCGCUCCCCUCCCAUUGUCUU	659	GACAAUGGGAGGGGAGCGGUU	2162
D-1655	252-270	252-270	CGCUCCCCUCCCAUUGUCCUU	660	GGACAAUGGGAGGGGAGCGUU	2163
D-1656	253-271	253-271	GCUCCCCUCCCAUUGUCCAUU	661	UGGACAAUGGGAGGGGAGCUU	2164
D-1657	254-272	254-272	CUCCCCUCCCAUUGUCCACUU	662	GUGGACAAUGGGAGGGGAGUU	2165
D-1658	25-43	25-43	GGUGACUGGCAUGUGUGGGUU	663	CCCACACAUGCCAGUCACCUU	2166
D-1659	255-273	255-273	UCCCCUCCCAUUGUCCACGUU	664	CGUGGACAAUGGGAGGGGAUU	2167
D-1660	256-274	256-274	CCCCUCCCAUUGUCCACGGUU	665	CCGUGGACAAUGGGAGGGGUU	2168
D-1661	257-275	257-275	CCCUCCCAUUGUCCACGGCUU	666	GCCGUGGACAAUGGGAGGGUU	2169

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1662	258-276	258-276	CCUCCCAUUGUCCACGGCUUU	667	AGCCGUGGACAAUGGGAGGUU	2170
D-1663	259-277	259-277	CUCCCAUUGUCCACGGCUGUU	668	CAGCCGUGGACAAUGGGAGUU	2171
D-1664	260-278	260-278	UCCCAUUGUCCACGGCUGUUU	669	ACAGCCGUGGACAAUGGGAUU	2172
D-1665	261-279	261-279	CCCAUUGUCCACGGCUGUCUU	670	GACAGCCGUGGACAAUGGGUU	2173
D-1666	262-280	262-280	CCAUUGUCCACGGCUGUCCUU	671	GGACAGCCGUGGACAAUGGUU	2174
D-1667	263-281	263-281	CAUUGUCCACGGCUGUCCGUU	672	CGGACAGCCGUGGACAAUGUU	2175
D-1668	264-282	264-282	AUUGUCCACGGCUGUCCGCUU	673	GCGGACAGCCGUGGACAAUUU	2176
D-1669	26-44	26-44	GUGACUGGCAUGUGUGGGGUU	674	CCCCACACAUGCCAGUCACUU	2177
D-1670	265-283	265-283	UUGUCCACGGCUGUCCGCCUU	675	GGCGGACAGCCGUGGACAAUU	2178
D-1671	266-284	266-284	UGUCCACGGCUGUCCGCCCUU	676	GGGCGGACAGCCGUGGACAUU	2179
D-1672	267-285	267-285	GUCCACGGCUGUCCGCCCAUU	677	UGGGCGGACAGCCGUGGACUU	2180
D-1673	268-286	268-286	UCCACGGCUGUCCGCCCACUU	678	GUGGGCGGACAGCCGUGGAUU	2181
D-1674	269-287	269-287	CCACGGCUGUCCGCCCACCUU	679	GGUGGGCGGACAGCCGUGGUU	2182
D-1675	270-288	270-288	CACGGCUGUCCGCCCACCCUU	680	GGGUGGGCGGACAGCCGUGUU	2183
D-1676	271-289	271-289	ACGGCUGUCCGCCCACCCCUU	681	GGGGUGGGCGGACAGCCGUUU	2184
D-1677	272-290	272-290	CGGCUGUCCGCCCACCCCCUU	682	GGGGGUGGGCGGACAGCCGUU	2185
D-1678	273-291	273-291	GGCUGUCCGCCCACCCCCAUU	683	UGGGGGUGGGCGGACAGCCUU	2186
D-1679	274-292	274-292	GCUGUCCGCCCACCCCCAUUU	684	AUGGGGGUGGGCGGACAGCUU	2187
D-1680	27-45	27-45	UGACUGGCAUGUGUGGGGGUU	685	CCCCCACACAUGCCAGUCAUU	2188
D-1681	275-293	275-293	CUGUCCGCCCACCCCCAUUUU	686	AAUGGGGGUGGGCGGACAGUU	2189
D-1682	276-294	276-294	UGUCCGCCCACCCCCAUUCUU	687	GAAUGGGGGUGGGCGGACAUU	2190
D-1683	277-295	277-295	GUCCGCCCACCCCCAUUCUUU	688	AGAAUGGGGGUGGGCGGACUU	2191
D-1684	278-296	278-296	UCCGCCCACCCCCAUUCUCUU	689	GAGAAUGGGGGUGGGCGGAUU	2192
D-1685	279-297	279-297	CCGCCCACCCCCAUUCUCCUU	690	GGAGAAUGGGGGUGGGCGGUU	2193
D-1686	280-298	280-298	CGCCCACCCCCAUUCUCCAUU	691	UGGAGAAUGGGGGUGGGCGUU	2194
D-1687	281-299	281-299	GCCCACCCCCAUUCUCCAAUU	692	UUGGAGAAUGGGGGUGGGCUU	2195
D-1688	282-300	282-300	CCCACCCCCAUUCUCCAAGUU	693	CUUGGAGAAUGGGGGUGGGUU	2196
D-1689	283-301	283-301	CCACCCCCAUUCUCCAAGCUU	694	GCUUGGAGAAUGGGGGUGGUU	2197
D-1690	284-302	284-302	CACCCCCAUUCUCCAAGCUUU	695	AGCUUGGAGAAUGGGGGUGUU	2198
D-1691	28-46	28-46	GACUGGCAUGUGUGGGGGCUU	696	GCCCCCACACAUGCCAGUCUU	2199
D-1692	285-303	285-303	ACCCCCAUUCUCCAAGCUUUU	697	AAGCUUGGAGAAUGGGGGUUU	2200
D-1693	286-304	286-304	CCCCCAUUCUCCAAGCUUCUU	698	GAAGCUUGGAGAAUGGGGGUU	2201
D-1694	287-305	287-305	CCCCAUUCUCCAAGCUUCAUU	699	UGAAGCUUGGAGAAUGGGGUU	2202
D-1695	288-306	288-306	CCCAUUCUCCAAGCUUCAGUU	700	CUGAAGCUUGGAGAAUGGGUU	2203
D-1696	289-307	289-307	CCAUUCUCCAAGCUUCAGCUU	701	GCUGAAGCUUGGAGAAUGGUU	2204
D-1697	290-308	290-308	CAUUCUCCAAGCUUCAGCCUU	702	GGCUGAAGCUUGGAGAAUGUU	2205

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1698	291-309	291-309	AUUCUCCAAGCUUCAGCCCUU	703	GGGCUGAAGCUUGGAGAAUUU	2206
D-1699	292-310	292-310	UUCUCCAAGCUUCAGCCCCUU	704	GGGGCUGAAGCUUGGAGAAUU	2207
D-1700	293-311	293-311	UCUCCAAGCUUCAGCCCCCUU	705	GGGGGCUGAAGCUUGGAGAUU	2208
D-1701	294-312	294-312	CUCCAAGCUUCAGCCCCCUUU	706	AGGGGGCUGAAGCUUGGAGUU	2209
D-1702	29-47	29-47	ACUGGCAUGUGUGGGGGCAUU	707	UGCCCCCACACAUGCCAGUUU	2210
D-1703	295-313	295-313	UCCAAGCUUCAGCCCCCUCUU	708	GAGGGGGCUGAAGCUUGGAUU	2211
D-1704	296-314	296-314	CCAAGCUUCAGCCCCCUCCUU	709	GGAGGGGGCUGAAGCUUGGUU	2212
D-1705	297-315	297-315	CAAGCUUCAGCCCCCUCCUUU	710	AGGAGGGGGCUGAAGCUUGUU	2213
D-1706	298-316	298-316	AAGCUUCAGCCCCCUCCUUUU	711	AAGGAGGGGGCUGAAGCUUUU	2214
D-1707	299-317	299-317	AGCUUCAGCCCCCUCCUUAUU	712	UAAGGAGGGGGCUGAAGCUUU	2215
D-1708	300-318	300-318	GCUUCAGCCCCCUCCUUAGUU	713	CUAAGGAGGGGGCUGAAGCUU	2216
D-1709	301-319	301-319	CUUCAGCCCCCUCCUUAGUUU	714	ACUAAGGAGGGGGCUGAAGUU	2217
D-1710	302-320	302-320	UUCAGCCCCCUCCUUAGUUUU	715	AACUAAGGAGGGGGCUGAAUU	2218
D-1711	303-321	303-321	UCAGCCCCCUCCUUAGUUCUU	716	GAACUAAGGAGGGGGCUGAUU	2219
D-1712	304-322	304-322	CAGCCCCCUCCUUAGUUCGUU	717	CGAACUAAGGAGGGGGCUGUU	2220
D-1713	30-48	30-48	CUGGCAUGUGUGGGGGCAAUU	718	UUGCCCCCACACAUGCCAGUU	2221
D-1714	305-323	305-323	AGCCCCCUCCUUAGUUCGGUU	719	CCGAACUAAGGAGGGGGCUUU	2222
D-1715	306-324	306-324	GCCCCCUCCUUAGUUCGGCUU	720	GCCGAACUAAGGAGGGGGCUU	2223
D-1716	307-325	307-325	CCCCCUCCUUAGUUCGGCAUU	721	UGCCGAACUAAGGAGGGGGUU	2224
D-1717	308-326	308-326	CCCCUCCUUAGUUCGGCAUUU	722	AUGCCGAACUAAGGAGGGGUU	2225
D-1718	309-327	309-327	CCCUCCUUAGUUCGGCAUCUU	723	GAUGCCGAACUAAGGAGGGUU	2226
D-1719	310-328	310-328	CCUCCUUAGUUCGGCAUCUUU	724	AGAUGCCGAACUAAGGAGGUU	2227
D-1720	311-329	311-329	CUCCUUAGUUCGGCAUCUGUU	725	CAGAUGCCGAACUAAGGAGUU	2228
D-1721	312-330	312-330	UCCUUAGUUCGGCAUCUGCUU	726	GCAGAUGCCGAACUAAGGAUU	2229
D-1722	313-331	313-331	CCUUAGUUCGGCAUCUGCAUU	727	UGCAGAUGCCGAACUAAGGUU	2230
D-1723	314-332	314-332	CUUAGUUCGGCAUCUGCACUU	728	GUGCAGAUGCCGAACUAAGUU	2231
D-1724	31-49	31-49	UGGCAUGUGUGGGGGCAACUU	729	GUUGCCCCCACACAUGCCAUU	2232
D-1725	315-333	315-333	UUAGUUCGGCAUCUGCACAUU	730	UGUGCAGAUGCCGAACUAAUU	2233
D-1726	316-334	316-334	UAGUUCGGCAUCUGCACAGUU	731	CUGUGCAGAUGCCGAACUAUU	2234
D-1727	317-335	317-335	AGUUCGGCAUCUGCACAGCUU	732	GCUGUGCAGAUGCCGAACUUU	2235
D-1728	318-336	318-336	GUUCGGCAUCUGCACAGCAUU	733	UGCUGUGCAGAUGCCGAACUU	2236
D-1729	319-337	319-337	UUCGGCAUCUGCACAGCACUU	734	GUGCUGUGCAGAUGCCGAAUU	2237
D-1730	320-338	320-338	UCGGCAUCUGCACAGCACUUU	735	AGUGCUGUGCAGAUGCCGAUU	2238
D-1731	3-21	3-21	CAAACGGUGCACGGAAGAGUU	736	CUCUUCCGUGCACCGUUUGUU	2239
D-1732	321-339	321-339	CGGCAUCUGCACAGCACUGUU	737	CAGUGCUGUGCAGAUGCCGUU	2240
D-1733	322-340	322-340	GGCAUCUGCACAGCACUGAUU	738	UCAGUGCUGUGCAGAUGCCUU	2241

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1734	323-341	323-341	GCAUCUGCACAGCACUGAAUU	739	UUCAGUGCUGUGCAGAUGCUU	2242
D-1735	324-342	324-342	CAUCUGCACAGCACUGAAGUU	740	CUUCAGUGCUGUGCAGAUGUU	2243
D-1736	32-50	32-50	GGCAUGUGUGGGGGCAACAUU	741	UGUUGCCCCCACACAUGCCUU	2244
D-1737	325-343	325-343	AUCUGCACAGCACUGAAGAUU	742	UCUUCAGUGCUGUGCAGAUUU	2245
D-1738	326-344	326-344	UCUGCACAGCACUGAAGAAUU	743	UUCUUCAGUGCUGUGCAGAUU	2246
D-1739	327-345	327-345	CUGCACAGCACUGAAGAACUU	744	GUUCUUCAGUGCUGUGCAGUU	2247
D-1740	328-346	328-346	UGCACAGCACUGAAGAACCUU	745	GGUUCUUCAGUGCUGUGCAUU	2248
D-1741	329-347	329-347	GCACAGCACUGAAGAACCUUU	746	AGGUUCUUCAGUGCUGUGCUU	2249
D-1742	330-348	330-348	CACAGCACUGAAGAACCUGUU	747	CAGGUUCUUCAGUGCUGUGUU	2250
D-1743	331-349	331-349	ACAGCACUGAAGAACCUGGUU	748	CCAGGUUCUUCAGUGCUGUUU	2251
D-1744	332-350	332-350	CAGCACUGAAGAACCUGGGUU	749	CCCAGGUUCUUCAGUGCUGUU	2252
D-1745	333-351	333-351	AGCACUGAAGAACCUGGGAUU	750	UCCCAGGUUCUUCAGUGCUUU	2253
D-1746	334-352	334-352	GCACUGAAGAACCUGGGAAUU	751	UUCCCAGGUUCUUCAGUGCUU	2254
D-1747	33-51	33-51	GCAUGUGUGGGGGCAACACUU	752	GUGUUGCCCCCACACAUGCUU	2255
D-1748	335-353	335-353	CACUGAAGAACCUGGGAAUUU	753	AUUCCCAGGUUCUUCAGUGUU	2256
D-1749	336-354	336-354	ACUGAAGAACCUGGGAAUCUU	754	GAUUCCCAGGUUCUUCAGUUU	2257
D-1750	337-355	337-355	CUGAAGAACCUGGGAAUCAUU	755	UGAUUCCCAGGUUCUUCAGUU	2258
D-1751	338-356	338-356	UGAAGAACCUGGGAAUCAGUU	756	CUGAUUCCCAGGUUCUUCAUU	2259
D-1752	339-357	339-357	GAAGAACCUGGGAAUCAGAUU	757	UCUGAUUCCCAGGUUCUUCUU	2260
D-1753	340-358	340-358	AAGAACCUGGGAAUCAGACUU	758	GUCUGAUUCCCAGGUUCUUUU	2261
D-1754	341-359	341-359	AGAACCUGGGAAUCAGACCUU	759	GGUCUGAUUCCCAGGUUCUUU	2262
D-1755	342-360	342-360	GAACCUGGGAAUCAGACCCUU	760	GGGUCUGAUUCCCAGGUUCUU	2263
D-1756	343-361	343-361	AACCUGGGAAUCAGACCCUUU	761	AGGGUCUGAUUCCCAGGUUUU	2264
D-1757	344-362	344-362	ACCUGGGAAUCAGACCCUGUU	762	CAGGGUCUGAUUCCCAGGUUU	2265
D-1758	34-52	34-52	CAUGUGUGGGGGCAACACGUU	763	CGUGUUGCCCCCACACAUGUU	2266
D-1759	345-363	345-363	CCUGGGAAUCAGACCCUGAUU	764	UCAGGGUCUGAUUCCCAGGUU	2267
D-1760	346-364	346-364	CUGGGAAUCAGACCCUGAGUU	765	CUCAGGGUCUGAUUCCCAGUU	2268
D-1761	347-365	347-365	UGGGAAUCAGACCCUGAGAUU	766	UCUCAGGGUCUGAUUCCCAUU	2269
D-1762	348-366	348-366	GGGAAUCAGACCCUGAGACUU	767	GUCUCAGGGUCUGAUUCCCUU	2270
D-1763	349-367	349-367	GGAAUCAGACCCUGAGACCUU	768	GGUCUCAGGGUCUGAUUCCUU	2271
D-1764	350-368	350-368	GAAUCAGACCCUGAGACCCUU	769	GGGUCUCAGGGUCUGAUUCUU	2272
D-1765	351-369	351-369	AAUCAGACCCUGAGACCCUUU	770	AGGGUCUCAGGGUCUGAUUUU	2273
D-1766	352-370	352-370	AUCAGACCCUGAGACCCUGUU	771	CAGGGUCUCAGGGUCUGAUUU	2274
D-1767	353-371	353-371	UCAGACCCUGAGACCCUGAUU	772	UCAGGGUCUCAGGGUCUGAUU	2275
D-1768	354-372	354-372	CAGACCCUGAGACCCUGAGUU	773	CUCAGGGUCUCAGGGUCUGUU	2276
D-1769	35-53	35-53	AUGUGUGGGGGCAACACGAUU	774	UCGUGUUGCCCCCACACAUUU	2277

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1770	355-373	355-373	AGACCCUGAGACCCUGAGCUU	775	GCUCAGGGUCUCAGGGUCUUU	2278
D-1771	356-374	356-374	GACCCUGAGACCCUGAGCAUU	776	UGCUCAGGGUCUCAGGGUCUU	2279
D-1772	357-375	357-375	ACCCUGAGACCCUGAGCAAUU	777	UUGCUCAGGGUCUCAGGGUUU	2280
D-1773	358-376	358-376	CCCUGAGACCCUGAGCAAUUU	778	AUUGCUCAGGGUCUCAGGGUU	2281
D-1774	359-377	359-377	CCUGAGACCCUGAGCAAUCUU	779	GAUUGCUCAGGGUCUCAGGUU	2282
D-1775	360-378	360-378	CUGAGACCCUGAGCAAUCCUU	780	GGAUUGCUCAGGGUCUCAGUU	2283
D-1776	361-379	361-379	UGAGACCCUGAGCAAUCCCUU	781	GGGAUUGCUCAGGGUCUCAUU	2284
D-1777	362-380	362-380	GAGACCCUGAGCAAUCCCAUU	782	UGGGAUUGCUCAGGGUCUCUU	2285
D-1778	363-381	363-381	AGACCCUGAGCAAUCCCAGUU	783	CUGGGAUUGCUCAGGGUCUUU	2286
D-1779	364-382	364-382	GACCCUGAGCAAUCCCAGGUU	784	CCUGGGAUUGCUCAGGGUCUU	2287
D-1780	365-383	365-383	ACCCUGAGCAAUCCCAGGUUU	785	ACCUGGGAUUGCUCAGGGUUU	2288
D-1781	36-54	36-54	UGUGUGGGGGCAACACGAUUU	786	AUCGUGUUGCCCCCACACAUU	2289
D-1782	366-384	366-384	CCCUGAGCAAUCCCAGGUCUU	787	GACCUGGGAUUGCUCAGGGUU	2290
D-1783	367-385	367-385	CCUGAGCAAUCCCAGGUCCUU	788	GGACCUGGGAUUGCUCAGGUU	2291
D-1784	368-386	368-386	CUGAGCAAUCCCAGGUCCAUU	789	UGGACCUGGGAUUGCUCAGUU	2292
D-1785	369-387	369-387	UGAGCAAUCCCAGGUCCAGUU	790	CUGGACCUGGGAUUGCUCAUU	2293
D-1786	370-388	370-388	GAGCAAUCCCAGGUCCAGCUU	791	GCUGGACCUGGGAUUGCUCUU	2294
D-1787	371-389	371-389	AGCAAUCCCAGGUCCAGCGUU	792	CGCUGGACCUGGGAUUGCUUU	2295
D-1788	372-390	372-390	GCAAUCCCAGGUCCAGCGCUU	793	GCGCUGGACCUGGGAUUGCUU	2296
D-1789	373-391	373-391	CAAUCCCAGGUCCAGCGCCUU	794	GGCGCUGGACCUGGGAUUGUU	2297
D-1790	374-392	374-392	AAUCCCAGGUCCAGCGCCAUU	795	UGGCGCUGGACCUGGGAUUUU	2298
D-1791	375-393	375-393	AUCCCAGGUCCAGCGCCAGUU	796	CUGGCGCUGGACCUGGGAUUU	2299
D-1792	37-55	37-55	GUGUGGGGGCAACACGAUUUU	797	AAUCGUGUUGCCCCCACACUU	2300
D-1793	376-394	376-394	UCCCAGGUCCAGCGCCAGCUU	798	GCUGGCGCUGGACCUGGGAUU	2301
D-1794	377-395	377-395	CCCAGGUCCAGCGCCAGCCUU	799	GGCUGGCGCUGGACCUGGGUU	2302
D-1795	378-396	378-396	CCAGGUCCAGCGCCAGCCCUU	800	GGGCUGGCGCUGGACCUGGUU	2303
D-1796	379-397	379-397	CAGGUCCAGCGCCAGCCCUUU	801	AGGGCUGGCGCUGGACCUGUU	2304
D-1797	380-398	380-398	AGGUCCAGCGCCAGCCCUAUU	802	UAGGGCUGGCGCUGGACCUUU	2305
D-1798	381-399	381-399	GGUCCAGCGCCAGCCCUAUUU	803	AUAGGGCUGGCGCUGGACCUU	2306
D-1799	382-400	382-400	GUCCAGCGCCAGCCCUAUCUU	804	GAUAGGGCUGGCGCUGGACUU	2307
D-1800	383-401	383-401	UCCAGCGCCAGCCCUAUCAUU	805	UGAUAGGGCUGGCGCUGGAUU	2308
D-1801	384-402	384-402	CCAGCGCCAGCCCUAUCAUUU	806	AUGAUAGGGCUGGCGCUGGUU	2309
D-1802	385-403	385-403	CAGCGCCAGCCCUAUCAUGUU	807	CAUGAUAGGGCUGGCGCUGUU	2310
D-1803	38-56	38-56	UGUGGGGGCAACACGAUUCUU	808	GAAUCGUGUUGCCCCCACAUU	2311
D-1804	386-404	386-404	AGCGCCAGCCCUAUCAUGAUU	809	UCAUGAUAGGGCUGGCGCUUU	2312
D-1805	387-405	387-405	GCGCCAGCCCUAUCAUGACUU	810	GUCAUGAUAGGGCUGGCGCUU	2313

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1806	388-406	388-406	CGCCAGCCCUAUCAUGACCUU	811	GGUCAUGAUAGGGCUGGCGUU	2314
D-1807	389-407	389-407	GCCAGCCCUAUCAUGACCAUU	812	UGGUCAUGAUAGGGCUGGCUU	2315
D-1808	390-408	390-408	CCAGCCCUAUCAUGACCAAUU	813	UUGGUCAUGAUAGGGCUGGUU	2316
D-1809	391-409	391-409	CAGCCCUAUCAUGACCAAGUU	814	CUUGGUCAUGAUAGGGCUGUU	2317
D-1810	392-410	392-410	AGCCCUAUCAUGACCAAGGUU	815	CCUUGGUCAUGAUAGGGCUUU	2318
D-1811	393-411	393-411	GCCCUAUCAUGACCAAGGAUU	816	UCCUUGGUCAUGAUAGGGCUU	2319
D-1812	394-412	394-412	CCCUAUCAUGACCAAGGAGUU	817	CUCCUUGGUCAUGAUAGGGUU	2320
D-1813	395-413	395-413	CCUAUCAUGACCAAGGAGUUU	818	ACUCCUUGGUCAUGAUAGGUU	2321
D-1814	39-57	39-57	GUGGGGGCAACACGAUUCUUU	819	AGAAUCGUGUUGCCCCCACUU	2322
D-1815	396-414	396-414	CUAUCAUGACCAAGGAGUAUU	820	UACUCCUUGGUCAUGAUAGUU	2323
D-1816	397-415	397-415	UAUCAUGACCAAGGAGUAUUU	821	AUACUCCUUGGUCAUGAUAUU	2324
D-1817	398-416	398-416	AUCAUGACCAAGGAGUAUCUU	822	GAUACUCCUUGGUCAUGAUUU	2325
D-1818	399-417	399-417	UCAUGACCAAGGAGUAUCAUU	823	UGAUACUCCUUGGUCAUGAUU	2326
D-1819	400-418	400-418	CAUGACCAAGGAGUAUCAAUU	824	UUGAUACUCCUUGGUCAUGUU	2327
D-1820	401-419	401-419	AUGACCAAGGAGUAUCAAGUU	825	CUUGAUACUCCUUGGUCAUUU	2328
D-1821	402-420	402-420	UGACCAAGGAGUAUCAAGAUU	826	UCUUGAUACUCCUUGGUCAUU	2329
D-1822	403-421	403-421	GACCAAGGAGUAUCAAGACUU	827	GUCUUGAUACUCCUUGGUCUU	2330
D-1823	404-422	404-422	ACCAAGGAGUAUCAAGACCUU	828	GGUCUUGAUACUCCUUGGUUU	2331
D-1824	405-423	405-423	CCAAGGAGUAUCAAGACCUUU	829	AGGUCUUGAUACUCCUUGGUU	2332
D-1825	40-58	40-58	UGGGGGCAACACGAUUCUCUU	830	GAGAAUCGUGUUGCCCCCAUU	2333
D-1826	406-424	406-424	CAAGGAGUAUCAAGACCUUUU	831	AAGGUCUUGAUACUCCUUGUU	2334
D-1827	407-425	407-425	AAGGAGUAUCAAGACCUUCUU	832	GAAGGUCUUGAUACUCCUUUU	2335
D-1828	408-426	408-426	AGGAGUAUCAAGACCUUCAUU	833	UGAAGGUCUUGAUACUCCUUU	2336
D-1829	409-427	409-427	GGAGUAUCAAGACCUUCAGUU	834	CUGAAGGUCUUGAUACUCCUU	2337
D-1830	410-428	410-428	GAGUAUCAAGACCUUCAGCUU	835	GCUGAAGGUCUUGAUACUCUU	2338
D-1831	411-429	411-429	AGUAUCAAGACCUUCAGCAUU	836	UGCUGAAGGUCUUGAUACUUU	2339
D-1832	412-430	412-430	GUAUCAAGACCUUCAGCAUUU	837	AUGCUGAAGGUCUUGAUACUU	2340
D-1833	413-431	413-431	UAUCAAGACCUUCAGCAUCUU	838	GAUGCUGAAGGUCUUGAUAUU	2341
D-1834	414-432	414-432	AUCAAGACCUUCAGCAUCUUU	839	AGAUGCUGAAGGUCUUGAUUU	2342
D-1835	415-433	415-433	UCAAGACCUUCAGCAUCUGUU	840	CAGAUGCUGAAGGUCUUGAUU	2343
D-1836	41-59	41-59	GGGGGCAACACGAUUCUCCUU	841	GGAGAAUCGUGUUGCCCCCUU	2344
D-1837	416-434	416-434	CAAGACCUUCAGCAUCUGGUU	842	CCAGAUGCUGAAGGUCUUGUU	2345
D-1838	417-435	417-435	AAGACCUUCAGCAUCUGGAUU	843	UCCAGAUGCUGAAGGUCUUUU	2346
D-1839	418-436	418-436	AGACCUUCAGCAUCUGGACUU	844	GUCCAGAUGCUGAAGGUCUUU	2347
D-1840	419-437	419-437	GACCUUCAGCAUCUGGACAUU	845	UGUCCAGAUGCUGAAGGUCUU	2348
D-1841	420-438	420-438	ACCUUCAGCAUCUGGACAAUU	846	UUGUCCAGAUGCUGAAGGUUU	2349

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-1842	421-439	421-439	CCUUCAGCAUCUGGACAAUUU	847	AUUGUCCAGAUGCUGAAGGUU	2350
D-1843	4-22	4-22	AAACGGUGCACGGAAGAGUUU	848	ACUCUUCCGUGCACCGUUUUU	2351
D-1844	422-440	422-440	CUUCAGCAUCUGGACAAUGUU	849	CAUUGUCCAGAUGCUGAAGUU	2352
D-1845	423-441	423-441	UUCAGCAUCUGGACAAUGAUU	850	UCAUUGUCCAGAUGCUGAAUU	2353
D-1846	424-442	424-442	UCAGCAUCUGGACAAUGAGUU	851	CUCAUUGUCCAGAUGCUGAUU	2354
D-1847	425-443	425-443	CAGCAUCUGGACAAUGAGGUU	852	CCUCAUUGUCCAGAUGCUGUU	2355
D-1848	42-60	42-60	GGGGCAACACGAUUCUCCUUU	853	AGGAGAAUCGUGUUGCCCCUU	2356
D-1849	426-444	426-444	AGCAUCUGGACAAUGAGGAUU	854	UCCUCAUUGUCCAGAUGCUUU	2357
D-1850	427-445	427-445	GCAUCUGGACAAUGAGGAGUU	855	CUCCUCAUUGUCCAGAUGCUU	2358
D-1851	428-446	428-446	CAUCUGGACAAUGAGGAGAUU	856	UCUCCUCAUUGUCCAGAUGUU	2359
D-1852	429-447	429-447	AUCUGGACAAUGAGGAGAGUU	857	CUCUCCUCAUUGUCCAGAUUU	2360
D-1853	430-448	430-448	UCUGGACAAUGAGGAGAGUUU	858	ACUCUCCUCAUUGUCCAGAUU	2361
D-1854	431-449	431-449	CUGGACAAUGAGGAGAGUGUU	859	CACUCUCCUCAUUGUCCAGUU	2362
D-1855	432-450	432-450	UGGACAAUGAGGAGAGUGAUU	860	UCACUCUCCUCAUUGUCCAUU	2363
D-1856	433-451	433-451	GGACAAUGAGGAGAGUGACUU	861	GUCACUCUCCUCAUUGUCCUU	2364
D-1857	434-452	434-452	GACAAUGAGGAGAGUGACCUU	862	GGUCACUCUCCUCAUUGUCUU	2365
D-1858	435-453	435-453	ACAAUGAGGAGAGUGACCAUU	863	UGGUCACUCUCCUCAUUGUUU	2366
D-1859	43-61	43-61	GGGCAACACGAUUCUCCUCUU	864	GAGGAGAAUCGUGUUGCCCUU	2367
D-1860	436-454	436-454	CAAUGAGGAGAGUGACCACUU	865	GUGGUCACUCUCCUCAUUGUU	2368
D-1861	437-455	437-455	AAUGAGGAGAGUGACCACCUU	866	GGUGGUCACUCUCCUCAUUUU	2369
D-1862	438-456	438-456	AUGAGGAGAGUGACCACCAUU	867	UGGUGGUCACUCUCCUCAUUU	2370
D-1863	439-457	439-457	UGAGGAGAGUGACCACCAUUU	868	AUGGUGGUCACUCUCCUCAUU	2371
D-1864	440-458	440-458	GAGGAGAGUGACCACCAUCUU	869	GAUGGUGGUCACUCUCCUCUU	2372
D-1865	441-459	441-459	AGGAGAGUGACCACCAUCAUU	870	UGAUGGUGGUCACUCUCCUUU	2373
D-1866	442-460	442-460	GGAGAGUGACCACCAUCAGUU	871	CUGAUGGUGGUCACUCUCCUU	2374
D-1867	443-461	443-461	GAGAGUGACCACCAUCAGCUU	872	GCUGAUGGUGGUCACUCUCUU	2375
D-1868	444-462	444-462	AGAGUGACCACCAUCAGCUUU	873	AGCUGAUGGUGGUCACUCUUU	2376
D-1869	445-463	445-463	GAGUGACCACCAUCAGCUCUU	874	GAGCUGAUGGUGGUCACUCUU	2377
D-1870	44-62	44-62	GGCAACACGAUUCUCCUCCUU	875	GGAGGAGAAUCGUGUUGCCUU	2378
D-1871	446-464	446-464	AGUGACCACCAUCAGCUCAUU	876	UGAGCUGAUGGUGGUCACUUU	2379
D-1872	447-465	447-465	GUGACCACCAUCAGCUCAGUU	877	CUGAGCUGAUGGUGGUCACUU	2380
D-1873	448-466	448-466	UGACCACCAUCAGCUCAGAUU	878	UCUGAGCUGAUGGUGGUCAUU	2381
D-1874	449-467	449-467	GACCACCAUCAGCUCAGAAUU	879	UUCUGAGCUGAUGGUGGUCUU	2382
D-1875	450-468	450-468	ACCACCAUCAGCUCAGAAAUU	880	UUUCUGAGCUGAUGGUGGUUU	2383
D-1876	451-469	451-469	CCACCAUCAGCUCAGAAAAUU	881	UUUUCUGAGCUGAUGGUGGUU	2384
D-1877	452-470	452-470	CACCAUCAGCUCAGAAAAGUU	882	CUUUUCUGAGCUGAUGGUGUU	2385

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1878	453-471	—	ACCAUCAGCUCAGAAAAGGUU	883	CCUUUUCUGAGCUGAUGGUUU	2386
D-1879	454-472	—	CCAUCAGCUCAGAAAAGGGUU	884	CCCUUUUCUGAGCUGAUGGUU	2387
D-1880	455-473	—	CAUCAGCUCAGAAAAGGGCUU	885	GCCCUUUUCUGAGCUGAUGUU	2388
D-1881	45-63	45-63	GCAACACGAUUCUCCUCCCUU	886	GGGAGGAGAAUCGUGUUGCUU	2389
D-1882	456-474	—	AUCAGCUCAGAAAAGGGCCUU	887	GGCCCUUUUCUGAGCUGAUUU	2390
D-1883	457-475	—	UCAGCUCAGAAAAGGGCCAUU	888	UGGCCCUUUUCUGAGCUGAUU	2391
D-1884	458-476	—	CAGCUCAGAAAAGGGCCACUU	889	GUGGCCCUUUUCUGAGCUGUU	2392
D-1885	459-477	—	AGCUCAGAAAAGGGCCACCUU	890	GGUGGCCCUUUUCUGAGCUUU	2393
D-1886	460-478	—	GCUCAGAAAAGGGCCACCUUU	891	AGGUGGCCCUUUUCUGAGCUU	2394
D-1887	461-479	—	CUCAGAAAAGGGCCACCUCUU	892	GAGGUGGCCCUUUUCUGAGUU	2395
D-1888	462-480	—	UCAGAAAAGGGCCACCUCCUU	893	GGAGGUGGCCCUUUUCUGAUU	2396
D-1889	463-481	—	CAGAAAAGGGCCACCUCCUUU	894	AGGAGGUGGCCCUUUUCUGUU	2397
D-1890	464-482	—	AGAAAAGGGCCACCUCCUCUU	895	GAGGAGGUGGCCCUUUUCUUU	2398
D-1891	465-483	—	GAAAAGGGCCACCUCCUCCUU	896	GGAGGAGGUGGCCCUUUUCUU	2399
D-1892	46-64	46-64	CAACACGAUUCUCCUCCCUUU	897	AGGGAGGAGAAUCGUGUUGUU	2400
D-1893	466-484	—	AAAAGGGCCACCUCCUCCCUU	898	GGGAGGAGGUGGCCCUUUUUU	2401
D-1894	467-485	—	AAAGGGCCACCUCCUCCCCUU	899	GGGGAGGAGGUGGCCCUUUUU	2402
D-1895	468-486	—	AAGGGCCACCUCCUCCCCAUU	900	UGGGGAGGAGGUGGCCCUUUU	2403
D-1896	469-487	—	AGGGCCACCUCCUCCCCAGUU	901	CUGGGGAGGAGGUGGCCCUUU	2404
D-1897	470-488	—	GGGCCACCUCCUCCCCAGCUU	902	GCUGGGGAGGAGGUGGCCCUU	2405
D-1898	471-489	—	GGCCACCUCCUCCCCAGCCUU	903	GGCUGGGGAGGAGGUGGCCUU	2406
D-1899	472-490	—	GCCACCUCCUCCCCAGCCCUU	904	GGGCUGGGGAGGAGGUGGCUU	2407
D-1900	473-491	—	CCACCUCCUCCCCAGCCCCUU	905	GGGGCUGGGGAGGAGGUGGUU	2408
D-1901	474-492	—	CACCUCCUCCCCAGCCCCUUU	906	AGGGGCUGGGGAGGAGGUGUU	2409
D-1902	475-493	—	ACCUCCUCCCCAGCCCCUCUU	907	GAGGGGCUGGGGAGGAGGUUU	2410
D-1903	476-494	—	CCUCCUCCCCAGCCCCUCCUU	908	GGAGGGGCUGGGGAGGAGGUU	2411
D-1904	47-65	47-65	AACACGAUUCUCCUCCCUGUU	909	CAGGGAGGAGAAUCGUGUUUU	2412
D-1905	477-495	—	CUCCUCCCCAGCCCCUCCUUU	910	AGGAGGGGCUGGGGAGGAGUU	2413
D-1906	478-496	—	UCCUCCCCAGCCCCUCCUGUU	911	CAGGAGGGGCUGGGGAGGAUU	2414
D-1907	479-497	—	CCUCCCCAGCCCCUCCUGCUU	912	GCAGGAGGGGCUGGGGAGGUU	2415
D-1908	480-498	—	CUCCCCAGCCCCUCCUGCAUU	913	UGCAGGAGGGGCUGGGGAGUU	2416
D-1909	481-499	—	UCCCCAGCCCCUCCUGCAGUU	914	CUGCAGGAGGGGCUGGGGAUU	2417
D-1910	482-500	—	CCCCAGCCCCUCCUGCAGCUU	915	GCUGCAGGAGGGGCUGGGGUU	2418
D-1911	483-501	—	CCCAGCCCCUCCUGCAGCGUU	916	CGCUGCAGGAGGGGCUGGGUU	2419
D-1912	484-502	—	CCAGCCCCUCCUGCAGCGUUU	917	ACGCUGCAGGAGGGGCUGGUU	2420
D-1913	485-503	—	CAGCCCCUCCUGCAGCGUCUU	918	GACGCUGCAGGAGGGGCUGUU	2421

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1914	486-504	—	AGCCCCUCCUGCAGCGUCUUU	919	AGACGCUGCAGGAGGGGCUUU	2422
D-1915	48-66	48-66	ACACGAUUCUCCUCCCUGGUU	920	CCAGGGAGGAGAAUCGUGUUU	2423
D-1916	487-505	—	GCCCCUCCUGCAGCGUCUCUU	921	GAGACGCUGCAGGAGGGGCUU	2424
D-1917	488-506	—	CCCCUCCUGCAGCGUCUCUUU	922	AGAGACGCUGCAGGAGGGGUU	2425
D-1918	489-507	—	CCCUCCUGCAGCGUCUCUGUU	923	CAGAGACGCUGCAGGAGGGUU	2426
D-1919	490-508	—	CCUCCUGCAGCGUCUCUGCUU	924	GCAGAGACGCUGCAGGAGGUU	2427
D-1920	491-509	—	CUCCUGCAGCGUCUCUGCUUU	925	AGCAGAGACGCUGCAGGAGUU	2428
D-1921	492-510	—	UCCUGCAGCGUCUCUGCUCUU	926	GAGCAGAGACGCUGCAGGAUU	2429
D-1922	493-511	—	CCUGCAGCGUCUCUGCUCCUU	927	GGAGCAGAGACGCUGCAGGUU	2430
D-1923	494-512	—	CUGCAGCGUCUCUGCUCCGUU	928	CGGAGCAGAGACGCUGCAGUU	2431
D-1924	495-513	—	UGCAGCGUCUCUGCUCCGGUU	929	CCGGAGCAGAGACGCUGCAUU	2432
D-1925	496-514	—	GCAGCGUCUCUGCUCCGGAUU	930	UCCGGAGCAGAGACGCUGCUU	2433
D-1926	49-67	49-67	CACGAUUCUCCUCCCUGGGUU	931	CCCAGGGAGGAGAAUCGUGUU	2434
D-1927	497-515	—	CAGCGUCUCUGCUCCGGACUU	932	GUCCGGAGCAGAGACGCUGUU	2435
D-1928	498-516	—	AGCGUCUCUGCUCCGGACCUU	933	GGUCCGGAGCAGAGACGCUUU	2436
D-1929	499-517	—	GCGUCUCUGCUCCGGACCUUU	934	AGGUCCGGAGCAGAGACGCUU	2437
D-1930	500-518	—	CGUCUCUGCUCCGGACCUCUU	935	GAGGUCCGGAGCAGAGACGUU	2438
D-1931	501-519	—	GUCUCUGCUCCGGACCUCGUU	936	CGAGGUCCGGAGCAGAGACUU	2439
D-1932	502-520	—	UCUCUGCUCCGGACCUCGCUU	937	GCGAGGUCCGGAGCAGAGAUU	2440
D-1933	503-521	—	CUCUGCUCCGGACCUCGCCUU	938	GGCGAGGUCCGGAGCAGAGUU	2441
D-1934	504-522	—	UCUGCUCCGGACCUCGCCUUU	939	AGGCGAGGUCCGGAGCAGAUU	2442
D-1935	505-523	—	CUGCUCCGGACCUCGCCUCUU	940	GAGGCGAGGUCCGGAGCAGUU	2443
D-1936	506-524	—	UGCUCCGGACCUCGCCUCCUU	941	GGAGGCGAGGUCCGGAGCAUU	2444
D-1937	50-68	50-68	ACGAUUCUCCUCCCUGGGGUU	942	CCCCAGGGAGGAGAAUCGUUU	2445
D-1938	507-525	—	GCUCCGGACCUCGCCUCCUUU	943	AGGAGGCGAGGUCCGGAGCUU	2446
D-1939	508-526	—	CUCCGGACCUCGCCUCCUCUU	944	GAGGAGGCGAGGUCCGGAGUU	2447
D-1940	509-527	—	UCCGGACCUCGCCUCCUCCUU	945	GGAGGAGGCGAGGUCCGGAUU	2448
D-1941	510-528	—	CCGGACCUCGCCUCCUCCUUU	946	AGGAGGAGGCGAGGUCCGGUU	2449
D-1942	511-529	—	CGGACCUCGCCUCCUCCUGUU	947	CAGGAGGAGGCGAGGUCCGUU	2450
D-1943	512-530	—	GGACCUCGCCUCCUCCUGCUU	948	GCAGGAGGAGGCGAGGUCCUU	2451
D-1944	513-531	—	GACCUCGCCUCCUCCUGCUUU	949	AGCAGGAGGAGGCGAGGUCUU	2452
D-1945	514-532	—	ACCUCGCCUCCUCCUGCUCUU	950	GAGCAGGAGGAGGCGAGGUUU	2453
D-1946	515-533	—	CCUCGCCUCCUCCUGCUCUUU	951	AGAGCAGGAGGAGGCGAGGUU	2454
D-1947	516-534	—	CUCGCCUCCUCCUGCUCUCUU	952	GAGAGCAGGAGGAGGCGAGUU	2455
D-1948	51-69	51-69	CGAUUCUCCUCCCUGGGGAUU	953	UCCCCAGGGAGGAGAAUCGUU	2456
D-1949	517-535	—	UCGCCUCCUCCUGCUCUCCUU	954	GGAGAGCAGGAGGAGGCGAUU	2457

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1950	518-536	—	CGCCUCCUCCUGCUCUCCCUU	955	GGGAGAGCAGGAGGAGGCGUU	2458
D-1951	519-537	—	GCCUCCUCCUGCUCUCCCUUU	956	AGGGAGAGCAGGAGGAGGCUU	2459
D-1952	520-538	—	CCUCCUCCUGCUCUCCCUGUU	957	CAGGGAGAGCAGGAGGAGGUU	2460
D-1953	521-539	—	CUCCUCCUGCUCUCCCUGGUU	958	CCAGGGAGAGCAGGAGGAGUU	2461
D-1954	522-540	—	UCCUCCUGCUCUCCCUGGGUU	959	CCCAGGGAGAGCAGGAGGAUU	2462
D-1955	5-23	5-23	AACGGUGCACGGAAGAGUGUU	960	CACUCUUCCGUGCACCGUUUU	2463
D-1956	523-541	—	CCUCCUGCUCUCCCUGGGCUU	961	GCCCAGGGAGAGCAGGAGGUU	2464
D-1957	524-542	—	CUCCUGCUCUCCCUGGGCCUU	962	GGCCCAGGGAGAGCAGGAGUU	2465
D-1958	525-543	—	UCCUGCUCUCCCUGGGCCUUU	963	AGGCCCAGGGAGAGCAGGAUU	2466
D-1959	526-544	—	CCUGCUCUCCCUGGGCCUCUU	964	GAGGCCCAGGGAGAGCAGGUU	2467
D-1960	52-70	52-70	GAUUCUCCUCCCUGGGGAGUU	965	CUCCCCAGGGAGGAGAAUCUU	2468
D-1961	527-545	—	CUGCUCUCCCUGGGCCUCAUU	966	UGAGGCCCAGGGAGAGCAGUU	2469
D-1962	528-546	—	UGCUCUCCCUGGGCCUCAGUU	967	CUGAGGCCCAGGGAGAGCAUU	2470
D-1963	529-547	—	GCUCUCCCUGGGCCUCAGCUU	968	GCUGAGGCCCAGGGAGAGCUU	2471
D-1964	530-548	—	CUCUCCCUGGGCCUCAGCCUU	969	GGCUGAGGCCCAGGGAGAGUU	2472
D-1965	531-549	—	UCUCCCUGGGCCUCAGCCUUU	970	AGGCUGAGGCCCAGGGAGAUU	2473
D-1966	532-550	—	CUCCCUGGGCCUCAGCCUCUU	971	GAGGCUGAGGCCCAGGGAGUU	2474
D-1967	533-551	—	UCCCUGGGCCUCAGCCUCCUU	972	GGAGGCUGAGGCCCAGGGAUU	2475
D-1968	534-552	—	CCCUGGGCCUCAGCCUCCUUU	973	AGGAGGCUGAGGCCCAGGGUU	2476
D-1969	535-553	—	CCUGGGCCUCAGCCUCCUGUU	974	CAGGAGGCUGAGGCCCAGGUU	2477
D-1970	536-554	—	CUGGGCCUCAGCCUCCUGCUU	975	GCAGGAGGCUGAGGCCCAGUU	2478
D-1971	53-71	53-71	AUUCUCCUCCCUGGGGAGCUU	976	GCUCCCCAGGGAGGAGAAUUU	2479
D-1972	537-555	—	UGGGCCUCAGCCUCCUGCUUU	977	AGCAGGAGGCUGAGGCCCAUU	2480
D-1973	538-556	—	GGGCCUCAGCCUCCUGCUGUU	978	CAGCAGGAGGCUGAGGCCCUU	2481
D-1974	539-557	—	GGCCUCAGCCUCCUGCUGCUU	979	GCAGCAGGAGGCUGAGGCCUU	2482
D-1975	540-558	—	GCCUCAGCCUCCUGCUGCUUU	980	AGCAGCAGGAGGCUGAGGCUU	2483
D-1976	541-559	—	CCUCAGCCUCCUGCUGCUUUU	981	AAGCAGCAGGAGGCUGAGGUU	2484
D-1977	542-560	—	CUCAGCCUCCUGCUGCUUGUU	982	CAAGCAGCAGGAGGCUGAGUU	2485
D-1978	543-561	—	UCAGCCUCCUGCUGCUUGUUU	983	ACAAGCAGCAGGAGGCUGAUU	2486
D-1979	544-562	—	CAGCCUCCUGCUGCUUGUGUU	984	CACAAGCAGCAGGAGGCUGUU	2487
D-1980	545-563	—	AGCCUCCUGCUGCUUGUGGUU	985	CCACAAGCAGCAGGAGGCUUU	2488
D-1981	546-564	—	GCCUCCUGCUGCUUGUGGUUU	986	ACCACAAGCAGCAGGAGGCUU	2489
D-1982	54-72	54-72	UUCUCCUCCCUGGGGAGCAUU	987	UGCUCCCCAGGGAGGAGAAUU	2490
D-1983	547-565	—	CCUCCUGCUGCUUGUGGUUUU	988	AACCACAAGCAGCAGGAGGUU	2491
D-1984	548-566	—	CUCCUGCUGCUUGUGGUUGUU	989	CAACCACAAGCAGCAGGAGUU	2492
D-1985	549-567	—	UCCUGCUGCUUGUGGUUGUUU	990	ACAACCACAAGCAGCAGGAUU	2493

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-1986	550-568	—	CCUGCUGCUUGUGGUUGUCUU	991	GACAACCACAAGCAGCAGGUU	2494
D-1987	551-569	—	CUGCUGCUUGUGGUUGUCUUU	992	AGACAACCACAAGCAGCAGUU	2495
D-1988	552-570	—	UGCUGCUUGUGGUUGUCUGUU	993	CAGACAACCACAAGCAGCAUU	2496
D-1989	553-571	—	GCUGCUUGUGGUUGUCUGUUU	994	ACAGACAACCACAAGCAGCUU	2497
D-1990	554-572	—	CUGCUUGUGGUUGUCUGUGUU	995	CACAGACAACCACAAGCAGUU	2498
D-1991	555-573	—	UGCUUGUGGUUGUCUGUGUUU	996	ACACAGACAACCACAAGCAUU	2499
D-1992	556-574	—	GCUUGUGGUUGUCUGUGUGUU	997	CACACAGACAACCACAAGCUU	2500
D-1993	55-73	55-73	UCUCCUCCCUGGGGAGCAGUU	998	CUGCUCCCCAGGGAGGAGAUU	2501
D-1994	557-575	—	CUUGUGGUUGUCUGUGUGAUU	999	UCACACAGACAACCACAAGUU	2502
D-1995	558-576	—	UUGUGGUUGUCUGUGUGAUUU	1000	AUCACACAGACAACCACAAUU	2503
D-1996	559-577	—	UGUGGUUGUCUGUGUGAUCUU	1001	GAUCACACAGACAACCACAUU	2504
D-1997	560-578	—	GUGGUUGUCUGUGUGAUCGUU	1002	CGAUCACACAGACAACCACUU	2505
D-1998	561-579	—	UGGUUGUCUGUGUGAUCGGUU	1003	CCGAUCACACAGACAACCAUU	2506
D-1999	562-580	—	GGUUGUCUGUGUGAUCGGAUU	1004	UCCGAUCACACAGACAACCUU	2507
D-2000	563-581	—	GUUGUCUGUGUGAUCGGAUUU	1005	AUCCGAUCACACAGACAACUU	2508
D-2001	564-582	—	UUGUCUGUGUGAUCGGAUCUU	1006	GAUCCGAUCACACAGACAAUU	2509
D-2002	565-583	—	UGUCUGUGUGAUCGGAUCCUU	1007	GGAUCCGAUCACACAGACAUU	2510
D-2003	566-584	—	GUCUGUGUGAUCGGAUCCCUU	1008	GGGAUCCGAUCACACAGACUU	2511
D-2004	56-74	56-74	CUCCUCCCUGGGGAGCAGAUU	1009	UCUGCUCCCCAGGGAGGAGUU	2512
D-2005	567-585	—	UCUGUGUGAUCGGAUCCCAUU	1010	UGGGAUCCGAUCACACAGAUU	2513
D-2006	568-586	—	CUGUGUGAUCGGAUCCCAAUU	1011	UUGGGAUCCGAUCACACAGUU	2514
D-2007	569-587	—	UGUGUGAUCGGAUCCCAAAUU	1012	UUUGGGAUCCGAUCACACAUU	2515
D-2008	570-588	—	GUGUGAUCGGAUCCCAAAAUU	1013	UUUUGGGAUCCGAUCACACUU	2516
D-2009	571-589	—	UGUGAUCGGAUCCCAAAACUU	1014	GUUUUGGGAUCCGAUCACAUU	2517
D-2010	572-590	—	GUGAUCGGAUCCCAAAACUUU	1015	AGUUUUGGGAUCCGAUCACUU	2518
D-2011	573-591	—	UGAUCGGAUCCCAAAACUCUU	1016	GAGUUUUGGGAUCCGAUCAUU	2519
D-2012	574-592	—	GAUCGGAUCCCAAAACUCCUU	1017	GGAGUUUUGGGAUCCGAUCUU	2520
D-2013	575-593	—	AUCGGAUCCCAAAACUCCCUU	1018	GGGAGUUUUGGGAUCCGAUUU	2521
D-2014	576-594	—	UCGGAUCCCAAAACUCCCAUU	1019	UGGGAGUUUUGGGAUCCGAUU	2522
D-2015	57-75	57-75	UCCUCCCUGGGGAGCAGAGUU	1020	CUCUGCUCCCCAGGGAGGAUU	2523
D-2016	577-595	—	CGGAUCCCAAAACUCCCAGUU	1021	CUGGGAGUUUUGGGAUCCGUU	2524
D-2017	578-596	—	GGAUCCCAAAACUCCCAGCUU	1022	GCUGGGAGUUUUGGGAUCCUU	2525
D-2018	579-597	—	GAUCCCAAAACUCCCAGCUUU	1023	AGCUGGGAGUUUUGGGAUCUU	2526
D-2019	580-598	—	AUCCCAAAACUCCCAGCUGUU	1024	CAGCUGGGAGUUUUGGGAUUU	2527
D-2020	581-599	—	UCCCAAAACUCCCAGCUGCUU	1025	GCAGCUGGGAGUUUUGGGAUU	2528
D-2021	582-600	—	CCCAAAACUCCCAGCUGCAUU	1026	UGCAGCUGGGAGUUUUGGGUU	2529

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2022	583-601	—	CCAAAACUCCCAGCUGCAGUU	1027	CUGCAGCUGGGAGUUUUGGUU	2530
D-2023	584-602	—	CAAAACUCCCAGCUGCAGGUU	1028	CCUGCAGCUGGGAGUUUUGUU	2531
D-2024	585-603	—	AAAACUCCCAGCUGCAGGAUU	1029	UCCUGCAGCUGGGAGUUUUUU	2532
D-2025	586-604	—	AAACUCCCAGCUGCAGGAGUU	1030	CUCCUGCAGCUGGGAGUUUUU	2533
D-2026	58-76	58-76	CCUCCCUGGGGAGCAGAGCUU	1031	GCUCUGCUCCCCAGGGAGGUU	2534
D-2027	587-605	—	AACUCCCAGCUGCAGGAGGUU	1032	CCUCCUGCAGCUGGGAGUUUU	2535
D-2028	588-606	471-489	ACUCCCAGCUGCAGGAGGAUU	1033	UCCUCCUGCAGCUGGGAGUUU	2536
D-2029	589-607	472-490	CUCCCAGCUGCAGGAGGAGUU	1034	CUCCUCCUGCAGCUGGGAGUU	2537
D-2030	590-608	473-491	UCCCAGCUGCAGGAGGAGCUU	1035	GCUCCUCCUGCAGCUGGGAUU	2538
D-2031	591-609	474-492	CCCAGCUGCAGGAGGAGCUUU	1036	AGCUCCUCCUGCAGCUGGGUU	2539
D-2032	592-610	475-493	CCAGCUGCAGGAGGAGCUGUU	1037	CAGCUCCUCCUGCAGCUGGUU	2540
D-2033	593-611	476-494	CAGCUGCAGGAGGAGCUGCUU	1038	GCAGCUCCUCCUGCAGCUGUU	2541
D-2034	594-612	477-495	AGCUGCAGGAGGAGCUGCGUU	1039	CGCAGCUCCUCCUGCAGCUUU	2542
D-2035	595-613	478-496	GCUGCAGGAGGAGCUGCGGUU	1040	CCGCAGCUCCUCCUGCAGCUU	2543
D-2036	596-614	479-497	CUGCAGGAGGAGCUGCGGGUU	1041	CCCGCAGCUCCUCCUGCAGUU	2544
D-2037	597-615	480-498	UGCAGGAGGAGCUGCGGGGUU	1042	CCCCGCAGCUCCUCCUGCAUU	2545
D-2038	59-77	59-77	CUCCCUGGGGAGCAGAGCAUU	1043	UGCUCUGCUCCCCAGGGAGUU	2546
D-2039	598-616	481-499	GCAGGAGGAGCUGCGGGGCUU	1044	GCCCCGCAGCUCCUCCUGCUU	2547
D-2040	599-617	482-500	CAGGAGGAGCUGCGGGGCCUU	1045	GGCCCCGCAGCUCCUCCUGUU	2548
D-2041	600-618	483-501	AGGAGGAGCUGCGGGGCCUUU	1046	AGGCCCCGCAGCUCCUCCUUU	2549
D-2042	601-619	484-502	GGAGGAGCUGCGGGGCCUGUU	1047	CAGGCCCCGCAGCUCCUCCUU	2550
D-2043	602-620	485-503	GAGGAGCUGCGGGGCCUGAUU	1048	UCAGGCCCCGCAGCUCCUCUU	2551
D-2044	603-621	486-504	AGGAGCUGCGGGGCCUGAGUU	1049	CUCAGGCCCCGCAGCUCCUUU	2552
D-2045	604-622	487-505	GGAGCUGCGGGGCCUGAGAUU	1050	UCUCAGGCCCCGCAGCUCCUU	2553
D-2046	605-623	488-506	GAGCUGCGGGGCCUGAGAGUU	1051	CUCUCAGGCCCCGCAGCUCUU	2554
D-2047	606-624	489-507	AGCUGCGGGGCCUGAGAGAUU	1052	UCUCUCAGGCCCCGCAGCUUU	2555
D-2048	607-625	490-508	GCUGCGGGGCCUGAGAGAGUU	1053	CUCUCUCAGGCCCCGCAGCUU	2556
D-2049	60-78	60-78	UCCCUGGGGAGCAGAGCAGUU	1054	CUGCUCUGCUCCCCAGGGAUU	2557
D-2050	608-626	491-509	CUGCGGGGCCUGAGAGAGAUU	1055	UCUCUCUCAGGCCCCGCAGUU	2558
D-2051	609-627	492-510	UGCGGGGCCUGAGAGAGACUU	1056	GUCUCUCUCAGGCCCCGCAUU	2559
D-2052	610-628	493-511	GCGGGGCCUGAGAGAGACGUU	1057	CGUCUCUCUCAGGCCCCGCUU	2560
D-2053	611-629	494-512	CGGGGCCUGAGAGAGACGUUU	1058	ACGUCUCUCUCAGGCCCCGUU	2561
D-2054	612-630	495-513	GGGGCCUGAGAGAGACGUUUU	1059	AACGUCUCUCUCAGGCCCCUU	2562
D-2055	613-631	496-514	GGGCCUGAGAGAGACGUUCUU	1060	GAACGUCUCUCUCAGGCCCUU	2563
D-2056	614-632	497-515	GGCCUGAGAGAGACGUUCAUU	1061	UGAACGUCUCUCUCAGGCCUU	2564
D-2057	615-633	498-516	GCCUGAGAGAGACGUUCAGUU	1062	CUGAACGUCUCUCUCAGGCUU	2565

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2058	616-634	499-517	CCUGAGAGAGACGUUCAGCUU	1063	GCUGAACGUCUCUCUCAGGUU	2566
D-2059	617-635	500-518	CUGAGAGAGACGUUCAGCAUU	1064	UGCUGAACGUCUCUCUCAGUU	2567
D-2060	61-79	61-79	CCCUGGGGAGCAGAGCAGAUU	1065	UCUGCUCUGCUCCCCAGGGUU	2568
D-2061	618-636	501-519	UGAGAGAGACGUUCAGCAAUU	1066	UUGCUGAACGUCUCUCUCAUU	2569
D-2062	619-637	502-520	GAGAGAGACGUUCAGCAACUU	1067	GUUGCUGAACGUCUCUCUCUU	2570
D-2063	620-638	503-521	AGAGAGACGUUCAGCAACUUU	1068	AGUUGCUGAACGUCUCUCUUU	2571
D-2064	621-639	504-522	GAGAGACGUUCAGCAACUUUU	1069	AAGUUGCUGAACGUCUCUCUU	2572
D-2065	622-640	505-523	AGAGACGUUCAGCAACUUCUU	1070	GAAGUUGCUGAACGUCUCUUU	2573
D-2066	623-641	506-524	GAGACGUUCAGCAACUUCAUU	1071	UGAAGUUGCUGAACGUCUCUU	2574
D-2067	6-24	6-24	ACGGUGCACGGAAGAGUGAUU	1072	UCACUCUUCCGUGCACCGUUU	2575
D-2068	624-642	507-525	AGACGUUCAGCAACUUCACUU	1073	GUGAAGUUGCUGAACGUCUUU	2576
D-2069	625-643	508-526	GACGUUCAGCAACUUCACAUU	1074	UGUGAAGUUGCUGAACGUCUU	2577
D-2070	626-644	509-527	ACGUUCAGCAACUUCACAGUU	1075	CUGUGAAGUUGCUGAACGUUU	2578
D-2071	627-645	510-528	CGUUCAGCAACUUCACAGCUU	1076	GCUGUGAAGUUGCUGAACGUU	2579
D-2072	62-80	62-80	CCUGGGGAGCAGAGCAGAGUU	1077	CUCUGCUCUGCUCCCCAGGUU	2580
D-2073	628-646	511-529	GUUCAGCAACUUCACAGCGUU	1078	CGCUGUGAAGUUGCUGAACUU	2581
D-2074	629-647	512-530	UUCAGCAACUUCACAGCGAUU	1079	UCGCUGUGAAGUUGCUGAAUU	2582
D-2075	630-648	513-531	UCAGCAACUUCACAGCGAGUU	1080	CUCGCUGUGAAGUUGCUGAUU	2583
D-2076	631-649	514-532	CAGCAACUUCACAGCGAGCUU	1081	GCUCGCUGUGAAGUUGCUGUU	2584
D-2077	632-650	515-533	AGCAACUUCACAGCGAGCAUU	1082	UGCUCGCUGUGAAGUUGCUUU	2585
D-2078	633-651	516-534	GCAACUUCACAGCGAGCACUU	1083	GUGCUCGCUGUGAAGUUGCUU	2586
D-2079	634-652	517-535	CAACUUCACAGCGAGCACGUU	1084	CGUGCUCGCUGUGAAGUUGUU	2587
D-2080	635-653	518-536	AACUUCACAGCGAGCACGGUU	1085	CCGUGCUCGCUGUGAAGUUUU	2588
D-2081	636-654	519-537	ACUUCACAGCGAGCACGGAUU	1086	UCCGUGCUCGCUGUGAAGUUU	2589
D-2082	637-655	520-538	CUUCACAGCGAGCACGGAGUU	1087	CUCCGUGCUCGCUGUGAAGUU	2590
D-2083	63-81	63-81	CUGGGGAGCAGAGCAGAGGUU	1088	CCUCUGCUCUGCUCCCCAGUU	2591
D-2084	638-656	521-539	UUCACAGCGAGCACGGAGGUU	1089	CCUCCGUGCUCGCUGUGAAUU	2592
D-2085	639-657	522-540	UCACAGCGAGCACGGAGGCUU	1090	GCCUCCGUGCUCGCUGUGAUU	2593
D-2086	640-658	523-541	CACAGCGAGCACGGAGGCCUU	1091	GGCCUCCGUGCUCGCUGUGUU	2594
D-2087	641-659	524-542	ACAGCGAGCACGGAGGCCCUU	1092	GGGCCUCCGUGCUCGCUGUUU	2595
D-2088	642-660	525-543	CAGCGAGCACGGAGGCCCAUU	1093	UGGGCCUCCGUGCUCGCUGUU	2596
D-2089	643-661	526-544	AGCGAGCACGGAGGCCCAGUU	1094	CUGGGCCUCCGUGCUCGCUUU	2597
D-2090	644-662	527-545	GCGAGCACGGAGGCCCAGGUU	1095	CCUGGGCCUCCGUGCUCGCUU	2598
D-2091	645-663	528-546	CGAGCACGGAGGCCCAGGUUU	1096	ACCUGGGCCUCCGUGCUCGUU	2599
D-2092	646-664	529-547	GAGCACGGAGGCCCAGGUCUU	1097	GACCUGGGCCUCCGUGCUCUU	2600
D-2093	647-665	530-548	AGCACGGAGGCCCAGGUCAUU	1098	UGACCUGGGCCUCCGUGCUUU	2601

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2094	64-82	64-82	UGGGGAGCAGAGCAGAGGCUU	1099	GCCUCUGCUCUGCUCCCCAUU	2602
D-2095	648-666	531-549	GCACGGAGGCCCAGGUCAAUU	1100	UUGACCUGGGCCUCCGUGCUU	2603
D-2096	649-667	532-550	CACGGAGGCCCAGGUCAAGUU	1101	CUUGACCUGGGCCUCCGUGUU	2604
D-2097	650-668	533-551	ACGGAGGCCCAGGUCAAGGUU	1102	CCUUGACCUGGGCCUCCGUUU	2605
D-2098	651-669	534-552	CGGAGGCCCAGGUCAAGGGUU	1103	CCCUUGACCUGGGCCUCCGUU	2606
D-2099	652-670	535-553	GGAGGCCCAGGUCAAGGGCUU	1104	GCCCUUGACCUGGGCCUCCUU	2607
D-2100	653-671	536-554	GAGGCCCAGGUCAAGGGCUUU	1105	AGCCCUUGACCUGGGCCUCUU	2608
D-2101	654-672	537-555	AGGCCCAGGUCAAGGGCUUUU	1106	AAGCCCUUGACCUGGGCCUUU	2609
D-2102	655-673	538-556	GGCCCAGGUCAAGGGCUUGUU	1107	CAAGCCCUUGACCUGGGCCUU	2610
D-2103	656-674	539-557	GCCCAGGUCAAGGGCUUGAUU	1108	UCAAGCCCUUGACCUGGGCUU	2611
D-2104	657-675	540-558	CCCAGGUCAAGGGCUUGAGUU	1109	CUCAAGCCCUUGACCUGGGUU	2612
D-2105	65-83	65-83	GGGGAGCAGAGCAGAGGCAUU	1110	UGCCUCUGCUCUGCUCCCCUU	2613
D-2106	658-676	541-559	CCAGGUCAAGGGCUUGAGCUU	1111	GCUCAAGCCCUUGACCUGGUU	2614
D-2107	659-677	542-560	CAGGUCAAGGGCUUGAGCAUU	1112	UGCUCAAGCCCUUGACCUGUU	2615
D-2108	660-678	543-561	AGGUCAAGGGCUUGAGCACUU	1113	GUGCUCAAGCCCUUGACCUUU	2616
D-2109	661-679	544-562	GGUCAAGGGCUUGAGCACCUU	1114	GGUGCUCAAGCCCUUGACCUU	2617
D-2110	662-680	545-563	GUCAAGGGCUUGAGCACCCUU	1115	GGGUGCUCAAGCCCUUGACUU	2618
D-2111	663-681	546-564	UCAAGGGCUUGAGCACCCAUU	1116	UGGGUGCUCAAGCCCUUGAUU	2619
D-2112	664-682	547-565	CAAGGGCUUGAGCACCCAGUU	1117	CUGGGUGCUCAAGCCCUUGUU	2620
D-2113	665-683	548-566	AAGGGCUUGAGCACCCAGGUU	1118	CCUGGGUGCUCAAGCCCUUUU	2621
D-2114	666-684	549-567	AGGGCUUGAGCACCCAGGGUU	1119	CCCUGGGUGCUCAAGCCCUUU	2622
D-2115	667-685	550-568	GGGCUUGAGCACCCAGGGAUU	1120	UCCCUGGGUGCUCAAGCCCUU	2623
D-2116	66-84	66-84	GGGAGCAGAGCAGAGGCAAUU	1121	UUGCCUCUGCUCUGCUCCCUU	2624
D-2117	668-686	551-569	GGCUUGAGCACCCAGGGAGUU	1122	CUCCCUGGGUGCUCAAGCCUU	2625
D-2118	669-687	552-570	GCUUGAGCACCCAGGGAGGUU	1123	CCUCCCUGGGUGCUCAAGCUU	2626
D-2119	670-688	553-571	CUUGAGCACCCAGGGAGGCUU	1124	GCCUCCCUGGGUGCUCAAGUU	2627
D-2120	671-689	554-572	UUGAGCACCCAGGGAGGCAUU	1125	UGCCUCCCUGGGUGCUCAAUU	2628
D-2121	672-690	555-573	UGAGCACCCAGGGAGGCAAUU	1126	UUGCCUCCCUGGGUGCUCAUU	2629
D-2122	673-691	556-574	GAGCACCCAGGGAGGCAAUUU	1127	AUUGCCUCCCUGGGUGCUCUU	2630
D-2123	674-692	557-575	AGCACCCAGGGAGGCAAUGUU	1128	CAUUGCCUCCCUGGGUGCUUU	2631
D-2124	675-693	558-576	GCACCCAGGGAGGCAAUGUUU	1129	ACAUUGCCUCCCUGGGUGCUU	2632
D-2125	676-694	559-577	CACCCAGGGAGGCAAUGUGUU	1130	CACAUUGCCUCCCUGGGUGUU	2633
D-2126	677-695	560-578	ACCCAGGGAGGCAAUGUGGUU	1131	CCACAUUGCCUCCCUGGGUUU	2634
D-2127	67-85	67-85	GGAGCAGAGCAGAGGCAACUU	1132	GUUGCCUCUGCUCUGCUCCUU	2635
D-2128	678-696	561-579	CCCAGGGAGGCAAUGUGGGUU	1133	CCCACAUUGCCUCCCUGGGUU	2636
D-2129	679-697	562-580	CCAGGGAGGCAAUGUGGGAUU	1134	UCCCACAUUGCCUCCCUGGUU	2637

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2130	680-698	563-581	CAGGGAGGCAAUGUGGGAAUU	1135	UUCCCACAUUGCCUCCCUGUU	2638
D-2131	681-699	564-582	AGGGAGGCAAUGUGGGAAGUU	1136	CUUCCCACAUUGCCUCCCUUU	2639
D-2132	682-700	565-583	GGGAGGCAAUGUGGGAAGAUU	1137	UCUUCCCACAUUGCCUCCCUU	2640
D-2133	683-701	566-584	GGAGGCAAUGUGGGAAGAAUU	1138	UUCUUCCCACAUUGCCUCCUU	2641
D-2134	684-702	567-585	GAGGCAAUGUGGGAAGAAAUU	1139	UUUCUUCCCACAUUGCCUCUU	2642
D-2135	685-703	568-586	AGGCAAUGUGGGAAGAAAGUU	1140	CUUUCUUCCCACAUUGCCUUU	2643
D-2136	686-704	569-587	GGCAAUGUGGGAAGAAAGAUU	1141	UCUUUCUUCCCACAUUGCCUU	2644
D-2137	687-705	570-588	GCAAUGUGGGAAGAAAGAUUU	1142	AUCUUUCUUCCCACAUUGCUU	2645
D-2138	68-86	68-86	GAGCAGAGCAGAGGCAACCUU	1143	GGUUGCCUCUGCUCUGCUCUU	2646
D-2139	688-706	571-589	CAAUGUGGGAAGAAAGAUGUU	1144	CAUCUUUCUUCCCACAUUGUU	2647
D-2140	689-707	572-590	AAUGUGGGAAGAAAGAUGAUU	1145	UCAUCUUUCUUCCCACAUUUU	2648
D-2141	690-708	573-591	AUGUGGGAAGAAAGAUGAAUU	1146	UUCAUCUUUCUUCCCACAUUU	2649
D-2142	691-709	574-592	UGUGGGAAGAAAGAUGAAGUU	1147	CUUCAUCUUUCUUCCCACAUU	2650
D-2143	692-710	575-593	GUGGGAAGAAAGAUGAAGUUU	1148	ACUUCAUCUUUCUUCCCACUU	2651
D-2144	693-711	576-594	UGGGAAGAAAGAUGAAGUCUU	1149	GACUUCAUCUUUCUUCCCAUU	2652
D-2145	694-712	577-595	GGGAAGAAAGAUGAAGUCGUU	1150	CGACUUCAUCUUUCUUCCCUU	2653
D-2146	695-713	578-596	GGAAGAAAGAUGAAGUCGCUU	1151	GCGACUUCAUCUUUCUUCCUU	2654
D-2147	696-714	579-597	GAAGAAAGAUGAAGUCGCUUU	1152	AGCGACUUCAUCUUUCUUCUU	2655
D-2148	697-715	580-598	AAGAAAGAUGAAGUCGCUAUU	1153	UAGCGACUUCAUCUUUCUUUU	2656
D-2149	69-87	69-87	AGCAGAGCAGAGGCAACCCUU	1154	GGGUUGCCUCUGCUCUGCUUU	2657
D-2150	698-716	581-599	AGAAAGAUGAAGUCGCUAGUU	1155	CUAGCGACUUCAUCUUUCUUU	2658
D-2151	699-717	581-600	GAAAGAUGAAGUCGCUAGAUU	1156	UCUAGCGACUUCAUCUUUCUU	2659
D-2152	700-718	581-601	AAAGAUGAAGUCGCUAGAGUU	1157	CUCUAGCGACUUCAUCUUUUU	2660
D-2153	701-719	581-602	AAGAUGAAGUCGCUAGAGUUU	1158	ACUCUAGCGACUUCAUCUUUU	2661
D-2154	702-720	581-603	AGAUGAAGUCGCUAGAGUCUU	1159	GACUCUAGCGACUUCAUCUUU	2662
D-2155	703-721	581-604	GAUGAAGUCGCUAGAGUCCUU	1160	GGACUCUAGCGACUUCAUCUU	2663
D-2156	704-722	581-605	AUGAAGUCGCUAGAGUCCCUU	1161	GGGACUCUAGCGACUUCAUUU	2664
D-2157	705-723	581-606	UGAAGUCGCUAGAGUCCCAUU	1162	UGGGACUCUAGCGACUUCAUU	2665
D-2158	706-724	581-607	GAAGUCGCUAGAGUCCCAGUU	1163	CUGGGACUCUAGCGACUUCUU	2666
D-2159	707-725	581-608	AAGUCGCUAGAGUCCCAGCUU	1164	GCUGGGACUCUAGCGACUUUU	2667
D-2160	708-726	581-609	AGUCGCUAGAGUCCCAGCUUU	1165	AGCUGGGACUCUAGCGACUUU	2668
D-2161	70-88	70-88	GCAGAGCAGAGGCAACCCAUU	1166	UGGGUUGCCUCUGCUCUGCUU	2669
D-2162	709-727	592-610	GUCGCUAGAGUCCCAGCUGUU	1167	CAGCUGGGACUCUAGCGACUU	2670
D-2163	710-728	593-611	UCGCUAGAGUCCCAGCUGGUU	1168	CCAGCUGGGACUCUAGCGAUU	2671
D-2164	711-729	594-612	CGCUAGAGUCCCAGCUGGAUU	1169	UCCAGCUGGGACUCUAGCGUU	2672
D-2165	712-730	595-613	GCUAGAGUCCCAGCUGGAGUU	1170	CUCCAGCUGGGACUCUAGCUU	2673

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2166	713-731	596-614	CUAGAGUCCCAGCUGGAGAUU	1171	UCUCCAGCUGGGACUCUAGUU	2674
D-2167	714-732	597-615	UAGAGUCCCAGCUGGAGAAUU	1172	UUCUCCAGCUGGGACUCUAUU	2675
D-2168	715-733	598-616	AGAGUCCCAGCUGGAGAAAUU	1173	UUUCUCCAGCUGGGACUCUUU	2676
D-2169	716-734	599-617	GAGUCCCAGCUGGAGAAACUU	1174	GUUUCUCCAGCUGGGACUCUU	2677
D-2170	717-735	600-618	AGUCCCAGCUGGAGAAACAUU	1175	UGUUUCUCCAGCUGGGACUUU	2678
D-2171	718-736	601-619	GUCCCAGCUGGAGAAACAGUU	1176	CUGUUUCUCCAGCUGGGACUU	2679
D-2172	71-89	71-89	CAGAGCAGAGGCAACCCAUUU	1177	AUGGGUUGCCUCUGCUCUGUU	2680
D-2173	719-737	602-620	UCCCAGCUGGAGAAACAGCUU	1178	GCUGUUUCUCCAGCUGGGAUU	2681
D-2174	720-738	603-621	CCCAGCUGGAGAAACAGCAUU	1179	UGCUGUUUCUCCAGCUGGGUU	2682
D-2175	721-739	604-622	CCAGCUGGAGAAACAGCAGUU	1180	CUGCUGUUUCUCCAGCUGGUU	2683
D-2176	722-740	605-623	CAGCUGGAGAAACAGCAGAUU	1181	UCUGCUGUUUCUCCAGCUGUU	2684
D-2177	723-741	606-624	AGCUGGAGAAACAGCAGAAUU	1182	UUCUGCUGUUUCUCCAGCUUU	2685
D-2178	724-742	607-625	GCUGGAGAAACAGCAGAAGUU	1183	CUUCUGCUGUUUCUCCAGCUU	2686
D-2179	7-25	7-25	CGGUGCACGGAAGAGUGAGUU	1184	CUCACUCUUCCGUGCACCGUU	2687
D-2180	725-743	608-626	CUGGAGAAACAGCAGAAGGUU	1185	CCUUCUGCUGUUUCUCCAGUU	2688
D-2181	726-744	609-627	UGGAGAAACAGCAGAAGGAUU	1186	UCCUUCUGCUGUUUCUCCAUU	2689
D-2182	727-745	610-628	GGAGAAACAGCAGAAGGACUU	1187	GUCCUUCUGCUGUUUCUCCUU	2690
D-2183	728-746	611-629	GAGAAACAGCAGAAGGACCUU	1188	GGUCCUUCUGCUGUUUCUCUU	2691
D-2184	72-90	72-90	AGAGCAGAGGCAACCCAUCUU	1189	GAUGGGUUGCCUCUGCUCUUU	2692
D-2185	729-747	612-630	AGAAACAGCAGAAGGACCUUU	1190	AGGUCCUUCUGCUGUUUCUUU	2693
D-2186	730-748	613-631	GAAACAGCAGAAGGACCUGUU	1191	CAGGUCCUUCUGCUGUUUCUU	2694
D-2187	731-749	614-632	AAACAGCAGAAGGACCUGAUU	1192	UCAGGUCCUUCUGCUGUUUUU	2695
D-2188	732-750	615-633	AACAGCAGAAGGACCUGAGUU	1193	CUCAGGUCCUUCUGCUGUUUU	2696
D-2189	733-751	616-634	ACAGCAGAAGGACCUGAGUUU	1194	ACUCAGGUCCUUCUGCUGUUU	2697
D-2190	734-752	617-635	CAGCAGAAGGACCUGAGUGUU	1195	CACUCAGGUCCUUCUGCUGUU	2698
D-2191	735-753	618-636	AGCAGAAGGACCUGAGUGAUU	1196	UCACUCAGGUCCUUCUGCUUU	2699
D-2192	736-754	619-637	GCAGAAGGACCUGAGUGAAUU	1197	UUCACUCAGGUCCUUCUGCUU	2700
D-2193	737-755	620-638	CAGAAGGACCUGAGUGAAGUU	1198	CUUCACUCAGGUCCUUCUGUU	2701
D-2194	738-756	621-639	AGAAGGACCUGAGUGAAGAUU	1199	UCUUCACUCAGGUCCUUCUUU	2702
D-2195	73-91	73-91	GAGCAGAGGCAACCCAUCCUU	1200	GGAUGGGUUGCCUCUGCUCUU	2703
D-2196	739-757	622-640	GAAGGACCUGAGUGAAGAUUU	1201	AUCUUCACUCAGGUCCUUCUU	2704
D-2197	740-758	623-641	AAGGACCUGAGUGAAGAUCUU	1202	GAUCUUCACUCAGGUCCUUUU	2705
D-2198	741-759	624-642	AGGACCUGAGUGAAGAUCAUU	1203	UGAUCUUCACUCAGGUCCUUU	2706
D-2199	742-760	625-643	GGACCUGAGUGAAGAUCACUU	1204	GUGAUCUUCACUCAGGUCCUU	2707
D-2200	743-761	626-644	GACCUGAGUGAAGAUCACUUU	1205	AGUGAUCUUCACUCAGGUCUU	2708
D-2201	744-762	627-645	ACCUGAGUGAAGAUCACUCUU	1206	GAGUGAUCUUCACUCAGGUUU	2709

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2202	745-763	628-646	CCUGAGUGAAGAUCACUCCUU	1207	GGAGUGAUCUUCACUCAGGUU	2710
D-2203	746-764	629-647	CUGAGUGAAGAUCACUCCAUU	1208	UGGAGUGAUCUUCACUCAGUU	2711
D-2204	747-765	630-648	UGAGUGAAGAUCACUCCAGUU	1209	CUGGAGUGAUCUUCACUCAUU	2712
D-2205	748-766	631-649	GAGUGAAGAUCACUCCAGCUU	1210	GCUGGAGUGAUCUUCACUCUU	2713
D-2206	74-92	74-92	AGCAGAGGCAACCCAUCCCUU	1211	GGGAUGGGUUGCCUCUGCUUU	2714
D-2207	749-767	632-650	AGUGAAGAUCACUCCAGCCUU	1212	GGCUGGAGUGAUCUUCACUUU	2715
D-2208	750-768	633-651	GUGAAGAUCACUCCAGCCUUU	1213	AGGCUGGAGUGAUCUUCACUU	2716
D-2209	751-769	634-652	UGAAGAUCACUCCAGCCUGUU	1214	CAGGCUGGAGUGAUCUUCAUU	2717
D-2210	752-770	635-653	GAAGAUCACUCCAGCCUGCUU	1215	GCAGGCUGGAGUGAUCUUCUU	2718
D-2211	753-771	636-654	AAGAUCACUCCAGCCUGCUUU	1216	AGCAGGCUGGAGUGAUCUUUU	2719
D-2212	754-772	637-655	AGAUCACUCCAGCCUGCUGUU	1217	CAGCAGGCUGGAGUGAUCUUU	2720
D-2213	755-773	638-656	GAUCACUCCAGCCUGCUGCUU	1218	GCAGCAGGCUGGAGUGAUCUU	2721
D-2214	756-774	639-657	AUCACUCCAGCCUGCUGCUUU	1219	AGCAGCAGGCUGGAGUGAUUU	2722
D-2215	757-775	640-658	UCACUCCAGCCUGCUGCUCUU	1220	GAGCAGCAGGCUGGAGUGAUU	2723
D-2216	758-776	641-659	CACUCCAGCCUGCUGCUCCUU	1221	GGAGCAGCAGGCUGGAGUGUU	2724
D-2217	75-93	75-93	GCAGAGGCAACCCAUCCCCUU	1222	GGGGAUGGGUUGCCUCUGCUU	2725
D-2218	759-777	642-660	ACUCCAGCCUGCUGCUCCAUU	1223	UGGAGCAGCAGGCUGGAGUUU	2726
D-2219	760-778	643-661	CUCCAGCCUGCUGCUCCACUU	1224	GUGGAGCAGCAGGCUGGAGUU	2727
D-2220	761-779	644-662	UCCAGCCUGCUGCUCCACGUU	1225	CGUGGAGCAGCAGGCUGGAUU	2728
D-2221	762-780	645-663	CCAGCCUGCUGCUCCACGUUU	1226	ACGUGGAGCAGCAGGCUGGUU	2729
D-2222	763-781	646-664	CAGCCUGCUGCUCCACGUGUU	1227	CACGUGGAGCAGCAGGCUGUU	2730
D-2223	764-782	647-665	AGCCUGCUGCUCCACGUGAUU	1228	UCACGUGGAGCAGCAGGCUUU	2731
D-2224	765-783	648-666	GCCUGCUGCUCCACGUGAAUU	1229	UUCACGUGGAGCAGCAGGCUU	2732
D-2225	766-784	649-667	CCUGCUGCUCCACGUGAAGUU	1230	CUUCACGUGGAGCAGCAGGUU	2733
D-2226	767-785	650-668	CUGCUGCUCCACGUGAAGCUU	1231	GCUUCACGUGGAGCAGCAGUU	2734
D-2227	768-786	651-669	UGCUGCUCCACGUGAAGCAUU	1232	UGCUUCACGUGGAGCAGCAUU	2735
D-2228	76-94	76-94	CAGAGGCAACCCAUCCCCCUU	1233	GGGGGAUGGGUUGCCUCUGUU	2736
D-2229	769-787	652-670	GCUGCUCCACGUGAAGCAGUU	1234	CUGCUUCACGUGGAGCAGCUU	2737
D-2230	770-788	653-671	CUGCUCCACGUGAAGCAGUUU	1235	ACUGCUUCACGUGGAGCAGUU	2738
D-2231	771-789	654-672	UGCUCCACGUGAAGCAGUUUU	1236	AACUGCUUCACGUGGAGCAUU	2739
D-2232	772-790	655-673	GCUCCACGUGAAGCAGUUCUU	1237	GAACUGCUUCACGUGGAGCUU	2740
D-2233	773-791	656-674	CUCCACGUGAAGCAGUUCGUU	1238	CGAACUGCUUCACGUGGAGUU	2741
D-2234	774-792	657-675	UCCACGUGAAGCAGUUCGUUU	1239	ACGAACUGCUUCACGUGGAUU	2742
D-2235	775-793	658-676	CCACGUGAAGCAGUUCGUGUU	1240	CACGAACUGCUUCACGUGGUU	2743
D-2236	776-794	659-677	CACGUGAAGCAGUUCGUGUUU	1241	ACACGAACUGCUUCACGUGUU	2744
D-2237	777-795	660-678	ACGUGAAGCAGUUCGUGUCUU	1242	GACACGAACUGCUUCACGUUU	2745

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2238	778-796	661-679	CGUGAAGCAGUUCGUGUCUUU	1243	AGACACGAACUGCUUCACGUU	2746
D-2239	77-95	77-95	AGAGGCAACCCAUCCCCCAUU	1244	UGGGGGAUGGGUUGCCUCUUU	2747
D-2240	779-797	662-680	GUGAAGCAGUUCGUGUCUGUU	1245	CAGACACGAACUGCUUCACUU	2748
D-2241	780-798	663-681	UGAAGCAGUUCGUGUCUGAUU	1246	UCAGACACGAACUGCUUCAUU	2749
D-2242	781-799	664-682	GAAGCAGUUCGUGUCUGACUU	1247	GUCAGACACGAACUGCUUCUU	2750
D-2243	782-800	665-683	AAGCAGUUCGUGUCUGACCUU	1248	GGUCAGACACGAACUGCUUUU	2751
D-2244	783-801	666-684	AGCAGUUCGUGUCUGACCUUU	1249	AGGUCAGACACGAACUGCUUU	2752
D-2245	784-802	667-685	GCAGUUCGUGUCUGACCUGUU	1250	CAGGUCAGACACGAACUGCUU	2753
D-2246	785-803	668-686	CAGUUCGUGUCUGACCUGCUU	1251	GCAGGUCAGACACGAACUGUU	2754
D-2247	786-804	669-687	AGUUCGUGUCUGACCUGCGUU	1252	CGCAGGUCAGACACGAACUUU	2755
D-2248	787-805	670-688	GUUCGUGUCUGACCUGCGGUU	1253	CCGCAGGUCAGACACGAACUU	2756
D-2249	788-806	671-689	UUCGUGUCUGACCUGCGGAUU	1254	UCCGCAGGUCAGACACGAAUU	2757
D-2250	78-96	78-96	GAGGCAACCCAUCCCCCACUU	1255	GUGGGGGAUGGGUUGCCUCUU	2758
D-2251	789-807	672-690	UCGUGUCUGACCUGCGGAGUU	1256	CUCCGCAGGUCAGACACGAUU	2759
D-2252	790-808	673-691	CGUGUCUGACCUGCGGAGCUU	1257	GCUCCGCAGGUCAGACACGUU	2760
D-2253	791-809	674-692	GUGUCUGACCUGCGGAGCCUU	1258	GGCUCCGCAGGUCAGACACUU	2761
D-2254	792-810	675-693	UGUCUGACCUGCGGAGCCUUU	1259	AGGCUCCGCAGGUCAGACAUU	2762
D-2255	793-811	676-694	GUCUGACCUGCGGAGCCUGUU	1260	CAGGCUCCGCAGGUCAGACUU	2763
D-2256	794-812	677-695	UCUGACCUGCGGAGCCUGAUU	1261	UCAGGCUCCGCAGGUCAGAUU	2764
D-2257	795-813	678-696	CUGACCUGCGGAGCCUGAGUU	1262	CUCAGGCUCCGCAGGUCAGUU	2765
D-2258	796-814	679-697	UGACCUGCGGAGCCUGAGCUU	1263	GCUCAGGCUCCGCAGGUCAUU	2766
D-2259	797-815	680-698	GACCUGCGGAGCCUGAGCUUU	1264	AGCUCAGGCUCCGCAGGUCUU	2767
D-2260	798-816	681-699	ACCUGCGGAGCCUGAGCUGUU	1265	CAGCUCAGGCUCCGCAGGUUU	2768
D-2261	79-97	79-97	AGGCAACCCAUCCCCCACUUU	1266	AGUGGGGGAUGGGUUGCCUUU	2769
D-2262	799-817	682-700	CCUGCGGAGCCUGAGCUGUUU	1267	ACAGCUCAGGCUCCGCAGGUU	2770
D-2263	800-818	683-701	CUGCGGAGCCUGAGCUGUCUU	1268	GACAGCUCAGGCUCCGCAGUU	2771
D-2264	801-819	684-702	UGCGGAGCCUGAGCUGUCAUU	1269	UGACAGCUCAGGCUCCGCAUU	2772
D-2265	802-820	685-703	GCGGAGCCUGAGCUGUCAGUU	1270	CUGACAGCUCAGGCUCCGCUU	2773
D-2266	803-821	686-704	CGGAGCCUGAGCUGUCAGAUU	1271	UCUGACAGCUCAGGCUCCGUU	2774
D-2267	804-822	687-705	GGAGCCUGAGCUGUCAGAUUU	1272	AUCUGACAGCUCAGGCUCCUU	2775
D-2268	805-823	688-706	GAGCCUGAGCUGUCAGAUGUU	1273	CAUCUGACAGCUCAGGCUCUU	2776
D-2269	806-824	689-707	AGCCUGAGCUGUCAGAUGGUU	1274	CCAUCUGACAGCUCAGGCUUU	2777
D-2270	807-825	690-708	GCCUGAGCUGUCAGAUGGCUU	1275	GCCAUCUGACAGCUCAGGCUU	2778
D-2271	808-826	691-709	CCUGAGCUGUCAGAUGGCGUU	1276	CGCCAUCUGACAGCUCAGGUU	2779
D-2272	80-98	80-98	GGCAACCCAUCCCCCACUCUU	1277	GAGUGGGGGAUGGGUUGCCUU	2780
D-2273	809-827	692-710	CUGAGCUGUCAGAUGGCGGUU	1278	CCGCCAUCUGACAGCUCAGUU	2781

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2274	810-828	693-711	UGAGCUGUCAGAUGGCGGCUU	1279	GCCGCCAUCUGACAGCUCAUU	2782
D-2275	811-829	694-712	GAGCUGUCAGAUGGCGGCGUU	1280	CGCCGCCAUCUGACAGCUCUU	2783
D-2276	812-830	695-713	AGCUGUCAGAUGGCGGCGCUU	1281	GCGCCGCCAUCUGACAGCUUU	2784
D-2277	813-831	696-714	GCUGUCAGAUGGCGGCGCUUU	1282	AGCGCCGCCAUCUGACAGCUU	2785
D-2278	814-832	697-715	CUGUCAGAUGGCGGCGCUCUU	1283	GAGCGCCGCCAUCUGACAGUU	2786
D-2279	815-833	698-716	UGUCAGAUGGCGGCGCUCCUU	1284	GGAGCGCCGCCAUCUGACAUU	2787
D-2280	816-834	699-717	GUCAGAUGGCGGCGCUCCAUU	1285	UGGAGCGCCGCCAUCUGACUU	2788
D-2281	817-835	700-718	UCAGAUGGCGGCGCUCCAGUU	1286	CUGGAGCGCCGCCAUCUGAUU	2789
D-2282	818-836	701-719	CAGAUGGCGGCGCUCCAGGUU	1287	CCUGGAGCGCCGCCAUCUGUU	2790
D-2283	819-837	702-720	AGAUGGCGGCGCUCCAGGGUU	1288	CCCUGGAGCGCCGCCAUCUUU	2791
D-2284	81-99	81-99	GCAACCCAUCCCCCACUCCUU	1289	GGAGUGGGGGAUGGGUUGCUU	2792
D-2285	820-838	703-721	GAUGGCGGCGCUCCAGGGCUU	1290	GCCCUGGAGCGCCGCCAUCUU	2793
D-2286	82-100	82-100	CAACCCAUCCCCCACUCCCUU	1291	GGGAGUGGGGGAUGGGUUGUU	2794
D-2287	821-839	704-722	AUGGCGGCGCUCCAGGGCAUU	1292	UGCCCUGGAGCGCCGCCAUUU	2795
D-2288	822-840	705-723	UGGCGGCGCUCCAGGGCAAUU	1293	UUGCCCUGGAGCGCCGCCAUU	2796
D-2289	823-841	706-724	GGCGGCGCUCCAGGGCAAUUU	1294	AUUGCCCUGGAGCGCCGCCUU	2797
D-2290	824-842	707-725	GCGGCGCUCCAGGGCAAUGUU	1295	CAUUGCCCUGGAGCGCCGCUU	2798
D-2291	825-843	708-726	CGGCGCUCCAGGGCAAUGGUU	1296	CCAUUGCCCUGGAGCGCCGUU	2799
D-2292	8-26	8-26	GGUGCACGGAAGAGUGAGGUU	1297	CCUCACUCUUCCGUGCACCUU	2800
D-2293	826-844	709-727	GGCGCUCCAGGGCAAUGGCUU	1298	GCCAUUGCCCUGGAGCGCCUU	2801
D-2294	827-845	710-728	GCGCUCCAGGGCAAUGGCUUU	1299	AGCCAUUGCCCUGGAGCGCUU	2802
D-2295	828-846	711-729	CGCUCCAGGGCAAUGGCUCUU	1300	GAGCCAUUGCCCUGGAGCGUU	2803
D-2296	829-847	712-730	GCUCCAGGGCAAUGGCUCAUU	1301	UGAGCCAUUGCCCUGGAGCUU	2804
D-2297	830-848	713-731	CUCCAGGGCAAUGGCUCAGUU	1302	CUGAGCCAUUGCCCUGGAGUU	2805
D-2298	83-101	83-101	AACCCAUCCCCCACUCCCAUU	1303	UGGGAGUGGGGGAUGGGUUUU	2806
D-2299	831-849	714-732	UCCAGGGCAAUGGCUCAGAUU	1304	UCUGAGCCAUUGCCCUGGAUU	2807
D-2300	832-850	715-733	CCAGGGCAAUGGCUCAGAAUU	1305	UUCUGAGCCAUUGCCCUGGUU	2808
D-2301	833-851	716-734	CAGGGCAAUGGCUCAGAAAUU	1306	UUUCUGAGCCAUUGCCCUGUU	2809
D-2302	834-852	717-735	AGGGCAAUGGCUCAGAAAGUU	1307	CUUUCUGAGCCAUUGCCCUUU	2810
D-2303	835-853	718-736	GGGCAAUGGCUCAGAAAGGUU	1308	CCUUUCUGAGCCAUUGCCCUU	2811
D-2304	836-854	719-737	GGCAAUGGCUCAGAAAGGAUU	1309	UCCUUUCUGAGCCAUUGCCUU	2812
D-2305	837-855	720-738	GCAAUGGCUCAGAAAGGACUU	1310	GUCCUUUCUGAGCCAUUGCUU	2813
D-2306	838-856	721-739	CAAUGGCUCAGAAAGGACCUU	1311	GGUCCUUUCUGAGCCAUUGUU	2814
D-2307	839-857	722-740	AAUGGCUCAGAAAGGACCUUU	1312	AGGUCCUUUCUGAGCCAUUUU	2815
D-2308	840-858	723-741	AUGGCUCAGAAAGGACCUGUU	1313	CAGGUCCUUUCUGAGCCAUUU	2816
D-2309	84-102	84-102	ACCCAUCCCCCACUCCCACUU	1314	GUGGGAGUGGGGGAUGGGUUU	2817

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2310	841-859	724-742	UGGCUCAGAAAGGACCUGCUU	1315	GCAGGUCCUUUCUGAGCCAUU	2818
D-2311	842-860	725-743	GGCUCAGAAAGGACCUGCUUU	1316	AGCAGGUCCUUUCUGAGCCUU	2819
D-2312	843-861	726-744	GCUCAGAAAGGACCUGCUGUU	1317	CAGCAGGUCCUUUCUGAGCUU	2820
D-2313	844-862	727-745	CUCAGAAAGGACCUGCUGCUU	1318	GCAGCAGGUCCUUUCUGAGUU	2821
D-2314	845-863	728-746	UCAGAAAGGACCUGCUGCCUU	1319	GGCAGCAGGUCCUUUCUGAUU	2822
D-2315	846-864	729-747	CAGAAAGGACCUGCUGCCCUU	1320	GGGCAGCAGGUCCUUUCUGUU	2823
D-2316	847-865	730-748	AGAAAGGACCUGCUGCCCGUU	1321	CGGGCAGCAGGUCCUUUCUUU	2824
D-2317	848-866	731-749	GAAAGGACCUGCUGCCCGGUU	1322	CCGGGCAGCAGGUCCUUUCUU	2825
D-2318	849-867	732-750	AAAGGACCUGCUGCCCGGUUU	1323	ACCGGGCAGCAGGUCCUUUUU	2826
D-2319	850-868	733-751	AAGGACCUGCUGCCCGGUCUU	1324	GACCGGGCAGCAGGUCCUUUU	2827
D-2320	85-103	85-103	CCCAUCCCCCACUCCCACCUU	1325	GGUGGGAGUGGGGGAUGGGUU	2828
D-2321	851-869	734-752	AGGACCUGCUGCCCGGUCAUU	1326	UGACCGGGCAGCAGGUCCUUU	2829
D-2322	852-870	735-753	GGACCUGCUGCCCGGUCAAUU	1327	UUGACCGGGCAGCAGGUCCUU	2830
D-2323	853-871	736-754	GACCUGCUGCCCGGUCAACUU	1328	GUUGACCGGGCAGCAGGUCUU	2831
D-2324	854-872	737-755	ACCUGCUGCCCGGUCAACUUU	1329	AGUUGACCGGGCAGCAGGUUU	2832
D-2325	855-873	738-756	CCUGCUGCCCGGUCAACUGUU	1330	CAGUUGACCGGGCAGCAGGUU	2833
D-2326	856-874	739-757	CUGCUGCCCGGUCAACUGGUU	1331	CCAGUUGACCGGGCAGCAGUU	2834
D-2327	857-875	740-758	UGCUGCCCGGUCAACUGGGUU	1332	CCCAGUUGACCGGGCAGCAUU	2835
D-2328	858-876	741-759	GCUGCCCGGUCAACUGGGUUU	1333	ACCCAGUUGACCGGGCAGCUU	2836
D-2329	859-877	742-760	CUGCCCGGUCAACUGGGUGUU	1334	CACCCAGUUGACCGGGCAGUU	2837
D-2330	860-878	743-761	UGCCCGGUCAACUGGGUGGUU	1335	CCACCCAGUUGACCGGGCAUU	2838
D-2331	86-104	86-104	CCAUCCCCCACUCCCACCCUU	1336	GGGUGGGAGUGGGGGAUGGUU	2839
D-2332	861-879	744-762	GCCCGGUCAACUGGGUGGAUU	1337	UCCACCCAGUUGACCGGGCUU	2840
D-2333	862-880	745-763	CCCGGUCAACUGGGUGGAGUU	1338	CUCCACCCAGUUGACCGGGUU	2841
D-2334	863-881	746-764	CCGGUCAACUGGGUGGAGCUU	1339	GCUCCACCCAGUUGACCGGUU	2842
D-2335	864-882	747-765	CGGUCAACUGGGUGGAGCAUU	1340	UGCUCCACCCAGUUGACCGUU	2843
D-2336	865-883	748-766	GGUCAACUGGGUGGAGCACUU	1341	GUGCUCCACCCAGUUGACCUU	2844
D-2337	866-884	749-767	GUCAACUGGGUGGAGCACGUU	1342	CGUGCUCCACCCAGUUGACUU	2845
D-2338	867-885	750-768	UCAACUGGGUGGAGCACGAUU	1343	UCGUGCUCCACCCAGUUGAUU	2846
D-2339	868-886	751-769	CAACUGGGUGGAGCACGAGUU	1344	CUCGUGCUCCACCCAGUUGUU	2847
D-2340	869-887	752-770	AACUGGGUGGAGCACGAGCUU	1345	GCUCGUGCUCCACCCAGUUUU	2848
D-2341	870-888	753-771	ACUGGGUGGAGCACGAGCGUU	1346	CGCUCGUGCUCCACCCAGUUU	2849
D-2342	87-105	87-105	CAUCCCCCACUCCCACCCCUU	1347	GGGGUGGGAGUGGGGGAUGUU	2850
D-2343	871-889	754-772	CUGGGUGGAGCACGAGCGCUU	1348	GCGCUCGUGCUCCACCCAGUU	2851
D-2344	872-890	755-773	UGGGUGGAGCACGAGCGCAUU	1349	UGCGCUCGUGCUCCACCCAUU	2852
D-2345	873-891	756-774	GGGUGGAGCACGAGCGCAGUU	1350	CUGCGCUCGUGCUCCACCCUU	2853

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2346	874-892	757-775	GGUGGAGCACGAGCGCAGCUU	1351	GCUGCGCUCGUGCUCCACCUU	2854
D-2347	875-893	758-776	GUGGAGCACGAGCGCAGCUUU	1352	AGCUGCGCUCGUGCUCCACUU	2855
D-2348	876-894	759-777	UGGAGCACGAGCGCAGCUGUU	1353	CAGCUGCGCUCGUGCUCCAUU	2856
D-2349	877-895	760-778	GGAGCACGAGCGCAGCUGCUU	1354	GCAGCUGCGCUCGUGCUCCUU	2857
D-2350	878-896	761-779	GAGCACGAGCGCAGCUGCUUU	1355	AGCAGCUGCGCUCGUGCUCUU	2858
D-2351	879-897	762-780	AGCACGAGCGCAGCUGCUAUU	1356	UAGCAGCUGCGCUCGUGCUUU	2859
D-2352	880-898	763-781	GCACGAGCGCAGCUGCUACUU	1357	GUAGCAGCUGCGCUCGUGCUU	2860
D-2353	88-106	88-106	AUCCCCCACUCCCACCCCCUU	1358	GGGGGUGGGAGUGGGGGAUUU	2861
D-2354	881-899	764-782	CACGAGCGCAGCUGCUACUUU	1359	AGUAGCAGCUGCGCUCGUGUU	2862
D-2355	882-900	765-783	ACGAGCGCAGCUGCUACUGUU	1360	CAGUAGCAGCUGCGCUCGUUU	2863
D-2356	883-901	766-784	CGAGCGCAGCUGCUACUGGUU	1361	CCAGUAGCAGCUGCGCUCGUU	2864
D-2357	884-902	767-785	GAGCGCAGCUGCUACUGGUUU	1362	ACCAGUAGCAGCUGCGCUCUU	2865
D-2358	885-903	768-786	AGCGCAGCUGCUACUGGUUUU	1363	AACCAGUAGCAGCUGCGCUUU	2866
D-2359	886-904	769-787	GCGCAGCUGCUACUGGUUCUU	1364	GAACCAGUAGCAGCUGCGCUU	2867
D-2360	887-905	770-788	CGCAGCUGCUACUGGUUCUUU	1365	AGAACCAGUAGCAGCUGCGUU	2868
D-2361	888-906	771-789	GCAGCUGCUACUGGUUCUCUU	1366	GAGAACCAGUAGCAGCUGCUU	2869
D-2362	889-907	772-790	CAGCUGCUACUGGUUCUCUUU	1367	AGAGAACCAGUAGCAGCUGUU	2870
D-2363	890-908	773-791	AGCUGCUACUGGUUCUCUCUU	1368	GAGAGAACCAGUAGCAGCUUU	2871
D-2364	89-107	89-107	UCCCCCACUCCCACCCCCAUU	1369	UGGGGGUGGGAGUGGGGGAUU	2872
D-2365	891-909	774-792	GCUGCUACUGGUUCUCUCGUU	1370	CGAGAGAACCAGUAGCAGCUU	2873
D-2366	892-910	775-793	CUGCUACUGGUUCUCUCGCUU	1371	GCGAGAGAACCAGUAGCAGUU	2874
D-2367	893-911	776-794	UGCUACUGGUUCUCUCGCUUU	1372	AGCGAGAGAACCAGUAGCAUU	2875
D-2368	894-912	777-795	GCUACUGGUUCUCUCGCUCUU	1373	GAGCGAGAGAACCAGUAGCUU	2876
D-2369	895-913	778-796	CUACUGGUUCUCUCGCUCCUU	1374	GGAGCGAGAGAACCAGUAGUU	2877
D-2370	896-914	779-797	UACUGGUUCUCUCGCUCCGUU	1375	CGGAGCGAGAGAACCAGUAUU	2878
D-2371	897-915	780-798	ACUGGUUCUCUCGCUCCGGUU	1376	CCGGAGCGAGAGAACCAGUUU	2879
D-2372	898-916	781-799	CUGGUUCUCUCGCUCCGGGUU	1377	CCCGGAGCGAGAGAACCAGUU	2880
D-2373	899-917	782-800	UGGUUCUCUCGCUCCGGGAUU	1378	UCCCGGAGCGAGAGAACCAUU	2881
D-2374	900-918	783-801	GGUUCUCUCGCUCCGGGAAUU	1379	UUCCCGGAGCGAGAGAACCUU	2882
D-2375	90-108	90-108	CCCCCACUCCCACCCCCACUU	1380	GUGGGGGUGGGAGUGGGGGUU	2883
D-2376	901-919	784-802	GUUCUCUCGCUCCGGGAAGUU	1381	CUUCCCGGAGCGAGAGAACUU	2884
D-2377	902-920	785-803	UUCUCUCGCUCCGGGAAGGUU	1382	CCUUCCCGGAGCGAGAGAAUU	2885
D-2378	903-921	786-804	UCUCUCGCUCCGGGAAGGCUU	1383	GCCUUCCCGGAGCGAGAGAUU	2886
D-2379	904-922	787-805	CUCUCGCUCCGGGAAGGCCUU	1384	GGCCUUCCCGGAGCGAGAGUU	2887
D-2380	905-923	788-806	UCUCGCUCCGGGAAGGCCUUU	1385	AGGCCUUCCCGGAGCGAGAUU	2888
D-2381	906-924	789-807	CUCGCUCCGGGAAGGCCUGUU	1386	CAGGCCUUCCCGGAGCGAGUU	2889

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5'-3')	SEQ ID NO: sense	Antisense Sequence (5'-3')	SEQ ID NO: antisense
D-2382	907-925	790-808	UCGCUCCGGGAAGGCCUGGUU	1387	CCAGGCCUUCCCGGAGCGAUU	2890
D-2383	908-926	791-809	CGCUCCGGGAAGGCCUGGGUU	1388	CCCAGGCCUUCCCGGAGCGUU	2891
D-2384	909-927	792-810	GCUCCGGGAAGGCCUGGGCUU	1389	GCCCAGGCCUUCCCGGAGCUU	2892
D-2385	910-928	793-811	CUCCGGGAAGGCCUGGGCUUU	1390	AGCCCAGGCCUUCCCGGAGUU	2893
D-2386	91-109	91-109	CCCCACUCCCACCCCCACAUU	1391	UGUGGGGGUGGGAGUGGGGUU	2894
D-2387	911-929	794-812	UCCGGGAAGGCCUGGGCUGUU	1392	CAGCCCAGGCCUUCCCGGAUU	2895
D-2388	912-930	795-813	CCGGGAAGGCCUGGGCUGAUU	1393	UCAGCCCAGGCCUUCCCGGUU	2896
D-2389	913-931	796-814	CGGGAAGGCCUGGGCUGACUU	1394	GUCAGCCCAGGCCUUCCCGUU	2897
D-2390	914-932	797-815	GGGAAGGCCUGGGCUGACGUU	1395	CGUCAGCCCAGGCCUUCCCUU	2898
D-2391	915-933	798-816	GGAAGGCCUGGGCUGACGCUU	1396	GCGUCAGCCCAGGCCUUCCUU	2899
D-2392	916-934	799-817	GAAGGCCUGGGCUGACGCCUU	1397	GGCGUCAGCCCAGGCCUUCUU	2900
D-2393	917-935	800-818	AAGGCCUGGGCUGACGCCGUU	1398	CGGCGUCAGCCCAGGCCUUUU	2901
D-2394	918-936	801-819	AGGCCUGGGCUGACGCCGAUU	1399	UCGGCGUCAGCCCAGGCCUUU	2902
D-2395	919-937	802-820	GGCCUGGGCUGACGCCGACUU	1400	GUCGGCGUCAGCCCAGGCCUU	2903
D-2396	920-938	803-821	GCCUGGGCUGACGCCGACAUU	1401	UGUCGGCGUCAGCCCAGGCUU	2904
D-2397	92-110	92-110	CCCACUCCCACCCCCACACUU	1402	GUGUGGGGGUGGGAGUGGGUU	2905
D-2398	921-939	804-822	CCUGGGCUGACGCCGACAAUU	1403	UUGUCGGCGUCAGCCCAGGUU	2906
D-2399	922-940	805-823	CUGGGCUGACGCCGACAACUU	1404	GUUGUCGGCGUCAGCCCAGUU	2907
D-2400	923-941	806-824	UGGGCUGACGCCGACAACUUU	1405	AGUUGUCGGCGUCAGCCCAUU	2908
D-2401	924-942	807-825	GGGCUGACGCCGACAACUAUU	1406	UAGUUGUCGGCGUCAGCCCUU	2909
D-2402	925-943	808-826	GGCUGACGCCGACAACUACUU	1407	GUAGUUGUCGGCGUCAGCCUU	2910
D-2403	926-944	809-827	GCUGACGCCGACAACUACUUU	1408	AGUAGUUGUCGGCGUCAGCUU	2911
D-2404	9-27	9-27	GUGCACGGAAGAGUGAGGUUU	1409	ACCUCACUCUUCCGUGCACUU	2912
D-2405	927-945	810-828	CUGACGCCGACAACUACUGUU	1410	CAGUAGUUGUCGGCGUCAGUU	2913
D-2406	928-946	811-829	UGACGCCGACAACUACUGCUU	1411	GCAGUAGUUGUCGGCGUCAUU	2914
D-2407	929-947	812-830	GACGCCGACAACUACUGCCUU	1412	GGCAGUAGUUGUCGGCGUCUU	2915
D-2408	930-948	813-831	ACGCCGACAACUACUGCCGUU	1413	CGGCAGUAGUUGUCGGCGUUU	2916
D-2409	93-111	93-111	CCACUCCCACCCCCACACUUU	1414	AGUGUGGGGGUGGGAGUGGUU	2917
D-2410	931-949	814-832	CGCCGACAACUACUGCCGGUU	1415	CCGGCAGUAGUUGUCGGCGUU	2918
D-2411	932-950	815-833	GCCGACAACUACUGCCGGCUU	1416	GCCGGCAGUAGUUGUCGGCUU	2919
D-2412	933-951	816-834	CCGACAACUACUGCCGGCUUU	1417	AGCCGGCAGUAGUUGUCGGUU	2920
D-2413	934-952	817-835	CGACAACUACUGCCGGCUGUU	1418	CAGCCGGCAGUAGUUGUCGUU	2921
D-2414	935-953	818-836	GACAACUACUGCCGGCUGGUU	1419	CCAGCCGGCAGUAGUUGUCUU	2922
D-2415	936-954	819-837	ACAACUACUGCCGGCUGGAUU	1420	UCCAGCCGGCAGUAGUUGUUU	2923
D-2416	937-955	820-838	CAACUACUGCCGGCUGGAGUU	1421	CUCCAGCCGGCAGUAGUUGUU	2924
D-2417	938-956	821-839	AACUACUGCCGGCUGGAGGUU	1422	CCUCCAGCCGGCAGUAGUUUU	2925

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2418	939-957	822-840	ACUACUGCCGGCUGGAGGAUU	1423	UCCUCCAGCCGGCAGUAGUUU	2926
D-2419	940-958	823-841	CUACUGCCGGCUGGAGGACUU	1424	GUCCUCCAGCCGGCAGUAGUU	2927
D-2420	94-112	94-112	CACUCCCACCCCCACACUCUU	1425	GAGUGUGGGGGUGGGAGUGUU	2928
D-2421	941-959	824-842	UACUGCCGGCUGGAGGACGUU	1426	CGUCCUCCAGCCGGCAGUAUU	2929
D-2422	942-960	825-843	ACUGCCGGCUGGAGGACGCUU	1427	GCGUCCUCCAGCCGGCAGUUU	2930
D-2423	943-961	826-844	CUGCCGGCUGGAGGACGCGUU	1428	CGCGUCCUCCAGCCGGCAGUU	2931
D-2424	944-962	827-845	UGCCGGCUGGAGGACGCGCUU	1429	GCGCGUCCUCCAGCCGGCAUU	2932
D-2425	945-963	828-846	GCCGGCUGGAGGACGCGCAUU	1430	UGCGCGUCCUCCAGCCGGCUU	2933
D-2426	946-964	829-847	CCGGCUGGAGGACGCGCACUU	1431	GUGCGCGUCCUCCAGCCGGUU	2934
D-2427	947-965	830-848	CGGCUGGAGGACGCGCACCUU	1432	GGUGCGCGUCCUCCAGCCGUU	2935
D-2428	948-966	831-849	GGCUGGAGGACGCGCACCUUU	1433	AGGUGCGCGUCCUCCAGCCUU	2936
D-2429	949-967	832-850	GCUGGAGGACGCGCACCUGUU	1434	CAGGUGCGCGUCCUCCAGCUU	2937
D-2430	950-968	833-851	CUGGAGGACGCGCACCUGGUU	1435	CCAGGUGCGCGUCCUCCAGUU	2938
D-2431	95-113	95-113	ACUCCCACCCCCACACUCCUU	1436	GGAGUGUGGGGGUGGGAGUUU	2939
D-2432	951-969	834-852	UGGAGGACGCGCACCUGGUUU	1437	ACCAGGUGCGCGUCCUCCAUU	2940
D-2433	952-970	835-853	GGAGGACGCGCACCUGGUGUU	1438	CACCAGGUGCGCGUCCUCCUU	2941
D-2434	953-971	836-854	GAGGACGCGCACCUGGUGGUU	1439	CCACCAGGUGCGCGUCCUCUU	2942
D-2435	954-972	837-855	AGGACGCGCACCUGGUGGUUU	1440	ACCACCAGGUGCGCGUCCUUU	2943
D-2436	955-973	838-856	GGACGCGCACCUGGUGGUGUU	1441	CACCACCAGGUGCGCGUCCUU	2944
D-2437	956-974	839-857	GACGCGCACCUGGUGGUGGUU	1442	CCACCACCAGGUGCGCGUCUU	2945
D-2438	957-975	840-858	ACGCGCACCUGGUGGUGGUUU	1443	ACCACCACCAGGUGCGCGUUU	2946
D-2439	958-976	841-859	CGCGCACCUGGUGGUGGUCUU	1444	GACCACCACCAGGUGCGCGUU	2947
D-2440	959-977	842-860	GCGCACCUGGUGGUGGUCAUU	1445	UGACCACCACCAGGUGCGCUU	2948
D-2441	960-978	843-861	CGCACCUGGUGGUGGUCACUU	1446	GUGACCACCACCAGGUGCGUU	2949
D-2442	96-114	96-114	CUCCCACCCCCACACUCCCUU	1447	GGGAGUGUGGGGGUGGGAGUU	2950
D-2443	961-979	844-862	GCACCUGGUGGUGGUCACGUU	1448	CGUGACCACCACCAGGUGCUU	2951
D-2444	962-980	845-863	CACCUGGUGGUGGUCACGUUU	1449	ACGUGACCACCACCAGGUGUU	2952
D-2445	963-981	846-864	ACCUGGUGGUGGUCACGUCUU	1450	GACGUGACCACCACCAGGUUU	2953
D-2446	964-982	847-865	CCUGGUGGUGGUCACGUCCUU	1451	GGACGUGACCACCACCAGGUU	2954
D-2447	965-983	848-866	CUGGUGGUGGUCACGUCCUUU	1452	AGGACGUGACCACCACCAGUU	2955
D-2448	966-984	849-867	UGGUGGUGGUCACGUCCUGUU	1453	CAGGACGUGACCACCACCAUU	2956
D-2449	967-985	850-868	GGUGGUGGUCACGUCCUGGUU	1454	CCAGGACGUGACCACCACCUU	2957
D-2450	968-986	851-869	GUGGUGGUCACGUCCUGGGUU	1455	CCCAGGACGUGACCACCACUU	2958
D-2451	969-987	852-870	UGGUGGUCACGUCCUGGGAUU	1456	UCCCAGGACGUGACCACCAUU	2959
D-2452	970-988	853-871	GGUGGUCACGUCCUGGGAGUU	1457	CUCCCAGGACGUGACCACCUU	2960
D-2453	97-115	97-115	UCCCACCCCCACACUCCCCUU	1458	GGGGAGUGUGGGGGUGGGAUU	2961

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2454	971-989	854-872	GUGGUCACGUCCUGGGAGGUU	1459	CCUCCCAGGACGUGACCACUU	2962
D-2455	972-990	855-873	UGGUCACGUCCUGGGAGGAUU	1460	UCCUCCCAGGACGUGACCAUU	2963
D-2456	973-991	856-874	GGUCACGUCCUGGGAGGAGUU	1461	CUCCUCCCAGGACGUGACCUU	2964
D-2457	974-992	857-875	GUCACGUCCUGGGAGGAGCUU	1462	GCUCCUCCCAGGACGUGACUU	2965
D-2458	975-993	858-876	UCACGUCCUGGGAGGAGCAUU	1463	UGCUCCUCCCAGGACGUGAUU	2966
D-2459	976-994	859-877	CACGUCCUGGGAGGAGCAGUU	1464	CUGCUCCUCCCAGGACGUGUU	2967
D-2460	977-995	860-878	ACGUCCUGGGAGGAGCAGAUU	1465	UCUGCUCCUCCCAGGACGUUU	2968
D-2461	978-996	861-879	CGUCCUGGGAGGAGCAGAAUU	1466	UUCUGCUCCUCCCAGGACGUU	2969
D-2462	979-997	862-880	GUCCUGGGAGGAGCAGAAAUU	1467	UUUCUGCUCCUCCCAGGACUU	2970
D-2463	980-998	863-881	UCCUGGGAGGAGCAGAAAUUU	1468	AUUUCUGCUCCUCCCAGGAUU	2971
D-2464	98-116	98-116	CCCACCCCCACACUCCCCUUU	1469	AGGGGAGUGUGGGGGUGGGUU	2972
D-2465	981-999	864-882	CCUGGGAGGAGCAGAAAUUUU	1470	AAUUUCUGCUCCUCCCAGGUU	2973
D-2466	982-1000	865-883	CUGGGAGGAGCAGAAAUUUUU	1471	AAAUUUCUGCUCCUCCCAGUU	2974
D-2467	983-1001	866-884	UGGGAGGAGCAGAAAUUUGUU	1472	CAAAUUUCUGCUCCUCCCAUU	2975
D-2468	984-1002	867-885	GGGAGGAGCAGAAAUUUGUUU	1473	ACAAAUUUCUGCUCCUCCCUU	2976
D-2469	985-1003	868-886	GGAGGAGCAGAAAUUUGUCUU	1474	GACAAAUUUCUGCUCCUCCUU	2977
D-2470	986-1004	869-887	GAGGAGCAGAAAUUUGUCCUU	1475	GGACAAAUUUCUGCUCCUCUU	2978
D-2471	987-1005	870-888	AGGAGCAGAAAUUUGUCCAUU	1476	UGGACAAAUUUCUGCUCCUUU	2979
D-2472	988-1006	871-889	GGAGCAGAAAUUUGUCCAGUU	1477	CUGGACAAAUUUCUGCUCCUU	2980
D-2473	989-1007	872-890	GAGCAGAAAUUUGUCCAGCUU	1478	GCUGGACAAAUUUCUGCUCUU	2981
D-2474	990-1008	873-891	AGCAGAAAUUUGUCCAGCAUU	1479	UGCUGGACAAAUUUCUGCUUU	2982
D-2475	991-1009	874-892	GCAGAAAUUUGUCCAGCACUU	1480	GUGCUGGACAAAUUUCUGCUU	2983
D-2476	99-117	99-117	CCACCCCCACACUCCCCUAUU	1481	UAGGGGAGUGUGGGGGUGGUU	2984
D-2477	992-1010	875-893	CAGAAAUUUGUCCAGCACCUU	1482	GGUGCUGGACAAAUUUCUGUU	2985
D-2478	993-1011	876-894	AGAAAUUUGUCCAGCACCAUU	1483	UGGUGCUGGACAAAUUUCUUU	2986
D-2479	994-1012	877-895	GAAAUUUGUCCAGCACCACUU	1484	GUGGUGCUGGACAAAUUUCUU	2987
D-2480	995-1013	878-896	AAAUUUGUCCAGCACCACAUU	1485	UGUGGUGCUGGACAAAUUUUU	2988
D-2481	996-1014	879-897	AAUUUGUCCAGCACCACAUUU	1486	AUGUGGUGCUGGACAAAUUUU	2989
D-2482	997-1015	880-898	AUUUGUCCAGCACCACAUAUU	1487	UAUGUGGUGCUGGACAAAUUU	2990
D-2483	998-1016	881-899	UUUGUCCAGCACCACAUAGUU	1488	CUAUGUGGUGCUGGACAAAUU	2991
D-2484	999-1017	882-900	UUGUCCAGCACCACAUAGGUU	1489	CCUAUGUGGUGCUGGACAAUU	2992
D-2485	—	453-471	ACCAUCAGCUCAGAAAAGAUU	1490	UCUUUUCUGAGCUGAUGGUUU	2993
D-2486	—	454-472	CCAUCAGCUCAGAAAAGACUU	1491	GUCUUUUCUGAGCUGAUGGUU	2994
D-2487	—	455-473	CAUCAGCUCAGAAAAGACUUU	1492	AGUCUUUUCUGAGCUGAUGUU	2995
D-2488	—	456-474	AUCAGCUCAGAAAAGACUCUU	1493	GAGUCUUUUCUGAGCUGAUUU	2996
D-2489	—	457-475	UCAGCUCAGAAAAGACUCCUU	1494	GGAGUCUUUUCUGAGCUGAUU	2997

Duplex No.	Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 001197216.2	Sense Sequence (5′-3′)	SEQ ID NO: sense	Antisense Sequence (5′-3′)	SEQ ID NO: antisense
D-2490	—	458-476	CAGCUCAGAAAAGACUCCCUU	1495	GGGAGUCUUUUCUGAGCUGUU	2998
D-2491	—	459-477	AGCUCAGAAAAGACUCCCAUU	1496	UGGGAGUCUUUUCUGAGCUUU	2999
D-2492	—	460-478	GCUCAGAAAAGACUCCCAGUU	1497	CUGGGAGUCUUUUCUGAGCUU	3000
D-2493	—	461-479	CUCAGAAAAGACUCCCAGCUU	1498	GCUGGGAGUCUUUUCUGAGUU	3001
D-2494	—	462-480	UCAGAAAAGACUCCCAGCUUU	1499	AGCUGGGAGUCUUUUCUGAUU	3002
D-2495	—	463-481	CAGAAAAGACUCCCAGCUGUU	1500	CAGCUGGGAGUCUUUUCUGUU	3003
D-2496	—	464-482	AGAAAAGACUCCCAGCUGCUU	1501	GCAGCUGGGAGUCUUUUCUUU	3004
D-2497	—	465-483	GAAAAGACUCCCAGCUGCAUU	1502	UGCAGCUGGGAGUCUUUUCUU	3005
D-2498	—	466-484	AAAAGACUCCCAGCUGCAGUU	1503	CUGCAGCUGGGAGUCUUUUUU	3006
D-2499	—	467-485	AAAGACUCCCAGCUGCAGGUU	1504	CCUGCAGCUGGGAGUCUUUUU	3007
D-2500	—	468-486	AAGACUCCCAGCUGCAGGAUU	1505	UCCUGCAGCUGGGAGUCUUUU	3008
D-2501	—	469-487	AGACUCCCAGCUGCAGGAGUU	1506	CUCCUGCAGCUGGGAGUCUUU	3009
D-2502	—	470-488	GACUCCCAGCUGCAGGAGGUU	1507	CCUCCUGCAGCUGGGAGUCUU	3010

Example 2. Efficacy of ASGR1 siRNA Molecules In Vitro

[0187] The siRNA molecules in Tier 1 and Tier 2 screening sets were synthesized without chemical modifications. Each siRNA molecule was comprised of a 21 nucleotide sense strand and 21 nucleotide antisense strand that hybridized to form a duplex region of 19 base pairs with a 2 nucleotide overhang at the 3′ end of each strand. The efficacy of each of the siRNA molecules in reducing ASGR1 expression was assessed using a 384-well format *in vitro* immunoassay, which quantifies levels of ASGR1 protein on the cell surface of Hep3B or HepG2 cells.

[0188] Transfection complexes of the siRNA molecules and RNAiMax transfection reagent (Life Technologies) in EMEM media (ATCC 30-2003) were prepared in 384-well plates in accordance with manufacturer's recommendations. Human hepatocellular carcinoma Hep3B (ATCC HB-8064) or HepG2 (ATCC HB-8065) cells in EMEM media supplemented with 10% fetal bovine serum and 1% antibiotic/antimycotic were added to each well. Cells were incubated for 4 days at 37 °C and 5% CO_2. Four days after siRNA transfection, cells were fixed in formaldehyde, blocked with bovine serum albumin, and subsequently stained with an anti-ASGR1 primary antibody (Amgen clone 7E11, light and heavy chain sequences provided below (SEQ ID NOs: 3 and 4)) for either 1 hour at room temperature or overnight at 4 °C. Plates were

washed three times with phosphate buffered saline (PBS). Cells were then incubated in the dark for 45 minutes at room temperature with Alexa488-conjugated anti-human IgG secondary antibody and nuclear stain DRAQ5 (ThermoFisher #62251), which was included to assess cell number. Following three PBS washes, the plates were imaged on an Opera Phenix high-content screening system (PerkinElmer) using the 488 and 640 channels to measure anti-ASGR1 antibody staining and nuclear staining, respectively. Data was analyzed using Columbus image analysis software and GeneData Screener software to quantify several measures of ASGR1 protein levels, cell count, and cell morphology on a per cell and per well basis.

[0189] Anti-ASGR1 primary antibody light chain amino acid sequence:
DIQMTQSPSSLSASVGDRVTIACRASQNIISYLNWYQQKPGKAPKFLIYTASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFAIYYCQQTYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS
KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 3)

[0190] Anti-ASGR1 primary antibody heavy chain amino acid sequence:
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSFGMHWVRQAPGKGLEWVAIIWHDGSNK
YYADSVKGRFTISRDNSKNTLYLQMSSLRAEDTAVYYCARDLSMGGMDVWGQGTTVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS
CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID
NO: 4)

[0191] Activity of each siRNA molecule was measured using a "Normalized Alexa 488 Mean Intensity" readout, which quantifies ASGR1 protein expression based on cell population analysis relative to ASGR1 expression in control cell populations. Cells transfected with non-targeting siRNA duplexes (i.e. siRNAs that do not have a 100% sequence match to any human gene sequences) were used as controls on each plate and a "central reference value" was calculated from these control cells. Specifically, the "central reference value" was the median value of the Alexa 488 intensity of the multiple wells containing cells transfected with non-targeting siRNAs. The "Normalized Alexa 488 Mean Intensity" was calculated for each well as follows. Nuclei and

cytoplasm were segmented using the DRAQ5 counterstain. The mean Alexa488 fluorescence intensity for each cell (i.e. the entire cellular region, including cytoplasm and nucleus) was measured. Individual cell values were averaged to produce a mean Alexa 488 intensity value for each well. This mean intensity value was then normalized to the central reference value to arrive at the "Normalized Alexa 488 Mean Intensity" value, which represents an ASGR1 expression measurement as a percent of control. Thus, negative "Normalized Alexa 488 Mean Intensity" values represent a reduced ASGR1 expression relative to control cells. Cell counts as assessed by the DRAQ5 stain were also normalized to cell counts for control cells and thus, represent a cell viability measurement as a percent of control.

[0192] The Tier 1 siRNA molecules were tested in duplicate at three different concentrations (0.3 nM, 1.25 nM, and 5 nM) in the *in vitro* immunoassay in both Hep3B cells and HepG2 cells. The reduction in ASGR1 cell surface expression relative to expression in cells transfected with non-targeting siRNAs in Hep3B cells for each siRNA molecule is shown in Table 2 below. Cell count measurements are also provided. For clarity, the data for the lowest concentration (0.3 nM) and the data for the HepG2 cells are not shown. The data shown in Table 2 are the results from two independent transfections of each siRNA (e.g. Run 1 and Run 2).

Table 2. *In vitro* efficacy of Tier 1 ASGR1 siRNA molecules in immunoassay screen

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-1011	16.51	-51.78	0.13	-14.40	25.37	-51.83	3.76	-28.05
D-1018	-17.30	-55.17	2.29	-16.02	-34.78	-52.13	30.89	-7.73
D-1024	-29.00	-18.51	-0.82	12.30	1.97	14.82	6.60	4.61
D-1036	-46.65	10.97	-10.56	7.07	-18.48	71.68	1.10	12.95
D-1055	10.56	-13.14	-1.08	-9.93	7.75	-24.90	11.92	-7.81
D-1063	9.47	-18.69	-2.54	-11.47	-25.16	-50.11	-10.17	-18.86
D-1069	-20.87	-41.89	-4.27	3.93	-11.39	-28.60	12.28	7.84
D-1082	17.70	-48.78	-8.32	-14.13	-0.15	-55.38	-5.13	-50.19
D-1089	-35.75	-60.09	-12.25	-36.42	-25.97	-57.46	-7.24	-51.34
D-1091	-18.99	-31.14	-13.76	5.02	-27.59	-20.03	3.02	-6.61
D-1098	6.89	-54.37	-2.80	-34.02	-14.23	-59.04	-11.92	-53.04

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-1135	10.36	-7.69	-15.39	-4.17	24.96	-24.64	3.57	-5.25
D-1147	20.97	-3.11	4.36	1.69	11.90	5.13	13.93	4.34
D-1151	-4.71	-14.13	-15.57	-17.87	-12.91	-34.11	-1.19	-14.79
D-1158	26.52	-10.17	23.24	8.03	28.20	-6.52	18.06	-2.88
D-1162	-40.01	-55.60	-22.04	-36.60	-35.29	-52.50	-14.02	-41.72
D-1165	-3.62	-54.73	-7.63	-23.22	-0.86	-51.86	15.67	-18.51
D-1166	-3.32	-41.79	-11.34	-13.26	-0.25	-14.66	-4.12	-15.13
D-1167	-53.20	-59.29	-6.34	-16.20	-34.68	-52.65	2.38	-24.06
D-1168	-31.18	-46.37	-1.51	-9.31	-4.10	-34.17	-15.22	-20.42
D-1170	-12.35	-53.90	-3.32	-42.65	-23.85	-56.63	5.59	-32.93
D-1171	3.82	-31.95	-14.62	-23.16	-12.00	-49.39	9.90	-28.40
D-1172	-45.07	-58.26	-1.94	3.83	-40.15	-56.40	-18.42	-45.04
D-1173	-25.53	-57.81	5.39	-8.67	-12.00	-58.53	-24.75	-56.05
D-1174	11.06	-32.05	3.06	-15.60	-18.38	-54.41	-13.38	-40.99
D-1175	-35.25	-47.56	-9.96	-1.38	-31.75	-44.76	-24.47	-34.12
D-1176	-21.07	-48.99	-12.46	-22.28	-55.65	-30.89	-4.67	-34.03
D-1206	-20.58	-58.56	-5.65	-42.60	-4.41	-58.69	13.47	-45.33
D-1234	0.74	-45.36	-6.51	4.14	13.42	-37.24	-0.46	-19.91
D-1235	-11.85	-55.44	-20.74	-53.47	-36.41	-59.01	-20.26	-54.37
D-1237	-20.08	-20.98	5.99	19.18	4.30	-22.26	0.55	-4.37
D-1246	18.79	-44.97	-0.22	-40.27	-18.38	-57.87	7.97	-44.91
D-1250	-6.10	-51.90	0.82	2.19	0.15	-58.42	10.08	-49.16
D-1257	-10.36	-55.00	5.39	16.17	-20.30	-53.64	-15.58	-41.86
D-1285	-15.32	-50.05	8.93	9.74	-18.08	-56.70	-12.37	-45.36
D-1286	-30.00	-55.94	-0.69	-28.77	-11.19	-48.78	-2.70	-42.37
D-1288	-26.13	-60.85	3.32	-3.82	-9.16	-56.60	8.07	-36.50
D-1289	-11.95	-48.94	-13.41	-9.24	-3.49	-53.30	-9.72	-31.07
D-1291	-21.57	-62.92	-2.37	4.10	10.28	-57.93	-5.22	-46.85
D-1293	7.88	-59.68	-4.18	-17.53	-1.47	-60.64	1.56	-48.52
D-1294	-13.93	-61.42	9.01	-8.13	4.20	-58.50	7.79	-49.89
D-1296	32.37	-35.87	-3.58	-26.73	21.72	-42.10	28.96	-8.80
D-1299	9.97	-15.14	5.99	-4.68	14.33	-12.03	-4.77	-16.17
D-1301	42.98	8.71	10.05	11.59	18.48	-7.91	1.65	0.99
D-1302	8.78	-15.98	11.08	4.83	4.61	-11.01	-0.73	-2.26
D-1303	18.39	8.99	15.05	3.34	34.38	16.39	4.95	0.93

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-1335	-4.41	-57.42	-7.81	-12.59	-2.78	-53.97	-5.32	-38.92
D-1340	15.42	-56.65	12.63	-47.35	18.08	-56.73	11.55	-47.26
D-1342	-1.34	-55.68	1.60	-30.81	-14.13	-55.74	24.66	-34.02
D-1350	12.25	-46.29	16.43	-17.81	8.86	-45.60	11.73	-15.78
D-1364	-36.14	-58.31	-7.81	-45.74	-31.95	-57.24	-2.47	-42.87
D-1365	-45.46	-59.21	1.08	-39.04	-54.43	-55.49	-9.26	-47.65
D-1367	-2.23	-49.60	27.47	-0.24	0.35	-55.94	15.49	-40.01
D-1373	29.80	-55.97	22.64	-34.90	-9.37	-57.64	15.40	-50.30
D-1376	9.37	-54.03	4.61	-6.55	-18.48	-58.89	23.74	-40.26
D-1387	-15.62	-60.74	12.03	-24.43	-22.84	-59.13	-0.46	-55.15
D-1389	37.33	-60.30	-1.68	-58.97	-6.03	-59.85	6.51	-56.49
D-1390	-7.09	-62.69	1.94	-19.96	18.08	-60.28	11.92	-58.45
D-1397	-17.90	-62.94	10.13	-56.73	25.06	-60.77	4.12	-56.43
D-1398	-7.09	-61.91	9.27	-39.40	-6.43	-56.41	27.77	-34.30
D-1399	-33.81	-62.45	12.59	-17.06	2.08	-59.75	11.14	-50.83
D-1400	46.65	-59.41	13.50	-36.58	16.15	-59.11	11.92	-48.21
D-1403	24.74	-0.88	20.40	4.38	-19.29	-29.75	11.27	4.71
D-1405	-7.78	-10.82	8.24	-5.29	4.30	-1.20	-4.03	-5.98
D-1406	-3.92	-9.59	-1.85	-8.89	-5.01	-9.40	23.74	15.19
D-1407	18.69	-3.89	-7.29	-12.59	-4.30	-19.11	9.90	-6.78
D-1408	8.73	-49.20	-12.98	-42.77	-1.47	-53.33	12.19	-35.80
D-1426	-6.79	-61.40	-12.46	-51.50	-4.30	-59.00	-19.34	-56.51
D-1431	5.30	-58.85	-8.50	-53.37	-3.19	-57.76	0.18	-47.13
D-1432	-16.11	-61.98	-2.72	-45.35	-22.53	-58.60	3.76	-47.92
D-1438	7.09	-61.80	23.59	-55.97	3.49	-58.39	21.45	-54.63
D-1443	-10.76	-62.32	2.98	-59.31	3.80	-59.01	8.98	-54.86
D-1452	-0.79	-56.32	14.27	-45.83	-31.70	-56.68	10.91	-52.19
D-1453	12.05	-56.42	31.87	-26.99	-32.86	-57.12	13.47	-56.95
D-1454	-25.83	-60.61	2.63	-24.99	-23.95	-59.91	9.62	-55.41
D-1455	19.58	-55.42	-6.34	-27.92	8.46	-58.89	0.27	-51.97
D-1472	29.80	-55.21	-2.89	-22.04	-13.42	-58.75	21.91	-52.79
D-1478	-3.12	-60.56	7.03	-3.28	4.81	-58.19	12.01	-43.07
D-1479	20.38	-59.07	-15.14	-22.23	-7.95	-58.41	10.08	-42.61
D-1484	-6.30	-62.62	9.87	-39.24	13.01	-58.78	3.76	-51.54
D-1494	-13.73	-63.95	6.34	-41.07	-11.19	-60.62	22.64	-59.92

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-1495	8.28	-62.15	4.70	-27.22	18.89	-60.38	20.16	-55.68
D-1497	26.13	-59.97	4.96	-58.89	0.05	-60.05	14.12	-58.30
D-1502	14.97	-45.58	1.94	-38.33	-4.76	-54.72	5.77	-38.10
D-1505	-8.28	-59.54	-12.25	-17.83	-14.08	-59.50	3.02	-36.43
D-1506	8.18	-57.99	20.91	-9.71	-2.48	-58.59	2.11	-41.88
D-1511	-0.74	-15.67	-2.63	-10.15	1.16	-14.97	13.84	-0.23
D-1516	12.05	-4.94	-1.08	0.63	4.51	1.35	-1.19	-17.05
D-1518	-4.21	-26.51	-13.58	-8.51	-4.00	-3.46	13.57	-3.88
D-1521	18.29	-23.36	6.68	1.40	20.81	15.51	-3.85	-13.25
D-1536	16.31	-15.47	1.25	5.23	27.70	-11.54	6.14	0.40
D-1554	13.24	-13.40	-4.70	0.95	6.63	-32.03	3.30	-0.92
D-1556	-26.52	-41.44	3.49	6.92	-3.19	-13.71	-1.47	-10.81
D-1572	26.62	-24.09	20.31	5.52	5.62	-1.00	24.01	11.58
D-1578	-4.71	-44.74	-12.89	-14.92	2.78	-23.50	5.22	-5.92
D-1581	-23.05	-27.51	-16.17	-14.43	-22.53	-12.89	-2.38	-15.63
D-1623	-22.46	-30.62	-11.69	-6.55	-25.27	-32.19	13.47	4.71
D-1627	12.25	-23.19	-4.96	-29.97	-10.89	-38.16	1.56	-25.15
D-1653	11.06	-32.19	9.44	0.09	-4.71	-32.15	19.52	0.81
D-1656	5.60	-38.39	1.51	-22.78	-21.42	-49.42	3.94	-21.36
D-1678	-32.77	-50.41	-16.52	-23.47	-15.04	-44.98	5.50	-6.64
D-1683	11.65	-32.74	4.53	-1.23	4.81	-26.86	13.75	-6.80
D-1686	2.63	-31.87	-13.15	-4.49	13.42	-13.30	23.37	-3.19
D-1687	-1.54	-38.12	-0.56	-8.62	-17.37	-40.05	21.08	-7.89
D-1694	-15.82	-54.86	8.58	-24.98	-29.82	-48.50	14.02	-28.37
D-1708	-17.80	-55.25	-2.03	-31.77	-34.99	-52.79	9.62	-30.91
D-1709	-8.28	-48.76	10.65	-2.99	9.06	-33.13	33.36	-2.17
D-1713	-6.40	-19.58	-18.76	10.36	-7.85	-17.32	10.91	10.44
D-1716	14.03	-45.60	22.38	-5.99	18.78	-49.38	8.71	-45.19
D-1719	-17.50	-53.30	8.75	-6.89	-29.92	-56.30	17.69	-20.17
D-1722	22.06	-49.25	6.94	-6.97	2.99	-53.32	16.96	-42.54
D-1734	27.32	-44.60	14.19	0.24	-7.04	-56.49	1.10	-44.07
D-1741	-2.63	-45.97	2.80	-2.87	-32.15	-55.22	16.68	-18.26
D-1748	7.09	-50.05	11.51	-16.11	-34.28	-57.38	8.98	-36.62
D-1750	39.91	-43.78	12.81	15.45	30.63	-43.98	24.38	-12.48
D-1752	1.54	-56.17	-3.23	-14.35	15.54	-53.71	10.91	-34.83

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-1773	-11.25	-61.04	7.72	-10.35	-19.80	-58.31	20.53	-50.30
D-1777	-11.16	-53.95	-1.51	-27.84	-0.05	-50.07	14.57	-28.05
D-1792	4.51	-10.06	7.98	2.31	31.44	-0.79	15.67	-0.52
D-1798	-29.00	-58.63	6.17	-49.28	-32.05	-58.49	8.71	-54.61
D-1801	19.58	-52.66	-11.00	-46.00	-13.62	-58.81	12.65	-45.62
D-1807	14.33	-36.45	-3.41	-8.24	1.57	-47.37	6.87	-33.08
D-1808	21.77	-50.54	5.48	-1.08	-25.16	-58.30	14.12	-44.68
D-1811	26.92	-48.75	-9.27	-37.36	10.89	-59.48	-2.38	-43.87
D-1813	15.82	-59.88	5.30	-5.72	48.86	-55.18	12.83	-51.46
D-1814	9.47	-11.40	-4.10	5.65	-6.53	-25.64	6.97	6.28
D-1815	20.18	-57.38	0.39	-46.20	3.80	-59.35	8.07	-49.05
D-1819	-14.33	-53.70	-4.53	-25.39	-21.62	-29.60	-2.02	-34.84
D-1824	8.58	-61.67	2.03	-52.48	-1.97	-60.35	0.73	-48.34
D-1826	-1.14	-59.23	3.75	-55.52	-1.47	-59.41	0.82	-56.95
D-1832	22.06	-57.11	-7.63	-32.20	-8.25	-59.70	-12.01	-58.04
D-1840	18.89	-48.93	12.29	-24.02	-14.33	-57.91	8.52	-41.61
D-1842	8.18	-57.58	-2.63	-11.59	-22.63	-59.42	9.99	-52.24
D-1848	3.12	1.44	-12.81	-3.07	-24.35	-34.25	-14.57	-5.02
D-1874	-1.14	-8.57	-3.88	1.72	-24.25	0.91	-13.79	-3.21
D-1876	12.10	-54.54	-0.78	-5.14	17.01	-53.11	5.18	-29.31
D-1929	-4.51	-53.02	-8.50	-37.65	-9.97	-56.26	15.86	-35.66
D-1975	-1.83	-60.71	-8.06	-22.41	24.86	-59.22	6.05	-45.07
D-1981	4.81	-59.13	-3.67	-21.74	19.29	-57.31	12.56	-49.72
D-1983	25.63	-60.82	-6.94	-53.04	18.28	-59.21	13.38	-50.18
D-1987	-0.25	-51.50	-17.12	-5.68	-7.34	-56.91	-0.37	-49.23
D-1989	25.93	-59.04	-0.22	-56.06	19.70	-59.14	-0.37	-57.37
D-1994	-30.59	-40.01	16.08	-2.53	-26.18	-40.53	-20.81	-34.18
D-1999	-5.30	-59.22	-0.22	-28.91	-3.90	-54.46	-11.00	-58.90
D-2000	-6.40	-52.51	-10.22	-41.18	-13.92	-56.51	-6.78	-47.04
D-2006	-6.10	-56.48	-11.00	-34.67	-23.75	-59.18	-17.14	-47.29
D-2008	1.54	-54.28	3.67	-27.83	-17.27	-59.63	-12.37	-44.60
D-2010	-6.69	-53.88	-4.27	-9.69	-11.39	-58.47	4.58	-44.37
D-2021	-10.96	-53.49	-18.84	-40.95	-1.27	-53.90	13.38	-33.91
D-2045	-26.82	-58.06	4.87	-22.24	-22.13	-56.67	-14.48	-39.83
D-2050	-5.01	-32.58	-17.81	-23.38	-13.52	-49.82	-11.82	-31.36

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-2054	14.33	-46.36	-18.50	-38.37	-11.90	-53.12	2.20	-26.56
D-2056	6.89	-56.26	-21.26	-48.12	-5.22	-60.11	0.09	-45.21
D-2059	-25.53	-60.64	-4.01	-12.60	-29.52	-59.15	-7.79	-56.33
D-2064	-42.29	-55.85	-2.37	-0.05	-37.01	-59.20	2.57	-49.72
D-2066	-27.12	-62.04	0.56	-21.81	-19.39	-58.62	-9.17	-56.56
D-2069	-2.63	-61.10	0.04	-43.17	14.13	-57.57	2.84	-43.86
D-2081	-16.66	-47.70	-3.41	-8.40	17.62	-54.09	3.16	-27.64
D-2095	-4.51	-59.69	-7.72	-31.26	-3.90	-56.37	13.84	-27.54
D-2107	-40.01	-57.62	0.73	-1.33	-19.70	-48.12	-0.64	-30.71
D-2115	-39.12	-41.56	-26.35	-31.43	-40.86	-31.71	-3.21	-20.71
D-2122	-42.09	-54.90	-19.62	-36.56	-37.22	-56.76	0.82	-33.96
D-2124	-8.08	-46.96	-14.19	-0.08	-17.37	-47.88	-21.54	-22.67
D-2130	-5.40	-22.16	3.41	11.97	-17.57	-33.56	-18.52	-18.45
D-2133	-25.93	-46.79	-19.97	-5.63	-36.51	-50.48	8.16	-10.25
D-2134	-39.81	-61.69	-16.26	-31.95	-22.43	-59.20	-1.74	-34.15
D-2136	-11.80	-42.20	-6.34	-4.68	-21.87	-56.73	-6.32	-21.07
D-2137	-30.59	-61.11	-10.74	-24.82	5.62	-49.50	17.42	-17.59
D-2142	-26.82	-56.29	14.79	3.81	2.68	-46.12	6.51	-21.91
D-2143	-35.25	-56.55	-11.08	-41.09	-21.32	-58.35	13.84	-32.12
D-2172	7.29	-29.17	-1.34	12.93	-6.03	-34.12	13.11	11.63
D-2174	2.03	-51.87	4.79	4.73	6.84	-47.31	7.97	-30.31
D-2192	14.43	-41.72	15.48	-11.07	24.96	-44.47	21.91	-24.19
D-2196	1.64	-52.44	14.27	-0.40	-34.38	-55.66	-0.82	-47.45
D-2199	26.82	-56.29	-4.01	-2.81	20.71	-58.07	12.37	-38.76
D-2200	5.01	-38.18	8.50	9.77	12.51	-44.01	18.42	-25.19
D-2202	5.85	-5.08	-2.24	1.89	-1.47	6.11	1.37	-0.43
D-2210	-20.87	-58.61	2.29	-24.34	-1.57	-44.74	15.58	-23.79
D-2224	13.34	-54.07	14.70	-17.77	39.54	-51.64	2.57	-36.75
D-2230	-23.95	-40.70	-2.54	-5.35	-10.68	-6.76	20.26	15.29
D-2236	9.17	-55.50	-4.44	-35.30	4.51	-46.56	-3.57	-27.54
D-2238	16.01	-48.75	-9.79	-29.17	21.42	-42.21	6.14	-28.27
D-2266	8.08	-14.56	3.84	-18.65	6.73	-28.22	6.51	-12.90
D-2267	9.27	0.67	-1.60	3.64	-41.87	-43.95	14.85	15.50
D-2294	25.63	-7.76	14.01	6.68	-8.66	-31.02	17.78	4.99
D-2296	16.81	-28.11	-1.94	-17.85	-13.22	-41.06	17.32	-11.82

	Run 1				Run 2			
Duplex No.	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**	**Cell count 5 nM**	**Normalized Alexa 488 Mean Intensity 5nM**	**Cell count 1.25 nM**	**Normalized Alexa 488 Mean Intensity 1.25nM**
D-2300	-26.13	-57.30	8.32	0.46	-45.22	-53.30	3.94	-29.90
D-2301	-15.72	-38.46	22.38	5.62	-9.87	-38.50	-9.07	-20.00
D-2304	14.53	-53.06	4.79	-16.86	-20.91	-58.98	15.03	-42.20
D-2311	-60.73	-63.05	1.25	-54.94	-59.90	-59.83	6.78	-51.22
D-2322	9.07	-53.47	-1.60	-28.61	-3.70	-53.94	5.32	-34.29
D-2335	2.73	-59.25	7.46	-44.73	-3.09	-57.83	2.02	-37.63
D-2354	3.12	-52.45	16.77	7.77	7.04	-49.64	15.31	-39.67
D-2357	46.55	-51.86	14.45	-45.90	3.39	-59.31	3.85	-56.37
D-2360	22.46	-57.37	24.71	-13.55	19.49	-56.45	19.80	-34.93
D-2361	11.16	-50.62	10.31	-17.97	42.58	-57.92	12.37	-49.42
D-2362	24.54	-24.39	5.22	3.25	10.08	-36.37	17.14	-0.36
D-2374	32.97	-24.51	-9.10	1.81	13.01	-36.58	9.07	-25.51
D-2388	-18.59	-43.66	12.38	0.51	-10.58	-29.34	30.98	10.51
D-2399	-39.22	-56.10	-4.18	-28.95	-68.10	-59.66	-39.60	-51.94
D-2401	-30.49	-59.59	-1.25	-11.64	-40.30	-57.59	10.04	-34.66
D-2403	-8.97	-61.28	2.20	-9.13	-14.63	-57.17	38.59	-13.48
D-2412	15.62	6.15	12.89	11.91	2.18	-12.33	12.10	-4.72
D-2461	-19.78	-56.95	-6.34	-54.93	-35.49	-57.76	-7.52	-49.34
D-2462	18.79	-21.80	11.25	-2.95	-32.35	-52.99	-2.84	-24.30
D-2465	13.83	-55.08	7.89	-7.64	1.97	-58.56	20.90	-43.55
D-2466	28.90	-49.02	-7.29	-8.54	-17.47	-57.63	17.05	-43.13
D-2468	9.17	-52.16	-5.74	-14.25	43.70	-57.19	12.47	-48.60
D-2475	-28.90	-54.23	-7.12	-5.24	-47.75	-56.37	5.04	-38.94
D-2481	12.94	-55.66	3.23	-12.64	3.70	-54.71	18.42	-28.59
D-2487	17.50	-10.84	-4.01	-0.05	9.37	-7.38	14.12	1.83

[0193] Of the 211 unmodified siRNA molecules screened in Tier 1, at the 5 nM concentration, about 168 siRNA molecules reduced ASGR1 cell surface expression relative to control cells by at least 30%, about 119 siRNA molecules reduced ASGR1 cell surface expression relative to control cells by at least 50%, and about 30 siRNA molecules reduced ASGR1 cell surface expression relative to control cells by at least 60%. Some of the siRNA molecules exhibited no or marginal reduction in ASGR1 cell surface expression relative to control cells.

[0194] A subset of the siRNA molecules from this initial screen of the Tier 1 molecules were selected for further testing in a 10-point dose response format (0.004nM to 83nM) in the *in vitro* anti-ASGR1 immunoassay in Hep3B cells. IC50 values for each of these 55 siRNA molecules were calculated from the dose-response curves and are shown in Table 3 below. Data from two independent transfections of each siRNA molecule (Run 1 and Run 2) are shown. At least 18 of the siRNA molecules had IC50 values of about 0.30 nM or less. Compounds D-1983, D-1098, D-1438, D-1246, and D-1494 were among the most potent with average IC50 values less than 0.15 nM.

Table 3. IC50 values determined by immunoassay for select ASGR1 siRNA molecules

Duplex No.	Run 1 IC50 (nM)	Run 2 IC50 (nM)	Duplex No.	Run 1 IC50 (nM)	Run 2 IC50 (nM)
D-1055	>83.33	>83.33	D-1708	0.66	0.56
D-1082	0.72	1.10	D-1798	0.48	0.52
D-1089	0.15	0.24	D-1801	0.50	0.76
D-1098	0.08	0.09	D-1811	0.73	0.57
D-1168	1.98	1.74	D-1813	0.29	0.29
D-1170	0.32	0.20	D-1815	0.80	0.24
D-1171	1.01	0.56	D-1824	0.39	0.33
D-1173	0.64	0.23	D-1826	1.08	0.07
D-1176	1.48	0.95	D-1832	0.26	0.12
D-1206	0.74	0.25	D-1981	1.33	0.46
D-1235	0.58	0.35	D-1983	0.05	0.05
D-1246	0.17	0.11	D-1989	1.35	0.83
D-1340	0.31	0.44	D-1999	0.23	0.14
D-1364	0.51	0.72	D-2000	0.67	0.45
D-1373	0.22	0.32	D-2006	0.52	0.55
D-1389	0.19	0.12	D-2045	0.14	0.21
D-1397	0.47	0.08	D-2056	0.27	0.19
D-1408	0.90	0.44	D-2069	1.33	1.33
D-1426	0.26	0.43	D-2122	0.80	1.41
D-1431	0.41	0.54	D-2142	2.07	1.12
D-1432	3.39	3.31	D-2143	1.12	0.68
D-1438	0.10	0.16	D-2311	0.56	0.46
D-1443	0.53	0.28	D-2335	0.28	0.23
D-1472	0.57	0.60	D-2357	0.38	0.28

Duplex No.	Run 1 IC50 (nM)	Run 2 IC50 (nM)	Duplex No.	Run 1 IC50 (nM)	Run 2 IC50 (nM)
D-1484	0.29	0.17	D-2361	0.75	0.70
D-1494	0.21	0.07	D-2401	0.99	0.76
D-1497	1.50	0.15	D-2461	1.05	0.91
D-1686	27.78	>83.33			

[0195] All of the Tier 2 siRNA molecules, except for 8 siRNA molecules targeting the 5′ and 3′ ends of the human ASGR1 transcript, were tested in the *in vitro* anti-ASGR1 immunoassay in Hep3B cells at two different concentrations (1.25 nM and 5 nM). The reduction in ASGR1 cell surface expression relative to expression in cells transfected with non-targeting siRNAs in Hep3B cells for each siRNA molecule is shown in Table 4 below. Cell count measurements are also provided.

Table 4. *In vitro* efficacy of Tier 2 ASGR1 siRNA molecules in immunoassay screen

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1000	-7.89	-69.66	14.36	-16.59	D-1766	0.52	4.89	14.20	-11.31
D-1001	-37.89	-69.18	2.85	-24.50	D-1767	18.43	-46.54	19.50	0.02
D-1002	-31.79	-57.03	11.54	-1.83	D-1768	12.02	-74.19	2.92	-14.64
D-1003	-3.36	37.23	9.55	-2.29	D-1769	-0.34	-55.25	-2.90	-21.94
D-1004	1.60	-59.64	8.80	-8.51	D-1770	3.43	-35.46	1.33	-9.24
D-1005	3.05	-28.72	-1.24	2.39	D-1771	-1.18	-35.96	18.93	-2.23
D-1006	-32.96	-57.28	-7.05	-9.66	D-1772	-32.57	-78.62	60.42	3.61
D-1007	-27.69	-70.79	14.31	-3.33	D-1774	24.50	-76.51	20.00	-23.79
D-1008	30.65	9.28	20.79	12.22	D-1775	21.92	-1.67	20.58	3.16
D-1009	-23.35	-73.69	11.67	-2.29	D-1776	-0.64	-69.08	3.51	-14.00
D-1010	35.43	-55.89	3.56	-22.96	D-1778	14.85	-43.29	7.13	3.09
D-1012	16.98	-75.78	10.37	-34.40	D-1779	45.23	9.53	7.47	-2.55
D-1013	24.10	12.20	8.33	2.11	D-1780	6.36	-53.12	16.21	5.81
D-1014	7.31	-65.21	12.97	-6.17	D-1781	-9.63	-55.20	3.01	-13.99
D-1015	-7.71	-73.25	16.15	-4.04	D-1782	-7.40	-37.94	-2.35	-13.41
D-1016	-60.21	-61.66	6.81	14.15	D-1783	-11.80	-39.91	15.38	-0.50
D-1017	11.83	-56.24	4.70	2.01	D-1784	-27.14	-62.76	7.72	-15.32

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1019	29.84	-64.73	-1.46	-12.82	D-1785	-24.69	-56.81	0.57	-20.48
D-1020	25.65	-53.00	-2.67	-10.04	D-1786	-53.14	-57.69	7.62	-13.19
D-1021	-26.83	-75.10	2.11	-12.78	D-1787	-1.98	-67.56	14.61	-14.64
D-1022	-0.55	-59.91	-3.68	-22.68	D-1788	22.85	-27.66	11.40	-4.65
D-1023	-0.29	13.64	11.80	2.03	D-1789	-57.57	-60.25	3.65	-2.84
D-1025	27.98	-1.15	7.76	-2.93	D-1790	18.68	-77.95	16.25	-18.72
D-1026	-18.53	-56.89	13.22	8.74	D-1791	-7.31	-74.76	15.24	-6.11
D-1027	55.59	-36.50	11.10	1.38	D-1793	28.65	16.33	12.45	5.71
D-1028	-32.96	-19.81	5.19	-0.71	D-1794	-17.68	-20.87	1.46	-7.31
D-1029	-20.89	-63.26	13.44	-5.46	D-1795	17.95	-73.95	-1.74	-27.64
D-1030	27.16	-43.18	5.36	-9.83	D-1796	5.95	-23.80	7.30	-7.46
D-1031	6.49	-13.65	23.42	2.27	D-1797	-6.72	-51.09	11.70	-3.05
D-1032	-1.16	-10.97	-4.20	-13.77	D-1798	12.40	-2.59	-8.59	-8.33
D-1033	-30.24	-69.98	-0.58	-13.92	D-1799	8.91	-59.33	-2.27	-19.09
D-1034	-28.53	-23.08	9.46	3.34	D-1800	18.52	17.09	2.45	-4.63
D-1035	25.32	-65.71	3.16	-16.06	D-1801	-18.92	-22.39	11.12	-12.94
D-1037	-3.94	-52.11	11.55	-9.25	D-1802	-3.58	-78.22	2.34	-13.75
D-1038	-7.40	-57.60	16.02	-6.46	D-1803	7.69	-66.70	-0.66	-17.72
D-1039	14.47	-71.31	9.64	-34.96	D-1804	-22.94	-78.51	16.40	-15.98
D-1040	-4.57	-54.21	14.10	-0.10	D-1805	12.14	-36.01	17.76	9.49
D-1041	-11.52	-69.09	-6.14	-14.98	D-1806	-10.65	-73.01	-1.86	-36.31
D-1042	-30.28	-38.43	-4.52	-15.31	D-1809	-2.23	-62.22	-3.38	-12.14
D-1043	36.88	-29.24	6.55	-7.92	D-1810	-2.27	-50.18	-7.88	-12.36
D-1044	2.11	33.99	18.08	14.48	D-1811	20.62	-78.33	10.83	-4.71
D-1045	-51.56	-57.05	6.11	-6.29	D-1812	6.46	-63.75	15.80	5.89
D-1046	-4.10	-54.90	18.23	4.76	D-1813	26.26	-34.46	3.24	-5.20
D-1047	2.37	-61.85	10.29	5.28	D-1815	21.72	24.33	-0.91	-15.26
D-1048	47.43	-78.54	22.26	-40.26	D-1816	-1.27	-62.68	0.65	-15.01
D-1049	-21.19	-48.21	18.33	3.60	D-1817	-37.56	-48.82	-8.49	-10.71
D-1050	-48.89	-66.58	2.19	-5.94	D-1818	-20.79	-49.64	0.32	-14.74
D-1051	-24.11	-78.56	9.89	-3.84	D-1820	1.94	-66.41	-12.77	-12.94
D-1052	20.98	-65.51	-1.22	-10.60	D-1821	-27.34	-55.96	-5.69	-15.96
D-1053	-24.22	-33.53	16.74	0.96	D-1822	15.72	-13.71	5.89	-8.21
D-1054	13.12	-66.55	-6.19	-20.07	D-1823	36.98	-54.48	7.03	-7.59
D-1055	-1.47	-30.04	5.24	-6.10	D-1824	15.05	-38.99	12.20	-4.28
D-1056	-5.32	-74.11	21.67	-19.44	D-1825	-17.23	-62.99	17.95	-0.48
D-1057	-4.16	8.07	-2.83	-19.78	D-1826	-1.74	-79.64	8.73	-30.66

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1058	15.98	-60.00	9.56	-6.36	D-1827	-9.29	-36.07	0.00	-8.87
D-1059	48.61	-77.08	1.54	-3.17	D-1828	32.08	-63.24	-1.16	-20.15
D-1060	-15.59	-38.07	4.82	2.38	D-1829	-12.97	-80.27	17.54	-16.16
D-1061	-23.58	-28.91	13.89	-4.03	D-1830	-18.62	-21.58	0.81	-16.10
D-1062	6.14	-17.75	38.76	11.62	D-1831	-25.78	-74.69	16.99	-12.92
D-1064	0.34	-47.84	4.56	-9.18	D-1832	9.24	16.76	-10.29	-21.96
D-1065	-6.79	-66.80	6.78	-22.67	D-1833	31.56	-68.81	13.34	-1.42
D-1066	-65.89	-80.55	2.45	-7.49	D-1834	-10.26	-74.52	-1.21	-27.17
D-1067	-33.03	-50.01	-10.13	-11.57	D-1835	-12.48	-67.28	3.77	0.84
D-1068	24.92	34.77	12.70	-11.13	D-1836	-13.17	-7.34	20.13	17.39
D-1070	-2.32	-77.56	4.69	-41.44	D-1837	-11.36	-20.19	3.48	4.61
D-1071	-13.75	-49.58	-4.45	-27.30	D-1838	-14.31	-32.03	14.06	1.71
D-1072	-17.16	-71.02	5.27	-11.02	D-1839	10.51	-63.37	11.43	-5.04
D-1073	3.53	-70.15	0.08	-20.71	D-1841	-16.26	-72.93	-5.25	-20.49
D-1074	-2.69	-52.58	-3.32	-13.23	D-1843	-46.20	-72.45	7.14	-13.01
D-1075	-29.75	-69.26	1.62	1.87	D-1844	-4.79	-42.61	15.60	9.77
D-1076	-19.38	-47.86	-12.97	-23.12	D-1845	35.78	-30.99	15.31	-11.75
D-1077	9.29	-65.14	9.30	-6.34	D-1846	30.49	-44.75	4.53	-10.21
D-1078	-23.33	-40.07	5.01	-3.70	D-1847	13.03	-44.91	9.72	-12.37
D-1079	-42.01	-63.78	0.89	0.06	D-1849	4.40	-50.27	4.32	-11.51
D-1080	-17.33	-44.28	2.34	2.62	D-1850	22.87	-19.62	9.48	2.97
D-1081	13.97	-12.08	12.60	0.04	D-1851	10.16	-50.32	10.83	-2.40
D-1082	31.36	-61.76	-6.47	-45.11	D-1852	-2.03	3.30	6.39	-10.53
D-1083	-4.22	-78.92	24.94	-13.91	D-1853	8.76	-34.41	11.54	-0.96
D-1084	-0.24	-78.23	0.59	-7.50	D-1854	-10.75	-32.54	1.86	-1.55
D-1085	-11.36	-44.47	0.49	-16.32	D-1855	6.49	-75.79	9.86	-13.88
D-1086	-7.98	-30.62	16.32	1.09	D-1856	-11.66	-70.52	-4.07	-27.14
D-1087	-4.69	-48.31	14.94	-7.65	D-1857	-7.50	-2.38	13.44	-5.69
D-1088	34.69	-75.14	3.15	-32.99	D-1858	13.63	-54.80	2.27	-14.00
D-1089	-0.64	14.68	10.29	0.81	D-1859	-17.17	-75.64	6.56	-17.77
D-1090	24.33	-73.19	1.58	-29.18	D-1860	6.58	-76.19	-5.16	-13.59
D-1092	15.32	-38.05	22.85	7.63	D-1861	19.57	-39.30	16.86	13.06
D-1093	16.98	-66.40	5.15	-3.92	D-1862	-5.71	-73.94	4.85	-8.72
D-1094	-28.11	-76.79	9.05	-12.11	D-1863	-47.23	-81.66	41.00	-8.60
D-1095	-62.01	-80.60	-6.17	-18.12	D-1864	23.90	-75.44	-0.16	-26.92
D-1096	29.08	-59.93	22.01	-14.91	D-1865	-2.85	-33.66	17.34	-7.39
D-1097	-3.49	-57.96	13.47	-9.93	D-1866	-41.34	-73.70	4.20	-7.31

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1098	-4.13	-77.54	18.58	11.13	D-1867	7.01	-43.86	23.49	-4.81
D-1099	1.50	-37.43	13.86	-9.51	D-1868	27.33	-45.04	-15.44	-23.60
D-1100	36.33	-34.40	-4.77	-12.29	D-1869	-2.02	-38.29	16.32	0.19
D-1101	18.17	-67.20	-3.35	-12.05	D-1870	-3.25	-72.86	-3.89	-33.61
D-1102	-32.57	-36.16	7.11	-2.90	D-1871	-6.24	-59.17	6.53	-8.23
D-1103	14.19	-66.58	2.19	-4.37	D-1872	6.06	12.20	27.36	18.31
D-1104	-26.08	-71.40	-0.66	-21.29	D-1873	-19.65	-62.34	3.15	-7.44
D-1105	26.73	-18.96	3.08	-10.81	D-1875	11.66	-45.27	6.22	-6.88
D-1106	4.76	-60.72	7.37	6.57	D-1877	28.40	-51.53	4.40	-19.08
D-1107	0.97	-31.43	9.38	-3.31	D-1878	-13.50	-29.09	5.98	-8.53
D-1108	-8.06	-74.96	3.16	-35.88	D-1879	1.09	-29.39	12.09	-9.43
D-1109	16.36	-42.30	4.53	-4.72	D-1880	-2.56	-47.80	-0.17	-6.36
D-1110	12.49	-25.10	24.01	5.26	D-1881	58.17	-50.55	-2.26	-19.24
D-1111	30.30	-7.13	2.99	-8.86	D-1882	-26.82	-47.71	2.51	10.76
D-1112	-13.01	-16.74	27.80	11.70	D-1883	-22.50	-13.68	-13.61	-21.06
D-1113	6.34	-59.24	10.21	-0.62	D-1884	-2.70	-35.00	19.02	-4.66
D-1114	-24.13	-24.51	9.04	-7.34	D-1885	-7.50	-73.19	-4.56	-34.52
D-1115	-24.09	-75.18	-10.45	-43.54	D-1886	-8.82	-20.72	6.89	11.71
D-1116	-15.10	-30.34	12.21	-0.66	D-1887	11.23	-66.61	1.94	-17.52
D-1117	17.76	9.45	4.90	-8.17	D-1888	-4.79	-17.84	6.06	-4.70
D-1118	2.98	-22.01	21.22	1.82	D-1889	7.59	-57.31	15.07	-11.89
D-1119	-14.42	-29.69	-4.61	-9.83	D-1890	-32.37	-68.00	-4.48	-15.63
D-1120	-8.07	-59.22	2.09	-18.67	D-1891	38.80	-18.11	5.75	-12.54
D-1121	1.37	-38.92	0.00	-18.03	D-1892	3.63	-9.46	9.72	12.53
D-1122	-25.60	-13.63	-16.07	-5.83	D-1893	5.33	-62.04	13.70	8.34
D-1123	-23.76	-13.41	18.49	-0.36	D-1894	-16.08	-66.91	-3.48	-18.47
D-1124	29.36	-39.05	30.71	8.55	D-1895	-39.37	-54.73	10.65	-3.04
D-1125	15.34	-60.37	-1.83	-18.69	D-1896	-34.17	-68.67	20.94	2.68
D-1126	8.35	-20.20	11.35	14.70	D-1897	-12.55	-79.14	-1.18	-30.09
D-1127	13.94	-56.41	4.37	-23.47	D-1898	-6.96	-68.28	-1.78	-18.90
D-1128	-9.29	-43.79	11.18	7.39	D-1899	20.72	26.23	-11.80	-14.61
D-1129	-36.45	-70.33	7.05	19.91	D-1900	-3.73	-64.22	-2.82	-23.57
D-1130	7.87	-58.39	-6.32	-12.47	D-1901	6.36	-58.44	5.35	-2.99
D-1131	-4.69	-60.73	11.29	-12.42	D-1902	1.26	21.40	23.69	10.04
D-1132	13.53	3.34	20.18	10.44	D-1903	3.94	-74.24	-0.25	-14.16
D-1133	6.11	-32.84	10.06	-9.99	D-1904	0.68	50.23	2.51	-9.54
D-1134	-8.48	-55.96	5.75	-15.23	D-1905	-19.08	-76.82	10.88	-17.12

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1136	-23.95	-25.01	15.68	-0.43	D-1906	17.08	-43.53	9.46	-4.79
D-1137	-31.73	-70.89	5.75	-7.02	D-1907	-19.00	-52.03	0.34	-20.98
D-1138	25.27	3.96	10.59	-5.05	D-1908	-21.93	-49.22	18.58	14.88
D-1139	36.30	16.88	9.30	0.56	D-1909	17.59	12.47	0.41	-5.27
D-1140	38.80	-11.18	8.96	-9.00	D-1910	12.10	-37.19	2.43	-10.38
D-1141	-9.08	-59.67	1.92	-3.78	D-1911	4.31	-60.58	19.92	7.26
D-1142	-2.57	-29.79	4.60	-9.26	D-1912	-7.69	-34.13	2.59	-5.43
D-1143	10.00	-23.14	18.41	3.98	D-1913	4.68	-7.14	21.84	10.42
D-1144	-22.41	-67.81	5.16	-4.68	D-1914	-9.95	-40.94	20.02	0.05
D-1145	-11.01	-39.40	14.98	-5.93	D-1915	-9.20	-12.41	0.40	-10.13
D-1146	20.61	-60.09	5.83	-14.30	D-1916	-90.09	-69.70	-1.42	10.86
D-1148	-32.46	-42.55	24.90	13.98	D-1917	7.80	-21.88	21.09	3.31
D-1149	-9.39	-20.73	-4.28	-13.98	D-1918	-13.11	-77.48	6.72	-61.74
D-1150	16.11	-22.00	7.88	-9.56	D-1919	0.14	-38.79	-5.67	-17.31
D-1152	-54.17	-60.99	7.05	-4.58	D-1920	-29.72	-58.58	19.83	9.16
D-1153	11.52	-30.76	-12.21	-20.90	D-1921	-12.68	-59.75	1.05	-14.09
D-1154	-0.73	-46.96	6.97	-6.28	D-1922	-19.56	-54.13	6.68	-10.08
D-1155	7.26	-13.95	3.23	-13.24	D-1923	-5.61	-43.21	16.29	12.59
D-1156	3.05	-46.25	13.69	-5.66	D-1924	12.82	-72.06	17.18	-2.29
D-1157	12.93	-59.47	16.23	-11.64	D-1925	16.97	-17.78	19.41	-2.83
D-1159	-29.47	-55.55	1.70	-4.00	D-1926	-15.49	-11.77	68.39	-20.57
D-1160	-0.42	-73.42	-0.81	-10.76	D-1927	11.32	4.87	-4.40	-23.95
D-1161	18.25	-23.94	6.32	6.22	D-1928	-6.06	-28.46	24.85	9.59
D-1163	-44.43	-63.99	13.02	-0.59	D-1930	-6.58	-79.22	17.16	-29.12
D-1164	-7.43	-49.38	8.03	-6.32	D-1931	-3.39	-62.32	5.61	-16.80
D-1168	1.65	-40.89	4.12	-19.65	D-1932	9.76	-2.23	10.05	7.37
D-1169	-19.55	-49.51	13.74	-5.68	D-1933	4.31	-53.82	5.06	-1.69
D-1170	-26.61	-71.74	7.70	-2.54	D-1934	-14.29	-22.36	15.56	8.75
D-1171	4.11	-75.01	22.41	11.35	D-1935	-3.85	-49.95	2.34	-6.40
D-1173	45.33	-49.69	7.69	-11.52	D-1936	-9.91	22.02	0.59	-6.11
D-1176	-14.04	39.10	14.23	10.32	D-1937	-3.73	-61.11	4.32	-21.53
D-1177	-25.04	-68.88	3.57	-5.82	D-1938	-35.33	-77.39	-7.36	-22.69
D-1178	18.05	-75.84	9.63	-21.29	D-1939	11.46	7.47	3.24	-6.37
D-1179	9.45	-28.67	5.52	1.22	D-1940	-42.29	-45.97	12.47	-5.61
D-1180	-11.55	0.73	-1.94	-1.98	D-1941	-8.16	-45.74	-2.27	-7.42
D-1181	-30.55	-78.57	15.31	-17.01	D-1942	-3.00	-55.85	16.65	-10.14
D-1182	-40.88	-57.42	9.63	-11.33	D-1943	33.68	-31.48	3.72	-12.52

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1183	24.63	-66.53	5.98	-10.91	D-1944	11.42	-58.08	3.04	-16.01
D-1184	-13.11	-33.62	8.80	-6.36	D-1945	-31.07	-68.98	10.70	-6.84
D-1185	-16.61	-39.82	12.97	5.82	D-1946	-36.79	-48.50	19.41	12.95
D-1186	19.94	-59.27	9.32	-5.26	D-1947	5.52	-18.81	-7.54	-11.92
D-1187	-0.73	-68.89	-3.98	-15.07	D-1948	0.24	-72.84	12.53	-1.26
D-1188	-32.58	-53.36	-10.13	-28.19	D-1949	22.59	8.84	14.94	-0.84
D-1189	-11.28	-72.46	8.12	-12.36	D-1950	19.69	13.83	0.08	-9.03
D-1190	-13.36	-51.18	6.31	-13.35	D-1951	-23.67	-77.04	2.43	-12.37
D-1191	-18.43	-12.80	8.62	-7.05	D-1952	-25.79	-72.15	7.29	4.56
D-1192	5.78	-70.90	11.63	-38.66	D-1953	-41.63	-54.76	-4.37	-19.62
D-1193	-12.63	-39.72	13.11	-2.18	D-1954	-16.50	-74.90	26.47	-9.31
D-1194	-7.12	59.76	23.34	19.24	D-1955	-21.01	-16.60	16.01	9.73
D-1195	-39.18	-71.13	0.73	-0.80	D-1956	-8.95	-74.13	13.94	-22.70
D-1196	19.11	3.83	20.58	7.12	D-1957	-15.05	-73.45	19.25	-5.72
D-1197	-3.58	-53.14	10.96	-4.07	D-1958	-17.04	-42.99	-8.57	-21.64
D-1198	11.37	-60.62	44.32	7.61	D-1959	-0.24	-74.53	10.37	-52.59
D-1199	2.66	-40.94	-10.62	-20.63	D-1960	5.66	-39.86	0.50	-6.53
D-1200	-31.07	-78.56	2.19	-15.79	D-1961	-15.14	-39.35	4.27	3.43
D-1201	-8.03	-18.56	9.05	3.62	D-1962	15.69	-64.81	3.10	-12.12
D-1202	6.39	19.18	11.88	10.69	D-1963	0.62	-55.52	-5.16	-14.03
D-1203	-23.94	-38.26	11.97	-7.76	D-1964	-16.11	-8.15	4.15	0.01
D-1204	18.53	-34.62	14.06	-0.10	D-1965	18.91	-68.13	16.29	5.58
D-1205	51.91	-39.17	-3.16	-17.83	D-1966	7.31	-66.61	18.67	2.02
D-1206	-37.20	-73.16	-3.16	-20.83	D-1967	-31.59	-27.69	-1.33	-18.19
D-1207	-45.60	-78.35	4.10	-17.84	D-1968	14.95	-50.53	10.04	2.00
D-1208	17.42	-61.26	3.15	-27.63	D-1969	-39.37	-49.73	11.83	3.08
D-1209	0.09	-22.29	3.77	1.55	D-1970	-30.04	-71.01	10.46	-3.76
D-1210	-7.52	-0.01	7.11	-3.27	D-1971	-1.36	-0.35	7.76	-3.39
D-1212	-25.06	-80.96	-10.57	-28.32	D-1972	-10.99	92.17	5.92	8.11
D-1213	-16.69	-70.97	-1.58	-20.96	D-1973	-26.54	-38.10	1.22	-7.75
D-1214	19.94	-18.87	-14.23	-21.87	D-1974	14.04	-47.50	8.73	-4.02
D-1215	-3.19	-64.93	12.37	-10.03	D-1976	-14.47	-28.64	10.05	2.14
D-1216	-20.89	-56.88	5.19	-8.45	D-1977	13.03	-14.91	6.78	8.02
D-1217	-4.76	-59.77	-0.32	0.60	D-1978	-17.61	-72.14	-0.25	-34.74
D-1218	8.81	-1.56	1.67	-13.50	D-1979	12.20	-66.67	0.40	-20.96
D-1219	8.72	-15.45	5.43	4.40	D-1980	4.78	-7.88	8.03	-4.08
D-1220	-3.92	-54.00	10.62	-3.14	D-1981	22.46	-78.74	11.96	-23.68

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1221	-9.45	-78.87	25.02	-19.76	D-1982	7.06	-42.71	13.64	-14.16
D-1222	24.49	16.25	9.14	-7.22	D-1983	147.43	-45.73	7.46	-4.83
D-1223	-4.11	-38.73	16.18	3.39	D-1984	-9.43	-56.18	18.85	8.40
D-1224	5.78	-63.52	11.05	-0.39	D-1985	-7.26	-78.52	-2.18	-23.49
D-1225	-27.52	-39.12	12.80	-6.49	D-1986	11.55	-54.27	10.78	-0.74
D-1226	25.32	-71.53	3.43	-7.69	D-1988	18.49	-80.12	-1.70	-32.09
D-1227	-2.40	-60.87	22.20	3.16	D-1989	32.04	-77.89	18.27	2.40
D-1228	20.18	-11.50	25.69	15.83	D-1990	17.46	-18.79	3.90	-13.24
D-1229	-21.59	-40.96	7.68	-3.08	D-1991	-7.01	-59.92	1.99	-11.66
D-1230	-6.72	-60.01	8.80	-12.19	D-1992	-82.84	-61.20	-12.64	2.49
D-1231	-11.10	-17.77	11.88	-0.38	D-1993	-9.27	-46.43	-3.01	-10.66
D-1232	-23.04	-56.57	4.37	-16.21	D-1995	-0.19	-75.26	-6.87	-30.20
D-1233	-46.59	-69.92	4.90	-24.43	D-1996	-11.66	-50.74	-13.03	-29.47
D-1235	6.78	-71.94	8.16	-14.27	D-1997	-25.96	-44.39	-5.94	-21.93
D-1236	-8.53	-53.49	23.18	1.28	D-1998	19.63	-42.79	14.23	-2.70
D-1238	31.17	-33.38	1.70	-12.57	D-1999	3.87	-79.84	21.26	-32.79
D-1239	15.59	-59.21	-6.06	-21.61	D-2000	5.27	-19.03	1.00	-3.02
D-1240	14.47	-42.60	4.23	-12.99	D-2001	-15.70	-39.55	-3.40	-20.23
D-1241	-3.73	-15.54	6.14	-4.81	D-2002	-0.19	-12.14	1.13	-15.73
D-1242	-27.39	-44.26	11.51	12.06	D-2003	-9.36	-42.27	3.51	-10.63
D-1243	26.82	-64.75	7.28	-30.55	D-2004	19.17	-13.09	-0.59	-8.71
D-1244	-36.97	-53.39	-8.20	-18.44	D-2005	27.82	-62.21	4.40	-23.84
D-1245	13.97	-59.19	6.09	-5.81	D-2006	7.31	-26.36	9.24	3.49
D-1246	12.21	13.16	-1.62	-24.75	D-2007	-52.29	-25.86	-13.89	0.39
D-1247	-12.88	-32.06	3.88	-6.32	D-2009	15.41	-56.60	30.54	4.40
D-1248	-38.80	-68.71	16.29	12.31	D-2011	5.07	-7.16	0.42	-6.12
D-1249	-1.75	6.92	14.79	-13.93	D-2012	3.49	14.31	9.62	5.80
D-1251	30.27	-79.34	7.61	-20.01	D-2013	29.17	-28.96	10.62	-13.66
D-1252	2.23	-50.19	4.37	-3.52	D-2014	-9.43	-56.66	23.92	3.59
D-1253	-32.85	-29.67	2.99	2.33	D-2015	-5.66	-13.26	-4.48	-19.19
D-1254	-36.45	-76.52	8.02	-21.55	D-2016	-7.79	-48.27	6.22	-11.50
D-1255	-3.39	-64.64	-4.77	-14.70	D-2017	-29.08	-10.09	8.46	6.59
D-1256	1.01	-3.30	25.61	14.58	D-2018	-12.29	-42.04	5.01	-18.67
D-1258	-49.01	-54.26	4.65	-6.34	D-2019	-9.38	-27.60	2.27	3.19
D-1259	-21.83	-49.68	9.72	-2.72	D-2020	5.41	-67.72	14.31	-3.73
D-1260	23.21	-65.48	8.03	-4.15	D-2022	6.39	-35.46	6.31	-0.92
D-1261	-31.64	-57.04	-9.89	-13.26	D-2023	19.27	-72.15	26.28	-23.46

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1262	-29.72	-66.74	-5.61	15.96	D-2024	4.76	-55.12	10.21	8.48
D-1263	-8.33	-65.33	0.08	-11.83	D-2025	24.01	0.84	5.82	-4.60
D-1264	36.01	-20.16	4.61	-14.46	D-2026	-9.82	-31.92	13.44	2.43
D-1265	-1.65	-51.45	-3.48	-6.13	D-2027	-10.47	-39.71	-13.78	-16.75
D-1266	-13.01	-19.17	-5.06	-8.27	D-2028	25.85	-25.14	7.11	-6.77
D-1267	-5.05	-31.71	11.97	-0.60	D-2029	9.58	-27.90	18.84	-6.92
D-1268	1.11	10.61	0.33	-5.81	D-2030	25.17	-4.33	-1.05	-8.23
D-1269	-5.56	-53.51	10.62	-3.13	D-2031	-46.06	-61.25	15.98	-1.88
D-1270	1.10	-60.09	17.57	-2.00	D-2032	-1.28	-54.49	-8.62	-19.41
D-1271	-5.05	-68.78	-0.50	-21.76	D-2033	37.48	-27.95	-7.46	-21.48
D-1272	-14.37	-50.90	-1.83	-18.13	D-2034	20.28	33.72	6.95	3.41
D-1273	-31.36	-62.83	15.04	-1.17	D-2035	-27.81	-53.97	19.10	-7.38
D-1274	-7.69	-21.09	9.88	-0.30	D-2036	-9.78	-59.60	8.25	-7.34
D-1275	25.07	-72.64	5.58	-25.02	D-2037	-16.17	-59.12	14.10	4.42
D-1276	-4.59	-35.87	-3.35	-11.79	D-2038	-2.48	-78.15	26.11	-3.69
D-1277	46.09	-35.72	-3.63	-25.23	D-2039	-17.52	-77.24	4.94	-0.89
D-1278	8.53	-70.41	14.59	-19.50	D-2040	-7.25	-54.11	11.63	0.72
D-1279	5.96	-4.96	22.09	28.38	D-2041	9.57	-11.47	-7.05	-6.10
D-1280	-14.29	-58.65	7.86	-3.32	D-2042	-18.34	-29.19	-1.05	-8.78
D-1281	10.07	-32.98	8.49	0.81	D-2043	-3.12	-66.07	11.63	1.50
D-1282	-28.56	-74.04	-3.80	-35.39	D-2044	-37.56	-32.28	21.91	8.04
D-1283	-18.30	-34.79	9.14	2.84	D-2045	-22.65	-75.89	2.02	-21.05
D-1284	-12.11	-36.83	11.05	4.28	D-2046	-13.91	-74.75	-1.46	-20.68
D-1287	11.71	-21.34	-12.29	-28.09	D-2047	-16.88	-53.39	-9.96	-30.30
D-1290	-2.13	-78.34	-3.56	-11.58	D-2048	-13.58	-76.86	16.90	-27.20
D-1292	-23.43	-28.70	-0.57	-16.42	D-2049	-36.21	-9.07	7.60	5.07
D-1295	25.46	-57.29	15.12	-1.18	D-2051	2.56	-51.79	3.24	-1.81
D-1297	3.21	-63.31	25.77	22.14	D-2052	-18.34	-46.56	12.48	15.60
D-1298	-3.92	-68.03	-9.71	-34.14	D-2053	20.23	-39.84	3.72	-13.74
D-1300	-10.33	-49.32	0.97	2.06	D-2055	7.15	-78.38	7.69	-15.41
D-1304	21.30	-10.48	-1.29	-11.82	D-2056	-2.39	-26.69	17.99	7.25
D-1305	41.65	13.01	8.80	-1.54	D-2057	-3.21	-61.15	1.76	-13.42
D-1306	29.33	-7.63	8.81	-6.33	D-2058	15.87	-21.62	3.63	-12.54
D-1307	22.31	-29.34	-1.52	-13.70	D-2060	-48.44	-77.63	6.86	-42.35
D-1308	15.60	-20.06	7.53	-4.85	D-2061	14.50	-79.48	19.67	-3.72
D-1309	-14.33	-52.52	16.98	-9.89	D-2062	-16.59	-70.67	-3.65	-21.31
D-1310	-6.36	-76.66	2.35	-10.23	D-2063	-7.01	-76.15	9.71	-28.36

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D-1311	14.29	-65.01	-12.32	-29.59	D-2065	-4.40	14.16	14.19	0.97
D-1312	-8.48	-79.39	-0.42	-14.88	D-2067	21.53	3.99	-8.46	-21.68
D-1313	-44.04	-74.66	0.67	-4.61	D-2068	23.43	-75.39	-3.40	-26.63
D-1314	-11.91	-43.05	10.02	-5.56	D-2069	2.42	-79.04	22.39	-11.16
D-1315	8.16	-46.22	-0.32	2.27	D-2070	9.38	-61.91	19.53	-0.10
D-1316	17.17	27.34	-1.49	-3.64	D-2071	0.52	-65.61	9.08	7.54
D-1317	-2.23	-55.09	5.58	-11.09	D-2072	-5.23	-78.42	7.28	-24.05
D-1318	11.27	-47.32	18.80	-7.48	D-2073	22.59	-3.89	21.08	10.82
D-1319	14.66	-25.03	16.29	13.59	D-2074	21.01	-72.33	3.07	-21.93
D-1320	19.79	-0.18	8.88	-7.73	D-2075	30.14	-58.62	-3.65	-14.55
D-1321	9.10	-76.11	17.02	-0.59	D-2076	5.13	-54.39	17.95	-0.94
D-1322	-44.56	-69.34	3.57	-13.82	D-2077	5.76	-53.36	-6.31	-22.62
D-1323	28.21	-15.42	0.41	-11.61	D-2078	-2.95	-27.45	5.31	-6.53
D-1324	21.72	-62.51	-10.04	-6.03	D-2079	-9.00	-76.93	-1.94	-18.14
D-1325	18.72	0.07	6.16	4.25	D-2080	-20.91	-41.76	18.51	2.13
D-1326	-4.10	-72.25	-19.37	-33.56	D-2082	1.38	-3.34	-1.76	-12.55
D-1327	16.07	-68.74	2.99	-16.27	D-2083	13.85	12.36	23.10	10.70
D-1328	20.37	-69.18	-2.32	-18.28	D-2084	4.26	-45.51	3.64	-5.08
D-1329	-25.32	-44.99	-3.16	3.98	D-2085	-21.45	-69.45	-1.70	-12.65
D-1330	-16.33	-63.82	-5.69	-16.83	D-2086	14.31	-25.67	5.19	-9.77
D-1331	0.99	-35.15	11.59	-7.43	D-2087	-10.64	-72.79	11.30	-7.89
D-1332	-15.23	-53.20	23.43	7.37	D-2088	33.03	-49.42	11.55	-4.08
D-1333	-11.93	-39.12	-2.27	-4.03	D-2089	-12.31	-71.20	-0.16	-12.87
D-1334	-47.27	-65.62	9.21	-3.59	D-2090	2.23	-13.02	4.53	-8.06
D-1336	3.44	-18.99	12.97	3.86	D-2091	5.50	-30.25	3.26	-8.25
D-1337	4.67	-67.99	4.05	-14.59	D-2092	25.21	9.46	26.06	9.99
D-1338	10.50	-20.32	-13.20	-27.03	D-2093	-30.01	-56.61	-2.51	-10.01
D-1339	10.45	-57.10	18.11	-5.50	D-2094	3.24	-50.65	12.20	-1.38
D-1340	7.50	-75.18	-11.35	-51.99	D-2096	-7.87	-47.43	-6.81	-18.01
D-1341	-14.13	-42.79	7.28	-2.05	D-2097	3.08	-48.50	-3.72	-12.37
D-1343	32.45	-74.74	25.44	-8.83	D-2098	-5.85	-44.10	-15.52	-16.11
D-1344	21.49	-79.31	8.57	-41.53	D-2099	1.74	-30.12	27.36	8.16
D-1345	5.56	-71.98	4.40	-14.59	D-2100	-1.85	-27.99	-0.85	-15.43
D-1346	10.84	-47.45	-2.43	-21.79	D-2101	9.57	-15.62	-13.37	-32.49
D-1347	11.85	-38.12	6.72	-16.62	D-2102	17.20	-17.54	8.11	-13.47
D-1348	-4.77	-76.11	-1.17	-20.86	D-2103	18.26	-14.51	19.92	-2.74
D-1349	-36.51	-61.19	10.46	11.03	D-2104	-20.60	-52.42	15.88	9.47

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D-1351	-15.32	-73.27	4.78	-8.76	D-2105	-13.44	-36.40	0.16	-2.69
D-1352	10.36	-63.16	3.64	-5.33	D-2106	7.45	-24.35	-6.14	-8.94
D-1353	1.21	-8.18	5.23	-10.04	D-2108	-26.79	-47.50	8.03	-6.12
D-1354	3.34	-75.94	4.23	-15.74	D-2109	28.75	-61.84	7.03	-18.38
D-1355	7.71	11.27	19.92	11.87	D-2110	-15.98	-64.33	11.83	-4.94
D-1356	-10.85	-63.81	6.34	0.13	D-2111	3.58	-25.27	11.63	-0.29
D-1357	1.31	-37.05	-14.02	-16.27	D-2112	-30.49	-70.57	-7.11	-23.03
D-1358	24.49	41.10	28.13	20.76	D-2113	-21.34	-45.95	-7.97	-11.53
D-1359	5.56	-23.75	13.20	-2.77	D-2114	2.37	-38.94	15.52	4.19
D-1360	17.08	37.58	1.08	-11.99	D-2116	-0.77	-16.52	7.68	0.82
D-1361	-22.77	-47.82	7.21	-9.44	D-2117	-34.56	-77.15	-0.97	-27.34
D-1362	19.55	-59.93	8.97	-23.28	D-2118	39.37	1.68	17.34	4.87
D-1363	-51.44	-77.04	7.78	-22.46	D-2119	35.75	-62.09	19.42	-3.86
D-1364	23.06	-10.37	9.40	-4.87	D-2120	-15.98	-37.99	-3.57	-10.72
D-1366	-9.36	-51.45	5.94	6.52	D-2121	-20.70	-45.64	-0.65	-0.80
D-1368	-2.29	-52.35	11.55	-12.22	D-2122	-28.27	-75.45	-8.49	-10.90
D-1369	-9.85	-46.01	-7.70	-10.96	D-2123	-3.00	-30.45	-12.77	-21.76
D-1370	-41.93	-78.44	12.97	-28.38	D-2125	-20.37	-46.48	12.20	-8.72
D-1371	-17.16	-36.27	4.02	-4.25	D-2126	15.87	-14.95	15.23	-8.82
D-1372	-19.19	-63.22	10.94	7.71	D-2127	-14.04	-41.88	-0.89	-20.13
D-1373	22.27	-76.68	0.97	-24.18	D-2128	-0.37	-32.88	9.54	6.92
D-1374	-24.95	-73.67	8.54	-38.43	D-2129	-5.66	-42.51	-2.74	-16.04
D-1375	-38.52	-63.20	2.67	-9.04	D-2131	-5.23	-60.82	17.74	0.02
D-1377	-59.82	-77.46	9.62	-16.34	D-2132	-7.91	-58.89	14.37	-3.66
D-1378	17.43	-27.46	0.08	-1.36	D-2135	-9.68	-76.64	10.59	1.08
D-1379	39.59	-77.99	8.65	-21.47	D-2138	32.66	-43.04	15.77	3.66
D-1380	16.50	-68.50	-2.57	-24.69	D-2139	-6.65	-37.39	10.37	0.22
D-1381	5.13	-34.48	0.49	-0.75	D-2140	-12.02	-44.16	2.93	-13.13
D-1382	-21.97	-80.36	12.13	-23.38	D-2141	-25.79	-65.81	0.00	-3.03
D-1383	-4.29	-46.09	16.86	1.03	D-2142	18.26	-9.97	11.72	12.29
D-1384	1.74	-78.01	14.64	-24.12	D-2143	-40.37	-41.64	10.54	6.24
D-1385	-26.66	-15.55	9.21	4.44	D-2144	17.30	-77.66	-0.73	-30.74
D-1386	-2.76	-22.47	-9.79	-16.76	D-2145	15.14	-73.75	7.55	-20.41
D-1388	11.93	-28.38	16.90	18.95	D-2146	-12.43	-66.84	9.71	-17.02
D-1389	-35.23	-75.62	13.47	3.46	D-2147	-2.79	-80.26	8.20	-11.80
D-1391	-9.54	-55.57	1.76	8.01	D-2148	-13.12	-50.55	6.17	-16.80
D-1392	-25.60	-69.12	-6.44	-31.51	D-2149	-14.10	-73.21	1.05	-16.43

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1393	4.95	-72.52	4.21	0.75	D-2150	8.57	-11.20	-2.20	-15.48
D-1394	7.16	-77.18	8.33	-7.38	D-2151	3.25	16.20	-11.67	-16.45
D-1395	30.60	-72.67	3.81	-29.55	D-2152	-27.82	-27.09	3.07	-9.90
D-1396	-7.43	-77.70	2.43	-28.95	D-2153	-8.20	-28.11	14.71	2.34
D-1397	25.07	-80.00	5.34	-32.68	D-2154	8.26	-57.95	5.69	-6.42
D-1401	0.05	6.64	-11.54	-12.09	D-2155	29.28	-26.90	-0.16	-8.87
D-1402	-14.85	-66.16	0.32	-2.45	D-2156	-8.63	-39.94	4.29	-1.85
D-1404	1.69	-41.85	17.51	0.44	D-2157	40.98	-49.72	15.81	-7.89
D-1408	32.66	-74.78	5.23	-9.30	D-2158	1.27	-64.90	-20.18	-19.77
D-1409	-10.30	-74.45	-1.58	-32.92	D-2159	-11.46	-62.75	-5.51	-19.74
D-1410	-37.77	-55.14	9.16	4.08	D-2160	4.74	-52.84	-2.34	-16.92
D-1411	-9.71	-61.25	5.83	-11.94	D-2161	51.01	-43.91	6.03	-11.46
D-1412	-4.40	-62.34	15.06	1.14	D-2162	-10.09	-45.16	5.61	-2.10
D-1413	-38.99	-26.13	8.91	13.59	D-2163	3.12	-48.22	51.05	6.96
D-1414	0.68	-48.38	11.08	-5.56	D-2164	39.79	-69.13	8.00	-19.97
D-1415	30.11	-79.94	14.79	-8.31	D-2165	-0.53	-74.56	-4.32	-27.16
D-1416	9.00	-72.55	-8.25	-27.91	D-2166	-2.18	-65.81	11.45	-16.77
D-1417	20.52	-1.74	14.23	4.17	D-2167	24.40	-53.07	27.98	16.39
D-1418	-23.30	-66.73	15.23	-0.48	D-2168	-25.14	-30.88	7.53	5.06
D-1419	9.36	-78.21	13.31	-33.52	D-2169	7.45	-56.17	16.17	2.89
D-1420	-25.30	-63.31	-10.54	-25.54	D-2170	-37.06	-62.46	6.69	-14.30
D-1421	-36.82	-71.74	-7.14	-31.17	D-2171	0.90	-53.35	-5.11	-15.32
D-1422	-1.31	-72.73	0.50	-31.24	D-2173	39.14	5.84	12.37	8.02
D-1423	6.97	-32.14	5.77	-0.11	D-2175	1.55	-63.15	-1.46	-11.53
D-1424	-0.05	-25.55	3.32	-13.94	D-2176	8.07	48.04	-6.19	-6.21
D-1425	14.42	-32.00	-3.96	-15.93	D-2177	18.72	22.15	-4.54	-9.19
D-1426	-10.30	-22.92	13.20	2.02	D-2178	-10.11	0.12	-0.66	-4.23
D-1427	-8.53	-61.49	11.51	-10.59	D-2179	0.00	-27.63	1.62	-13.12
D-1428	19.28	-18.07	5.43	-4.47	D-2180	11.04	13.22	0.17	-3.68
D-1429	5.81	-78.39	3.48	-41.33	D-2181	-28.17	-16.03	2.76	-10.31
D-1430	9.87	-77.50	-2.26	-28.08	D-2182	-25.91	-41.36	0.08	-11.30
D-1431	-20.64	-79.16	2.76	-35.67	D-2183	24.88	-43.72	-2.67	-10.89
D-1432	-12.59	-48.84	7.21	-14.06	D-2184	18.20	18.68	11.96	11.68
D-1433	-18.88	-77.44	-0.49	-19.75	D-2185	-20.32	-41.43	-7.54	-26.81
D-1434	30.88	-31.72	25.22	7.46	D-2186	-10.37	-73.28	11.38	-12.70
D-1435	3.97	-79.61	2.51	-31.91	D-2187	19.46	-20.05	10.59	10.67
D-1436	8.08	-71.76	-1.08	-28.30	D-2188	1.02	-70.09	-1.74	-15.96

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1437	-17.56	-72.82	15.27	8.76	D-2189	-14.50	-38.26	1.42	-14.19
D-1438	-13.50	-49.08	1.49	-14.23	D-2190	-18.24	-61.71	-9.79	-17.99
D-1439	21.43	-63.70	17.18	-0.95	D-2191	-15.04	-62.87	15.80	4.20
D-1440	-0.52	-65.90	5.51	-21.92	D-2193	9.58	-59.04	7.44	-1.72
D-1441	0.09	-38.28	3.85	-9.17	D-2194	-11.18	-44.01	14.69	-2.00
D-1442	2.66	-55.33	-3.43	-26.16	D-2195	19.07	-44.55	15.76	5.22
D-1443	-24.24	-30.45	11.54	-0.89	D-2197	13.12	-25.85	6.61	-12.79
D-1444	33.58	-65.83	24.85	-0.39	D-2198	-4.68	-35.17	4.02	-10.32
D-1445	-22.79	-16.47	14.20	-7.26	D-2199	-8.27	-48.07	14.61	-3.49
D-1446	22.30	-16.81	8.46	-8.89	D-2201	12.39	-68.13	13.26	-8.12
D-1447	6.18	-68.19	16.29	-11.29	D-2203	5.96	-47.61	22.26	-0.47
D-1448	4.01	-49.66	1.54	-7.00	D-2204	17.20	-2.70	14.12	-7.52
D-1449	-40.41	-15.22	3.08	-10.87	D-2205	-0.37	-2.53	3.93	0.78
D-1450	-0.77	-77.98	9.78	-23.68	D-2206	-1.94	-36.37	16.57	-4.49
D-1451	-6.58	-69.35	20.12	-8.13	D-2207	-34.95	-53.37	19.41	-3.59
D-1456	-16.75	-79.94	2.10	-14.80	D-2208	15.05	-61.50	8.37	-14.17
D-1457	-17.33	-80.91	3.56	-39.89	D-2209	21.64	-73.66	-10.21	-41.26
D-1458	26.04	-29.22	8.57	-4.40	D-2211	-30.08	-42.14	9.89	-7.13
D-1459	-12.84	-76.97	9.47	-15.64	D-2212	29.46	-73.39	7.72	-15.28
D-1460	-3.29	-76.01	-4.45	-25.68	D-2213	2.69	-46.37	1.86	8.25
D-1461	-5.61	-77.92	-1.70	-19.63	D-2214	38.33	-53.84	-5.92	-11.50
D-1462	2.08	-63.16	-6.72	-26.68	D-2215	-23.67	-54.98	17.74	2.12
D-1463	-16.61	-67.89	1.09	2.56	D-2216	-55.59	-72.78	1.86	-11.28
D-1464	-8.48	-54.92	8.11	-14.13	D-2217	29.27	-69.54	14.23	-22.52
D-1465	5.76	-71.09	18.59	0.96	D-2218	-26.43	-76.79	-6.39	-27.46
D-1466	20.46	-37.62	23.18	-2.68	D-2219	-10.55	-50.41	7.52	-16.12
D-1467	20.32	-13.04	-17.34	-15.71	D-2220	5.52	-13.82	-3.40	-2.47
D-1468	31.45	-64.41	-2.19	-4.79	D-2221	30.40	-61.88	-2.59	-19.75
D-1469	12.68	5.48	-7.28	-20.26	D-2222	43.30	-48.47	4.32	-3.69
D-1470	6.92	-66.88	9.38	-12.70	D-2223	24.63	-62.30	3.32	-5.52
D-1471	-22.22	-74.37	13.02	-13.21	D-2225	-6.63	-42.35	-9.38	-21.15
D-1472	-11.81	-79.47	15.36	-19.74	D-2226	-38.62	-62.87	10.46	-8.69
D-1473	-38.46	-72.40	-0.17	-21.43	D-2227	-23.94	-50.40	9.29	10.89
D-1474	2.97	-57.92	-5.19	-16.96	D-2228	20.09	-29.75	14.14	0.05
D-1475	-16.93	-44.54	3.65	2.15	D-2229	-18.06	-31.06	11.10	-14.24
D-1476	-5.89	-52.67	12.80	-3.85	D-2231	9.00	-61.35	-13.34	-22.09
D-1477	-17.89	-60.62	-3.68	-2.20	D-2232	14.77	-76.09	17.15	-3.37

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1480	28.79	10.79	-3.24	-16.12	D-2233	7.21	-8.78	0.17	-10.36
D-1481	6.70	-41.49	3.35	-21.34	D-2234	1.28	-72.80	15.23	-43.35
D-1482	7.43	-19.68	17.91	6.02	D-2235	-37.16	-74.11	20.67	2.73
D-1483	1.98	-21.91	4.90	-5.20	D-2237	-8.85	-51.03	0.25	-19.94
D-1484	-16.51	-55.79	1.51	6.85	D-2239	-27.30	-73.35	0.97	-14.70
D-1485	-36.43	-80.11	9.81	-11.66	D-2240	-27.96	-75.24	-4.46	-17.10
D-1486	5.42	-62.97	5.50	-13.09	D-2241	11.91	-72.70	20.45	3.61
D-1487	10.89	-23.86	-5.81	-11.30	D-2242	-0.33	-35.08	14.34	7.58
D-1488	-14.71	-68.13	6.06	-5.50	D-2243	-36.81	-74.89	4.31	-11.89
D-1489	-21.55	-76.48	-5.83	-18.03	D-2244	30.62	38.57	13.86	4.28
D-1490	26.04	-80.46	0.57	-46.23	D-2245	-18.07	-41.66	7.87	-9.64
D-1491	32.72	-80.10	1.78	-26.10	D-2246	-6.14	56.28	29.46	28.50
D-1492	39.08	-37.64	6.69	4.14	D-2247	-25.60	-73.58	-4.44	-16.28
D-1493	3.54	-74.86	14.02	-7.60	D-2248	11.51	-20.86	2.87	-9.83
D-1494	-19.75	-43.37	20.10	2.38	D-2249	-16.91	-39.16	0.34	-14.24
D-1496	-16.08	-70.55	4.54	-21.74	D-2250	15.77	-73.36	10.48	-8.70
D-1497	32.26	-81.52	17.58	-27.07	D-2251	0.43	-79.99	10.74	-17.83
D-1498	12.11	-40.01	51.46	25.60	D-2252	6.05	-65.41	5.15	-14.74
D-1499	-24.39	-79.00	2.34	4.18	D-2253	11.10	-54.80	38.74	15.88
D-1500	-51.56	-70.59	5.02	-16.85	D-2254	22.21	-14.24	10.79	-10.26
D-1501	46.47	-65.12	-19.40	-28.47	D-2255	41.07	18.44	6.97	-2.34
D-1503	-31.92	-69.56	9.89	-10.48	D-2256	-8.23	-46.19	2.59	3.33
D-1504	5.50	-37.04	22.85	5.61	D-2257	-6.65	-9.03	-2.27	-7.54
D-1507	8.48	-55.73	23.50	-8.71	D-2258	-7.71	-76.29	5.44	-7.30
D-1508	-11.65	-68.55	12.47	-16.00	D-2259	14.95	68.74	-17.68	-12.68
D-1509	-17.76	-55.16	2.07	-15.48	D-2260	9.67	-20.49	0.97	4.43
D-1510	-4.36	-29.45	7.68	-3.23	D-2261	-24.00	-45.64	13.13	-0.23
D-1512	0.33	-33.83	6.40	5.03	D-2262	-10.92	-17.68	17.57	-0.15
D-1513	-40.09	-64.18	17.24	-2.88	D-2263	3.34	-74.25	4.98	-19.68
D-1514	-19.65	-33.00	1.86	-10.55	D-2264	-8.47	-74.97	8.13	-7.51
D-1515	-24.63	-55.52	3.73	0.05	D-2265	-11.80	-58.43	28.74	27.99
D-1517	-47.61	-74.57	8.95	-9.97	D-2268	-4.67	-42.18	-9.56	-9.46
D-1519	11.56	-29.26	-12.37	-18.89	D-2269	-8.42	-50.28	5.98	-6.48
D-1520	32.24	3.14	15.60	-0.57	D-2270	8.82	-56.73	-3.81	-31.28
D-1522	32.14	8.88	0.97	-13.70	D-2271	-15.05	-41.32	12.61	5.63
D-1523	-7.43	-50.43	-1.00	-11.45	D-2272	-2.18	-51.38	-13.44	-20.07
D-1524	15.49	-8.69	2.02	0.13	D-2273	0.87	7.40	2.43	-10.08

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1525	-22.79	-63.32	13.36	7.28	D-2274	6.84	-68.97	-7.29	-31.31
D-1526	10.45	-12.02	-9.30	-17.56	D-2275	17.04	-20.30	-4.20	-17.23
D-1527	-7.16	-39.49	14.64	10.43	D-2276	-19.08	-59.63	8.45	-16.02
D-1528	30.78	16.18	-8.65	-26.51	D-2277	-5.23	-9.32	10.54	8.24
D-1529	5.41	-34.44	5.52	9.61	D-2278	16.94	-47.09	5.58	-2.28
D-1530	23.04	-14.77	2.10	-12.78	D-2279	10.98	-57.75	3.98	-13.27
D-1531	36.53	-1.44	0.50	-11.53	D-2280	10.99	0.50	17.83	8.21
D-1532	-11.19	-22.94	18.16	2.41	D-2281	3.78	-7.60	7.76	-7.03
D-1533	11.38	-70.75	7.78	-6.32	D-2282	-37.16	-66.11	12.47	-6.97
D-1541	-3.76	-50.19	30.21	23.94	D-2283	-8.81	-13.66	17.66	-1.44
D-1542	4.74	-17.47	9.54	1.27	D-2284	-6.53	-56.80	18.51	1.11
D-1543	11.93	-76.40	7.70	-42.72	D-2285	9.68	-18.56	3.96	-9.57
D-1544	-42.33	-52.93	14.69	-0.38	D-2286	-16.88	-62.09	15.77	-11.21
D-1545	-9.67	-41.93	4.13	-9.45	D-2287	-7.59	-35.92	9.08	-6.25
D-1546	-14.76	-71.93	9.54	-7.00	D-2288	4.20	-68.32	-11.91	-18.58
D-1547	-45.14	-63.59	10.29	-7.72	D-2289	5.56	-52.09	17.51	4.86
D-1548	7.53	-32.51	-6.85	-8.07	D-2290	47.89	3.79	15.98	-2.50
D-1549	12.78	-59.45	15.20	-24.86	D-2291	4.59	-58.65	-8.12	-6.02
D-1550	5.96	-73.04	23.10	-3.15	D-2292	5.27	-66.33	-4.90	-20.75
D-1551	-3.17	-50.57	-4.48	-10.38	D-2293	16.75	-52.01	21.10	6.47
D-1552	17.08	-3.57	3.49	-13.28	D-2295	38.62	12.59	-12.72	-10.00
D-1553	-37.67	-70.41	-11.02	-23.50	D-2297	10.83	15.03	2.26	6.34
D-1555	-19.85	-47.96	1.54	-8.57	D-2298	-4.69	-2.09	-2.32	-13.00
D-1557	-22.96	-65.81	4.46	-6.26	D-2299	-32.86	-69.77	4.05	-13.11
D-1558	15.05	-10.38	16.99	13.12	D-2302	26.26	-51.02	7.13	4.49
D-1559	-11.13	-11.60	10.59	-5.72	D-2303	11.28	-45.64	-3.77	-19.21
D-1560	-14.95	-70.17	10.29	-4.46	D-2305	17.40	-23.21	0.41	-10.26
D-1561	-2.81	-53.50	-3.31	-23.23	D-2306	22.94	-53.98	10.63	-13.70
D-1562	-0.90	-70.55	8.91	-2.19	D-2307	19.46	-39.96	-1.46	-13.70
D-1563	6.74	-36.12	-1.70	-11.00	D-2308	9.36	-64.54	7.53	-13.04
D-1564	-0.33	-76.38	9.89	-9.36	D-2309	14.37	-72.06	6.47	-19.58
D-1565	11.74	-70.09	17.57	3.84	D-2310	24.72	-29.06	8.38	-9.31
D-1566	-19.26	-36.08	4.12	-20.01	D-2311	-11.17	-39.70	8.91	9.42
D-1567	-36.21	-26.16	16.33	8.05	D-2312	19.21	-71.67	12.28	-11.47
D-1568	-22.17	-29.62	8.89	-0.71	D-2313	19.65	-21.49	3.15	-11.19
D-1569	21.63	-2.09	10.46	-5.42	D-2314	26.15	-33.61	14.56	-7.81
D-1570	22.11	-76.43	14.14	-32.88	D-2315	-13.03	-53.10	10.65	-9.69

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1571	-0.82	-37.92	5.89	-14.85	D-2316	2.42	-29.40	10.91	-11.39
D-1573	-10.18	-64.73	4.44	-1.95	D-2317	-24.49	-67.65	8.33	-5.38
D-1574	-2.61	-35.69	2.26	-15.60	D-2318	9.72	-40.13	8.70	-3.99
D-1575	15.97	-5.44	-9.22	-15.32	D-2319	23.72	-77.03	5.51	-63.69
D-1576	-10.11	-49.40	-16.68	-16.01	D-2320	25.70	8.69	8.27	-0.77
D-1577	-36.79	-70.90	22.18	3.36	D-2321	8.13	-69.42	-17.95	-37.39
D-1579	-13.84	-42.68	7.44	-10.53	D-2323	28.07	2.72	20.42	3.41
D-1580	-16.15	-0.78	11.21	1.18	D-2324	2.89	-56.23	12.76	-8.95
D-1582	-29.33	-70.31	4.61	-9.18	D-2325	13.50	-77.16	-4.23	-14.43
D-1583	-3.91	-72.50	-5.83	-22.00	D-2326	-3.05	-59.64	21.16	-9.55
D-1584	-17.49	-69.74	14.91	-4.97	D-2327	-12.00	-46.84	6.14	-3.12
D-1585	29.70	-51.61	6.85	-9.20	D-2328	6.84	-40.50	10.62	8.44
D-1586	-10.36	-24.80	-3.64	-14.72	D-2329	-1.31	-9.41	7.72	-7.80
D-1587	-12.24	-16.84	-4.32	-14.95	D-2330	4.59	-69.60	10.79	-8.67
D-1588	0.39	-1.95	13.34	-2.91	D-2331	-9.54	-73.22	-9.79	-29.41
D-1589	40.88	0.52	14.26	6.47	D-2332	-6.55	-72.41	8.51	-6.94
D-1590	-5.61	22.64	-0.97	-7.11	D-2333	11.17	-2.82	15.48	11.15
D-1591	2.31	-30.67	-3.48	-13.93	D-2334	-2.66	-75.33	12.72	-9.84
D-1592	-19.75	-38.53	3.55	-6.58	D-2335	-23.27	-67.78	10.62	2.39
D-1593	19.01	6.07	19.17	16.66	D-2336	-11.80	40.65	-1.01	-6.78
D-1594	-17.20	-57.14	-1.44	-15.06	D-2337	-15.32	-76.42	-2.59	-32.42
D-1595	-15.97	-57.16	19.00	7.35	D-2338	15.49	-74.04	21.13	-1.29
D-1596	-15.98	-42.84	9.16	8.17	D-2339	20.66	15.26	-14.02	-26.53
D-1597	1.66	-71.11	7.27	-23.62	D-2340	26.04	-1.14	7.03	4.64
D-1598	-4.22	-63.19	7.03	-6.96	D-2341	-7.40	-74.83	20.50	3.23
D-1599	11.04	-39.72	-1.13	-20.46	D-2342	-15.34	-55.08	4.90	-10.82
D-1600	17.62	-38.11	9.86	-16.81	D-2343	-12.29	-46.10	-10.21	-20.14
D-1601	35.77	-77.17	11.75	-26.16	D-2344	-23.43	-48.16	4.54	5.25
D-1602	-33.82	-69.95	5.89	-13.32	D-2345	-33.71	-27.73	-9.81	-24.68
D-1603	31.45	-71.55	-2.35	-30.03	D-2346	6.88	13.79	2.68	-10.88
D-1604	20.89	-1.24	-1.30	-9.64	D-2347	-18.07	-43.48	20.00	28.83
D-1605	6.55	-53.67	3.48	-9.38	D-2348	-47.43	-50.28	-6.14	-19.13
D-1606	2.69	-23.77	2.27	-1.67	D-2349	-5.71	-72.76	0.40	-30.56
D-1607	-17.91	-51.36	6.31	10.90	D-2350	-2.48	-3.02	11.13	12.54
D-1608	27.20	-32.06	18.56	3.72	D-2351	20.23	-0.55	14.59	16.95
D-1609	18.06	-19.53	7.54	-5.72	D-2352	-26.04	-79.85	2.83	-41.79
D-1610	0.29	-5.19	-1.21	-14.22	D-2353	-26.97	-3.97	11.30	-9.21

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1611	7.55	36.89	5.34	-0.83	D-2355	13.01	-62.85	7.05	-10.93
D-1612	-12.84	-19.84	24.77	13.24	D-2356	22.02	-42.24	4.27	-3.90
D-1613	-12.97	-75.43	19.45	-2.76	D-2357	24.78	-73.44	-0.32	-16.90
D-1614	41.14	37.89	14.31	-4.57	D-2358	28.79	-18.62	1.16	-9.13
D-1615	27.30	-41.74	23.10	14.97	D-2359	16.26	-75.14	0.89	-50.36
D-1616	12.94	3.94	24.94	30.37	D-2361	42.98	-75.85	2.67	-15.94
D-1617	-12.74	-28.74	11.92	-7.36	D-2363	-8.25	-40.20	-1.94	-1.25
D-1618	-21.59	-33.88	21.75	9.98	D-2364	11.83	-29.04	14.99	7.35
D-1620	12.43	-59.95	-6.31	-6.82	D-2365	39.82	-71.52	27.63	-14.32
D-1621	-26.08	-48.87	-11.78	-11.89	D-2366	15.79	17.44	3.57	-1.02
D-1622	-11.28	6.47	13.22	4.49	D-2367	-34.63	-60.76	6.17	-13.96
D-1624	11.89	-55.62	15.64	-2.82	D-2368	-10.37	-68.39	18.24	-21.70
D-1625	-23.14	-30.97	13.42	-0.85	D-2369	-12.78	-49.28	5.09	-0.64
D-1626	-48.99	-63.51	17.15	-3.64	D-2370	0.19	-52.13	-14.96	-30.52
D-1628	-1.56	-38.82	-1.09	-13.60	D-2371	-21.17	-76.37	-5.27	-26.92
D-1629	22.68	-43.27	-2.76	-9.65	D-2372	-22.46	-77.36	12.13	-17.20
D-1630	42.94	-59.46	13.31	-0.07	D-2373	25.98	-27.45	11.37	-10.77
D-1631	-7.87	-61.54	-5.43	-11.47	D-2375	6.51	-70.26	9.54	-30.77
D-1632	31.45	40.65	3.40	1.39	D-2376	-18.34	-34.30	7.94	2.16
D-1633	-1.02	-42.12	2.32	-10.80	D-2377	-0.05	-19.93	11.29	-7.45
D-1634	9.14	-31.08	16.35	-8.94	D-2378	-8.76	-55.07	0.08	-17.21
D-1635	-21.74	-62.17	3.57	-6.98	D-2379	-42.39	-67.16	-1.86	-19.30
D-1636	19.09	-24.92	8.88	-24.34	D-2380	9.85	-50.55	6.24	-15.88
D-1637	24.00	-50.62	-9.16	-13.04	D-2381	-18.14	-72.98	28.13	10.21
D-1638	-26.95	-66.99	10.06	-9.12	D-2382	-7.36	-26.01	13.66	10.26
D-1639	1.01	-36.90	8.95	-4.91	D-2383	-39.36	-62.24	18.58	13.73
D-1640	-11.91	-64.78	-0.16	-9.43	D-2384	-12.59	-56.52	14.75	9.42
D-1641	4.60	-48.90	5.64	-16.05	D-2385	-10.79	-48.93	1.58	-5.69
D-1642	0.58	-41.02	18.35	1.62	D-2386	46.35	-44.45	-5.59	-14.76
D-1643	-8.85	-76.54	9.54	-15.54	D-2387	-15.88	-46.20	2.10	-19.49
D-1644	10.51	-52.89	20.58	14.19	D-2389	13.76	-78.69	-3.01	-28.91
D-1645	12.87	-71.23	12.16	-0.54	D-2390	9.10	-30.45	17.67	2.11
D-1646	-5.78	-74.08	-4.69	-27.01	D-2391	12.29	-56.75	4.93	-21.32
D-1647	-4.45	-5.92	6.63	-8.13	D-2392	-23.49	-74.83	5.02	-33.62
D-1648	13.46	34.26	22.88	4.87	D-2393	16.84	3.98	14.39	1.42
D-1649	-47.63	-56.76	4.12	8.02	D-2394	-2.71	-70.98	13.26	-11.62
D-1650	32.58	-59.12	4.05	-9.81	D-2395	7.89	-27.03	4.65	2.79

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1651	1.84	-64.00	-3.73	-17.15	D-2396	16.82	-16.14	16.91	-3.49
D-1652	15.30	-41.66	4.28	-10.21	D-2397	2.12	-35.82	3.89	-3.96
D-1654	-5.23	-33.75	3.00	3.66	D-2398	9.57	-41.40	18.96	-0.05
D-1655	6.87	-42.73	14.47	8.55	D-2399	-47.71	-61.72	28.20	0.37
D-1657	-2.37	-52.43	4.98	-15.30	D-2400	-8.35	-72.99	17.07	-18.54
D-1658	2.03	-18.81	19.00	8.79	D-2401	-28.01	-75.77	1.16	-14.75
D-1659	-9.57	-59.55	23.74	-15.69	D-2402	-33.04	-76.71	18.09	-77.25
D-1660	-26.48	-74.55	19.78	-2.82	D-2404	-7.61	-67.29	-1.09	-41.79
D-1661	17.81	-38.33	41.55	0.20	D-2405	0.05	-17.64	3.00	-0.09
D-1662	14.45	-52.42	-0.59	-27.08	D-2406	-9.58	-33.64	-10.59	-25.33
D-1663	4.07	-58.51	2.59	-16.05	D-2407	-9.63	-62.24	-0.08	-13.96
D-1664	15.20	-53.44	6.39	-8.56	D-2408	14.42	-3.00	-6.79	-16.32
D-1665	-23.06	-68.84	21.96	14.62	D-2409	27.04	-34.28	-4.73	-20.25
D-1666	13.84	-40.77	3.64	2.18	D-2410	-18.30	-67.46	16.81	-7.29
D-1667	-24.50	-45.47	-9.04	6.51	D-2411	-21.28	-57.25	12.72	-8.07
D-1668	6.61	-78.38	9.62	-24.13	D-2413	4.95	-60.16	10.46	-0.22
D-1669	25.32	-65.31	27.36	-27.95	D-2414	-17.33	-64.07	-14.55	-6.78
D-1670	9.53	20.77	-11.62	-24.98	D-2415	-15.05	-65.69	-9.46	-17.88
D-1671	14.18	-38.83	-1.66	-12.03	D-2416	-0.99	-75.16	11.26	-3.94
D-1672	10.69	-42.66	-1.83	-19.00	D-2417	3.05	-76.41	-0.91	-33.96
D-1673	-6.87	-12.52	12.45	-2.14	D-2418	-1.93	-24.85	29.04	17.48
D-1674	-3.44	-30.88	17.10	12.97	D-2419	-24.40	-47.12	4.18	-3.30
D-1675	-41.19	-75.58	12.13	-15.82	D-2420	16.06	-58.83	4.35	-25.40
D-1676	-12.87	-60.60	15.24	-7.71	D-2421	-1.37	-74.32	9.56	-21.07
D-1677	-13.84	-38.01	2.26	-9.77	D-2422	-38.14	-48.49	-11.91	-24.13
D-1679	6.72	-42.72	10.87	1.76	D-2423	-20.41	-60.80	-0.41	-9.66
D-1680	-0.82	-58.97	2.49	-4.77	D-2424	-48.40	-65.04	-2.10	-8.61
D-1681	2.40	-70.08	3.89	-16.35	D-2425	28.94	15.14	14.20	6.12
D-1682	-22.79	-48.92	10.87	-4.47	D-2426	7.89	-47.66	16.10	2.93
D-1684	16.50	-50.83	-2.16	-13.61	D-2427	-19.09	-23.01	1.62	-3.94
D-1685	-16.42	-79.02	7.62	-61.49	D-2428	5.56	-11.55	11.62	-5.34
D-1686	4.79	-74.35	6.72	-13.30	D-2429	0.52	-33.21	-11.43	-24.16
D-1688	-16.27	-49.27	-6.81	-19.80	D-2430	4.41	-37.30	-3.55	-16.45
D-1689	3.43	-73.67	0.91	-18.82	D-2431	-37.67	-67.95	-1.54	-9.79
D-1690	-22.68	-21.68	-5.75	-7.62	D-2432	-25.32	-68.85	-4.13	-20.36
D-1691	15.82	-72.63	0.75	-33.93	D-2433	0.52	-71.18	-7.86	-31.49
D-1692	-8.53	-65.87	23.18	-2.19	D-2434	10.40	-37.19	10.54	-13.54

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1693	-6.53	-52.63	2.49	-13.30	D-2435	4.86	-57.38	17.34	20.49
D-1695	18.62	-73.01	0.73	-16.64	D-2436	18.88	-35.44	23.12	-12.39
D-1696	-27.53	-41.20	12.86	11.56	D-2437	25.79	-40.05	15.35	1.03
D-1697	-0.63	-76.21	33.11	-5.40	D-2438	15.05	9.99	6.80	-9.53
D-1698	10.73	5.15	24.35	24.10	D-2439	21.63	-41.11	18.17	2.50
D-1699	7.59	-49.15	-2.19	-15.43	D-2440	37.57	-0.17	2.20	-12.17
D-1700	-5.47	-42.44	24.90	13.63	D-2441	-8.06	-54.57	13.61	7.61
D-1701	7.02	-9.16	9.08	5.69	D-2442	36.79	57.61	5.61	-6.44
D-1702	-47.80	-24.11	13.81	-4.71	D-2443	11.36	-66.78	2.92	-13.62
D-1703	-2.85	-61.94	9.13	-4.88	D-2444	-38.81	-72.85	8.54	-3.71
D-1704	-27.90	-8.32	9.89	-13.37	D-2445	-11.04	-64.66	8.08	-2.29
D-1705	-37.01	-46.48	3.32	-9.17	D-2446	3.82	-42.52	-10.45	-14.16
D-1706	-19.28	-32.88	1.70	-8.36	D-2447	-7.91	-58.98	13.44	-4.86
D-1707	7.69	-21.74	9.05	-6.05	D-2448	7.34	-12.66	4.65	-11.66
D-1708	-16.50	-57.74	6.64	-3.44	D-2449	-31.64	-2.57	-7.05	-21.21
D-1710	-16.79	-65.45	6.80	-10.38	D-2450	-18.81	-37.87	-0.24	-4.80
D-1711	-28.36	-56.25	7.76	-4.87	D-2451	-9.05	-65.54	8.96	-5.60
D-1712	17.37	-18.44	3.32	-13.05	D-2452	7.97	-72.48	-5.11	-13.04
D-1714	26.79	-33.16	7.78	-4.00	D-2453	-4.77	-45.85	12.38	-13.76
D-1715	4.22	-53.78	11.83	-10.35	D-2454	21.10	-54.04	-4.37	-13.62
D-1717	0.87	-57.74	7.92	-3.01	D-2455	8.18	-71.54	5.31	-22.07
D-1718	35.62	-38.40	-0.40	-11.07	D-2456	11.23	-30.35	-2.67	-15.16
D-1720	-5.71	-66.00	5.50	-9.46	D-2457	5.60	-60.92	1.84	-1.91
D-1721	29.47	45.96	20.42	15.01	D-2458	21.64	-76.04	4.05	-4.69
D-1723	9.72	-28.91	0.00	-30.34	D-2459	32.73	-39.55	12.68	2.47
D-1724	-9.58	-71.18	3.80	-9.56	D-2460	-13.78	-51.39	10.57	11.22
D-1725	-12.29	-58.30	5.17	-5.90	D-2461	-18.30	-80.09	-13.02	-48.39
D-1726	18.53	8.84	8.13	-5.66	D-2463	-24.85	-9.05	6.56	-10.92
D-1727	-8.35	-79.86	14.31	-27.31	D-2464	8.42	-30.80	13.50	-8.82
D-1728	-14.50	-78.33	6.36	-27.01	D-2467	-8.91	-35.24	-1.05	-16.07
D-1729	17.39	-6.03	29.92	11.54	D-2469	9.90	-74.91	12.09	-2.50
D-1730	-45.31	-77.60	20.83	1.51	D-2470	-16.83	-18.78	9.64	4.78
D-1731	15.79	-18.18	1.78	-9.77	D-2471	-13.11	-39.34	17.59	-0.33
D-1732	-16.21	-4.72	17.10	4.67	D-2472	-51.91	-74.29	0.08	-22.90
D-1733	-0.64	-75.43	17.74	-13.23	D-2473	-23.85	-64.30	4.48	-3.65
D-1735	16.55	-62.74	7.52	-11.28	D-2474	-18.97	-73.74	-9.30	-20.23
D-1736	-19.47	-52.32	-3.00	-9.23	D-2476	-12.39	-39.15	-5.50	-14.58

Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM	Duplex No.	Cell count 5 nM	Normalized Alexa 488 Mean Intensity 5nM	Cell count 1.25 nM	Normalized Alexa 488 Mean Intensity 1.25nM
D-1737	5.41	-9.57	25.94	15.76	D-2477	-36.35	-71.63	-9.00	-8.89
D-1738	5.35	-35.18	15.13	-10.09	D-2478	5.73	-71.48	-7.35	-21.50
D-1739	-10.18	-57.04	15.48	-15.92	D-2479	29.53	-66.03	6.47	-17.15
D-1740	10.75	-73.85	0.42	-21.93	D-2480	13.11	-73.36	1.49	-45.78
D-1742	13.07	-19.18	-4.93	-6.50	D-2482	-1.37	-14.22	26.88	7.58
D-1743	-2.56	-27.26	-4.73	-11.73	D-2483	-26.46	-76.11	9.13	-15.10
D-1744	-7.60	-70.94	10.71	-1.73	D-2484	-7.16	-76.11	14.31	-8.27
D-1745	-1.21	-44.21	1.16	-15.57	D-2485	-6.97	-64.92	-0.65	2.47
D-1746	-19.08	-74.88	14.64	-18.38	D-2486	-38.05	-65.90	10.21	-3.14
D-1747	6.70	16.51	0.42	-12.56	D-2488	4.40	-65.48	23.24	-1.45
D-1749	2.52	-40.74	10.35	2.28	D-2489	10.61	-50.59	2.76	-16.97
D-1751	2.95	-76.84	7.05	-18.50	D-2490	-6.92	-56.48	13.36	-5.04
D-1753	2.02	15.57	12.97	19.69	D-2491	-28.11	-69.71	10.95	-11.63
D-1754	17.30	-1.58	-7.05	-21.69	D-2492	4.59	34.94	21.34	-5.76
D-1755	-20.55	-74.51	8.79	-16.00	D-2493	9.43	-74.40	19.78	-3.04
D-1756	-45.60	-12.19	16.17	-1.67	D-2494	-8.07	-59.67	-2.85	-15.61
D-1757	-26.04	-61.16	12.21	-7.81	D-2495	0.92	-8.01	22.82	8.68
D-1758	-0.34	-73.97	47.63	-8.80	D-2496	23.04	-8.86	14.79	2.59
D-1759	-63.51	-69.49	-24.07	-41.37	D-2497	6.97	-9.77	-5.74	-17.82
D-1760	5.76	-43.12	-0.91	-9.97	D-2498	-0.92	-30.75	5.10	-9.22
D-1761	42.43	-57.23	18.09	8.26	D-2499	3.63	-39.99	12.48	-5.26
D-1762	0.10	-69.14	10.67	-6.73	D-2500	-0.48	13.29	22.96	11.73
D-1763	-5.81	-62.90	34.11	14.42	D-2501	-7.36	-19.71	-3.48	-6.31
D-1764	6.21	-72.39	5.92	-22.06	D-2502	-17.21	-41.54	16.86	-1.63
D-1765	-11.10	-37.69	-1.76	-2.05					

[0196] The results from the screening assay of the Tier 2 molecules revealed an additional 663 potent siRNA molecules that reduced ASGR1 cell surface expression relative to control cells by at least 50% when tested at 5 nM. These siRNA molecules were not included in Tier 1 and were not identified from the bioinformatics analysis of the transcript sequences. At least 263 of these new siRNA molecules reduced ASGR1 cell surface expression relative to control cells by at least 70% and at least 14 siRNA molecules reduced ASGR1 cell surface expression relative to control cells by at least 80% when tested at 5 nM.

Example 3. Efficacy of Select ASGR1 siRNA molecules in RNA FISH Assay

[0197] To assess the potency of a subgroup of ASGR1 siRNA molecules in reducing ASGR1 expression at the mRNA level, IC50 values were determined for each siRNA in an ASGR1 RNA Fluorescence In Situ Hybridization (FISH) assay. Hep3B cells (ATCC HB-8064) were transfected with siRNA using Lipofectamine RNAiMAX transfection reagent (ThermoFisher Scientific 13378-150), at 0.035µL/reaction. Human ASGR1 siRNAs were tested in a 10 point dose response format, 3-fold dilutions, ranging from 0-83.3nM, final concentration. Control siRNAs were tested at 5nM, final concentration and included: a Neutral Control (used for normalization): Non-Targeting RcsC2 (UUACAUCGUUAAUGCGUUA (SEQ ID NO: 4316), an Inhibitor Positive Control: human ASGR1 (ACUUCACAGCGAGCACGGA (SEQ ID NO: 4317), and a Transfection Control: human EIF4A3 (GCAUCUUGGUGAAACGUGA (SEQ ID NO: 4318). Cells were seeded over the transfection complex at 2000 cells per reaction in Perkin Elmer Cell Carrier PDL-coated 384 well assay plates (Perkin Elmer #6007580). The transfection period was 96 hours, after which cells were fixed with 4% methanol free formaldehyde, final concentration. Directly post fixation, cells were dehydrated in ethanol following the Dehydrating Cells for Storage or Shipping protocol within the manufacturer's protocol for the Affymetrix QuantiGene View RNA HC Screening Assay. Plates were sealed and stored at -20°C.

[0198] According to the manufacturer's protocol, cells were rehydrated and processed in the Affymetrix QuantiGene View RNA HC Screening Assay, an *in situ* hybridization method to quantify messenger RNA levels. In this instance, the multiplex assay detected human ASGR1 (NM_001671.4; SEQ ID NO: 1), human ASGR2 (NM_0080912.3 or NM_001181.4), and human PPIB (NM_000942.4). The assay was carried out using the QG ViewRNA HC Screening Assay Kit and the QG ViewRNA HC Screening Signal Amp Kit, 3-plex (Affymetrix QVP0011 and QVP0213, respectively) and probe sets for the detection of human ASGR1, ASGR2 and PPIB (Affymetrix, VA6-19401-01, custom type 4 probe, VA1-10148-01 respectively). Each probe set is labeled with a different fluorophore. Protease for the digestion step was added at 1:8000, final concentration. Post assay, nuclei and cytoplasm were counterstained using Hoechst 33342 nuclear stain and Cell Mask Blue reagents (ThermoFisher Scientific H3570 and H32720 at final concentrations of 10ng/µL and 4ng/µL, respectively). Plate was imaged on the Perkin Elmer Phenix reading Hoechst and Cell Mask Blue in the UV channel, PPIB/Type1 in the 488 channel,

ASGR2/Type4 in the 550 channel and ASGR1/Type6 in the 650 channel. Image acquisition and data analysis was completed in the Perkin Elmer Columbus software package and well normalization/IC50 value generation was completed in Genedata Screener.

[0199] The results of the assay are shown in Table 5. The IC50 values determined in the RNA FISH assay correlate with those determined in the immunoassay for ASGR1 protein levels described in Example 2. However, at the time points tested, the IC50 values determined in the RNA FISH assay are higher than those determined in the immunoassay.

Table 5. IC50 values determined by RNA FISH assay for select ASGR1 siRNA molecules

Duplex No.	IC50 (nM)	Duplex No.	IC50 (nM)
D-1168	>83.33	D-1815	1.18
D-1170	0.62	D-1826	3.47
D-1171	1.74	D-1981	1.81
D-1173	1.65	D-1989	2.07
D-1176	5.12	D-1999	0.27
D-1206	4.70	D-2000	7.04
D-1235	1.57	D-2142	9.26
D-1389	0.68	D-2143	4.42
D-1397	1.06	D-2357	0.40
D-1408	>83.33	D-2361	1.42
D-1443	0.58	D-2401	1.73
D-1497	3.65	D-2461	4.03
D-1708	0.05		

Example 4. Design and Synthesis of Modified ASGR1 siRNA Molecules

[0200] To improve the potency and *in vivo* stability of the ASGR1 siRNA molecules, chemical modifications were incorporated into a subset of the most potent ASGR1 siRNA molecules from the Tier 1 and Tier 2 screens, including five of the most potent ASGR1 siRNA molecules from the Tier1 screen that also had sequence homology with mouse Asgr1 mRNA and cynomolgus monkey ASGR1 mRNA. Specifically, 2′-O-methyl and 2′-fluoro modifications of the ribose sugar were incorporated at specific positions within the ASGR1 siRNAs. Phosphorothioate internucleotide linkages were also incorporated at the terminal ends of the antisense and/or sense sequences. Table 6 below depicts the modifications in the sense and antisense sequences for

each of the modified ASGR1 siRNAs. The nucleotide sequences in Table 6 are listed according to the following notations: A, U, G, and C = corresponding ribonucleotide; dT = deoxythymidine; a, u, g, and c = corresponding 2′-O-methyl ribonucleotide; Af, Uf, Gf, and Cf = corresponding 2′-deoxy-2′-fluoro (“2′-fluoro”) ribonucleotide. Insertion of an “s” in the sequence indicates that the two adjacent nucleotides are connected by a phosphorothiodiester group (e.g. a phosphorothioate internucleotide linkage). Unless indicated otherwise, all other nucleotides are connected by 3′-5′ phosphodiester groups. Each of the siRNA compounds in Table 6 comprises a 19 base pair duplex region with a 2 nucleotide overhang at the 3′ end of both strands.

Table 6. ASGR1 chemically modified siRNA Sequences

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3000	AGGcccuAccGcuGGGucudTsdT	3014	AGACCcAGCGGuAGGGCCUdTsdT	3665
D-3001	AfgGfcCfcUfAfCfCfGfcUfgGfgUfcUfuUf	3015	aGfaCfcCfaGfcgguaGfgGfcCfusUfsu	3666
D-3002	AfgGfcCfcUfAfcCfGfcUfgGfgUfcUfuUf	3016	aGfaCfcCfaGfcgGfuaGfgGfcCfusUfsu	3667
D-3003	AfgGfcCfcUfacCfGfcUfgGfgUfcUfuUf	3017	aGfaCfcCfaGfcgGfUfaGfgGfcCfusUfsu	3668
D-3004	AfgGfcCfcUfaCfCfGfCfUfgGfgUfcUfuUf	3018	aGfaCfcCfagcggUfaGfgGfcCfusUfsu	3669
D-3005	AfgGfcCfcUfaCfCfgCfUfgGfgUfcUfuUf	3019	aGfaCfcCfagCfggUfaGfgGfcCfusUfsu	3670
D-3006	AfgGfcCfcUfaCfCfgcUfgGfgUfcUfuUf	3020	aGfaCfcCfaGfCfggUfaGfgGfcCfusUfsu	3671
D-3007	AfgGfcCfcuAfCfcGfcUfgGfgUfcUfuUf	3021	aGfaCfcCfaGfcGfguAfGfgGfcCfusUfsu	3672
D-3008	AfgGfcCfcUfaCfcGfCfugGfgUfcUfuUf	3022	aGfaCfcCfAfgcGfgUfaGfgGfcCfusUfsu	3673
D-3009	AfsgsGfcCfcuAfCfcGfcUfgGfgUfcUfuUf	3023	asGfsaCfcCfaGfcGfguAfGfgGfcCfusUfsu	3674
D-3010	AfgGfcCfcuAfCfcGfcUfgGfgUfcUfuUf	3024	aGfaCfcCfaGfcGfguAfGfgGfcCfuUfu	3675
D-3011	AfsgsGfcCfcUfaCfcGfCfugGfgUfcUfuUf	3025	asGfsaCfcCfAfgcGfgUfaGfgGfcCfusUfsu	3676
D-3012	AfgGfcCfcUfaCfcGfCfugGfgUfcUfuUf	3026	aGfaCfcCfAfgcGfgUfaGfgGfcCfuUfu	3677
D-3013	AfgGfcCfCfuaCfcGfcUfgGfgUfcUfuUf	3027	aGfaCfcCfaGfcGfgUfAfggGfcCfusUfsu	3678
D-3014	AfgGfccCfUfaCfcGfcUfgGfgUfcUfuUf	3028	aGfaCfcCfaGfcGfgUfagGfGfcCfusUfsu	3679
D-3015	AfgGfCfccUfaCfcGfcUfgGfgUfcUfuUf	3029	aGfaCfcCfaGfcGfgUfaGfGfgcCfusUfsu	3680
D-3016	AfggCfCfcUfaCfcGfcUfgGfgUfcUfuUf	3030	aGfaCfcCfaGfcGfgUfaGfggCfCfusUfsu	3681
D-3017	AfGfgcCfcUfaCfcGfcUfgGfgUfcUfuUf	3031	aGfaCfcCfaGfcGfgUfaGfgGfCfcusUfsu	3682
D-3018	aGfGfcCfcUfaCfcGfcUfgGfgUfcUfuUf	3032	aGfaCfcCfaGfcGfgUfaGfgGfccUfsUfsu	3683
D-3019	agGfcCfcUfaCfcGfcUfgGfgUfcUfuUf	3033	aGfaCfcCfaGfcGfgUfaGfgGfcCfUfsusu	3684
D-3020	AfgGfcCfcUfaCfcGfcuGfGfgUfcUfuUf	3034	aGfaCfccAfGfcGfgUfaGfgGfcCfusUfsu	3685
D-3021	AfgGfcCfcUfaCfcGfcUfGfggUfcUfuUf	3035	aGfaCfCfcaGfcGfgUfaGfgGfcCfusUfsu	3686
D-3022	AfgGfcCfcUfaCfcGfcUfggGfUfcUfuUf	3036	aGfacCfCfaGfcGfgUfaGfgGfcCfusUfsu	3687
D-3023	AfgGfcCfcUfaCfcGfcUfgGfGfucUfuUf	3037	aGfAfccCfaGfcGfgUfaGfgGfcCfusUfsu	3688
D-3024	AfgGfcCfcUfaCfcGfcUfgGfguCfUfuUf	3038	agAfCfcCfaGfcGfgUfaGfgGfcCfusUfsu	3689
D-3025	AfgGfcCfcUfaCfcGfcUfgGfgUfCfuuUf	3039	AfgaCfcCfaGfcGfgUfaGfgGfcCfusUfsu	3690

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3026	AfgGfcCfcUfaCfcGfcUfgGfgUfcuUfUf	3040	AfGfaCfcCfaGfcGfgUfaGfgGfcCfusUfsu	3691
D-3027	AfGfgcCfCfuaCfCfgcUfGfggUfCfuuUf	3041	AfgaCfCfcaGfCfggUfAfggGfCfcusUfsUf	3692
D-3028	agGfCfccUfAfccGfCfugGfGfucUfUfu	3042	aGfAfccCfAfgcGfGfuaGfGfgcCfUfsusu	3693
D-3029	AfggCfCfcuAfCfcgCfUfggGfUfcuUfUf	3043	AfGfacCfCfagCfGfguAfGfggCfCfususUf	3694
D-3030	aGfGfccCfUfacCfGfcuGfGfguCfUfuu	3044	agAfCfccAfGfcgGfUfagGfGfccUfsUfsu	3695
D-3031	GuGGGAAGAAAGAuGAAGudTsdT	3045	ACUUcAUCUUUCUUCCcACdTsdT	3696
D-3032	GfuGfgGfaAfGfAfAfAfgAfuGfaAfgUfuUf	3046	aCfuUfcAfuCfuuucuUfcCfcAfcsUfsu	3697
D-3033	GfuGfgGfaAfGfaAfAfgAfuGfaAfgUfuUf	3047	aCfuUfcAfuCfuuUfcuUfcCfcAfcsUfsu	3698
D-3034	GfuGfgGfaAfgaAfAfgAfuGfaAfgUfuUf	3048	aCfuUfcAfuCfuuUfCfuUfcCfcAfcsUfsu	3699
D-3035	GfuGfgGfaAfgAfAfAfGfAfuGfaAfgUfuUf	3049	aCfuUfcAfucuuuCfuUfcCfcAfcsUfsu	3700
D-3036	GfuGfgGfaAfgAfAfaGfAfuGfaAfgUfuUf	3050	aCfuUfcAfucUfuuCfuUfcCfcAfcsUfsu	3701
D-3037	GfuGfgGfaAfgAfAfagAfuGfaAfgUfuUf	3051	aCfuUfcAfuCfUfuuCfuUfcCfcAfcsUfsu	3702
D-3038	GfuGfgGfaaGfAfaAfgAfuGfaAfgUfuUf	3052	aCfuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	3703
D-3039	GfuGfgGfaAfgAfaAfGfauGfaAfgUfuUf	3053	aCfuUfcAfUfcuUfuCfuUfcCfcAfcsUfsu	3704
D-3040	GfsusGfgGfaaGfAfaAfgAfuGfaAfgUfuUf	3054	asCfsuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	3705
D-3041	GfuGfgGfaaGfAfaAfgAfuGfaAfgUfuUf	3055	aCfuUfcAfuCfuUfucUfUfcCfcAfcUfu	3706
D-3042	GfsusGfgGfaAfgAfaAfGfauGfaAfgUfuUf	3056	asCfsuUfcAfUfcuUfuCfuUfcCfcAfcsUfsu	3707
D-3043	GfuGfgGfaAfgAfaAfGfauGfaAfgUfuUf	3057	aCfuUfcAfUfcuUfuCfuUfcCfcAfcUfu	3708
D-3044	GfuGfgGfAfagAfaAfgAfuGfaAfgUfuUf	3058	aCfuUfcAfuCfuUfuCfUfucCfcAfcsUfsu	3709
D-3045	GfuGfggAfAfgAfaAfgAfuGfaAfgUfuUf	3059	aCfuUfcAfuCfuUfuCfuuCfCfcAfcsUfsu	3710
D-3046	GfuGfGfgaAfgAfaAfgAfuGfaAfgUfuUf	3060	aCfuUfcAfuCfuUfuCfuUfCfccAfcsUfsu	3711
D-3047	GfugGfGfaAfgAfaAfgAfuGfaAfgUfuUf	3061	aCfuUfcAfuCfuUfuCfuUfccCfAfcsUfsu	3712
D-3048	GfUfggGfaAfgAfaAfgAfuGfaAfgUfuUf	3062	aCfuUfcAfuCfuUfuCfuUfcCfCfacsUfsu	3713
D-3049	gUfGfgGfaAfgAfaAfgAfuGfaAfgUfuUf	3063	aCfuUfcAfuCfuUfuCfuUfcCfcaCfsUfsu	3714
D-3050	guGfgGfaAfgAfaAfgAfuGfaAfgUfuUf	3064	aCfuUfcAfuCfuUfuCfuUfcCfcAfCfsusu	3715
D-3051	GfuGfgGfaAfgAfaAfgaUfGfaAfgUfuUf	3065	aCfuUfcaUfCfuUfuCfuUfcCfcAfcsUfsu	3716
D-3052	GfuGfgGfaAfgAfaAfgAfUfgaAfgUfuUf	3066	aCfuUfCfauCfuUfuCfuUfcCfcAfcsUfsu	3717
D-3053	GfuGfgGfaAfgAfaAfgAfugAfAfgUfuUf	3067	aCfuuCfAfuCfuUfuCfuUfcCfcAfcsUfsu	3718
D-3054	GfuGfgGfaAfgAfaAfgAfuGfAfagUfuUf	3068	aCfUfucAfuCfuUfuCfuUfcCfcAfcsUfsu	3719
D-3055	GfuGfgGfaAfgAfaAfgAfuGfaaGfUfuUf	3069	acUfUfcAfuCfuUfuCfuUfcCfcAfcsUfsu	3720
D-3056	GfuGfgGfaAfgAfaAfgAfuGfaAfGfuuUf	3070	AfcuUfcAfuCfuUfuCfuUfcCfcAfcsUfsu	3721
D-3057	GfuGfgGfaAfgAfaAfgAfuGfaAfguUfUf	3071	AfCfuUfcAfuCfuUfuCfuUfcCfcAfcsUfsu	3722
D-3058	GfUfggGfAfagAfAfagAfUfgaAfGfuuUf	3072	AfcuUfCfauCfUfuuCfUfucCfCfacsUfsUf	3723
D-3059	guGfGfgaAfGfaaAfGfauGfAfagUfUfu	3073	aCfUfucAfUfcuUfUfcuUfCfccAfCfsusu	3724
D-3060	GfugGfGfaaGfAfaaGfAfugAfAfguUfUf	3074	AfCfuuCfAfucUfUfucUfUfccCfAfcsusUf	3725
D-3061	gUfGfggAfAfgaAfAfgaUfGfaaGfUfuu	3075	acUfUfcaUfCfuuUfCfuuCfCfcaCfsUfsu	3726
D-3062	GAGAcGGGcuucAAGAAcudTsdT	3076	AGUUCUUGAAGCCCGUCUCdTsdT	3727
D-3063	GfaGfaCfgGfGfCfUfUfcAfaGfaAfcUfuUf	3077	aGfuUfcUfuGfaagccCfgUfcUfcsUfsu	3728
D-3064	GfaGfaCfgGfGfcUfUfcAfaGfaAfcUfuUf	3078	aGfuUfcUfuGfaaGfccCfgUfcUfcsUfsu	3729
D-3065	GfaGfaCfgGfgcUfUfcAfaGfaAfcUfuUf	3079	aGfuUfcUfuGfaaGfCfcCfgUfcUfcsUfsu	3730

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3066	GfaGfaCfgGfgCfUfUfCfAfaGfaAfcUfuUf	3080	aGfuUfcUfugaagCfcCfgUfcUfcsUfsu	3731
D-3067	GfaGfaCfgGfgCfUfuCfAfaGfaAfcUfuUf	3081	aGfuUfcUfugAfagCfcCfgUfcUfcsUfsu	3732
D-3068	GfaGfaCfgGfgCfUfucAfaGfaAfcUfuUf	3082	aGfuUfcUfuGfAfagCfcCfgUfcUfcsUfsu	3733
D-3069	GfaGfaCfggGfCfuUfcAfaGfaAfcUfuUf	3083	aGfuUfcUfuGfaAfgcCfCfgUfcUfcsUfsu	3734
D-3070	GfaGfaCfgGfgCfuUfCfaaGfaAfcUfuUf	3084	aGfuUfcUfUfgaAfgCfcCfgUfcUfcsUfsu	3735
D-3071	GfsasGfaCfggGfCfuUfcAfaGfaAfcUfuUf	3085	asGfsuUfcUfuGfaAfgcCfCfgUfcUfcsUfsu	3736
D-3072	GfaGfaCfggGfCfuUfcAfaGfaAfcUfuUf	3086	aGfuUfcUfuGfaAfgcCfCfgUfcUfcUfu	3737
D-3073	GfsasGfaCfgGfgCfuUfCfaaGfaAfcUfuUf	3087	asGfsuUfcUfUfgaAfgCfcCfgUfcUfcsUfsu	3738
D-3074	GfaGfaCfgGfgCfuUfCfaaGfaAfcUfuUf	3088	aGfuUfcUfUfgaAfgCfcCfgUfcUfcUfu	3739
D-3075	GfaGfaCfGfggCfuUfcAfaGfaAfcUfuUf	3089	aGfuUfcUfuGfaAfgCfCfcgUfcUfcsUfsu	3740
D-3076	GfaGfacGfGfgCfuUfcAfaGfaAfcUfuUf	3090	aGfuUfcUfuGfaAfgCfccGfUfcUfcsUfsu	3741
D-3077	GfaGfAfcgGfgCfuUfcAfaGfaAfcUfuUf	3091	aGfuUfcUfuGfaAfgCfcCfGfucUfcsUfsu	3742
D-3078	GfagAfCfgGfgCfuUfcAfaGfaAfcUfuUf	3092	aGfuUfcUfuGfaAfgCfcCfguCfUfcsUfsu	3743
D-3079	GfAfgaCfgGfgCfuUfcAfaGfaAfcUfuUf	3093	aGfuUfcUfuGfaAfgCfcCfgUfCfucsUfsu	3744
D-3080	gAfGfaCfgGfgCfuUfcAfaGfaAfcUfuUf	3094	aGfuUfcUfuGfaAfgCfcCfgUfcuCfsUfsu	3745
D-3081	gaGfaCfgGfgCfuUfcAfaGfaAfcUfuUf	3095	aGfuUfcUfuGfaAfgCfcCfgUfcUfCfsusu	3746
D-3082	GfaGfaCfgGfgCfuUfcaAfGfaAfcUfuUf	3096	aGfuUfcuUfGfaAfgCfcCfgUfcUfcsUfsu	3747
D-3083	GfaGfaCfgGfgCfuUfcAfAfgaAfcUfuUf	3097	aGfuUfCfuuGfaAfgCfcCfgUfcUfcsUfsu	3748
D-3084	GfaGfaCfgGfgCfuUfcAfagAfAfcUfuUf	3098	aGfuuCfUfuGfaAfgCfcCfgUfcUfcsUfsu	3749
D-3085	GfaGfaCfgGfgCfuUfcAfaGfAfacUfuUf	3099	aGfUfucUfuGfaAfgCfcCfgUfcUfcsUfsu	3750
D-3086	GfaGfaCfgGfgCfuUfcAfaGfaaCfUfuUf	3100	agUfUfcUfuGfaAfgCfcCfgUfcUfcsUfsu	3751
D-3087	GfaGfaCfgGfgCfuUfcAfaGfaAfCfuuUf	3101	AfguUfcUfuGfaAfgCfcCfgUfcUfcsUfsu	3752
D-3088	GfaGfaCfgGfgCfuUfcAfaGfaAfcuUfUf	3102	AfGfuUfcUfuGfaAfgCfcCfgUfcUfcsUfsu	3753
D-3089	GfAfgaCfGfggCfUfucAfAfgaAfCfuuUf	3103	AfguUfCfuuGfAfagCfCfcgUfCfucsUfsUf	3754
D-3090	gaGfAfcgGfGfcuUfCfaaGfAfacUfUfu	3104	aGfUfucUfUfgaAfGfccCfGfucUfCfsusu	3755
D-3091	GfagAfCfggGfCfuuCfAfagAfAfcuUfUf	3105	AfGfuuCfUfugAfAfgcCfCfguCfUfcsusUf	3756
D-3092	gAfGfacGfGfgcUfUfcaAfGfaaCfUfuu	3106	agUfUfcuUfGfaaGfCfccGfUfcuCfsUfsu	3757
D-3093	GAGcGcAGcuGcuAcuGGudTsdT	3107	ACcAGuAGcAGCUGCGCUCdTsdT	3758
D-3094	GfaGfcGfcAfGfCfUfGfcUfaCfuGfgUfuUf	3108	aCfcAfgUfaGfcagcuGfcGfcUfcsUfsu	3759
D-3095	GfaGfcGfcAfGfcUfGfcUfaCfuGfgUfuUf	3109	aCfcAfgUfaGfcaGfcuGfcGfcUfcsUfsu	3760
D-3096	GfaGfcGfcAfgcUfGfcUfaCfuGfgUfuUf	3110	aCfcAfgUfaGfcaGfCfuGfcGfcUfcsUfsu	3761
D-3097	GfaGfcGfcAfgCfUfGfCfUfaCfuGfgUfuUf	3111	aCfcAfgUfagcagCfuGfcGfcUfcsUfsu	3762
D-3098	GfaGfcGfcAfgCfUfgCfUfaCfuGfgUfuUf	3112	aCfcAfgUfagCfagCfuGfcGfcUfcsUfsu	3763
D-3099	GfaGfcGfcAfgCfUfgcUfaCfuGfgUfuUf	3113	aCfcAfgUfaGfCfagCfuGfcGfcUfcsUfsu	3764
D-3100	GfaGfcGfcaGfCfuGfcUfaCfuGfgUfuUf	3114	aCfcAfgUfaGfcAfgcUfGfcGfcUfcsUfsu	3765
D-3101	GfaGfcGfcAfgCfuGfCfuaCfuGfgUfuUf	3115	aCfcAfgUfAfgcAfgCfuGfcGfcUfcsUfsu	3766
D-3102	GfsasGfcGfcaGfCfuGfcUfaCfuGfgUfuUf	3116	asCfscAfgUfaGfcAfgcUfGfcGfcUfcsUfsu	3767
D-3103	GfaGfcGfcaGfCfuGfcUfaCfuGfgUfuUf	3117	aCfcAfgUfaGfcAfgcUfGfcGfcUfcUfu	3768
D-3104	GfsasGfcGfcAfgCfuGfCfuaCfuGfgUfuUf	3118	asCfscAfgUfAfgcAfgCfuGfcGfcUfcsUfsu	3769
D-3105	GfaGfcGfcAfgCfuGfCfuaCfuGfgUfuUf	3119	aCfcAfgUfAfgcAfgCfuGfcGfcUfcUfu	3770

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3106	GfaGfcGfCfagCfuGfcUfaCfuGfgUfuUf	3120	aCfcAfgUfaGfcAfgCfUfgcGfcUfcsUfsu	3771
D-3107	GfaGfcgCfAfgCfuGfcUfaCfuGfgUfuUf	3121	aCfcAfgUfaGfcAfgCfugCfGfcUfcsUfsu	3772
D-3108	GfaGfCfgcAfgCfuGfcUfaCfuGfgUfuUf	3122	aCfcAfgUfaGfcAfgCfuGfCfgcUfcsUfsu	3773
D-3109	GfagCfGfcAfgCfuGfcUfaCfuGfgUfuUf	3123	aCfcAfgUfaGfcAfgCfuGfcgCfUfcsUfsu	3774
D-3110	GfAfgcGfcAfgCfuGfcUfaCfuGfgUfuUf	3124	aCfcAfgUfaGfcAfgCfuGfcGfCfucsUfsu	3775
D-3111	gAfGfcGfcAfgCfuGfcUfaCfuGfgUfuUf	3125	aCfcAfgUfaGfcAfgCfuGfcGfcuCfsUfsu	3776
D-3112	gaGfcGfcAfgCfuGfcUfaCfuGfgUfuUf	3126	aCfcAfgUfaGfcAfgCfuGfcGfcUfCfsusu	3777
D-3113	GfaGfcGfcAfgCfuGfcuAfCfuGfgUfuUf	3127	aCfcAfguAfGfcAfgCfuGfcGfcUfcsUfsu	3778
D-3114	GfaGfcGfcAfgCfuGfcUfAfcuGfgUfuUf	3128	aCfcAfGfuaGfcAfgCfuGfcGfcUfcsUfsu	3779
D-3115	GfaGfcGfcAfgCfuGfcUfacUfGfgUfuUf	3129	aCfcaGfUfaGfcAfgCfuGfcGfcUfcsUfsu	3780
D-3116	GfaGfcGfcAfgCfuGfcUfaCfUfggUfuUf	3130	aCfCfagUfaGfcAfgCfuGfcGfcUfcsUfsu	3781
D-3117	GfaGfcGfcAfgCfuGfcUfaCfugGfUfuUf	3131	acCfAfgUfaGfcAfgCfuGfcGfcUfcsUfsu	3782
D-3118	GfaGfcGfcAfgCfuGfcUfaCfuGfGfuuUf	3132	AfccAfgUfaGfcAfgCfuGfcGfcUfcsUfsu	3783
D-3119	GfaGfcGfcAfgCfuGfcUfaCfuGfguUfUf	3133	AfCfcAfgUfaGfcAfgCfuGfcGfcUfcsUfsu	3784
D-3120	GfAfgcGfCfagCfUfgcUfAfcuGfGfuuUf	3134	AfccAfGfuaGfCfagCfUfgcGfCfucsUfsUf	3785
D-3121	gaGfCfgcAfGfcuGfCfuaCfUfggUfUfu	3135	aCfCfagUfAfgcAfGfcuGfCfgcUfCfsusu	3786
D-3122	GfagCfGfcaGfCfugCfUfacUfGfguUfUf	3136	AfCfcaGfUfagCfAfgcUfGfcgCfUfcsusUf	3787
D-3123	gAfGfcgCfAfgcUfGfcuAfCfugGfUfuu	3137	acCfAfguAfGfcaGfCfugCfGfcuCfsUfsu	3788
D-3124	GuuGucuGuGuGAucGGAudTsdT	3138	AUCCGAUcAcAcAGAcAACdTsdT	3789
D-3125	GfuUfgUfcUfGfUfGfUfgAfuCfgGfaUfuUf	3139	aUfcCfgAfuCfacacaGfaCfaAfcsUfsu	3790
D-3126	GfuUfgUfcUfGfuGfUfgAfuCfgGfaUfuUf	3140	aUfcCfgAfuCfacAfcaGfaCfaAfcsUfsu	3791
D-3127	GfuUfgUfcUfguGfUfgAfuCfgGfaUfuUf	3141	aUfcCfgAfuCfacAfCfaGfaCfaAfcsUfsu	3792
D-3128	GfuUfgUfcUfgUfGfUfGfAfuCfgGfaUfuUf	3142	aUfcCfgAfucacaCfaGfaCfaAfcsUfsu	3793
D-3129	GfuUfgUfcUfgUfGfuGfAfuCfgGfaUfuUf	3143	aUfcCfgAfucAfcaCfaGfaCfaAfcsUfsu	3794
D-3130	GfuUfgUfcUfgUfGfugAfuCfgGfaUfuUf	3144	aUfcCfgAfuCfAfcaCfaGfaCfaAfcsUfsu	3795
D-3131	GfuUfgUfcuGfUfgUfgAfuCfgGfaUfuUf	3145	aUfcCfgAfuCfaCfacAfGfaCfaAfcsUfsu	3796
D-3132	GfuUfgUfcUfgUfgUfGfauCfgGfaUfuUf	3146	aUfcCfgAfUfcaCfaCfaGfaCfaAfcsUfsu	3797
D-3133	GfsusUfgUfcuGfUfgUfgAfuCfgGfaUfuUf	3147	asUfscCfgAfuCfaCfacAfGfaCfaAfcsUfsu	3798
D-3134	GfuUfgUfcuGfUfgUfgAfuCfgGfaUfuUf	3148	aUfcCfgAfuCfaCfacAfGfaCfaAfcUfu	3799
D-3135	GfsusUfgUfcUfgUfgUfGfauCfgGfaUfuUf	3149	asUfscCfgAfUfcaCfaCfaGfaCfaAfcsUfsu	3800
D-3136	GfuUfgUfcUfgUfgUfGfauCfgGfaUfuUf	3150	aUfcCfgAfUfcaCfaCfaGfaCfaAfcUfu	3801
D-3137	GfuUfgUfCfugUfgUfgAfuCfgGfaUfuUf	3151	aUfcCfgAfuCfaCfaCfAfgaCfaAfcsUfsu	3802
D-3138	GfuUfguCfUfgUfgUfgAfuCfgGfaUfuUf	3152	aUfcCfgAfuCfaCfaCfagAfCfaAfcsUfsu	3803
D-3139	GfuUfGfucUfgUfgUfgAfuCfgGfaUfuUf	3153	aUfcCfgAfuCfaCfaCfaGfAfcaAfcsUfsu	3804
D-3140	GfuuGfUfcUfgUfgUfgAfuCfgGfaUfuUf	3154	aUfcCfgAfuCfaCfaCfaGfacAfAfcsUfsu	3805
D-3141	GfUfugUfcUfgUfgUfgAfuCfgGfaUfuUf	3155	aUfcCfgAfuCfaCfaCfaGfaCfAfacsUfsu	3806
D-3142	gUfUfgUfcUfgUfgUfgAfuCfgGfaUfuUf	3156	aUfcCfgAfuCfaCfaCfaGfaCfaaCfsUfsu	3807
D-3143	guUfgUfcUfgUfgUfgAfuCfgGfaUfuUf	3157	aUfcCfgAfuCfaCfaCfaGfaCfaAfCfsusu	3808
D-3144	GfuUfgUfcUfgUfgUfgaUfCfgGfaUfuUf	3158	aUfcCfgaUfCfaCfaCfaGfaCfaAfcsUfsu	3809
D-3145	GfuUfgUfcUfgUfgUfgAfUfcgGfaUfuUf	3159	aUfcCfGfauCfaCfaCfaGfaCfaAfcsUfsu	3810

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3146	GfuUfgUfcUfgUfgUfgAfucGfGfaUfuUf	3160	aUfccGfAfuCfaCfaCfaGfaCfaAfcsUfsu	3811
D-3147	GfuUfgUfcUfgUfgUfgAfuCfGfgaUfuUf	3161	aUfCfcgAfuCfaCfaCfaGfaCfaAfcsUfsu	3812
D-3148	GfuUfgUfcUfgUfgUfgAfuCfggAfUfuUf	3162	auCfCfgAfuCfaCfaCfaGfaCfaAfcsUfsu	3813
D-3149	GfuUfgUfcUfgUfgUfgAfuCfgGfAfuuUf	3163	AfucCfgAfuCfaCfaCfaGfaCfaAfcsUfsu	3814
D-3150	GfuUfgUfcUfgUfgUfgAfuCfgGfauUfUf	3164	AfUfcCfgAfuCfaCfaCfaGfaCfaAfcsUfsu	3815
D-3151	GfUfugUfCfugUfGfugAfUfcgGfAfuuUf	3165	AfucCfGfauCfAfcaCfAfgaCfAfacsUfsUf	3816
D-3152	guUfGfucUfGfugUfGfauCfGfgaUfUfu	3166	aUfCfcgAfUfcaCfAfcaGfAfcaAfCfsusu	3817
D-3153	GfuuGfUfcuGfUfguGfAfucGfGfauUfUf	3167	AfUfccGfAfucAfCfacAfGfacAfAfcsusUf	3818
D-3154	gUfUfguCfUfguGfUfgaUfCfggAfUfuu	3168	auCfCfgaUfCfacAfCfagAfCfaaCfsUfsu	3819
D-3155	GGAGcuGcGGGGccuGAGAdTsdT	3169	UCUcAGGCCCCGcAGCUCCdTsdT	3820
D-3156	GfgAfgCfuGfCfGfGfGfgCfcUfgAfgAfuUf	3170	uCfuCfaGfgCfcccgcAfgCfuCfcsUfsu	3821
D-3157	GfgAfgCfuGfCfgGfGfgCfcUfgAfgAfuUf	3171	uCfuCfaGfgCfccCfgcAfgCfuCfcsUfsu	3822
D-3158	GfgAfgCfuGfcgGfGfgCfcUfgAfgAfuUf	3172	uCfuCfaGfgCfccCfGfcAfgCfuCfcsUfsu	3823
D-3159	GfgAfgCfuGfcGfGfGfGfCfcUfgAfgAfuUf	3173	uCfuCfaGfgccccGfcAfgCfuCfcsUfsu	3824
D-3160	GfgAfgCfuGfcGfGfgGfCfcUfgAfgAfuUf	3174	uCfuCfaGfgcCfccGfcAfgCfuCfcsUfsu	3825
D-3161	GfgAfgCfuGfcGfGfggCfcUfgAfgAfuUf	3175	uCfuCfaGfgCfCfccGfcAfgCfuCfcsUfsu	3826
D-3162	GfgAfgCfugCfGfgGfgCfcUfgAfgAfuUf	3176	uCfuCfaGfgCfcCfcgCfAfgCfuCfcsUfsu	3827
D-3163	GfgAfgCfuGfcGfgGfGfccUfgAfgAfuUf	3177	uCfuCfaGfGfccCfcGfcAfgCfuCfcsUfsu	3828
D-3164	GfsgsAfgCfugCfGfgGfgCfcUfgAfgAfuUf	3178	usCfsuCfaGfgCfcCfcgCfAfgCfuCfcsUfsu	3829
D-3165	GfgAfgCfugCfGfgGfgCfcUfgAfgAfuUf	3179	uCfuCfaGfgCfcCfcgCfAfgCfuCfcUfu	3830
D-3166	GfsgsAfgCfuGfcGfgGfGfccUfgAfgAfuUf	3180	usCfsuCfaGfGfccCfcGfcAfgCfuCfcsUfsu	3831
D-3167	GfgAfgCfuGfcGfgGfGfccUfgAfgAfuUf	3181	uCfuCfaGfGfccCfcGfcAfgCfuCfcUfu	3832
D-3168	GfgAfgCfUfgcGfgGfgCfcUfgAfgAfuUf	3182	uCfuCfaGfgCfcCfcGfCfagCfuCfcsUfsu	3833
D-3169	GfgAfgcUfGfcGfgGfgCfcUfgAfgAfuUf	3183	uCfuCfaGfgCfcCfcGfcaGfCfuCfcsUfsu	3834
D-3170	GfgAfGfcuGfcGfgGfgCfcUfgAfgAfuUf	3184	uCfuCfaGfgCfcCfcGfcAfGfcuCfcsUfsu	3835
D-3171	GfgaGfCfuGfcGfgGfgCfcUfgAfgAfuUf	3185	uCfuCfaGfgCfcCfcGfcAfgcUfCfcsUfsu	3836
D-3172	GfGfagCfuGfcGfgGfgCfcUfgAfgAfuUf	3186	uCfuCfaGfgCfcCfcGfcAfgCfUfccsUfsu	3837
D-3173	gGfAfgCfuGfcGfgGfgCfcUfgAfgAfuUf	3187	uCfuCfaGfgCfcCfcGfcAfgCfucCfsUfsu	3838
D-3174	ggAfgCfuGfcGfgGfgCfcUfgAfgAfuUf	3188	uCfuCfaGfgCfcCfcGfcAfgCfuCfCfsusu	3839
D-3175	GfgAfgCfuGfcGfgGfgcCfUfgAfgAfuUf	3189	uCfuCfagGfCfcCfcGfcAfgCfuCfcsUfsu	3840
D-3176	GfgAfgCfuGfcGfgGfgCfCfugAfgAfuUf	3190	uCfuCfAfggCfcCfcGfcAfgCfuCfcsUfsu	3841
D-3177	GfgAfgCfuGfcGfgGfgCfcuGfAfgAfuUf	3191	uCfucAfGfgCfcCfcGfcAfgCfuCfcsUfsu	3842
D-3178	GfgAfgCfuGfcGfgGfgCfcUfGfagAfuUf	3192	uCfUfcaGfgCfcCfcGfcAfgCfuCfcsUfsu	3843
D-3179	GfgAfgCfuGfcGfgGfgCfcUfgaGfAfuUf	3193	ucUfCfaGfgCfcCfcGfcAfgCfuCfcsUfsu	3844
D-3180	GfgAfgCfuGfcGfgGfgCfcUfgAfGfauUf	3194	UfcuCfaGfgCfcCfcGfcAfgCfuCfcsUfsu	3845
D-3181	GfgAfgCfuGfcGfgGfgCfcUfgAfgaUfUf	3195	UfCfuCfaGfgCfcCfcGfcAfgCfuCfcsUfsu	3846
D-3182	GfGfagCfUfgcGfGfggCfCfugAfGfauUf	3196	UfcuCfAfggCfCfccGfCfagCfUfccsUfsUf	3847
D-3183	ggAfGfcuGfCfggGfGfccUfGfagAfUfu	3197	uCfUfcaGfGfccCfCfgcAfGfcuCfCfsusu	3848
D-3184	GfgaGfCfugCfGfggGfCfcuGfAfgaUfUf	3198	UfCfucAfGfgcCfCfcgCfAfgcUfCfcsusUf	3849
D-3185	gGfAfgcUfGfcgGfGfgcCfUfgaGfAfuu	3199	ucUfCfagGfCfccCfGfcaGfCfucCfsUfsu	3850

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3186	GccGcuGGAAcGAcGAcGudTsdT	3200	ACGUCGUCGUUCcAGCGGCdTsdT	3851
D-3187	GfcCfgCfuGfGfAfAfCfgAfcGfaCfgUfuUf	3201	aCfgUfcGfuCfguuccAfgCfgGfcsUfsu	3852
D-3188	GfcCfgCfuGfGfaAfCfgAfcGfaCfgUfuUf	3202	aCfgUfcGfuCfguUfccAfgCfgGfcsUfsu	3853
D-3189	GfcCfgCfuGfgaAfCfgAfcGfaCfgUfuUf	3203	aCfgUfcGfuCfguUfCfcAfgCfgGfcsUfsu	3854
D-3190	GfcCfgCfuGfgAfAfCfGfAfcGfaCfgUfuUf	3204	aCfgUfcGfucguuCfcAfgCfgGfcsUfsu	3855
D-3191	GfcCfgCfuGfgAfAfcGfAfcGfaCfgUfuUf	3205	aCfgUfcGfucGfuuCfcAfgCfgGfcsUfsu	3856
D-3192	GfcCfgCfuGfgAfAfcgAfcGfaCfgUfuUf	3206	aCfgUfcGfuCfGfuuCfcAfgCfgGfcsUfsu	3857
D-3193	GfcCfgCfugGfAfaCfgAfcGfaCfgUfuUf	3207	aCfgUfcGfuCfgUfucCfAfgCfgGfcsUfsu	3858
D-3194	GfcCfgCfuGfgAfaCfGfacGfaCfgUfuUf	3208	aCfgUfcGfUfcgUfuCfcAfgCfgGfcsUfsu	3859
D-3195	GfscsCfgCfugGfAfaCfgAfcGfaCfgUfuUf	3209	asCfsgUfcGfuCfgUfucCfAfgCfgGfcsUfsu	3860
D-3196	GfcCfgCfugGfAfaCfgAfcGfaCfgUfuUf	3210	aCfgUfcGfuCfgUfucCfAfgCfgGfcUfu	3861
D-3197	GfscsCfgCfuGfgAfaCfGfacGfaCfgUfuUf	3211	asCfsgUfcGfUfcgUfuCfcAfgCfgGfcsUfsu	3862
D-3198	GfcCfgCfuGfgAfaCfGfacGfaCfgUfuUf	3212	aCfgUfcGfUfcgUfuCfcAfgCfgGfcUfu	3863
D-3199	GfcCfgCfUfggAfaCfgAfcGfaCfgUfuUf	3213	aCfgUfcGfuCfgUfuCfCfagCfgGfcsUfsu	3864
D-3200	GfcCfgcUfGfgAfaCfgAfcGfaCfgUfuUf	3214	aCfgUfcGfuCfgUfuCfcaGfCfgGfcsUfsu	3865
D-3201	GfcCfGfcuGfgAfaCfgAfcGfaCfgUfuUf	3215	aCfgUfcGfuCfgUfuCfcAfGfcgGfcsUfsu	3866
D-3202	GfccGfCfuGfgAfaCfgAfcGfaCfgUfuUf	3216	aCfgUfcGfuCfgUfuCfcAfgcGfGfcsUfsu	3867
D-3203	GfCfcgCfuGfgAfaCfgAfcGfaCfgUfuUf	3217	aCfgUfcGfuCfgUfuCfcAfgCfGfgcsUfsu	3868
D-3204	gCfCfgCfuGfgAfaCfgAfcGfaCfgUfuUf	3218	aCfgUfcGfuCfgUfuCfcAfgCfggCfsUfsu	3869
D-3205	gcCfgCfuGfgAfaCfgAfcGfaCfgUfuUf	3219	aCfgUfcGfuCfgUfuCfcAfgCfgGfCfsusu	3870
D-3206	GfcCfgCfuGfgAfaCfgaCfGfaCfgUfuUf	3220	aCfgUfcgUfCfgUfuCfcAfgCfgGfcsUfsu	3871
D-3207	GfcCfgCfuGfgAfaCfgAfCfgaCfgUfuUf	3221	aCfgUfCfguCfgUfuCfcAfgCfgGfcsUfsu	3872
D-3208	GfcCfgCfuGfgAfaCfgAfcgAfCfgUfuUf	3222	aCfguCfGfuCfgUfuCfcAfgCfgGfcsUfsu	3873
D-3209	GfcCfgCfuGfgAfaCfgAfcGfAfcgUfuUf	3223	aCfGfucGfuCfgUfuCfcAfgCfgGfcsUfsu	3874
D-3210	GfcCfgCfuGfgAfaCfgAfcGfacGfUfuUf	3224	acGfUfcGfuCfgUfuCfcAfgCfgGfcsUfsu	3875
D-3211	GfcCfgCfuGfgAfaCfgAfcGfaCfGfuuUf	3225	AfcgUfcGfuCfgUfuCfcAfgCfgGfcsUfsu	3876
D-3212	GfcCfgCfuGfgAfaCfgAfcGfaCfguUfUf	3226	AfCfgUfcGfuCfgUfuCfcAfgCfgGfcsUfsu	3877
D-3213	GfCfcgCfUfggAfAfcgAfCfgaCfGfuuUf	3227	AfcgUfCfguCfGfuuCfCfagCfGfgcsUfsUf	3878
D-3214	gcCfGfcuGfGfaaCfGfacGfAfcgUfUfu	3228	aCfGfucGfUfcgUfUfccAfGfcgGfCfsusu	3879
D-3215	GfccGfCfugGfAfacGfAfcgAfCfguUfUf	3229	AfCfguCfGfucGfUfucCfAfgcGfGfcsusUf	3880
D-3216	gCfCfgcUfGfgaAfCfgaCfGfacGfUfuu	3230	acGfUfcgUfCfguUfCfcaGfCfggCfsUfsu	3881
D-3217	GcAGcuGcuAcuGGuucucdTsdT	3231	GAGAACcAGuAGcAGCUGCdTsdT	3882
D-3218	GfcAfgCfuGfCfUfAfCfuGfgUfuCfuCfuUf	3232	gAfgAfaCfcAfguagcAfgCfuGfcsUfsu	3883
D-3219	GfcAfgCfuGfCfuAfCfuGfgUfuCfuCfuUf	3233	gAfgAfaCfcAfguAfgcAfgCfuGfcsUfsu	3884
D-3220	GfcAfgCfuGfcuAfCfuGfgUfuCfuCfuUf	3234	gAfgAfaCfcAfguAfGfcAfgCfuGfcsUfsu	3885
D-3221	GfcAfgCfuGfcUfAfCfUfGfgUfuCfuCfuUf	3235	gAfgAfaCfcaguaGfcAfgCfuGfcsUfsu	3886
D-3222	GfcAfgCfuGfcUfAfcUfGfgUfuCfuCfuUf	3236	gAfgAfaCfcaGfuaGfcAfgCfuGfcsUfsu	3887
D-3223	GfcAfgCfuGfcUfAfcuGfgUfuCfuCfuUf	3237	gAfgAfaCfcAfGfuaGfcAfgCfuGfcsUfsu	3888
D-3224	GfcAfgCfugCfUfaCfuGfgUfuCfuCfuUf	3238	gAfgAfaCfcAfgUfagCfAfgCfuGfcsUfsu	3889
D-3225	GfcAfgCfuGfcUfaCfUfggUfuCfuCfuUf	3239	gAfgAfaCfCfagUfaGfcAfgCfuGfcsUfsu	3890

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3226	GfscsAfgCfugCfUfaCfuGfgUfuCfuCfuUf	3240	gsAfsgAfaCfcAfgUfagCfAfgCfuGfcsUfsu	3891
D-3227	GfcAfgCfugCfUfaCfuGfgUfuCfuCfuUf	3241	gAfgAfaCfcAfgUfagCfAfgCfuGfcUfu	3892
D-3228	GfscsAfgCfuGfcUfaCfUfggUfuCfuCfuUf	3242	gsAfsgAfaCfCfagUfaGfcAfgCfuGfcsUfsu	3893
D-3229	GfcAfgCfuGfcUfaCfUfggUfuCfuCfuUf	3243	gAfgAfaCfCfagUfaGfcAfgCfuGfcUfu	3894
D-3230	GfcAfgCfUfgcUfaCfuGfgUfuCfuCfuUf	3244	gAfgAfaCfcAfgUfaGfCfagCfuGfcsUfsu	3895
D-3231	GfcAfgcUfGfcUfaCfuGfgUfuCfuCfuUf	3245	gAfgAfaCfcAfgUfaGfcaGfCfuGfcsUfsu	3896
D-3232	GfcAfGfcuGfcUfaCfuGfgUfuCfuCfuUf	3246	gAfgAfaCfcAfgUfaGfcAfGfcuGfcsUfsu	3897
D-3233	GfcaGfCfuGfcUfaCfuGfgUfuCfuCfuUf	3247	gAfgAfaCfcAfgUfaGfcAfgcUfGfcsUfsu	3898
D-3234	GfCfagCfuGfcUfaCfuGfgUfuCfuCfuUf	3248	gAfgAfaCfcAfgUfaGfcAfgCfUfgcsUfsu	3899
D-3235	gCfAfgCfuGfcUfaCfuGfgUfuCfuCfuUf	3249	gAfgAfaCfcAfgUfaGfcAfgCfugCfsUfsu	3900
D-3236	gcAfgCfuGfcUfaCfuGfgUfuCfuCfuUf	3250	gAfgAfaCfcAfgUfaGfcAfgCfuGfCfsusu	3901
D-3237	GfcAfgCfuGfcUfaCfugGfUfuCfuCfuUf	3251	gAfgAfacCfAfgUfaGfcAfgCfuGfcsUfsu	3902
D-3238	GfcAfgCfuGfcUfaCfuGfGfuuCfuCfuUf	3252	gAfgAfAfccAfgUfaGfcAfgCfuGfcsUfsu	3903
D-3239	GfcAfgCfuGfcUfaCfuGfguUfCfuCfuUf	3253	gAfgaAfCfcAfgUfaGfcAfgCfuGfcsUfsu	3904
D-3240	GfcAfgCfuGfcUfaCfuGfgUfUfcuCfuUf	3254	gAfGfaaCfcAfgUfaGfcAfgCfuGfcsUfsu	3905
D-3241	GfcAfgCfuGfcUfaCfuGfgUfucUfCfuUf	3255	gaGfAfaCfcAfgUfaGfcAfgCfuGfcsUfsu	3906
D-3242	GfcAfgCfuGfcUfaCfuGfgUfuCfUfcuUf	3256	GfagAfaCfcAfgUfaGfcAfgCfuGfcsUfsu	3907
D-3243	GfcAfgCfuGfcUfaCfuGfgUfuCfucUfUf	3257	GfAfgAfaCfcAfgUfaGfcAfgCfuGfcsUfsu	3908
D-3244	GfCfagCfUfgcUfAfcuGfGfuuCfUfcuUf	3258	GfagAfAfccAfGfuaGfCfagCfUfgcsUfsUf	3909
D-3245	gcAfGfcuGfCfuaCfUfggUfUfcuCfUfu	3259	gAfGfaaCfCfagUfAfgcAfGfcuGfCfsusu	3910
D-3246	GfcaGfCfugCfUfacUfGfguUfCfucUfUf	3260	GfAfgaAfCfcaGfUfagCfAfgcUfGfcsusUf	3911
D-3247	gCfAfgcUfGfcuAfCfugGfUfucUfCfuu	3261	gaGfAfacCfAfguAfGfcaGfCfugCfsUfsu	3912
D-3248	GcuGGGucuGcGAGAcAGAdTsdT	3262	UCUGUCUCGcAGACCcAGCdTsdT	3913
D-3249	GfcUfgGfgUfCfUfGfCfgAfgAfcAfgAfuUf	3263	uCfuGfuCfuCfgcagaCfcCfaGfcsUfsu	3914
D-3250	GfcUfgGfgUfCfuGfCfgAfgAfcAfgAfuUf	3264	uCfuGfuCfuCfgcAfgaCfcCfaGfcsUfsu	3915
D-3251	GfcUfgGfgUfcuGfCfgAfgAfcAfgAfuUf	3265	uCfuGfuCfuCfgcAfGfaCfcCfaGfcsUfsu	3916
D-3252	GfcUfgGfgUfcUfGfCfGfAfgAfcAfgAfuUf	3266	uCfuGfuCfucgcaGfaCfcCfaGfcsUfsu	3917
D-3253	GfcUfgGfgUfcUfGfcGfAfgAfcAfgAfuUf	3267	uCfuGfuCfucGfcaGfaCfcCfaGfcsUfsu	3918
D-3254	GfcUfgGfgUfcUfGfcgAfgAfcAfgAfuUf	3268	uCfuGfuCfuCfGfcaGfaCfcCfaGfcsUfsu	3919
D-3255	GfcUfgGfguCfUfgCfgAfgAfcAfgAfuUf	3269	uCfuGfuCfuCfgCfagAfCfcCfaGfcsUfsu	3920
D-3256	GfcUfgGfgUfcUfgCfGfagAfcAfgAfuUf	3270	uCfuGfuCfUfcgCfaGfaCfcCfaGfcsUfsu	3921
D-3257	GfscsUfgGfguCfUfgCfgAfgAfcAfgAfuUf	3271	usCfsuGfuCfuCfgCfagAfCfcCfaGfcsUfsu	3922
D-3258	GfcUfgGfguCfUfgCfgAfgAfcAfgAfuUf	3272	uCfuGfuCfuCfgCfagAfCfcCfaGfcUfu	3923
D-3259	GfscsUfgGfgUfcUfgCfGfagAfcAfgAfuUf	3273	usCfsuGfuCfUfcgCfaGfaCfcCfaGfcsUfsu	3924
D-3260	GfcUfgGfgUfcUfgCfGfagAfcAfgAfuUf	3274	uCfuGfuCfUfcgCfaGfaCfcCfaGfcUfu	3925
D-3261	GfcUfgGfGfucUfgCfgAfgAfcAfgAfuUf	3275	uCfuGfuCfuCfgCfaGfAfccCfaGfcsUfsu	3926
D-3262	GfcUfggGfUfcUfgCfgAfgAfcAfgAfuUf	3276	uCfuGfuCfuCfgCfaGfacCfCfaGfcsUfsu	3927
D-3263	GfcUfGfggUfcUfgCfgAfgAfcAfgAfuUf	3277	uCfuGfuCfuCfgCfaGfaCfCfcaGfcsUfsu	3928
D-3264	GfcuGfGfgUfcUfgCfgAfgAfcAfgAfuUf	3278	uCfuGfuCfuCfgCfaGfaCfccAfGfcsUfsu	3929
D-3265	GfCfugGfgUfcUfgCfgAfgAfcAfgAfuUf	3279	uCfuGfuCfuCfgCfaGfaCfcCfAfgcsUfsu	3930

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3266	gCfUfgGfgUfcUfgCfgAfgAfcAfgAfuUf	3280	uCfuGfuCfuCfgCfaGfaCfcCfagCfsUfsu	3931
D-3267	gcUfgGfgUfcUfgCfgAfgAfcAfgAfuUf	3281	uCfuGfuCfuCfgCfaGfaCfcCfaGfCfsusu	3932
D-3268	GfcUfgGfgUfcUfgCfgaGfAfcAfgAfuUf	3282	uCfuGfucUfCfgCfaGfaCfcCfaGfcsUfsu	3933
D-3269	GfcUfgGfgUfcUfgCfgAfGfacAfgAfuUf	3283	uCfuGfUfcuCfgCfaGfaCfcCfaGfcsUfsu	3934
D-3270	GfcUfgGfgUfcUfgCfgAfgaCfAfgAfuUf	3284	uCfugUfCfuCfgCfaGfaCfcCfaGfcsUfsu	3935
D-3271	GfcUfgGfgUfcUfgCfgAfgAfCfagAfuUf	3285	uCfUfguCfuCfgCfaGfaCfcCfaGfcsUfsu	3936
D-3272	GfcUfgGfgUfcUfgCfgAfgAfcaGfAfuUf	3286	ucUfGfuCfuCfgCfaGfaCfcCfaGfcsUfsu	3937
D-3273	GfcUfgGfgUfcUfgCfgAfgAfcAfGfauUf	3287	UfcuGfuCfuCfgCfaGfaCfcCfaGfcsUfsu	3938
D-3274	GfcUfgGfgUfcUfgCfgAfgAfcAfgaUfUf	3288	UfCfuGfuCfuCfgCfaGfaCfcCfaGfcsUfsu	3939
D-3275	GfCfugGfGfucUfGfcgAfGfacAfGfauUf	3289	UfcuGfUfcuCfGfcaGfAfccCfAfgcsUfsUf	3940
D-3276	gcUfGfggUfCfugCfGfagAfCfagAfUfu	3290	uCfUfguCfUfcgCfAfgaCfCfcaGfCfsusu	3941
D-3277	GfcuGfGfguCfUfgcGfAfgaCfAfgaUfUf	3291	UfCfugUfCfucGfCfagAfCfccAfGfcsusUf	3942
D-3278	gCfUfggGfUfcuGfCfgaGfAfcaGfAfuu	3292	ucUfGfucUfCfgcAfGfacCfCfagCfsUfsu	3943
D-3279	GcuuucucGGGAAuuuucAdTsdT	3293	UGAAAAUUCCCGAGAAAGCdTsdT	3944
D-3280	GfcUfuUfcUfCfGfGfGfaAfuUfuUfcAfuUf	3294	uGfaAfaAfuUfcccgaGfaAfaGfcsUfsu	3945
D-3281	GfcUfuUfcUfCfgGfGfaAfuUfuUfcAfuUf	3295	uGfaAfaAfuUfccCfgaGfaAfaGfcsUfsu	3946
D-3282	GfcUfuUfcUfcgGfGfaAfuUfuUfcAfuUf	3296	uGfaAfaAfuUfccCfGfaGfaAfaGfcsUfsu	3947
D-3283	GfcUfuUfcUfcGfGfGfAfAfuUfuUfcAfuUf	3297	uGfaAfaAfuucccGfaGfaAfaGfcsUfsu	3948
D-3284	GfcUfuUfcUfcGfGfgAfAfuUfuUfcAfuUf	3298	uGfaAfaAfuuCfccGfaGfaAfaGfcsUfsu	3949
D-3285	GfcUfuUfcUfcGfGfgaAfuUfuUfcAfuUf	3299	uGfaAfaAfuUfCfccGfaGfaAfaGfcsUfsu	3950
D-3286	GfcUfuUfcuCfGfgGfaAfuUfuUfcAfuUf	3300	uGfaAfaAfuUfcCfcgAfGfaAfaGfcsUfsu	3951
D-3287	GfcUfuUfcUfcGfgGfAfauUfuUfcAfuUf	3301	uGfaAfaAfUfucCfcGfaGfaAfaGfcsUfsu	3952
D-3288	GfscsUfuUfcuCfGfgGfaAfuUfuUfcAfuUf	3302	usGfsaAfaAfuUfcCfcgAfGfaAfaGfcsUfsu	3953
D-3289	GfcUfuUfcuCfGfgGfaAfuUfuUfcAfuUf	3303	uGfaAfaAfuUfcCfcgAfGfaAfaGfcUfu	3954
D-3290	GfscsUfuUfcUfcGfgGfAfauUfuUfcAfuUf	3304	usGfsaAfaAfUfucCfcGfaGfaAfaGfcsUfsu	3955
D-3291	GfcUfuUfcUfcGfgGfAfauUfuUfcAfuUf	3305	uGfaAfaAfUfucCfcGfaGfaAfaGfcUfu	3956
D-3292	GfcUfuUfCfucGfgGfaAfuUfuUfcAfuUf	3306	uGfaAfaAfuUfcCfcGfAfgaAfaGfcsUfsu	3957
D-3293	GfcUfuuCfUfcGfgGfaAfuUfuUfcAfuUf	3307	uGfaAfaAfuUfcCfcGfagAfAfaGfcsUfsu	3958
D-3294	GfcUfUfucUfcGfgGfaAfuUfuUfcAfuUf	3308	uGfaAfaAfuUfcCfcGfaGfAfaaGfcsUfsu	3959
D-3295	GfcuUfUfcUfcGfgGfaAfuUfuUfcAfuUf	3309	uGfaAfaAfuUfcCfcGfaGfaaAfGfcsUfsu	3960
D-3296	GfCfuuUfcUfcGfgGfaAfuUfuUfcAfuUf	3310	uGfaAfaAfuUfcCfcGfaGfaAfAfgcsUfsu	3961
D-3297	gCfUfuUfcUfcGfgGfaAfuUfuUfcAfuUf	3311	uGfaAfaAfuUfcCfcGfaGfaAfagCfsUfsu	3962
D-3298	gcUfuUfcUfcGfgGfaAfuUfuUfcAfuUf	3312	uGfaAfaAfuUfcCfcGfaGfaAfaGfCfsusu	3963
D-3299	GfcUfuUfcUfcGfgGfaaUfUfuUfcAfuUf	3313	uGfaAfaaUfUfcCfcGfaGfaAfaGfcsUfsu	3964
D-3300	GfcUfuUfcUfcGfgGfaAfUfuuUfcAfuUf	3314	uGfaAfAfauUfcCfcGfaGfaAfaGfcsUfsu	3965
D-3301	GfcUfuUfcUfcGfgGfaAfuuUfUfcAfuUf	3315	uGfaaAfAfuUfcCfcGfaGfaAfaGfcsUfsu	3966
D-3302	GfcUfuUfcUfcGfgGfaAfuUfUfucAfuUf	3316	uGfAfaaAfuUfcCfcGfaGfaAfaGfcsUfsu	3967
D-3303	GfcUfuUfcUfcGfgGfaAfuUfuuCfAfuUf	3317	ugAfAfaAfuUfcCfcGfaGfaAfaGfcsUfsu	3968
D-3304	GfcUfuUfcUfcGfgGfaAfuUfuUfCfauUf	3318	UfgaAfaAfuUfcCfcGfaGfaAfaGfcsUfsu	3969
D-3305	GfcUfuUfcUfcGfgGfaAfuUfuUfcaUfUf	3319	UfGfaAfaAfuUfcCfcGfaGfaAfaGfcsUfsu	3970

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3306	GfCfuuUfCfucGfGfgaAfUfuuUfCfauUf	3320	UfgaAfAfauUfCfccGfAfgaAfAfgcsUfsUf	3971
D-3307	gcUfUfucUfCfggGfAfauUfUfucAfUfu	3321	uGfAfaaAfUfucCfCfgaGfAfaaGfCfsusu	3972
D-3308	GfcuUfUfcuCfGfggAfAfuuUfUfcaUfUf	3322	UfGfaaAfAfuuCfCfcgAfGfaaAfGfcsusUf	3973
D-3309	gCfUfuuCfUfcgGfGfaaUfUfuuCfAfuu	3323	ugAfAfaaUfUfccCfGfagAfAfagCfsUfsu	3974
D-3310	ccuccuGcuGcuuGuGGuudTsdT	3324	AACcAcAAGcAGcAGGAGGdTsdT	3975
D-3311	CfcUfcCfuGfCfUfGfCfuUfgUfgGfuUfuUf	3325	aAfcCfaCfaAfgcagcAfgGfaGfgsUfsu	3976
D-3312	CfcUfcCfuGfCfuGfCfuUfgUfgGfuUfuUf	3326	aAfcCfaCfaAfgcAfgcAfgGfaGfgsUfsu	3977
D-3313	CfcUfcCfuGfcuGfCfuUfgUfgGfuUfuUf	3327	aAfcCfaCfaAfgcAfGfcAfgGfaGfgsUfsu	3978
D-3314	CfcUfcCfuGfcUfGfCfUfUfgUfgGfuUfuUf	3328	aAfcCfaCfaagcaGfcAfgGfaGfgsUfsu	3979
D-3315	CfcUfcCfuGfcUfGfcUfUfgUfgGfuUfuUf	3329	aAfcCfaCfaaGfcaGfcAfgGfaGfgsUfsu	3980
D-3316	CfcUfcCfuGfcUfGfcuUfgUfgGfuUfuUf	3330	aAfcCfaCfaAfGfcaGfcAfgGfaGfgsUfsu	3981
D-3317	CfcUfcCfugCfUfgCfuUfgUfgGfuUfuUf	3331	aAfcCfaCfaAfgCfagCfAfgGfaGfgsUfsu	3982
D-3318	CfcUfcCfuGfcUfgCfUfugUfgGfuUfuUf	3332	aAfcCfaCfAfagCfaGfcAfgGfaGfgsUfsu	3983
D-3319	CfscsUfcCfugCfUfgCfuUfgUfgGfuUfuUf	3333	asAfscCfaCfaAfgCfagCfAfgGfaGfgsUfsu	3984
D-3320	CfcUfcCfugCfUfgCfuUfgUfgGfuUfuUf	3334	aAfcCfaCfaAfgCfagCfAfgGfaGfgUfu	3985
D-3321	CfscsUfcCfuGfcUfgCfUfugUfgGfuUfuUf	3335	asAfscCfaCfAfagCfaGfcAfgGfaGfgsUfsu	3986
D-3322	CfcUfcCfuGfcUfgCfUfugUfgGfuUfuUf	3336	aAfcCfaCfAfagCfaGfcAfgGfaGfgUfu	3987
D-3323	CfcUfcCfUfgcUfgCfuUfgUfgGfuUfuUf	3337	aAfcCfaCfaAfgCfaGfCfagGfaGfgsUfsu	3988
D-3324	CfcUfccUfGfcUfgCfuUfgUfgGfuUfuUf	3338	aAfcCfaCfaAfgCfaGfcaGfGfaGfgsUfsu	3989
D-3325	CfcUfCfcuGfcUfgCfuUfgUfgGfuUfuUf	3339	aAfcCfaCfaAfgCfaGfcAfGfgaGfgsUfsu	3990
D-3326	CfcuCfCfuGfcUfgCfuUfgUfgGfuUfuUf	3340	aAfcCfaCfaAfgCfaGfcAfggAfGfgsUfsu	3991
D-3327	CfCfucCfuGfcUfgCfuUfgUfgGfuUfuUf	3341	aAfcCfaCfaAfgCfaGfcAfgGfAfggsUfsu	3992
D-3328	cCfUfcCfuGfcUfgCfuUfgUfgGfuUfuUf	3342	aAfcCfaCfaAfgCfaGfcAfgGfagGfsUfsu	3993
D-3329	ccUfcCfuGfcUfgCfuUfgUfgGfuUfuUf	3343	aAfcCfaCfaAfgCfaGfcAfgGfaGfGfsusu	3994
D-3330	CfcUfcCfuGfcUfgCfuuGfUfgGfuUfuUf	3344	aAfcCfacAfAfgCfaGfcAfgGfaGfgsUfsu	3995
D-3331	CfcUfcCfuGfcUfgCfuUfGfugGfuUfuUf	3345	aAfcCfAfcaAfgCfaGfcAfgGfaGfgsUfsu	3996
D-3332	CfcUfcCfuGfcUfgCfuUfguGfGfuUfuUf	3346	aAfccAfCfaAfgCfaGfcAfgGfaGfgsUfsu	3997
D-3333	CfcUfcCfuGfcUfgCfuUfgUfGfguUfuUf	3347	aAfCfcaCfaAfgCfaGfcAfgGfaGfgsUfsu	3998
D-3334	CfcUfcCfuGfcUfgCfuUfgUfggUfUfuUf	3348	aaCfCfaCfaAfgCfaGfcAfgGfaGfgsUfsu	3999
D-3335	CfcUfcCfuGfcUfgCfuUfgUfgGfUfuuUf	3349	AfacCfaCfaAfgCfaGfcAfgGfaGfgsUfsu	4000
D-3336	CfcUfcCfuGfcUfgCfuUfgUfgGfuuUfUf	3350	AfAfcCfaCfaAfgCfaGfcAfgGfaGfgsUfsu	4001
D-3337	CfCfucCfUfgcUfGfcuUfGfugGfUfuuUf	3351	AfacCfAfcaAfGfcaGfCfagGfAfggsUfsUf	4002
D-3338	ccUfCfcuGfCfugCfUfugUfGfguUfUfu	3352	aAfCfcaCfAfagCfAfgcAfGfgaGfGfsusu	4003
D-3339	CfcuCfCfugCfUfgcUfUfguGfGfuuUfUf	3353	AfAfccAfCfaaGfCfagCfAfggAfGfgsusUf	4004
D-3340	cCfUfccUfGfcuGfCfuuGfUfggUfUfuu	3354	aaCfCfacAfAfgcAfGfcaGfGfagGfsUfsu	4005
D-3341	cuAucAuGAccAAGGAGuAdTsdT	3355	uACUCCUUGGUcAUGAuAGdTsdT	4006
D-3342	CfuAfuCfaUfGfAfCfCfaAfgGfaGfuAfuUf	3356	uAfcUfcCfuUfggucaUfgAfuAfgsUfsu	4007
D-3343	CfuAfuCfaUfGfaCfCfaAfgGfaGfuAfuUf	3357	uAfcUfcCfuUfggUfcaUfgAfuAfgsUfsu	4008
D-3344	CfuAfuCfaUfgaCfCfaAfgGfaGfuAfuUf	3358	uAfcUfcCfuUfggUfCfaUfgAfuAfgsUfsu	4009
D-3345	CfuAfuCfaUfgAfCfCfAfAfgGfaGfuAfuUf	3359	uAfcUfcCfuugguCfaUfgAfuAfgsUfsu	4010

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3346	CfuAfuCfaUfgAfCfcAfAfgGfaGfuAfuUf	3360	uAfcUfcCfuuGfguCfaUfgAfuAfgsUfsu	4011
D-3347	CfuAfuCfaUfgAfCfcaAfgGfaGfuAfuUf	3361	uAfcUfcCfuUfGfguCfaUfgAfuAfgsUfsu	4012
D-3348	CfuAfuCfauGfAfcCfaAfgGfaGfuAfuUf	3362	uAfcUfcCfuUfgGfucAfUfgAfuAfgsUfsu	4013
D-3349	CfuAfuCfaUfgAfcCfAfagGfaGfuAfuUf	3363	uAfcUfcCfUfugGfuCfaUfgAfuAfgsUfsu	4014
D-3350	CfsusAfuCfauGfAfcCfaAfgGfaGfuAfuUf	3364	usAfscUfcCfuUfgGfucAfUfgAfuAfgsUfsu	4015
D-3351	CfuAfuCfauGfAfcCfaAfgGfaGfuAfuUf	3365	uAfcUfcCfuUfgGfucAfUfgAfuAfgUfu	4016
D-3352	CfsusAfuCfaUfgAfcCfAfagGfaGfuAfuUf	3366	usAfscUfcCfUfugGfuCfaUfgAfuAfgsUfsu	4017
D-3353	CfuAfuCfaUfgAfcCfAfagGfaGfuAfuUf	3367	uAfcUfcCfUfugGfuCfaUfgAfuAfgUfu	4018
D-3354	CfuAfuCfAfugAfcCfaAfgGfaGfuAfuUf	3368	uAfcUfcCfuUfgGfuCfAfugAfuAfgsUfsu	4019
D-3355	CfuAfucAfUfgAfcCfaAfgGfaGfuAfuUf	3369	uAfcUfcCfuUfgGfuCfauGfAfuAfgsUfsu	4020
D-3356	CfuAfUfcaUfgAfcCfaAfgGfaGfuAfuUf	3370	uAfcUfcCfuUfgGfuCfaUfGfauAfgsUfsu	4021
D-3357	CfuaUfCfaUfgAfcCfaAfgGfaGfuAfuUf	3371	uAfcUfcCfuUfgGfuCfaUfgaUfAfgsUfsu	4022
D-3358	CfUfauCfaUfgAfcCfaAfgGfaGfuAfuUf	3372	uAfcUfcCfuUfgGfuCfaUfgAfUfagsUfsu	4023
D-3359	cUfAfuCfaUfgAfcCfaAfgGfaGfuAfuUf	3373	uAfcUfcCfuUfgGfuCfaUfgAfuaGfsUfsu	4024
D-3360	cuAfuCfaUfgAfcCfaAfgGfaGfuAfuUf	3374	uAfcUfcCfuUfgGfuCfaUfgAfuAfGfsusu	4025
D-3361	CfuAfuCfaUfgAfcCfaaGfGfaGfuAfuUf	3375	uAfcUfccUfUfgGfuCfaUfgAfuAfgsUfsu	4026
D-3362	CfuAfuCfaUfgAfcCfaAfGfgaGfuAfuUf	3376	uAfcUfCfcuUfgGfuCfaUfgAfuAfgsUfsu	4027
D-3363	CfuAfuCfaUfgAfcCfaAfggAfGfuAfuUf	3377	uAfcuCfCfuUfgGfuCfaUfgAfuAfgsUfsu	4028
D-3364	CfuAfuCfaUfgAfcCfaAfgGfAfguAfuUf	3378	uAfCfucCfuUfgGfuCfaUfgAfuAfgsUfsu	4029
D-3365	CfuAfuCfaUfgAfcCfaAfgGfagUfAfuUf	3379	uaCfUfcCfuUfgGfuCfaUfgAfuAfgsUfsu	4030
D-3366	CfuAfuCfaUfgAfcCfaAfgGfaGfUfauUf	3380	UfacUfcCfuUfgGfuCfaUfgAfuAfgsUfsu	4031
D-3367	CfuAfuCfaUfgAfcCfaAfgGfaGfuaUfUf	3381	UfAfcUfcCfuUfgGfuCfaUfgAfuAfgsUfsu	4032
D-3368	CfUfauCfAfugAfCfcaAfGfgaGfUfauUf	3382	UfacUfCfcuUfGfguCfAfugAfUfagsUfsUf	4033
D-3369	cuAfUfcaUfGfacCfAfagGfAfguAfUfu	3383	uAfCfucCfUfugGfUfcaUfGfauAfGfsusu	4034
D-3370	CfuaUfCfauGfAfccAfAfggAfGfuaUfUf	3384	UfAfcuCfCfuuGfGfucAfUfgaUfAfgsusUf	4035
D-3371	cUfAfucAfUfgaCfCfaaGfGfagUfAfuu	3385	uaCfUfccUfUfggUfCfauGfAfuaGfsUfsu	4036
D-3372	cGuccuGGGAGGAGcAGAAdTsdT	3386	UUCUGCUCCUCCcAGGACGdTsdT	4037
D-3373	CfgUfcCfuGfGfGfAfGfgAfgCfaGfaAfuUf	3387	uUfcUfgCfuCfcucccAfgGfaCfgsUfsu	4038
D-3374	CfgUfcCfuGfGfgAfGfgAfgCfaGfaAfuUf	3388	uUfcUfgCfuCfcuCfccAfgGfaCfgsUfsu	4039
D-3375	CfgUfcCfuGfggAfGfgAfgCfaGfaAfuUf	3389	uUfcUfgCfuCfcuCfCfcAfgGfaCfgsUfsu	4040
D-3376	CfgUfcCfuGfgGfAfGfGfAfgCfaGfaAfuUf	3390	uUfcUfgCfuccucCfcAfgGfaCfgsUfsu	4041
D-3377	CfgUfcCfuGfgGfAfgGfAfgCfaGfaAfuUf	3391	uUfcUfgCfucCfucCfcAfgGfaCfgsUfsu	4042
D-3378	CfgUfcCfuGfgGfAfggAfgCfaGfaAfuUf	3392	uUfcUfgCfuCfCfucCfcAfgGfaCfgsUfsu	4043
D-3379	CfgUfcCfugGfGfaGfgAfgCfaGfaAfuUf	3393	uUfcUfgCfuCfcUfccCfAfgGfaCfgsUfsu	4044
D-3380	CfgUfcCfuGfgGfaGfGfagCfaGfaAfuUf	3394	uUfcUfgCfUfccUfcCfcAfgGfaCfgsUfsu	4045
D-3381	CfsgsUfcCfugGfGfaGfgAfgCfaGfaAfuUf	3395	usUfscUfgCfuCfcUfccCfAfgGfaCfgsUfsu	4046
D-3382	CfgUfcCfugGfGfaGfgAfgCfaGfaAfuUf	3396	uUfcUfgCfuCfcUfccCfAfgGfaCfgUfu	4047
D-3383	CfsgsUfcCfuGfgGfaGfGfagCfaGfaAfuUf	3397	usUfscUfgCfUfccUfcCfcAfgGfaCfgsUfsu	4048
D-3384	CfgUfcCfuGfgGfaGfGfagCfaGfaAfuUf	3398	uUfcUfgCfUfccUfcCfcAfgGfaCfgUfu	4049
D-3385	CfgUfcCfUfggGfaGfgAfgCfaGfaAfuUf	3399	uUfcUfgCfuCfcUfcCfCfagGfaCfgsUfsu	4050

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3386	CfgUfccUfGfgGfaGfgAfgCfaGfaAfuUf	3400	uUfcUfgCfuCfcUfcCfcaGfGfaCfgsUfsu	4051
D-3387	CfgUfCfcuGfgGfaGfgAfgCfaGfaAfuUf	3401	uUfcUfgCfuCfcUfcCfcAfGfgaCfgsUfsu	4052
D-3388	CfguCfCfuGfgGfaGfgAfgCfaGfaAfuUf	3402	uUfcUfgCfuCfcUfcCfcAfggAfCfgsUfsu	4053
D-3389	CfGfucCfuGfgGfaGfgAfgCfaGfaAfuUf	3403	uUfcUfgCfuCfcUfcCfcAfgGfAfcgsUfsu	4054
D-3390	cGfUfcCfuGfgGfaGfgAfgCfaGfaAfuUf	3404	uUfcUfgCfuCfcUfcCfcAfgGfacGfsUfsu	4055
D-3391	cgUfcCfuGfgGfaGfgAfgCfaGfaAfuUf	3405	uUfcUfgCfuCfcUfcCfcAfgGfaCfGfsusu	4056
D-3392	CfgUfcCfuGfgGfaGfgaGfCfaGfaAfuUf	3406	uUfcUfgcUfCfcUfcCfcAfgGfaCfgsUfsu	4057
D-3393	CfgUfcCfuGfgGfaGfgAfGfcaGfaAfuUf	3407	uUfcUfGfcuCfcUfcCfcAfgGfaCfgsUfsu	4058
D-3394	CfgUfcCfuGfgGfaGfgAfgcAfGfaAfuUf	3408	uUfcuGfCfuCfcUfcCfcAfgGfaCfgsUfsu	4059
D-3395	CfgUfcCfuGfgGfaGfgAfgCfAfgaAfuUf	3409	uUfCfugCfuCfcUfcCfcAfgGfaCfgsUfsu	4060
D-3396	CfgUfcCfuGfgGfaGfgAfgCfagAfAfuUf	3410	uuCfUfgCfuCfcUfcCfcAfgGfaCfgsUfsu	4061
D-3397	CfgUfcCfuGfgGfaGfgAfgCfaGfAfauUf	3411	UfucUfgCfuCfcUfcCfcAfgGfaCfgsUfsu	4062
D-3398	CfgUfcCfuGfgGfaGfgAfgCfaGfaaUfUf	3412	UfUfcUfgCfuCfcUfcCfcAfgGfaCfgsUfsu	4063
D-3399	CfGfucCfUfggGfAfggAfGfcaGfAfauUf	3413	UfucUfGfcuCfCfucCfCfagGfAfcgsUfsUf	4064
D-3400	cgUfCfcuGfGfgaGfGfagCfAfgaAfUfu	3414	uUfCfugCfUfccUfCfccAfGfgaCfGfsusu	4065
D-3401	CfguCfCfugGfGfagGfAfgcAfGfaaUfUf	3415	UfUfcuGfCfucCfUfccCfAfggAfCfgsusUf	4066
D-3402	cGfUfccUfGfggAfGfgaGfCfagAfAfuu	3416	uuCfUfgcUfCfcuCfCfcaGfGfacGfsUfsu	4067
D-3403	cuGGGGGccucuucuGcuudTsdT	3417	AAGcAGAAGAGGCCCCcAGdTsdT	4068
D-3404	CfuGfgGfgGfCfCfUfCfuUfcUfgCfuUfuUf	3418	aAfgCfaGfaAfgaggcCfcCfcAfgsUfsu	4069
D-3405	CfuGfgGfgGfCfcUfCfuUfcUfgCfuUfuUf	3419	aAfgCfaGfaAfgaGfgcCfcCfcAfgsUfsu	4070
D-3406	CfuGfgGfgGfccUfCfuUfcUfgCfuUfuUf	3420	aAfgCfaGfaAfgaGfGfcCfcCfcAfgsUfsu	4071
D-3407	CfuGfgGfgGfcCfUfCfUfUfcUfgCfuUfuUf	3421	aAfgCfaGfaagagGfcCfcCfcAfgsUfsu	4072
D-3408	CfuGfgGfgGfcCfUfcUfUfcUfgCfuUfuUf	3422	aAfgCfaGfaaGfagGfcCfcCfcAfgsUfsu	4073
D-3409	CfuGfgGfgGfcCfUfcuUfcUfgCfuUfuUf	3423	aAfgCfaGfaAfGfagGfcCfcCfcAfgsUfsu	4074
D-3410	CfuGfgGfggCfCfuCfuUfcUfgCfuUfuUf	3424	aAfgCfaGfaAfgAfggCfCfcCfcAfgsUfsu	4075
D-3411	CfuGfgGfgGfcCfuCfUfucUfgCfuUfuUf	3425	aAfgCfaGfAfagAfgGfcCfcCfcAfgsUfsu	4076
D-3412	CfsusGfgGfggCfCfuCfuUfcUfgCfuUfuUf	3426	asAfsgCfaGfaAfgAfggCfCfcCfcAfgsUfsu	4077
D-3413	CfuGfgGfggCfCfuCfuUfcUfgCfuUfuUf	3427	aAfgCfaGfaAfgAfggCfCfcCfcAfgUfu	4078
D-3414	CfsusGfgGfgGfcCfuCfUfucUfgCfuUfuUf	3428	asAfsgCfaGfAfagAfgGfcCfcCfcAfgsUfsu	4079
D-3415	CfuGfgGfgGfcCfuCfUfucUfgCfuUfuUf	3429	aAfgCfaGfAfagAfgGfcCfcCfcAfgUfu	4080
D-3416	CfuGfgGfGfgcCfuCfuUfcUfgCfuUfuUf	3430	aAfgCfaGfaAfgAfgGfCfccCfcAfgsUfsu	4081
D-3417	CfuGfggGfGfcCfuCfuUfcUfgCfuUfuUf	3431	aAfgCfaGfaAfgAfgGfccCfCfcAfgsUfsu	4082
D-3418	CfuGfGfggGfcCfuCfuUfcUfgCfuUfuUf	3432	aAfgCfaGfaAfgAfgGfcCfCfccAfgsUfsu	4083
D-3419	CfugGfGfgGfcCfuCfuUfcUfgCfuUfuUf	3433	aAfgCfaGfaAfgAfgGfcCfccCfAfgsUfsu	4084
D-3420	CfUfggGfgGfcCfuCfuUfcUfgCfuUfuUf	3434	aAfgCfaGfaAfgAfgGfcCfcCfCfagsUfsu	4085
D-3421	cUfGfgGfgGfcCfuCfuUfcUfgCfuUfuUf	3435	aAfgCfaGfaAfgAfgGfcCfcCfcaGfsUfsu	4086
D-3422	cuGfgGfgGfcCfuCfuUfcUfgCfuUfuUf	3436	aAfgCfaGfaAfgAfgGfcCfcCfcAfGfsusu	4087
D-3423	CfuGfgGfgGfcCfuCfuuCfUfgCfuUfuUf	3437	aAfgCfagAfAfgAfgGfcCfcCfcAfgsUfsu	4088
D-3424	CfuGfgGfgGfcCfuCfuUfCfugCfuUfuUf	3438	aAfgCfAfgaAfgAfgGfcCfcCfcAfgsUfsu	4089
D-3425	CfuGfgGfgGfcCfuCfuUfcuGfCfuUfuUf	3439	aAfgcAfGfaAfgAfgGfcCfcCfcAfgsUfsu	4090

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3426	CfuGfgGfgGfcCfuCfuUfcUfGfcuUfuUf	3440	aAfGfcaGfaAfgAfgGfcCfcCfcAfgsUfsu	4091
D-3427	CfuGfgGfgGfcCfuCfuUfcUfgcUfUfuUf	3441	aaGfCfaGfaAfgAfgGfcCfcCfcAfgsUfsu	4092
D-3428	CfuGfgGfgGfcCfuCfuUfcUfgCfUfuuUf	3442	AfagCfaGfaAfgAfgGfcCfcCfcAfgsUfsu	4093
D-3429	CfuGfgGfgGfcCfuCfuUfcUfgCfuuUfUf	3443	AfAfgCfaGfaAfgAfgGfcCfcCfcAfgsUfsu	4094
D-3430	CfUfggGfGfgcCfUfcuUfCfugCfUfuuUf	3444	AfagCfAfgaAfGfagGfCfccCfCfagsUfsUf	4095
D-3431	cuGfGfggGfCfcuCfUfucUfGfcuUfUfu	3445	aAfGfcaGfAfagAfGfgcCfCfccAfGfsusu	4096
D-3432	CfugGfGfggCfCfucUfUfcuGfCfuuUfUf	3446	AfAfgcAfGfaaGfAfggCfCfccCfAfgsusUf	4097
D-3433	cUfGfggGfGfccUfCfuuCfUfgcUfUfuu	3447	aaGfCfagAfAfgaGfGfccCfCfcaGfsUfsu	4098
D-3434	ccuAucAuGAccAAGGAGudTsdT	3448	ACUCCUUGGUcAUGAuAGGdTsdT	4099
D-3435	CfcUfaUfcAfUfGfAfCfcAfaGfgAfgUfuUf	3449	aCfuCfcUfuGfgucauGfaUfaGfgsUfsu	4100
D-3436	CfcUfaUfcAfUfgAfCfcAfaGfgAfgUfuUf	3450	aCfuCfcUfuGfguCfauGfaUfaGfgsUfsu	4101
D-3437	CfcUfaUfcAfugAfCfcAfaGfgAfgUfuUf	3451	aCfuCfcUfuGfguCfAfuGfaUfaGfgsUfsu	4102
D-3438	CfcUfaUfcAfuGfAfCfCfAfaGfgAfgUfuUf	3452	aCfuCfcUfuggucAfuGfaUfaGfgsUfsu	4103
D-3439	CfcUfaUfcAfuGfAfcCfAfaGfgAfgUfuUf	3453	aCfuCfcUfugGfucAfuGfaUfaGfgsUfsu	4104
D-3440	CfcUfaUfcAfuGfAfccAfaGfgAfgUfuUf	3454	aCfuCfcUfuGfGfucAfuGfaUfaGfgsUfsu	4105
D-3441	CfcUfaUfcaUfGfaCfcAfaGfgAfgUfuUf	3455	aCfuCfcUfuGfgUfcaUfGfaUfaGfgsUfsu	4106
D-3442	CfcUfaUfcAfuGfaCfCfaaGfgAfgUfuUf	3456	aCfuCfcUfUfggUfcAfuGfaUfaGfgsUfsu	4107
D-3443	CfscsUfaUfcaUfGfaCfcAfaGfgAfgUfuUf	3457	asCfsuCfcUfuGfgUfcaUfGfaUfaGfgsUfsu	4108
D-3444	CfcUfaUfcaUfGfaCfcAfaGfgAfgUfuUf	3458	aCfuCfcUfuGfgUfcaUfGfaUfaGfgUfu	4109
D-3445	CfscsUfaUfcAfuGfaCfCfaaGfgAfgUfuUf	3459	asCfsuCfcUfUfggUfcAfuGfaUfaGfgsUfsu	4110
D-3446	CfcUfaUfcAfuGfaCfCfaaGfgAfgUfuUf	3460	aCfuCfcUfUfggUfcAfuGfaUfaGfgUfu	4111
D-3447	CfcUfaUfCfauGfaCfcAfaGfgAfgUfuUf	3461	aCfuCfcUfuGfgUfcAfUfgaUfaGfgsUfsu	4112
D-3448	CfcUfauCfAfuGfaCfcAfaGfgAfgUfuUf	3462	aCfuCfcUfuGfgUfcAfugAfUfaGfgsUfsu	4113
D-3449	CfcUfAfucAfuGfaCfcAfaGfgAfgUfuUf	3463	aCfuCfcUfuGfgUfcAfuGfAfuaGfgsUfsu	4114
D-3450	CfcuAfUfcAfuGfaCfcAfaGfgAfgUfuUf	3464	aCfuCfcUfuGfgUfcAfuGfauAfGfgsUfsu	4115
D-3451	CfCfuaUfcAfuGfaCfcAfaGfgAfgUfuUf	3465	aCfuCfcUfuGfgUfcAfuGfaUfAfggsUfsu	4116
D-3452	cCfUfaUfcAfuGfaCfcAfaGfgAfgUfuUf	3466	aCfuCfcUfuGfgUfcAfuGfaUfagGfsUfsu	4117
D-3453	ccUfaUfcAfuGfaCfcAfaGfgAfgUfuUf	3467	aCfuCfcUfuGfgUfcAfuGfaUfaGfGfsusu	4118
D-3454	CfcUfaUfcAfuGfaCfcaAfGfgAfgUfuUf	3468	aCfuCfcuUfGfgUfcAfuGfaUfaGfgsUfsu	4119
D-3455	CfcUfaUfcAfuGfaCfcAfAfggAfgUfuUf	3469	aCfuCfCfuuGfgUfcAfuGfaUfaGfgsUfsu	4120
D-3456	CfcUfaUfcAfuGfaCfcAfagGfAfgUfuUf	3470	aCfucCfUfuGfgUfcAfuGfaUfaGfgsUfsu	4121
D-3457	CfcUfaUfcAfuGfaCfcAfaGfGfagUfuUf	3471	aCfUfccUfuGfgUfcAfuGfaUfaGfgsUfsu	4122
D-3458	CfcUfaUfcAfuGfaCfcAfaGfgaGfUfuUf	3472	acUfCfcUfuGfgUfcAfuGfaUfaGfgsUfsu	4123
D-3459	CfcUfaUfcAfuGfaCfcAfaGfgAfGfuuUf	3473	AfcuCfcUfuGfgUfcAfuGfaUfaGfgsUfsu	4124
D-3460	CfcUfaUfcAfuGfaCfcAfaGfgAfguUfUf	3474	AfCfuCfcUfuGfgUfcAfuGfaUfaGfgsUfsu	4125
D-3461	CfCfuaUfCfauGfAfccAfAfggAfGfuuUf	3475	AfcuCfCfuuGfGfucAfUfgaUfAfggsUfsUf	4126
D-3462	ccUfAfucAfUfgaCfCfaaGfGfagUfUfu	3476	aCfUfccUfUfggUfCfauGfAfuaGfGfsusu	4127
D-3463	CfcuAfUfcaUfGfacCfAfagGfAfguUfUf	3477	AfCfucCfUfugGfUfcaUfGfauAfGfgsusUf	4128
D-3464	cCfUfauCfAfugAfCfcaAfGfgaGfUfuu	3478	acUfCfcuUfGfguCfAfugAfUfagGfsUfsu	4129
D-3465	uGuGGGAAGAAAGAuGAAGdTsdT	3479	CUUcAUCUUUCUUCCcAcAdTsdT	4130

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3466	UfgUfgGfgAfAfGfAfAfaGfaUfgAfaGfuUf	3480	cUfuCfaUfcUfuucuuCfcCfaCfasUfsu	4131
D-3467	UfgUfgGfgAfAfgAfAfaGfaUfgAfaGfuUf	3481	cUfuCfaUfcUfuuCfuuCfcCfaCfasUfsu	4132
D-3468	UfgUfgGfgAfagAfAfaGfaUfgAfaGfuUf	3482	cUfuCfaUfcUfuuCfUfuCfcCfaCfasUfsu	4133
D-3469	UfgUfgGfgAfaGfAfAfAfGfaUfgAfaGfuUf	3483	cUfuCfaUfcuuucUfuCfcCfaCfasUfsu	4134
D-3470	UfgUfgGfgAfaGfAfaAfGfaUfgAfaGfuUf	3484	cUfuCfaUfcuUfucUfuCfcCfaCfasUfsu	4135
D-3471	UfgUfgGfgAfaGfAfaaGfaUfgAfaGfuUf	3485	cUfuCfaUfcUfUfucUfuCfcCfaCfasUfsu	4136
D-3472	UfgUfgGfgaAfGfaAfaGfaUfgAfaGfuUf	3486	cUfuCfaUfcUfuUfcuUfCfcCfaCfasUfsu	4137
D-3473	UfgUfgGfgAfaGfaAfAfgaUfgAfaGfuUf	3487	cUfuCfaUfCfuuUfcUfuCfcCfaCfasUfsu	4138
D-3474	UfsgsUfgGfgaAfGfaAfaGfaUfgAfaGfuUf	3488	csUfsuCfaUfcUfuUfcuUfCfcCfaCfasUfsu	4139
D-3475	UfgUfgGfgaAfGfaAfaGfaUfgAfaGfuUf	3489	cUfuCfaUfcUfuUfcuUfCfcCfaCfaUfu	4140
D-3476	UfsgsUfgGfgAfaGfaAfAfgaUfgAfaGfuUf	3490	csUfsuCfaUfCfuuUfcUfuCfcCfaCfasUfsu	4141
D-3477	UfgUfgGfgAfaGfaAfAfgaUfgAfaGfuUf	3491	cUfuCfaUfCfuuUfcUfuCfcCfaCfaUfu	4142
D-3478	UfgUfgGfGfaaGfaAfaGfaUfgAfaGfuUf	3492	cUfuCfaUfcUfuUfcUfUfccCfaCfasUfsu	4143
D-3479	UfgUfggGfAfaGfaAfaGfaUfgAfaGfuUf	3493	cUfuCfaUfcUfuUfcUfucCfCfaCfasUfsu	4144
D-3480	UfgUfGfggAfaGfaAfaGfaUfgAfaGfuUf	3494	cUfuCfaUfcUfuUfcUfuCfCfcaCfasUfsu	4145
D-3481	UfguGfGfgAfaGfaAfaGfaUfgAfaGfuUf	3495	cUfuCfaUfcUfuUfcUfuCfccAfCfasUfsu	4146
D-3482	UfGfugGfgAfaGfaAfaGfaUfgAfaGfuUf	3496	cUfuCfaUfcUfuUfcUfuCfcCfAfcasUfsu	4147
D-3483	uGfUfgGfgAfaGfaAfaGfaUfgAfaGfuUf	3497	cUfuCfaUfcUfuUfcUfuCfcCfacAfsUfsu	4148
D-3484	ugUfgGfgAfaGfaAfaGfaUfgAfaGfuUf	3498	cUfuCfaUfcUfuUfcUfuCfcCfaCfAfsusu	4149
D-3485	UfgUfgGfgAfaGfaAfagAfUfgAfaGfuUf	3499	cUfuCfauCfUfuUfcUfuCfcCfaCfasUfsu	4150
D-3486	UfgUfgGfgAfaGfaAfaGfAfugAfaGfuUf	3500	cUfuCfAfucUfuUfcUfuCfcCfaCfasUfsu	4151
D-3487	UfgUfgGfgAfaGfaAfaGfauGfAfaGfuUf	3501	cUfucAfUfcUfuUfcUfuCfcCfaCfasUfsu	4152
D-3488	UfgUfgGfgAfaGfaAfaGfaUfGfaaGfuUf	3502	cUfUfcaUfcUfuUfcUfuCfcCfaCfasUfsu	4153
D-3489	UfgUfgGfgAfaGfaAfaGfaUfgaAfGfuUf	3503	cuUfCfaUfcUfuUfcUfuCfcCfaCfasUfsu	4154
D-3490	UfgUfgGfgAfaGfaAfaGfaUfgAfAfguUf	3504	CfuuCfaUfcUfuUfcUfuCfcCfaCfasUfsu	4155
D-3491	UfgUfgGfgAfaGfaAfaGfaUfgAfagUfUf	3505	CfUfuCfaUfcUfuUfcUfuCfcCfaCfasUfsu	4156
D-3492	UfGfugGfGfaaGfAfaaGfAfugAfAfguUf	3506	CfuuCfAfucUfUfucUfUfccCfAfcasUfsUf	4157
D-3493	ugUfGfggAfAfgaAfAfgaUfGfaaGfUfu	3507	cUfUfcaUfCfuuUfCfuuCfCfcaCfAfsusu	4158
D-3494	UfguGfGfgaAfGfaaAfGfauGfAfagUfUf	3508	CfUfucAfUfcuUfUfcuUfCfccAfCfasusUf	4159
D-3495	uGfUfggGfAfagAfAfagAfUfgaAfGfuu	3509	cuUfCfauCfUfuuCfUfucCfCfacAfsUfsu	4160
D-3496	AGGAcuGuGcccAcuucAcdTsdT	3510	GUGAAGUGGGcAcAGUCCUdTsdT	4161
D-3497	AfgGfaCfuGfUfGfCfCfcAfcUfuCfaCfuUf	3511	gUfgAfaGfuGfggcacAfgUfcCfusUfsu	4162
D-3498	AfgGfaCfuGfUfgCfCfcAfcUfuCfaCfuUf	3512	gUfgAfaGfuGfggCfacAfgUfcCfusUfsu	4163
D-3499	AfgGfaCfuGfugCfCfcAfcUfuCfaCfuUf	3513	gUfgAfaGfuGfggCfAfcAfgUfcCfusUfsu	4164
D-3500	AfgGfaCfuGfuGfCfCfCfAfcUfuCfaCfuUf	3514	gUfgAfaGfugggcAfcAfgUfcCfusUfsu	4165
D-3501	AfgGfaCfuGfuGfCfcCfAfcUfuCfaCfuUf	3515	gUfgAfaGfugGfgcAfcAfgUfcCfusUfsu	4166
D-3502	AfgGfaCfuGfuGfCfccAfcUfuCfaCfuUf	3516	gUfgAfaGfuGfGfgcAfcAfgUfcCfusUfsu	4167
D-3503	AfgGfaCfugUfGfcCfcAfcUfuCfaCfuUf	3517	gUfgAfaGfuGfgGfcaCfAfgUfcCfusUfsu	4168
D-3504	AfgGfaCfuGfuGfcCfCfacUfuCfaCfuUf	3518	gUfgAfaGfUfggGfcAfcAfgUfcCfusUfsu	4169
D-3505	AfsgsGfaCfugUfGfcCfcAfcUfuCfaCfuUf	3519	gsUfsgAfaGfuGfgGfcaCfAfgUfcCfusUfsu	4170

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3506	AfgGfaCfugUfGfcCfcAfcUfuCfaCfuUf	3520	gUfgAfaGfuGfgGfcaCfAfgUfcCfuUfu	4171
D-3507	AfsgsGfaCfuGfuGfcCfCfacUfuCfaCfuUf	3521	gsUfsgAfaGfUfggGfcAfcAfgUfcCfusUfsu	4172
D-3508	AfgGfaCfuGfuGfcCfCfacUfuCfaCfuUf	3522	gUfgAfaGfUfggGfcAfcAfgUfcCfuUfu	4173
D-3509	AfgGfaCfUfguGfcCfcAfcUfuCfaCfuUf	3523	gUfgAfaGfuGfgGfcAfCfagUfcCfusUfsu	4174
D-3510	AfgGfacUfGfuGfcCfcAfcUfuCfaCfuUf	3524	gUfgAfaGfuGfgGfcAfcaGfUfcCfusUfsu	4175
D-3511	AfgGfAfcuGfuGfcCfcAfcUfuCfaCfuUf	3525	gUfgAfaGfuGfgGfcAfcAfGfucCfusUfsu	4176
D-3512	AfggAfCfuGfuGfcCfcAfcUfuCfaCfuUf	3526	gUfgAfaGfuGfgGfcAfcAfguCfCfusUfsu	4177
D-3513	AfGfgaCfuGfuGfcCfcAfcUfuCfaCfuUf	3527	gUfgAfaGfuGfgGfcAfcAfgUfCfcusUfsu	4178
D-3514	aGfGfaCfuGfuGfcCfcAfcUfuCfaCfuUf	3528	gUfgAfaGfuGfgGfcAfcAfgUfccUfsUfsu	4179
D-3515	agGfaCfuGfuGfcCfcAfcUfuCfaCfuUf	3529	gUfgAfaGfuGfgGfcAfcAfgUfcCfUfsusu	4180
D-3516	AfgGfaCfuGfuGfcCfcaCfUfuCfaCfuUf	3530	gUfgAfagUfGfgGfcAfcAfgUfcCfusUfsu	4181
D-3517	AfgGfaCfuGfuGfcCfcAfCfuuCfaCfuUf	3531	gUfgAfAfguGfgGfcAfcAfgUfcCfusUfsu	4182
D-3518	AfgGfaCfuGfuGfcCfcAfcuUfCfaCfuUf	3532	gUfgaAfGfuGfgGfcAfcAfgUfcCfusUfsu	4183
D-3519	AfgGfaCfuGfuGfcCfcAfcUfUfcaCfuUf	3533	gUfGfaaGfuGfgGfcAfcAfgUfcCfusUfsu	4184
D-3520	AfgGfaCfuGfuGfcCfcAfcUfucAfCfuUf	3534	guGfAfaGfuGfgGfcAfcAfgUfcCfusUfsu	4185
D-3521	AfgGfaCfuGfuGfcCfcAfcUfuCfAfcuUf	3535	GfugAfaGfuGfgGfcAfcAfgUfcCfusUfsu	4186
D-3522	AfgGfaCfuGfuGfcCfcAfcUfuCfacUfUf	3536	GfUfgAfaGfuGfgGfcAfcAfgUfcCfusUfsu	4187
D-3523	AfGfgaCfUfguGfCfccAfCfuuCfAfcuUf	3537	GfugAfAfguGfGfgcAfCfagUfCfcusUfsUf	4188
D-3524	agGfAfcuGfUfgcCfCfacUfUfcaCfUfu	3538	gUfGfaaGfUfggGfCfacAfGfucCfUfsusu	4189
D-3525	AfggAfCfugUfGfccCfAfcuUfCfacUfUf	3539	GfUfgaAfGfugGfGfcaCfAfguCfCfususUf	4190
D-3526	aGfGfacUfGfugCfCfcaCfUfucAfCfuu	3540	guGfAfagUfGfggCfAfcaGfUfccUfsUfsu	4191
D-3527	GAuAGGGuGAuGuuccGAAdTsdT	3541	UUCGGAAcAUcACCCuAUCdTsdT	4192
D-3528	GfaUfaGfgGfUfGfAfUfgUfuCfcGfaAfuUf	3542	uUfcGfgAfaCfaucacCfcUfaUfcsUfsu	4193
D-3529	GfaUfaGfgGfUfgAfUfgUfuCfcGfaAfuUf	3543	uUfcGfgAfaCfauCfacCfcUfaUfcsUfsu	4194
D-3530	GfaUfaGfgGfugAfUfgUfuCfcGfaAfuUf	3544	uUfcGfgAfaCfauCfAfcCfcUfaUfcsUfsu	4195
D-3531	GfaUfaGfgGfuGfAfUfGfUfuCfcGfaAfuUf	3545	uUfcGfgAfacaucAfcCfcUfaUfcsUfsu	4196
D-3532	GfaUfaGfgGfuGfAfuGfUfuCfcGfaAfuUf	3546	uUfcGfgAfacAfucAfcCfcUfaUfcsUfsu	4197
D-3533	GfaUfaGfgGfuGfAfugUfuCfcGfaAfuUf	3547	uUfcGfgAfaCfAfucAfcCfcUfaUfcsUfsu	4198
D-3534	GfaUfaGfggUfGfaUfgUfuCfcGfaAfuUf	3548	uUfcGfgAfaCfaUfcaCfCfcUfaUfcsUfsu	4199
D-3535	GfaUfaGfgGfuGfaUfGfuuCfcGfaAfuUf	3549	uUfcGfgAfAfcaUfcAfcCfcUfaUfcsUfsu	4200
D-3536	GfsasUfaGfggUfGfaUfgUfuCfcGfaAfuUf	3550	usUfscGfgAfaCfaUfcaCfCfcUfaUfcsUfsu	4201
D-3537	GfaUfaGfggUfGfaUfgUfuCfcGfaAfuUf	3551	uUfcGfgAfaCfaUfcaCfCfcUfaUfcUfu	4202
D-3538	GfsasUfaGfgGfuGfaUfGfuuCfcGfaAfuUf	3552	usUfscGfgAfAfcaUfcAfcCfcUfaUfcsUfsu	4203
D-3539	GfaUfaGfgGfuGfaUfGfuuCfcGfaAfuUf	3553	uUfcGfgAfAfcaUfcAfcCfcUfaUfcUfu	4204
D-3540	GfaUfaGfGfguGfaUfgUfuCfcGfaAfuUf	3554	uUfcGfgAfaCfaUfcAfCfccUfaUfcsUfsu	4205
D-3541	GfaUfagGfGfuGfaUfgUfuCfcGfaAfuUf	3555	uUfcGfgAfaCfaUfcAfccCfUfaUfcsUfsu	4206
D-3542	GfaUfAfggGfuGfaUfgUfuCfcGfaAfuUf	3556	uUfcGfgAfaCfaUfcAfcCfCfuaUfcsUfsu	4207
D-3543	GfauAfGfgGfuGfaUfgUfuCfcGfaAfuUf	3557	uUfcGfgAfaCfaUfcAfcCfcuAfUfcsUfsu	4208
D-3544	GfAfuaGfgGfuGfaUfgUfuCfcGfaAfuUf	3558	uUfcGfgAfaCfaUfcAfcCfcUfAfucsUfsu	4209
D-3545	gAfUfaGfgGfuGfaUfgUfuCfcGfaAfuUf	3559	uUfcGfgAfaCfaUfcAfcCfcUfauCfsUfsu	4210

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3546	gaUfaGfgGfuGfaUfgUfuCfcGfaAfuUf	3560	uUfcGfgAfaCfaUfcAfcCfcUfaUfCfsusu	4211
D-3547	GfaUfaGfgGfuGfaUfguUfCfcGfaAfuUf	3561	uUfcGfgaAfCfaUfcAfcCfcUfaUfcsUfsu	4212
D-3548	GfaUfaGfgGfuGfaUfgUfUfccGfaAfuUf	3562	uUfcGfGfaaCfaUfcAfcCfcUfaUfcsUfsu	4213
D-3549	GfaUfaGfgGfuGfaUfgUfucCfGfaAfuUf	3563	uUfcgGfAfaCfaUfcAfcCfcUfaUfcsUfsu	4214
D-3550	GfaUfaGfgGfuGfaUfgUfuCfCfgaAfuUf	3564	uUfCfggAfaCfaUfcAfcCfcUfaUfcsUfsu	4215
D-3551	GfaUfaGfgGfuGfaUfgUfuCfcgAfAfuUf	3565	uuCfGfgAfaCfaUfcAfcCfcUfaUfcsUfsu	4216
D-3552	GfaUfaGfgGfuGfaUfgUfuCfcGfAfauUf	3566	UfucGfgAfaCfaUfcAfcCfcUfaUfcsUfsu	4217
D-3553	GfaUfaGfgGfuGfaUfgUfuCfcGfaaUfUf	3567	UfUfcGfgAfaCfaUfcAfcCfcUfaUfcsUfsu	4218
D-3554	GfAfuaGfGfguGfAfugUfUfccGfAfauUf	3568	UfucGfGfaaCfAfucAfCfccUfAfucsUfsUf	4219
D-3555	gaUfAfggGfUfgaUfGfuuCfCfgaAfUfu	3569	uUfCfggAfAfcaUfCfacCfCfuaUfCfsusu	4220
D-3556	GfauAfGfggUfGfauGfUfucCfGfaaUfUf	3570	UfUfcgGfAfacAfUfcaCfCfcuAfUfcsusUf	4221
D-3557	gAfUfagGfGfugAfUfguUfCfcgAfAfuu	3571	uuCfGfgaAfCfauCfAfccCfUfauCfsUfsu	4222
D-3558	GcAGuuuGcAGGuuAucAudTsdT	3572	AUGAuAACCUGcAAACUGCdTsdT	4223
D-3559	GfcAfgUfuUfGfCfAfGfgUfuAfuCfaUfuUf	3573	aUfgAfuAfaCfcugcaAfaCfuGfcsUfsu	4224
D-3560	GfcAfgUfuUfGfcAfGfgUfuAfuCfaUfuUf	3574	aUfgAfuAfaCfcuGfcaAfaCfuGfcsUfsu	4225
D-3561	GfcAfgUfuUfgcAfGfgUfuAfuCfaUfuUf	3575	aUfgAfuAfaCfcuGfCfaAfaCfuGfcsUfsu	4226
D-3562	GfcAfgUfuUfgCfAfGfGfUfuAfuCfaUfuUf	3576	aUfgAfuAfaccugCfaAfaCfuGfcsUfsu	4227
D-3563	GfcAfgUfuUfgCfAfgGfUfuAfuCfaUfuUf	3577	aUfgAfuAfacCfugCfaAfaCfuGfcsUfsu	4228
D-3564	GfcAfgUfuUfgCfAfggUfuAfuCfaUfuUf	3578	aUfgAfuAfaCfCfugCfaAfaCfuGfcsUfsu	4229
D-3565	GfcAfgUfuuGfCfaGfgUfuAfuCfaUfuUf	3579	aUfgAfuAfaCfcUfgcAfAfaCfuGfcsUfsu	4230
D-3566	GfcAfgUfuUfgCfaGfGfuuAfuCfaUfuUf	3580	aUfgAfuAfAfccUfgCfaAfaCfuGfcsUfsu	4231
D-3567	GfscsAfgUfuuGfCfaGfgUfuAfuCfaUfuUf	3581	asUfsgAfuAfaCfcUfgcAfAfaCfuGfcsUfsu	4232
D-3568	GfcAfgUfuuGfCfaGfgUfuAfuCfaUfuUf	3582	aUfgAfuAfaCfcUfgcAfAfaCfuGfcUfu	4233
D-3569	GfscsAfgUfuUfgCfaGfGfuuAfuCfaUfuUf	3583	asUfsgAfuAfAfccUfgCfaAfaCfuGfcsUfsu	4234
D-3570	GfcAfgUfuUfgCfaGfGfuuAfuCfaUfuUf	3584	aUfgAfuAfAfccUfgCfaAfaCfuGfcUfu	4235
D-3571	GfcAfgUfUfugCfaGfgUfuAfuCfaUfuUf	3585	aUfgAfuAfaCfcUfgCfAfaaCfuGfcsUfsu	4236
D-3572	GfcAfguUfUfgCfaGfgUfuAfuCfaUfuUf	3586	aUfgAfuAfaCfcUfgCfaaAfCfuGfcsUfsu	4237
D-3573	GfcAfGfuuUfgCfaGfgUfuAfuCfaUfuUf	3587	aUfgAfuAfaCfcUfgCfaAfAfcuGfcsUfsu	4238
D-3574	GfcaGfUfuUfgCfaGfgUfuAfuCfaUfuUf	3588	aUfgAfuAfaCfcUfgCfaAfacUfGfcsUfsu	4239
D-3575	GfCfagUfuUfgCfaGfgUfuAfuCfaUfuUf	3589	aUfgAfuAfaCfcUfgCfaAfaCfUfgcsUfsu	4240
D-3576	gCfAfgUfuUfgCfaGfgUfuAfuCfaUfuUf	3590	aUfgAfuAfaCfcUfgCfaAfaCfugCfsUfsu	4241
D-3577	gcAfgUfuUfgCfaGfgUfuAfuCfaUfuUf	3591	aUfgAfuAfaCfcUfgCfaAfaCfuGfCfsusu	4242
D-3578	GfcAfgUfuUfgCfaGfguUfAfuCfaUfuUf	3592	aUfgAfuaAfCfcUfgCfaAfaCfuGfcsUfsu	4243
D-3579	GfcAfgUfuUfgCfaGfgUfUfauCfaUfuUf	3593	aUfgAfUfaaCfcUfgCfaAfaCfuGfcsUfsu	4244
D-3580	GfcAfgUfuUfgCfaGfgUfuaUfCfaUfuUf	3594	aUfgaUfAfaCfcUfgCfaAfaCfuGfcsUfsu	4245
D-3581	GfcAfgUfuUfgCfaGfgUfuAfUfcaUfuUf	3595	aUfGfauAfaCfcUfgCfaAfaCfuGfcsUfsu	4246
D-3582	GfcAfgUfuUfgCfaGfgUfuAfucAfUfuUf	3596	auGfAfuAfaCfcUfgCfaAfaCfuGfcsUfsu	4247
D-3583	GfcAfgUfuUfgCfaGfgUfuAfuCfAfuuUf	3597	AfugAfuAfaCfcUfgCfaAfaCfuGfcsUfsu	4248
D-3584	GfcAfgUfuUfgCfaGfgUfuAfuCfauUfUf	3598	AfUfgAfuAfaCfcUfgCfaAfaCfuGfcsUfsu	4249
D-3585	GfCfagUfUfugCfAfggUfUfauCfAfuuUf	3599	AfugAfUfaaCfCfugCfAfaaCfUfgcsUfsUf	4250

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3586	gcAfGfuuUfGfcaGfGfuuAfUfcaUfUfu	3600	aUfGfauAfAfccUfGfcaAfAfcuGfCfsusu	4251
D-3587	GfcaGfUfuuGfCfagGfUfuaUfCfauUfUf	3601	AfUfgaUfAfacCfUfgcAfAfacUfGfcsusUf	4252
D-3588	gCfAfguUfUfgcAfGfguUfAfucAfUfuu	3602	auGfAfuaAfCfcuGfCfaaAfCfugCfsUfsu	4253
D-3589	GGuuGucuGuGuGAucGGAdTsdT	3603	UCCGAUcAcAcAGAcAACCdTsdT	4254
D-3590	GfgUfuGfuCfUfGfUfGfuGfaUfcGfgAfuUf	3604	uCfcGfaUfcAfcacagAfcAfaCfcsUfsu	4255
D-3591	GfgUfuGfuCfUfgUfGfuGfaUfcGfgAfuUf	3605	uCfcGfaUfcAfcaCfagAfcAfaCfcsUfsu	4256
D-3592	GfgUfuGfuCfugUfGfuGfaUfcGfgAfuUf	3606	uCfcGfaUfcAfcaCfAfgAfcAfaCfcsUfsu	4257
D-3593	GfgUfuGfuCfuGfUfGfUfGfaUfcGfgAfuUf	3607	uCfcGfaUfcacacAfgAfcAfaCfcsUfsu	4258
D-3594	GfgUfuGfuCfuGfUfgUfGfaUfcGfgAfuUf	3608	uCfcGfaUfcaCfacAfgAfcAfaCfcsUfsu	4259
D-3595	GfgUfuGfuCfuGfUfguGfaUfcGfgAfuUf	3609	uCfcGfaUfcAfCfacAfgAfcAfaCfcsUfsu	4260
D-3596	GfgUfuGfucUfGfuGfuGfaUfcGfgAfuUf	3610	uCfcGfaUfcAfcAfcaGfAfcAfaCfcsUfsu	4261
D-3597	GfgUfuGfuCfuGfuGfUfgaUfcGfgAfuUf	3611	uCfcGfaUfCfacAfcAfgAfcAfaCfcsUfsu	4262
D-3598	GfsgsUfuGfucUfGfuGfuGfaUfcGfgAfuUf	3612	usCfscGfaUfcAfcAfcaGfAfcAfaCfcsUfsu	4263
D-3599	GfgUfuGfucUfGfuGfuGfaUfcGfgAfuUf	3613	uCfcGfaUfcAfcAfcaGfAfcAfaCfcUfu	4264
D-3600	GfsgsUfuGfuCfuGfuGfUfgaUfcGfgAfuUf	3614	usCfscGfaUfCfacAfcAfgAfcAfaCfcsUfsu	4265
D-3601	GfgUfuGfuCfuGfuGfUfgaUfcGfgAfuUf	3615	uCfcGfaUfCfacAfcAfgAfcAfaCfcUfu	4266
D-3602	GfgUfuGfUfcuGfuGfuGfaUfcGfgAfuUf	3616	uCfcGfaUfcAfcAfcAfGfacAfaCfcsUfsu	4267
D-3603	GfgUfugUfCfuGfuGfuGfaUfcGfgAfuUf	3617	uCfcGfaUfcAfcAfcAfgaCfAfaCfcsUfsu	4268
D-3604	GfgUfUfguCfuGfuGfuGfaUfcGfgAfuUf	3618	uCfcGfaUfcAfcAfcAfgAfCfaaCfcsUfsu	4269
D-3605	GfguUfGfuCfuGfuGfuGfaUfcGfgAfuUf	3619	uCfcGfaUfcAfcAfcAfgAfcaAfCfcsUfsu	4270
D-3606	GfGfuuGfuCfuGfuGfuGfaUfcGfgAfuUf	3620	uCfcGfaUfcAfcAfcAfgAfcAfAfccsUfsu	4271
D-3607	gGfUfuGfuCfuGfuGfuGfaUfcGfgAfuUf	3621	uCfcGfaUfcAfcAfcAfgAfcAfacCfsUfsu	4272
D-3608	ggUfuGfuCfuGfuGfuGfaUfcGfgAfuUf	3622	uCfcGfaUfcAfcAfcAfgAfcAfaCfCfsusu	4273
D-3609	GfgUfuGfuCfuGfuGfugAfUfcGfgAfuUf	3623	uCfcGfauCfAfcAfcAfgAfcAfaCfcsUfsu	4274
D-3610	GfgUfuGfuCfuGfuGfuGfAfucGfgAfuUf	3624	uCfcGfAfucAfcAfcAfgAfcAfaCfcsUfsu	4275
D-3611	GfgUfuGfuCfuGfuGfuGfauCfGfgAfuUf	3625	uCfcgAfUfcAfcAfcAfgAfcAfaCfcsUfsu	4276
D-3612	GfgUfuGfuCfuGfuGfuGfaUfCfggAfuUf	3626	uCfCfgaUfcAfcAfcAfgAfcAfaCfcsUfsu	4277
D-3613	GfgUfuGfuCfuGfuGfuGfaUfcgGfAfuUf	3627	ucCfGfaUfcAfcAfcAfgAfcAfaCfcsUfsu	4278
D-3614	GfgUfuGfuCfuGfuGfuGfaUfcGfGfauUf	3628	UfccGfaUfcAfcAfcAfgAfcAfaCfcsUfsu	4279
D-3615	GfgUfuGfuCfuGfuGfuGfaUfcGfgaUfUf	3629	UfCfcGfaUfcAfcAfcAfgAfcAfaCfcsUfsu	4280
D-3616	GfGfuuGfUfcuGfUfguGfAfucGfGfauUf	3630	UfccGfAfucAfCfacAfGfacAfAfccsUfsUf	4281
D-3617	ggUfUfguCfUfguGfUfgaUfCfggAfUfu	3631	uCfCfgaUfCfacAfCfagAfCfaaCfCfsusu	4282
D-3618	GfguUfGfucUfGfugUfGfauCfGfgaUfUf	3632	UfCfcgAfUfcaCfAfcaGfAfcaAfCfcsusUf	4283
D-3619	gGfUfugUfCfugUfGfugAfUfcgGfAfuu	3633	ucCfGfauCfAfcaCfAfgaCfAfacCfsUfsu	4284
D-3620	cGGAcuAcGAGAcGGGcuudTsdT	3634	AAGCCCGUCUCGuAGUCCGdTsdT	4285
D-3621	CfgGfaCfuAfCfGfAfGfaCfgGfgCfuUfuUf	3635	aAfgCfcCfgUfcucguAfgUfcCfgsUfsu	4286
D-3622	CfgGfaCfuAfCfgAfGfaCfgGfgCfuUfuUf	3636	aAfgCfcCfgUfcuCfguAfgUfcCfgsUfsu	4287
D-3623	CfgGfaCfuAfcgAfGfaCfgGfgCfuUfuUf	3637	aAfgCfcCfgUfcuCfGfuAfgUfcCfgsUfsu	4288
D-3624	CfgGfaCfuAfcGfAfGfAfCfgGfgCfuUfuUf	3638	aAfgCfcCfgucucGfuAfgUfcCfgsUfsu	4289
D-3625	CfgGfaCfuAfcGfAfgAfCfgGfgCfuUfuUf	3639	aAfgCfcCfguCfucGfuAfgUfcCfgsUfsu	4290

Duplex No.	Sense Sequence (5′-3′)	SEQ ID NO: (sense)	Antisense Sequence (5′-3′)	SEQ ID NO: (antisense)
D-3626	CfgGfaCfuAfcGfAfgaCfgGfgCfuUfuUf	3640	aAfgCfcCfgUfCfucGfuAfgUfcCfgsUfsu	4291
D-3627	CfgGfaCfuaCfGfaGfaCfgGfgCfuUfuUf	3641	aAfgCfcCfgUfcUfcgUfAfgUfcCfgsUfsu	4292
D-3628	CfgGfaCfuAfcGfaGfAfcgGfgCfuUfuUf	3642	aAfgCfcCfGfucUfcGfuAfgUfcCfgsUfsu	4293
D-3629	CfsgsGfaCfuaCfGfaGfaCfgGfgCfuUfuUf	3643	asAfsgCfcCfgUfcUfcgUfAfgUfcCfgsUfsu	4294
D-3630	CfgGfaCfuaCfGfaGfaCfgGfgCfuUfuUf	3644	aAfgCfcCfgUfcUfcgUfAfgUfcCfgUfu	4295
D-3631	CfsgsGfaCfuAfcGfaGfAfcgGfgCfuUfuUf	3645	asAfsgCfcCfGfucUfcGfuAfgUfcCfgsUfsu	4296
D-3632	CfgGfaCfuAfcGfaGfAfcgGfgCfuUfuUf	3646	aAfgCfcCfGfucUfcGfuAfgUfcCfgUfu	4297
D-3633	CfgGfaCfUfacGfaGfaCfgGfgCfuUfuUf	3647	aAfgCfcCfgUfcUfcGfUfagUfcCfgsUfsu	4298
D-3634	CfgGfacUfAfcGfaGfaCfgGfgCfuUfuUf	3648	aAfgCfcCfgUfcUfcGfuaGfUfcCfgsUfsu	4299
D-3635	CfgGfAfcuAfcGfaGfaCfgGfgCfuUfuUf	3649	aAfgCfcCfgUfcUfcGfuAfGfucCfgsUfsu	4300
D-3636	CfggAfCfuAfcGfaGfaCfgGfgCfuUfuUf	3650	aAfgCfcCfgUfcUfcGfuAfguCfCfgsUfsu	4301
D-3637	CfGfgaCfuAfcGfaGfaCfgGfgCfuUfuUf	3651	aAfgCfcCfgUfcUfcGfuAfgUfCfcgsUfsu	4302
D-3638	cGfGfaCfuAfcGfaGfaCfgGfgCfuUfuUf	3652	aAfgCfcCfgUfcUfcGfuAfgUfccGfsUfsu	4303
D-3639	cgGfaCfuAfcGfaGfaCfgGfgCfuUfuUf	3653	aAfgCfcCfgUfcUfcGfuAfgUfcCfGfsusu	4304
D-3640	CfgGfaCfuAfcGfaGfacGfGfgCfuUfuUf	3654	aAfgCfccGfUfcUfcGfuAfgUfcCfgsUfsu	4305
D-3641	CfgGfaCfuAfcGfaGfaCfGfggCfuUfuUf	3655	aAfgCfCfcgUfcUfcGfuAfgUfcCfgsUfsu	4306
D-3642	CfgGfaCfuAfcGfaGfaCfggGfCfuUfuUf	3656	aAfgcCfCfgUfcUfcGfuAfgUfcCfgsUfsu	4307
D-3643	CfgGfaCfuAfcGfaGfaCfgGfGfcuUfuUf	3657	aAfGfccCfgUfcUfcGfuAfgUfcCfgsUfsu	4308
D-3644	CfgGfaCfuAfcGfaGfaCfgGfgcUfUfuUf	3658	aaGfCfcCfgUfcUfcGfuAfgUfcCfgsUfsu	4309
D-3645	CfgGfaCfuAfcGfaGfaCfgGfgCfUfuuUf	3659	AfagCfcCfgUfcUfcGfuAfgUfcCfgsUfsu	4310
D-3646	CfgGfaCfuAfcGfaGfaCfgGfgCfuuUfUf	3660	AfAfgCfcCfgUfcUfcGfuAfgUfcCfgsUfsu	4311
D-3647	CfGfgaCfUfacGfAfgaCfGfggCfUfuuUf	3661	AfagCfCfcgUfCfucGfUfagUfCfcgsUfsUf	4312
D-3648	cgGfAfcuAfCfgaGfAfcgGfGfcuUfUfu	3662	aAfGfccCfGfucUfCfguAfGfucCfGfsusu	4313
D-3649	CfggAfCfuaCfGfagAfCfggGfCfuuUfUf	3663	AfAfgcCfCfguCfUfcgUfAfguCfCfgsusUf	4314
D-3650	cGfGfacUfAfcgAfGfacGfGfgcUfUfuu	3664	aaGfCfccGfUfcuCfGfuaGfUfccGfsUfsu	4315

[0201] Synthesis of chemically modified siRNA sequences was performed on the GE AKTA OligoPilot 100.

Materials:

[0202] Acetonitrile (DNA Synthesis Grade, AXO152-2505, EMD)

[0203] Capping Reagent A (20% N-methylimidazole in acetonitrile, BI0224-0505, EMD, Lot# 56090)

[0204] Capping Reagent B1 (20% acetic anhydride in acetonitrile, BI0347-0505, EMD, Lot# 55015)

[0205] Capping Reagent B2 (30% 2,6-lutidine in aceotnitrile, BI0349-0505, EMD, Lot# 55176)

[0206] Capping Reagent B1 and B2 were mixed together 1:1 (v/v).

[0207] Activator (0.3 M benzylthiotetrazole (BTT) in acetonitrile, BI0166-1005, EMD Lot# 55106, over molecular sieves)

[0208] Detritylation Reagent (3% dichloroacetic acid in toluene, BIO832-2505, EMD, Lot# 55316)

[0209] Oxidation Reagent (0.05 M iodine in 90:10 pyridine/water, BIO424-1005, EMD, Lot# 54323)

[0210] Diethylamine solution (20% DEA in acetonitrile, NC0017-0505, EMD, Lot# 55202)

[0211] Ammonium hydroxide (concentrated, J. T. Baker)

[0212] Thiolation Reagent, 0.2 M phenylacetic disulfide (PADS, Aldrich) in 50:50 2-methylpyridine (picoline, Aldrich)/N-methylpyrrolidinone (NMP), Aldrich)

[0213] Thymidine (Thermo Fisher Scientific) and 2′-O-methyl and 2′-fluoro phosphoramidites of adenosine, guanosine, cytosine, and uridine (Thermo Fisher Scientific), 0.15 M in acetonitrile over ~10 mL of molecular sieves (J. T. Baker)

[0214] Primer Support 5G UnyLinker 350, Lot# 10236161, 343 μmol/g, 0.60 g (206 μmol) or Primer Support 5G Amino with GalNAc cluster

Synthesis:

[0215] Reagent solutions, phosphoramidite solutions, and solvents were attached to the instrument. Solid support was added to the column (6.3 mL), and the column was affixed to the instrument. The column was flushed with acetonitrile. The synthesis was started using the Unicorn software. The phosphoramidite and reagent solution lines were purged. The synthesis was accomplished by repetition of the deprotection/coupling/ oxidation /capping synthesis cycle. To the solid support was added detritylation reagent to remove the 5′-dimethoxytrityl (DMT) protecting group. The solid support was washed with acetonitrile. To the support was added phosphoramidite and activator solution followed by recycling to couple the incoming nucleotide to the free 5′-hydroxyl group. The support was washed with acetonitrile. To the support was added oxidation or thiolation reagent to convert the phosphite triester to the phosphate triester or phosphorothioate. To the support was added capping reagents A and B to terminate any unreacted oligonucleotide chains. The support was washed with acetonitrile. After the final

reaction cycle, the resin was washed with diethylamine solution to remove the 2-cyanoethyl protecting groups. The support was washed with acetonitrile.

Cleavage:

[0216] The synthesis column was removed from the synthesizer and dried under vacuum for 20 minutes. The column was opened, and the solid support was transferred to a 100 mL bottle. To the solid support was added 40 mL of concentrated ammonium hydroxide. The cap was tightly affixed to the bottle, and the mixture was heated at 65°C overnight. The bottle was moved to the freezer and cooled for 20 minutes before opening in the hood. The mixture was filtered through a 60 mL M fritted glass funnel. The bottle and solid support were rinsed with 20 mL of 50:50 ethanol/water and then 40 mL of water.

Analysis and Purification:

[0217] A portion of the combined filtrate was analyzed and purified by anion exchange chromatography. The pooled fractions were desalted by size exclusion chromatography and analyzed by ion pair-reversed phase HPLC. The pooled fractions were lyophilized to obtain a white amorphous powder.

Analytical anion exchange chromatography (AEX):

[0218] Column: Thermo DNAPac PA200RS (4.6 x 50 mm, 4μm)

[0219] Instrument: Agilent 1100 HPLC

[0220] Buffer A: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5

[0221] Buffer B: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5, 1 M sodium bromide

[0222] Flow rate: 1 mL/min at 40°C

[0223] Gradient: 20-65% B in 6.2 min

Preparative anion exchange chromatography (AEX):

[0224] Column: Tosoh TSK Gel SuperQ-5PW, 21 x 150 mm, 13 μm

[0225] Instrument: Agilent 1200 HPLC

[0226] Buffer A: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5

[0227] Buffer B: 20 mM sodium phosphate, 10% acetonitrile, pH 8.5, 1 M sodium bromide

[0228] Flow rate: 8 mL/min

[0229] Injection volume: 5 mL

[0230] Gradient: 35-55% B over 20 min

Preparative size exclusion chromatography (SEC):

[0231] Column: GE Hi-Prep 26/10

[0232] Instrument: GE AKTA Pure

[0233] Buffer: 20% ethanol in water

[0234] Flow Rate: 10 mL/min

[0235] Injection volume: 15 mL using sample loading pump

Ion Pair-Reversed Phase (IP-RP) HPLC:

[0236] Column: Water Xbridge BEH OST C18, 2.5 μm, 2.1 x 50 mm

[0237] Instrument: Agilent 1100 HPLC

[0238] Buffer A: 15.7 mM DIEA, 50 mM HFIP in water

[0239] Buffer B: 15.7 mM DIEA, 50 mM HFIP in 50:50 water/acetonitrile

[0240] Flow rate: 0.5 mL/min

[0241] Gradient: 10-30% B over 6 min

Annealing:

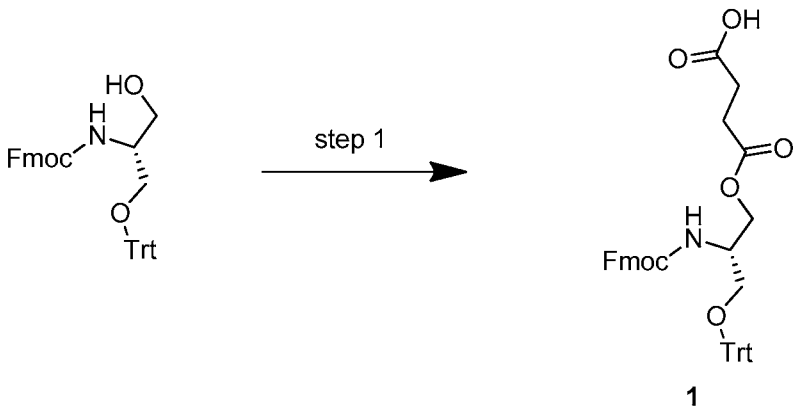
[0242] A small amount of the sense strand and the antisense strand were weighed into individual vials. To the vials was added siRNA reconstitution buffer (Qiagen) to an approximate concentration of 2 mM based on the dry weight. The actual sample concentration was measured on the NanoDrop One (ssDNA, extinction coefficient = 33 μg/OD260). The two strands were then mixed in an equimolar ratio, and the sample was heated for 3 minutes in a 90°C water bath and allowed to cool slowly to room temperature. The sample was analyzed by AEX. The RNA duplex was observed to have a longer retention time by analytical AEX than the single strands. The duplex was registered and submitted for *in vitro* (see methods described in Examples 2 and 3) and *in vivo* (see methods described in Example 6) testing.

Example 5. Synthesis of GalNAc-containing Ligand

[0243] This example describes the synthesis of a tetravalent GalNAc moiety, which can be conjugated to the double-stranded RNA molecules in the RNAi constructs of the invention to facilitate delivery and uptake of the RNAi constructs by the liver (e.g. hepatocytes). The synthetic scheme is depicted in Figure 5.

Resin-bound Tetraantennary GalNAc

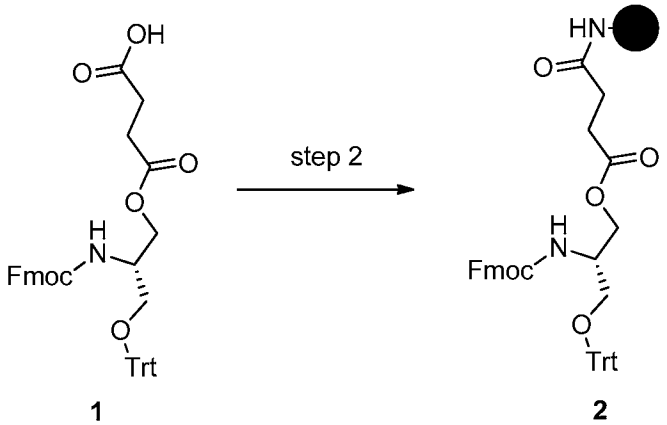
[0244] Step 1: (S)-4-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(trityloxy)propoxy)-4-oxobutanoic acid (**1**)



1

[0245] The (R)-(9H-fluoren-9-yl)methyl (1-hydroxy-3-(trityloxy)propan-2-yl)carbamate (20 g, 36.0 mmol), succinic anhydride (7.20 g, 72 mmol), polystyrene-supported DMAP (3 mmol/g, 24 g, 72 mmol) and triethylamine (10 mL, 72 mmol) were taken up in DCM (720 mL). The suspension was stirred at room temperature for 16 h. The reaction was filtered through Celite (to remove PS-dmap), and the filter cake was rinsed with DCM (200 mL). The combined filtrate was extracted with saturated aqueous NaCl (3 x 100 mL). The organic layer was dried over sodium sulfate and concentrated to afford the crude title compound (23.6 g, 36.0 mmol, 100% yield) which was used in the next step without further purification. MS *m/z* 678.2 (M+Na).

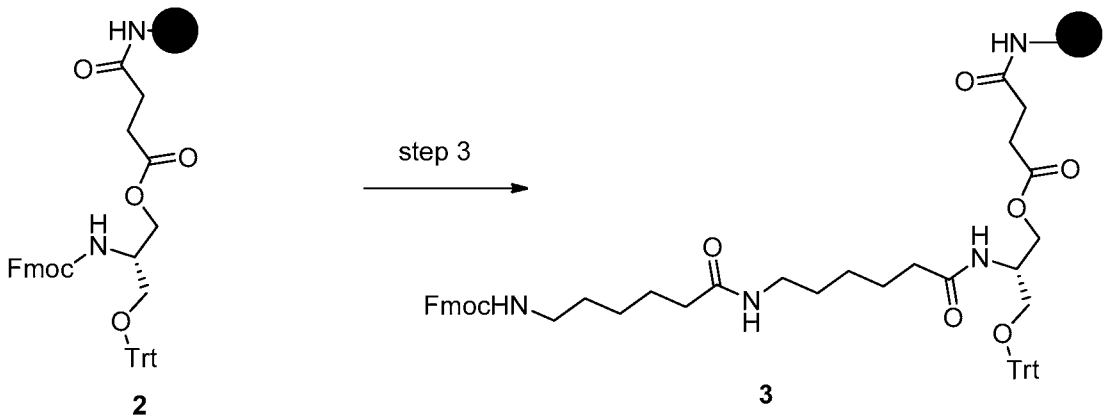
[0246] Step 2:



1 2

[0247] In a 50-mL conical tube, the activated hemisuccinate was prepared as follows: (S)-4-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(trityloxy)propoxy)-4-oxobutanoic acid (0.5 g, 0.763 mmol) and TATU (344 mg, 1.07 mmol) were dissolved in 5 mL of DMF, and the tube was swirled for 3 minutes. Hunig's base (0.400 mL, 2.29 mmol) was added. Meanwhile, the resin (Primer Support 5G Amino from GE Lifesciences, 0.46 mmol/g, 1.66 g, 0.763 mmol) was swelled in a 50-mL falcon tube in 10 mL of DMF. The activated hemisuccinate solution was added. The tube was gently shaken at room temperature at 400 rpm. The reaction mixture was filtered, then rinsed with DCM (50 mL), 10% MeOH-DCM (50 mL), then DCM (50 mL) and dried under vacuum. The resin was capped by adding a solution of acetic anhydride (5.625 mL, 59 mmol), pyridine (16.65 mL) and triethylamine (0.225 mL), and shaking at 400 rpm for 2 h at room temperature. The resin was filtered, rinsed with DCM (50 mL), 10% MeOH-DCM (50 mL), and DCM (50 mL) and dried under vacuum, to afford Intermediate **2** (2.55 g, 0.255 mmol/g, 0.65 mmol), which was used as is in the next step.

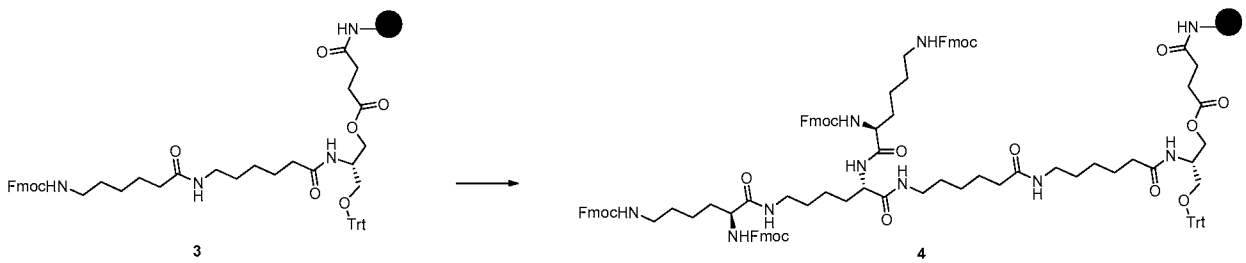
[0248] Step 3:



2 3

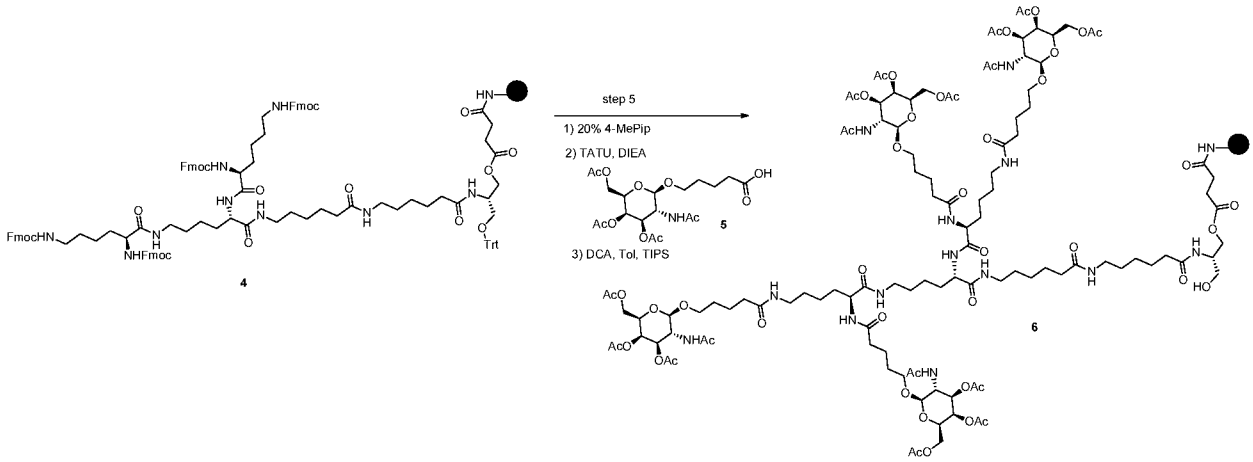
[0249] Intermediate **2** (2.55 g, 0.65 mmol) was suspended in a solution of 20% 4-methylpiperidine in DMF (15 mL) and stirred for 5 minutes. The solution was drained, and the process was repeated two more times to afford the deprotected intermediate. An activated solution of Fmoc-protected 6-aminohexanoic acid was made by dissolving Fmoc-protected 6-aminohexanoic acid (1.41 g, 4.0 mmol) and TATU (1.288 g, 4.0 mmol) in DMF (10 mL). After 5 minutes, Hunig's base (1.05 mL, 6.05 mmol) was added. This solution was added to the deprotected resin. The mixture was shaken at 400 rpm at room temperature overnight. The reaction was filtered, and the resin was washed with DMF (3 x 30 mL). The same procedure (deprotection, preparation of the activated acid, and coupling) was repeated to afford crude Intermediate **3** (2.40 g, 0.184 mmol/g, 0.442 mmol), which was used in the next step.

[0250] Step 4:



[0251] Intermediate **3** was suspended in a solution of 20% 4-methylpiperidine in DMF (15 mL) and stirred for 5 minutes. The solution was drained, and the process was repeated two more times to afford the deprotected intermediate. An activated solution of bis-Fmoc-protected lysine was prepared by dissolving bis-Fmoc-protected lysine (2.07 g, 3.5 mmol) and TATU (1.13 g, 3.5 mmol) in DMF (10 mL) and stirring for 5 minutes. Hunig's base (0.96 mL, 5.5 mmol) was added. This solution was added to the deprotected resin. The suspension was shaken at 400 rpm at room temperature overnight. The reaction mixture was filtered, and the resin was then washed with DMF (3 x 30 mL). The resin was deprotected using the procedure above. An activated solution of bis-Fmoc-protected lysine was prepared as above, except that the amount of bis-Fmoc-protected lysine was 2.96 g (5.0 mmol), the amount of TATU was 1.61 g (5.0 mmol), and the amount of Hunig's base was 1.31 mL (7.5 mmol), and the deprotected resin was coupled to the activated acid by shaking at 400 rpm at room temperature overnight. The resin was washed with DMF (3 x 30 mL) and then DCM (3 x 30 mL), and dried to afford crude Intermediate **4** (2.28 g, 0.165 mmol/g, 0.376 mmol).

[0252] Step 5:



[0253] Intermediate **4** (0.4 mmol) was suspended in a solution of 20% 4-methylpiperidine in DMF (25 mL) and stirred for 5 minutes. The solution was drained, and the process was repeated one more time to afford the deprotected intermediate. To a solution of 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid (5, 2.68 g, 6 mmol) in DMF (20 mL) was added TATU (1.92 g, 6.0 mmol) and the solution was stirred for 5 min. Hunig's base (1.57 mL, 9.0 mmol) was added to the solution and the mixture was then added to the deprotected intermediate. The suspension was kept at room temperature overnight and the solvent was drained. The resin was washed with DMF (3 x 30 mL) and DCM (3 x 30 mL). The resin was treated with 3% Dichloroacetic acid in Tol with 5% TIPS (25 mL) and after 5 min the solvent was drained. The process was repeated two more times to give intermediate **6**, which was used in the next step directly (e.g. conjugation reaction to 5′ or 3′ end of sense strand of an RNAi construct of the invention).

[0254] The chemically modified ASGR1 siRNAs alone or conjugated to the GalNAc moiety are evaluated for efficacy in reducing ASGR1 expression by the *in vitro* immunoassay described in Example 2, the RNA FISH assay described in Example 3, or the *in vivo* mouse model described in Example 6.

Example 6. In Vivo Efficacy of ASGR1 siRNA Molecules

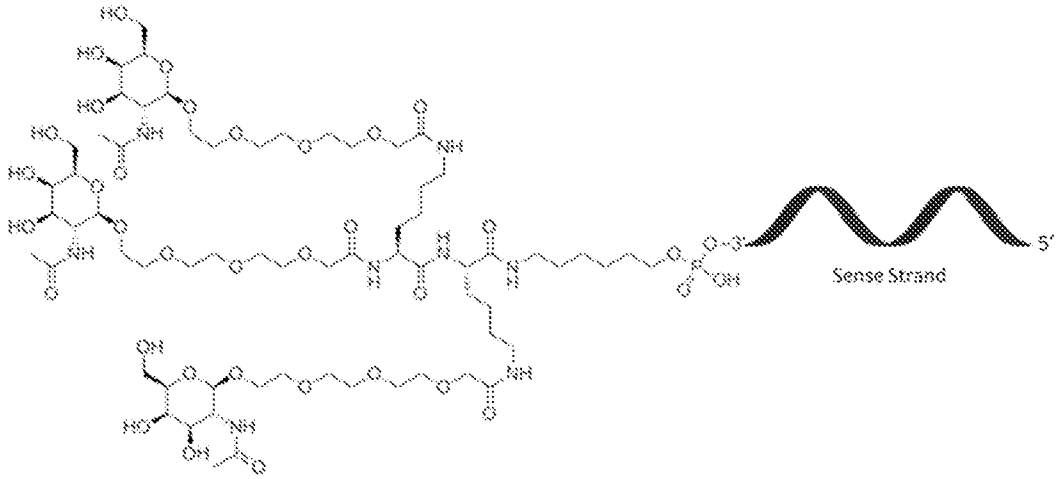
[0255] To assess the efficacy of chemically modified ASGR1 siRNA molecules in reducing ASGR1 liver expression *in vivo*, the modified ASGR1 siRNA molecules (complexed with Invivofectamine® reagent) or GalNAc-siRNA conjugates are administered to C57BL/6J mice

intravenously or subcutaneously. Specifically, mice are injected with buffer, indicated siRNA and matched control siRNA at 1-5 mg/kg body weight in 0.25 ml buffer on day 0. Animals are harvested for further analysis at day 2, day 4 and day 7. Liver total RNA from harvested animals is processed for qPCR analysis. The efficacy of the ASGR1 siRNA is assessed by comparing the amount of Asgr1 mRNA and ASGR1 protein in liver tissue of the siRNA-treated animals to the amount of Asgr1 mRNA and ASGR1 protein in liver tissue of animals injected with buffer or control siRNAs.

[0256] Serum levels of alkaline phosphatase and LDL cholesterol may also be measured in the mice at various times following injection with ASGR1 siRNA molecules or matched controls to assess the *in vivo* efficacy of ASGR1 siRNA molecules. Elevated serum alkaline phosphatase levels correlate with reduced serum levels of non-HDL cholesterol and reduced risk of coronary artery disease (Nioi *et al.*, New England Journal of Medicine, Vol. 374(22):2131-2141, 2016, which is hereby incorporated by reference in its entirety). Thus, serum alkaline phosphatase levels can be used as a surrogate biomarker of efficacy of a particular ASGR1 siRNA to reduce serum non-HDL cholesterol levels or risk of coronary artery disease. Efficacious ASGR1 siRNA molecules are those that produce reduced serum non-HDL cholesterol (e.g. LDL cholesterol) levels or increased serum alkaline phosphatase levels in treated animals as compared to the levels in animals injected with buffer or control siRNAs.

Example 7. In Vitro Efficacy of ASGR1 Chemically Modified siRNA Molecules

[0257] Select chemically modified siRNA molecules listed in Table 6 were conjugated to the triantennary GalNAc moiety shown in Formula VII, the structure of which is reproduced below. The GalNAc moiety was conjugated to the 3′ end of the sense strand of each duplex through a phosphodiester linkage.



[0258] The GalNAc-siRNA conjugates were evaluated for their ability to inhibit ASGR1 expression in the Hep3B cell transfection assay and human ASGR1 CHO cell free uptake assay. The Hep3B cell transfection immunoassay is described in Example 2 above. The free uptake assay utilizing Chinese Hamster Ovary (CHO) cells stably expressing human ASGR1 was conducted as follows. GalNAc-conjugated siRNA molecules in F-12K media (Corning Cellgro#10-025-CV) were prepared in 384-well plates. CHO cells stably expressing human ASGR1 in F-12K media supplemented with 10% fetal bovine serum and 1% antibiotic/antimycotic were added to each well. Cells were incubated for 4 days at 37 °C and 5% CO_2. Four days after siRNA delivery, cells were fixed in formaldehyde, blocked with bovine serum albumin, and subsequently stained with an anti-ASGR1 primary antibody (Amgen clone 7E11, light and heavy chain sequences provided in SEQ ID NOs: 3 and 4, respectively) for either 1 hour at room temperature or overnight at 4 °C. Plates were washed three times with phosphate buffered saline (PBS). Cells were then incubated in the dark for 45 minutes at room temperature with Alexa488-conjugated anti-human IgG secondary antibody and nuclear stain Hoechst 33342 (Invitrogen #H3570) to assess cell number. Following three PBS washes, the plates were imaged on an Opera Phenix high-content screening system (PerkinElmer) using 488/500-550 and 375/435-480 excitation/emission filter settings to measure anti-ASGR1 antibody staining and nuclear staining, respectively. Data were analyzed using Columbus image analysis software and GeneData Screener software to quantify several measures of ASGR1 protein levels, cell count, and cell morphology on a per cell and per well basis.

[0259] The GalNAc-siRNA conjugates were tested at twenty-two different doses ranging from 0.000012 to 25 μM in each of the assays and dose-response curves were constructed. IC50 values and maximum antagonist activity values (relative to control cells; -1.0 max antagonist activity represents complete inhibition) were calculated from the dose-response curves. The results of the assays are shown in Table 7 below.

Table 7. *In vitro* efficacy of GalNAc-ASGR1 siRNA conjugates

Duplex No.	Hep3B Transfected IC50 (μM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 (μM)	hASGR1 CHO Free Uptake Max Antagonist Activity
D-3033	0.00325	-0.84	> 0.5	-0.34
D-3034	>0.167	-0.46	> 0.5	-0.08
D-3036	0.00355	-0.97	> 0.5	-0.48
D-3037	0.00395	-0.96	> 0.5	-0.55
D-3044	>0.5	-0.05	> 0.5	0.13
D-3046	0.00481	-0.82	> 0.5	-0.14
D-3048	0.00288	-0.93	> 0.5	-0.31
D-3050	0.00386	-0.99	> 0.5	-0.36
D-3051	0.0124	-0.82	> 0.5	-0.51
D-3053	0.00349	-0.84	> 0.5	-0.48
D-3055	0.00346	-0.82	> 0.5	-0.26
D-3057	0.0021	-0.86	> 0.5	-0.58
D-3058	>0.5	0.04	> 0.5	0.26
D-3059	0.00966	-0.82	> 0.5	-0.12
D-3060	0.00527	-0.71	> 0.5	-0.06
D-3061	>0.5	0.14	> 0.5	-0.20
D-3063	0.00541	-1.0	0.395	-0.20
D-3071	0.00435	-0.9	> 12.5	-0.10
D-3094	0.00544	-0.9	> 25.0	-0.40
D-3102	0.00649	-0.9	> 12.5	-0.10
D-3125	0.00144	-0.9	0.694	-0.40
D-3133	0.00245	-0.8	> 12.5	-0.20
D-3156	0.00206	-0.5	> 25.0	-0.10
D-3164	1.17	-0.4	2.14	-0.10
D-3187	0.00653	-0.6	> 25.0	-0.10
D-3195	> 0.0977	-0.5	0.179	-0.10
D-3219	> 0.5	0.08	> 0.5	-0.09
D-3220	> 0.5	0.12	> 0.5	-0.11
D-3222	0.00406	-0.95	> 0.5	-0.14
D-3223	0.00818	-0.74	> 0.5	-0.07

Duplex No.	Hep3B Transfected IC50 (μM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 (μM)	hASGR1 CHO Free Uptake Max Antagonist Activity
D-3228	0.000479	-0.9	> 25.0	-0.20
D-3230	> 12.5	-0.2	> 25.0	-0.10
D-3231	> 12.5	-0.2	> 25.0	-0.20
D-3232	0.30214	-0.6	> 25.0	-0.10
D-3233	0.00468	-0.4	> 25.0	-0.10
D-3234	1.5879	-0.8	> 25.0	0.20
D-3235	0.00109	-0.9	> 25.0	0.10
D-3236	0.0047	-0.7	> 25.0	-0.20
D-3237	0.000178	-0.9	> 25.0	-0.20
D-3238	0.00336	-0.9	> 25.0	-0.30
D-3239	0.00394	-0.9	> 25.0	-0.20
D-3240	0.00458	-0.9	> 25.0	-0.20
D-3241	> 12.5	-0.2	> 25.0	-0.10
D-3242	> 12.5	-0.2	> 25.0	0.20
D-3243	0.00122	-0.9	> 25.0	-0.10
D-3244	> 12.5	-0.1	> 25.0	0.10
D-3245	> 12.5	-0.4	> 25.0	0.10
D-3246	> 12.5	-0.2	> 25.0	-0.20
D-3247	> 12.5	-0.2	> 25.0	-0.10
D-3249	0.0137	-0.6	> 25.0	0.00
D-3257	2.33	-0.4	> 12.5	-0.30
D-3280	0.00407	-1.0	> 25.0	-0.10
D-3288	0.011	-0.7	> 12.5	0.10
D-3311	0.0068	-0.8	> 25.0	-0.20
D-3319	> 12.5	-0.3	> 12.5	0.00
D-3342	0.00217	-0.9	0.703	-0.30
D-3350	0.00512	-0.7	> 12.5	-0.10
D-3373	0.00961	-0.6	> 25.0	0.00
D-3381	> 12.5	-0.2	> 12.5	-0.20
D-3404	0.00497	-0.8	> 25.0	-0.30
D-3412	0.00915	-0.6	> 12.5	-0.10
D-3435	0.00302	-0.7	> 25.0	0.10
D-3443	> 12.5	-0.3	> 6.25	-0.20
D-3467	0.00473	-0.7	> 25.0	-0.20
D-3468	> 12.5	-0.2	> 25.0	0.20
D-3470	0.079127	-0.9	> 25.0	-0.30
D-3471	0.38449	-0.9	> 25.0	-0.10
D-3474	0.648	-0.4	> 25.0	0.00
D-3476	0.23421	-0.9	> 25.0	-0.40

Duplex No.	Hep3B Transfected IC50 (μM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 (μM)	hASGR1 CHO Free Uptake Max Antagonist Activity
D-3478	> 12.5	-0.1	> 25.0	0.20
D-3479	0.948	-0.3	> 25.0	-0.10
D-3480	0.274	-0.5	> 25.0	0.10
D-3481	0.00181	-0.8	> 25.0	0.00
D-3482	0.54988	-0.9	> 25.0	-0.10
D-3483	0.35517	-0.9	> 25.0	-0.20
D-3484	1.3218	-0.9	> 25.0	-0.20
D-3485	0.00376	-0.9	1.71	-0.30
D-3486	0.0054	-0.9	> 25.0	-0.10
D-3487	0.00419	-0.8	> 25.0	-0.20
D-3488	0.00582	-0.9	> 25.0	-0.10
D-3489	0.737	-0.3	> 25.0	0.10
D-3490	> 12.5	0.0	> 25.0	-0.10
D-3491	0.00799	-0.8	2.53	-0.30
D-3505	> 12.5	-0.3	11	-0.30
D-3528	0.000536	-1.0	> 25.0	-0.10
D-3536	0.00559	-0.8	> 12.5	0.10
D-3559	0.00285	-1.0	> 25.0	0.00
D-3567	0.0027	-1.0	> 25.0	-0.20

[0260] Several of the GalNAc-siRNA conjugates knocked down ASGR1 expression by greater than 80% when transfected into Hep3B cells. In particular GalNAc-siRNA conjugates targeting nucleotides 692 to 710 of the human ASGR1 transcript variant 1 (NM_ 001671.4; SEQ ID NO: 1) having various chemical modification patterns (e.g. Duplex Nos. 3036, 3037, 3051, 3053, and 3057) exhibited low nanomolar IC50 values when transfected into Hep3B cells and about 50% maximum knockdown activity in the CHO cell free uptake assay. Changing the GalNAc moiety in the conjugates to other triantennary GalNAc structures described herein (e.g. Formula XVI) improved performance of the GalNAc-siRNA conjugates in the free uptake assay (data not shown).

Example 8. Design and Efficacy of Additional GalNAc-ASGR1 siRNA Molecules

[0261] Additional GalNAc-ASGR1 siRNA conjugates were made that had varying patterns of chemical modifications, different sequences, and different GalNAc moieties. Table 8 below lists the modifications in the sense and antisense sequences and the structure and site of conjugation

for the GalNAc moiety for each of the GalNAc-ASGR1 siRNA conjugates. The nucleotide sequences in Table 8 are listed according to the following notations: A, U, G, and C = corresponding ribonucleotide; dT, dA, dG, dC = corresponding deoxyribonucleotide; a, u, g, and c = corresponding 2′-O-methyl ribonucleotide; Af, Uf, Gf, and Cf = corresponding 2′-deoxy-2′-fluoro (“2′-fluoro”) ribonucleotide; Phos = terminal nucleotide has a monophosphate group at its 5′ end; and invAb = inverted abasic nucleotide (i.e. abasic nucleotide linked to adjacent nucleotide via a substitutent at its 3′ position (a 3′-3′ linkage)). Insertion of an “s” in the sequence indicates that the two adjacent nucleotides are connected by a phosphorothiodiester group (e.g. a phosphorothioate internucleotide linkage). Unless indicated otherwise, all other nucleotides are connected by 3′-5′ phosphodiester groups. GalNAc structures are shown in the referenced formulas, which are depicted above.

Table 8. GalNAc-ASGR1 siRNA Conjugates

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5′-3′)	SEQ ID NO:	Antisense Sequence (5′-3′)	SEQ ID NO:
D-3651	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaAfGfAfAfdAgAfuGfaAfgUfuUf	4319	{Phos}asCfsuUfcAfuCfuuucuUfcCfcAfcsUfsu	4513
D-3652	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaAfGfdAAfAfgAfuGfaAfgUfuUf	4320	{Phos}asCfsuUfcAfuCfuuucuUfcCfcAfcsUfsu	4513
D-3653	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaAfgdAAfAfGfAfuGfaAfgUfuUf	4321	{Phos}asCfsuUfcAfucuuuCfuUfcCfcAfcsUfsu	4514
D-3654	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaAfgAfAfdAGfAfuGfaAfgUfuUf	4322	{Phos}asCfsuUfcAfucuuuCfuUfcCfcAfcsUfsu	4514
D-3655	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaaGfAfadAgAfuGfaAfgUfuUf	4323	{Phos}asCfsuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	4515
D-3656	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaaGfAfdAAfgAfuGfaAfgUfuUf	4324	{Phos}asCfsuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	4515
D-3657	Formula VII	3′ end of sense strand	{Phos}GfsusGfgGfaaGfdAaAfgAfuGfaAfgUfuUf	4325	{Phos}asCfsuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	4515

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3658	Formula VII	3' end of sense strand	{Phos}gsusgggaAfgAfadAgaugaaguuu	4326	{Phos}asCfsuUfcAfuCfuUfuCfuUfcCfcacsusu	4516
D-3659	Formula VII	3' end of sense strand	{Phos}GfsusGfgGfaAfGfAfAfAfgAfuGfaAfguuu	4327	{Phos}asCfsuUfcAfuCfuuucuUfcCfcAfcsUfsu	4513
D-3660	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfaCfuGfgUfuCfuCfuUf	4328	{Phos}gsAfsgAfaCfcAfgUfaGfcAfgCfuGfcsUfsu	4517
D-3661	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfugCfUfAfCfuGfgUfuCfuCfuUf	4329	{Phos}gsAfsgAfaCfcAfguagCfAfgCfuGfcsUfsu	4518
D-3662	Formula VII	3' end of sense strand	{Phos}gsCfsaGfcUfgCfUfAfCfuGfgUfuCfuCfuUf	4330	{Phos}gsAfsgAfaCfcAfguagCfaGfcUfgCfsusUf	4519
D-3663	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfAfCfUfggUfuCfuCfuUf	4331	{Phos}gsAfsgAfaCfCfaguaGfcAfgCfuGfcsUfsu	4520
D-3664	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfAfCfUfgGfuUfcUfcUfu	4332	{Phos}GfsasGfaAfcCfaguaGfcAfgCfuGfcsUfsu	4521
D-3665	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfCfUfAfdCuGfgUfuCfuCfuUf	4333	{Phos}gsAfsgAfaCfcAfguagcAfgCfuGfcsUfsu	4522
D-3666	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfCfdTAfCfuGfgUfuCfuCfuUf	4334	{Phos}gsAfsgAfaCfcAfguagcAfgCfuGfcsUfsu	4522
D-3667	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfcdTAfCfUfGfgUfuCfuCfuUf	4335	{Phos}gsAfsgAfaCfcaguaGfcAfgCfuGfcsUfsu	4523
D-3668	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfAfdCUfGfgUfuCfuCfuUf	4336	{Phos}gsAfsgAfaCfcaguaGfcAfgCfuGfcsUfsu	4523
D-3669	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfugCfUfadCuGfgUfuCfuCfuUf	4337	{Phos}gsAfsgAfaCfcAfgUfagCfAfgCfuGfcsUfsu	4524
D-3670	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfugCfUfdACfuGfgUfuCfuCfuUf	4338	{Phos}gsAfsgAfaCfcAfgUfagCfAfgCfuGfcsUfsu	4524

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3671	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfugCfdTaCfuGfgUfuCfuCfuUf	4339	{Phos}gsAfsgAfaCfcAfgUfagCfAfgCfuGfcsUfsu	4524
D-3672	Formula VII	3' end of sense strand	{Phos}gscsagcuGfcUfadCugguucucuu	4340	{Phos}gsAfsgAfaCfcAfgUfaGfcAfgCfugcsusu	4525
D-3673	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfCfuAfCfuGfguucuCfuu	4341	{Phos}gsAfsgAfaCfcAfguagcAfgCfuGfcsUfsu	4522
D-3674	Formula VII	3' end of sense strand	{Phos}UfsgsUfgGfgAfaGfaAfaGfaUfgAfaGfuUf	4342	{Phos}csUfsuCfaUfcUfuUfcUfuCfcCfaCfasUfsu	4526
D-3675	Formula VII	3' end of sense strand	{Phos}UfsgsUfgGfgaAfGfAfAfaGfaUfgAfaGfuUf	4343	{Phos}csUfsuCfaUfcUfuucuUfCfcCfaCfasUfsu	4527
D-3676	Formula VII	3' end of sense strand	{Phos}usgsugggAfaGfadAagaugaaguu	4344	{Phos}csUfsuCfaUfcUfuUfcUfuCfcCfacasusu	4528
D-3677	Formula VII	3' end of sense strand	{Phos}usgsugGfgAfAfGfAfAfaGfaugaaGfuu	4345	{Phos}csUfsuCfaUfcUfuucuuCfcCfaCfasUfsu	4529
D-3678	Formula VII	3' end of sense strand	{Phos}GfuGfgGfaAfGfAfAfAfgAfuGfaAfgUfuUf	4346	{Phos}aCfuUfcAfuCfuuucuUfcCfcAfcUfu	4530
D-3679	Formula VII	3' end of sense strand	{Phos}GfcAfgCfuGfCfUfAfCfuGfgUfuCfuCfuUf	4347	{Phos}gAfgAfaCfcAfguagcAfgCfuGfcUfu	4531
D-3680	Formula VII	3' end of sense strand	{Phos}UfgUfgGfgAfAfGfAfAfaGfaUfgAfaGfuUf	4348	{Phos}cUfuCfaUfcUfuucuuCfcCfaCfaUfu	4532
D-3681	Formula VII	3' end of sense strand	{Phos}AfgGfaCfuGfUfGfCfCfcAfcUfuCfaCfuUf	4349	{Phos}gUfgAfaGfuGfggcacAfgUfcCfuUfu	4533
D-3682	Formula VII	3' end of sense strand	{Phos}GfaGfaCfgGfGfCfUfUfcAfaGfaAfcUfuUf	4350	{Phos}aGfuUfcUfuGfaagccCfgUfcUfcUfu	4534
D-3683	Formula VII	3' end of sense strand	{Phos}GfaGfcGfcAfGfCfUfGfcUfaCfuGfgUfuUf	4351	{Phos}aCfcAfgUfaGfcagcuGfcGfcUfcUfu	4535

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3684	Formula VII	3' end of sense strand	{Phos}GfuUfgUfcUfGfUfGfUfgAfuCfgGfaUfuUf	4352	{Phos}aUfcCfgAfuCfacacaGfaCfaAfcUfu	4536
D-3685	Formula VII	3' end of sense strand	{Phos}GfgAfgCfuGfCfGfGfGfgCfcUfgAfgAfuUf	4353	{Phos}uCfuCfaGfgCfcccgcAfgCfuCfcUfu	4537
D-3686	Formula VII	3' end of sense strand	{Phos}GfcCfgCfuGfGfAfAfCfgAfcGfaCfgUfuUf	4354	{Phos}aCfgUfcGfuCfguuccAfgCfgGfcUfu	4538
D-3687	Formula VII	3' end of sense strand	{Phos}GfcUfgGfgUfCfUfGfCfgAfgAfcAfgAfuUf	4355	{Phos}uCfuGfuCfuCfgcagaCfcCfaGfcUfu	4539
D-3688	Formula VII	3' end of sense strand	{Phos}GfcUfuUfcUfCfGfGfGfaAfuUfuUfcAfuUf	4356	{Phos}uGfaAfaAfuUfcccgaGfaAfaGfcUfu	4540
D-3689	Formula VII	3' end of sense strand	{Phos}CfcUfcCfuGfCfUfGfCfuUfgUfgGfuUfuUf	4357	{Phos}aAfcCfaCfaAfgcagcAfgGfaGfgUfu	4541
D-3690	Formula VII	3' end of sense strand	{Phos}CfuAfuCfaUfGfAfCfCfaAfgGfaGfuAfuUf	4358	{Phos}uAfcUfcCfuUfggucaUfgAfuAfgUfu	4542
D-3691	Formula VII	3' end of sense strand	{Phos}CfgUfcCfuGfGfGfAfGfgAfgCfaGfaAfuUf	4359	{Phos}uUfcUfgCfuCfcucccAfgGfaCfgUfu	4543
D-3692	Formula VII	3' end of sense strand	{Phos}CfuGfgGfgGfCfCfUfCfuUfcUfgCfuUfuUf	4360	{Phos}aAfgCfaGfaAfgaggcCfcCfcAfgUfu	4544
D-3693	Formula VII	3' end of sense strand	{Phos}CfcUfaUfcAfUfGfAfCfcAfaGfgAfgUfuUf	4361	{Phos}aCfuCfcUfuGfgucauGfaUfaGfgUfu	4545
D-3694	Formula VII	3' end of sense strand	{Phos}GfaUfaGfgGfUfGfAfUfgUfuCfcGfaAfuUf	4362	{Phos}uUfcGfgAfaCfaucacCfcUfaUfcUfu	4546
D-3695	Formula VII	3' end of sense strand	{Phos}GfcAfgUfuUfGfCfAfGfgUfuAfuCfaUfuUf	4363	{Phos}aUfgAfuAfaCfcugcaAfaCfuGfcUfu	4547
D-3696	Formula VII	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfAfAfgAfuGfaAfgUfcGf	4364	{Phos}csGfsaCfuUfcAfuCfuuuCfuUfcCfcAfcsUfsu	4548

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3697	Formula VII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfAfCfuGfgUfuCfuCfuCf	4365	{Phos}gsAfsgAfgAfaCfcAfguaGfcAfgCfuGfcsUfsu	4549
D-3698	Formula VII	3' end of sense strand	{Phos}UfsgsUfgGfgAfaGfAfAfaGfaUfgAfaGfuCf	4366	{Phos}gsAfscUfuCfaUfcUfuucUfuCfcCfaCfasUfsu	4550
D-3699	Formula VII	3' end of sense strand	{Phos}AfsusGfuGfgGfaAfGfAfaAfgAfuGfaAfgUf	4367	{Phos}asCfsuUfcAfuCfuUfucuUfcCfcAfcAfusUfsu	4551
D-3700	Formula VII	3' end of sense strand	{Phos}GfscsGfcAfgCfuGfCfUfaCfuGfgUfuCfuCf	4368	{Phos}gsAfsgAfaCfcAfgUfagcAfgCfuGfcGfcsUfsu	4552
D-3701	Formula VII	3' end of sense strand	{Phos}AfsasUfgUfgGfgAfAfGfaAfaGfaUfgAfaGf	4369	{Phos}csUfsuCfaUfcUfuUfcuuCfcCfaCfaUfusUfsu	4553
D-3702	Formula VII	3' end of sense strand	{Phos}GfsasCfgGfgAfcGfGfAfCfUfaCfgAfgAfuUf	4370	{Phos}usCfsuCfgUfaguccGfuCfcCfgUfcsUfsu	4554
D-3703	Formula VII	3' end of sense strand	{Phos}AfsgsCfcAfcCfuCfUfCfCfUfuUfaAfuUfuUf	4371	{Phos}asAfsuUfaAfaggagAfgGfuGfgCfusUfsu	4555
D-3704	Formula VII	3' end of sense strand	{Phos}UfsgsAfcCfuGfcGfGfAfGfCfcUfgAfgCfuUf	4372	{Phos}gsCfsuCfaGfgcuccGfcAfgGfuCfasUfsu	4556
D-3705	Formula VII	3' end of sense strand	{Phos}CfscsUfgCfuCfuCfCfCfUfGfgGfcCfuCfuUf	4373	{Phos}gsAfsgGfcCfcagggAfgAfgCfaGfgsUfsu	4557
D-3706	Formula VII	3' end of sense strand	{Phos}CfscsUfcCfuGfcUfCfUfCfCfcUfgGfgCfuUf	4374	{Phos}gsCfscCfaGfggagaGfcAfgGfaGfgsUfsu	4558
D-3707	Formula VII	3' end of sense strand	{Phos}GfscsUfgCfuAfcUfGfGfUfUfcUfcUfcGfuUf	4375	{Phos}csGfsaGfaGfaaccaGfuAfgCfaGfcsUfsu	4559
D-3708	Formula VII	3' end of sense strand	{Phos}CfscsCfaUfuCfuCfCfAfAfGfcUfuCfaGfuUf	4376	{Phos}csUfsgAfaGfcuuggAfgAfaUfgGfgsUfsu	4560
D-3709	Formula VII	3' end of sense strand	{Phos}AfscsUfgGfuUfcUfCfUfCfGfcUfcCfgGfuUf	4377	{Phos}csCfsgGfaGfcgagaGfaAfcCfaGfusUfsu	4561

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3710	Formula VII	3' end of sense strand	{Phos}GfsasCfgGfgAfCfGfGfAfcUfaCfgAfgAfuUf	4378	{Phos}usCfsuCfgUfaGfuccguCfcCfgUfcsUfsu	4562
D-3711	Formula VII	3' end of sense strand	{Phos}AfsgsCfcAfcCfUfCfUfCfcUfuUfaAfuUfuUf	4379	{Phos}asAfsuUfaAfaGfgagagGfuGfgCfusUfsu	4563
D-3712	Formula VII	3' end of sense strand	{Phos}GfscsAfcGfaGfCfGfCfAfgCfuGfcUfaCfuUf	4380	{Phos}gsUfsaGfcAfgCfugcgcUfcGfuGfcsUfsu	4564
D-3713	Formula VII	3' end of sense strand	{Phos}GfscsGfcAfgCfUfGfCfUfaCfuGfgUfuCfuUf	4381	{Phos}gsAfsaCfcAfgUfagcagCfuGfcGfcsUfsu	4565
D-3714	Formula VII	3' end of sense strand	{Phos}AfscsGfgGfaCfGfGfAfCfuAfcGfaGfaCfuUf	4382	{Phos}gsUfscUfcGfuAfguccgUfcCfcGfusUfsu	4566
D-3715	Formula VII	3' end of sense strand	{Phos}GfscsUfcCfaCfGfUfGfAfaGfcAfgUfuCfuUf	4383	{Phos}gsAfsaCfuGfcUfucacgUfgGfaGfcsUfsu	4567
D-3716	Formula VII	3' end of sense strand	{Phos}UfsgsAfcCfuGfCfGfGfAfgCfcUfgAfgCfuUf	4384	{Phos}gsCfsuCfaGfgCfuccgcAfgGfuCfasUfsu	4568
D-3717	Formula VII	3' end of sense strand	{Phos}GfscsUfgCfgGfGfGfCfCfuGfaGfaGfaGfuUf	4385	{Phos}csUfscUfcUfcAfggcccCfgCfaGfcsUfsu	4569
D-3718	Formula VII	3' end of sense strand	{Phos}UfsusCfaCfcGfAfCfGfAfcGfgCfcGfcUfuUf	4386	{Phos}asGfscGfgCfcGfucgucGfgUfgAfasUfsu	4570
D-3719	Formula VII	3' end of sense strand	{Phos}CfscsAfcGfaCfCfAfAfAfaCfgGfgCfcCfuUf	4387	{Phos}gsGfsgCfcCfgUfuuuggUfcGfuGfgsUfsu	4571
D-3720	Formula VII	3' end of sense strand	{Phos}CfscsUfgCfuCfUfCfCfCfuGfgGfcCfuCfuUf	4388	{Phos}gsAfsgGfcCfcAfgggagAfgCfaGfgsUfsu	4572
D-3721	Formula VII	3' end of sense strand	{Phos}CfscsUfcCfuGfCfUfCfUfcCfcUfgGfgCfuUf	4389	{Phos}gsCfscCfaGfgGfagagcAfgGfaGfgsUfsu	4573
D-3722	Formula VII	3' end of sense strand	{Phos}GfsgsGfaAfgAfAfAfGfAfuGfaAfgUfcGfuUf	4390	{Phos}csGfsaCfuUfcAfucuuuCfuUfcCfcsUfsu	4574

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3723	Formula VII	3' end of sense strand	{Phos}CfscsAfcUfuCfAfCfCfGfaCfgAfcGfgCfuUf	4391	{Phos}gsCfscGfuCfgUfcggugAfaGfuGfgsUfsu	4575
D-3724	Formula VII	3' end of sense strand	{Phos}GfscsUfgCfuAfCfUfGfGfuUfcUfcUfcGfuUf	4392	{Phos}csGfsaGfaGfaAfccaguAfgCfaGfcsUfsu	4576
D-3725	Formula VII	3' end of sense strand	{Phos}AfsasCfgGfgCfCfCfUfGfgAfaGfuGfgGfuUf	4393	{Phos}csCfscAfcUfuCfcagggCfcCfgUfusUfsu	4577
D-3726	Formula VII	3' end of sense strand	{Phos}AfsgsCfaGfcCfGfGfAfCfgAfcUfgGfuAfuUf	4394	{Phos}usAfscCfaGfuCfguccgGfcUfgCfusUfsu	4578
D-3727	Formula VII	3' end of sense strand	{Phos}CfsusGfcGfaGfAfCfAfGfaGfcUfgGfaCfuUf	4395	{Phos}gsUfscCfaGfcUfcugucUfcGfcAfgsUfsu	4579
D-3728	Formula VII	3' end of sense strand	{Phos}GfsgsAfgGfaCfGfCfGfCfaCfcUfgGfuGfuUf	4396	{Phos}csAfscCfaGfgUfgcgcgUfcCfuCfcsUfsu	4580
D-3729	Formula VII	3' end of sense strand	{Phos}UfscsAfcGfuCfCfUfGfGfgAfgGfaGfcAfuUf	4397	{Phos}usGfscUfcCfuCfccaggAfcGfuGfasUfsu	4581
D-3730	Formula VII	3' end of sense strand	{Phos}AfsasGfgAfcCfUfGfCfUfgCfcCfgGfuCfuUf	4398	{Phos}gsAfscCfgGfgCfagcagGfuCfcUfusUfsu	4582
D-3731	Formula VII	3' end of sense strand	{Phos}CfscsCfaUfuCfUfCfCfAfaGfcUfuCfaGfuUf	4399	{Phos}csUfsgAfaGfcUfuggagAfaUfgGfgsUfsu	4583
D-3732	Formula VII	3' end of sense strand	{Phos}AfsusGfgGfcCfUfCfCfAfcGfaCfcAfaAfuUf	4400	{Phos}usUfsuGfgUfcGfuggagGfcCfcAfusUfsu	4584
D-3733	Formula VII	3' end of sense strand	{Phos}CfsgsAfcGfgCfCfGfCfUfgGfaAfcGfaCfuUf	4401	{Phos}gsUfscGfuUfcCfagcggCfcGfuCfgsUfsu	4585
D-3734	Formula VII	3' end of sense strand	{Phos}AfscsUfgGfuUfCfUfCfUfcGfcUfcCfgGfuUf	4402	{Phos}csCfsgGfaGfcGfagagaAfcCfaGfusUfsu	4586
D-3735	Formula VII	3' end of sense strand	{Phos}CfsgsAfcCfaAfAfAfCfGfgGfcCfcUfgGfuUf	4403	{Phos}csCfsaGfgGfcCfcguuuUfgGfuCfgsUfsu	4587

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3736	Formula VII	3' end of sense strand	{Phos}GfsgsUfcUfgCfGfAfGfAfcAfgAfgCfuGfuUf	4404	{Phos}csAfsgCfuCfuGfucucgCfaGfaCfcsUfsu	4588
D-3737	Formula VII	3' end of sense strand	{Phos}GfaCfgGfgAfCfGfGfAfcUfaCfgAfgAfuUf	4405	{Phos}uCfuCfgUfaGfuccguCfcCfgUfcUfu	4589
D-3738	Formula VII	3' end of sense strand	{Phos}AfgCfcAfcCfUfCfUfCfcUfuUfaAfuUfuUf	4406	{Phos}aAfuUfaAfaGfgagagGfuGfgCfuUfu	4590
D-3739	Formula VII	3' end of sense strand	{Phos}UfgAfcCfuGfCfGfGfAfgCfcUfgAfgCfuUf	4407	{Phos}gCfuCfaGfgCfuccgcAfgGfuCfaUfu	4591
D-3740	Formula VII	3' end of sense strand	{Phos}CfcUfgCfuCfUfCfCfCfuGfgGfcCfuCfuUf	4408	{Phos}gAfgGfcCfcAfgggagAfgCfaGfgUfu	4592
D-3741	Formula VII	3' end of sense strand	{Phos}CfcUfcCfuGfCfUfCfUfcCfcUfgGfgCfuUf	4409	{Phos}gCfcCfaGfgGfagagcAfgGfaGfgUfu	4593
D-3742	Formula VII	3' end of sense strand	{Phos}GfcUfgCfuAfCfUfGfGfuUfcUfcUfcGfuUf	4410	{Phos}cGfaGfaGfaAfccaguAfgCfaGfcUfu	4594
D-3743	Formula VII	3' end of sense strand	{Phos}CfcCfaUfuCfUfCfCfAfaGfcUfuCfaGfuUf	4411	{Phos}cUfgAfaGfcUfuggagAfaUfgGfgUfu	4595
D-3744	Formula VII	3' end of sense strand	{Phos}AfcUfgGfuUfCfUfCfUfcGfcUfcCfgGfuUf	4412	{Phos}cCfgGfaGfcGfagagaAfcCfaGfuUfu	4596
D-3745	Formula XVI, k=3, n=1	5' end of sense strand	GfcAfgCfuGfcUfAfCfUfggUfuCfuCfsusUf	4413	{Phos}gsAfsgAfaCfCfaguaGfcAfgCfuGfcsUfsu	4520
D-3746	Formula VIII	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfAfAfGfauGfaAfgUfuUf	4414	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3747	Formula VIII	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfAfAfGfAfuGfaAfgUfuUf	4415	{Phos}asCfsuUfcAfucuuuCfuUfcCfcAfcsUfsu	4514
D-3748	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfAfuGfaAfgUfsusUf	4416	{Phos}asCfsuUfcAfucuuuCfuUfcCfcAfcsUfsu	4514

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3749	Formula VIII	3' end of sense strand	{Phos}GfuGfgGfaaGfAfaAfgAfuGfaAfgUfuUf	4417	{Phos}aCfuUfcAfuCfuUfucUfUfcCfcAfcUfu	4598
D-3750	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaaGfAfaAfgAfuGfaAfgUfsusUf	4418	{Phos}asCfsuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	4515
D-3751	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfaAfGfauGfaAfgUfsusUf	4419	{Phos}asCfsuUfcAfUfcuUfuCfuUfcCfcAfcsUfsu	4599
D-3752	Formula XXVI	5' end of sense strand	GfuGfgGfaAfgAfAfAfgAfuGfaAfgUfsusUf	4420	{Phos}asCfsuUfcAfuCfuuuCfuUfcCfcAfcsUfsu	4600
D-3753	None	N/A	{Phos}GfuGfgGfaAfgAfAfAfGfAfuGfaAfgUfuUf	4421	{Phos}aCfuUfcAfucuuuCfuUfcCfcAfcUfu	4601
D-3754	None	N/A	{Phos}GfuGfgGfaAfgAfaAfgAfuGfaAfguUfUf	4422	{Phos}AfCfuUfcAfuCfuUfuCfuUfcCfcAfcUfu	4602
D-3755	None	N/A	{Phos}GfuGfgGfaAfgAfAfAfGfauGfaAfgUfuUf	4423	{Phos}aCfuUfcAfUfcuuuCfuUfcCfcAfcUfu	4603
D-3756	None	N/A	{Phos}GfsusGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4424	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3757	None	N/A	{Phos}GfuGfgGfaAfgAfAfAfGfaUfgAfaGfuUfu	4425	{Phos}AfcUfuCfaUfcuuuCfuUfcCfcAfcUfu	4604
D-3758	Formula VIII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfAfCfUfGfgUfuCfuCfuUf	4426	{Phos}gsAfsgAfaCfcaguaGfcAfgCfuGfcsUfsu	4523
D-3759	Formula VIII	3' end of sense strand	{Phos}UfsgsUfgGfgAfaGfAfAfAfGfaUfgAfaGfuUf	4427	{Phos}csUfsuCfaUfcuuucUfuCfcCfaCfasUfsu	4605
D-3760	Formula VIII	3' end of sense strand	{Phos}GfsusGfgGfaaGfAfaAfgAfuGfaAfgUfuUf	4428	{Phos}asCfsuUfcAfuCfuUfucUfUfcCfcAfcsUfsu	4515
D-3761	Formula VIII	3' end of sense strand	{Phos}GfscsAfgCfugCfUfaCfuGfgUfuCfuCfuUf	4429	{Phos}gsAfsgAfaCfcAfgUfagCfAfgCfuGfcsUfsu	4524
D-3762	Formula VIII	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfaAfgAfuGfaAfgUfuUf	4430	{Phos}asCfsuUfcAfuCfuUfuCfuUfcCfcAfcsUfsUf	4606
D-3763	Formula VIII	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfaAfGfauGfaAfgUfuUf	4431	{Phos}asCfsuUfcAfUfcuUfuCfuUfcCfcAfcsUfsu	4599
D-3764	Formula VIII	3' end of sense strand	{Phos}GfsusGfggAfAfgAfaAfgAfuGfaAfgUfuUf	4432	{Phos}asCfsuUfcAfuCfuUfuCfuuCfCfcAfcsUfsu	4607

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3765	Formula VIII	3' end of sense strand	{Phos}GfsusgGfGfaAfgAfaAfgAfuGfaAfgUfuUf	4433	{Phos}asCfsuUfcAfuCfuUfuCfuUfccCfAfcsUfsu	4608
D-3766	Formula VIII	3' end of sense strand	{Phos}gsUfsGfgGfaAfgAfaAfgAfuGfaAfgUfuUf	4434	{Phos}asCfsuUfcAfuCfuUfuCfuUfcCfcaCfsUfsUf	4609
D-3767	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfaAfgAfUfgaAfgUfsusUf	4435	{Phos}asCfsuUfCfauCfuUfuCfuUfcCfcAfcsUfsu	4610
D-3768	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfaAfgAfuGfAfagUfsusUf	4436	{Phos}asCfsUfucAfuCfuUfuCfuUfcCfcAfcsUfsu	4611
D-3769	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfaAfgAfuGfaAfGfususUf	4437	{Phos}AfscsuUfcAfuCfuUfuCfuUfcCfcAfcsUfsu	4612
D-3770	Formula XVI, k=3, n=1	5' end of sense strand	gUfgGfgAfaGfAfAfAfgAfuGfaAfgUfsusUf	4438	{Phos}asCfsuUfcAfuCfuuucUfuCfcCfaCfsusUf	4613
D-3771	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3772	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfaUfgAfaGfusUfsu	4440	{Phos}AfscsUfuCfaUfcuuuCfuUfcCfcAfcsUfsu	4614
D-3773	Formula XVI, k=3, n=1	5' end of sense strand	GfcAfgCfuGfcUfAfCfUfGfgUfuCfuCfsusUf	4441	{Phos}gsAfsgAfaCfcaguaGfcAfgCfuGfcsUfsu	4523
D-3774	Formula XXIX	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfAfAfGfauGfaAfgUfuUf	4414	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3775	Formula XXIX	3' end of sense strand	{Phos}GfsusGfgGfaAfgAfaAfGfauGfaAfgUfuUf	4431	{Phos}asCfsuUfcAfUfcuUfuCfuUfcCfcAfcsUfsu	4599
D-3776	None	N/A	{Phos}GfscsAfgCfugCfUfaCfuGfgUfuCfuCfuUf	4429	{Phos}gsAfsgAfaCfcAfgUfagCfAfgCfuGfcsUfsUf	4615
D-3777	None	N/A	{Phos}GfscsAfgCfuGfcUfAfCfUfGfgUfuCfuCfuUf	4426	{Phos}gsAfsgAfaCfcaguaGfcAfgCfuGfcsUfsUf	4616
D-3778	Formula VIII	3' end of sense strand	{Phos}GfscsAfgCfuGfcUfaCfugGfUfuCfuCfuUf	4442	{Phos}gsAfsgAfacCfAfgUfaGfcAfgCfuGfcsUfsu	4617

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3779	Formula XVI, k=3, n=1	5' end of sense strand	GfcCfgCfuGfgAfAfCfGfacGfaCfgUfsusUf	4443	{Phos}asCfsgUfcGfUfcguuCfcAfgCfgGfcsUfsu	4618
D-3780	Formula XVI, k=3, n=1	5' end of sense strand	GfaUfaGfgGfuGfAfUfGfuuCfcGfaAfsusUf	4444	{Phos}usUfscGfgAfAfcaucAfcCfcUfaUfcsUfsu	4619
D-3781	Formula XVI, k=3, n=1	5' end of sense strand	CfcUfaUfcAfuGfAfCfCfaaGfgAfgUfsusUf	4445	{Phos}asCfsuCfcUfUfggucAfuGfaUfaGfgsUfsu	4620
D-3782	Formula XVI, k=3, n=1	5' end of sense strand	CfuAfuCfaUfgAfCfCfAfagGfaGfuAfsusUf	4446	{Phos}usAfscUfcCfUfugguCfaUfgAfuAfgsUfsu	4621
D-3783	Formula XVI, k=3, n=1	5' end of sense strand	AfaCfgGfgCfcCfUfGfGfaaGfuGfgGfsusUf	4447	{Phos}csCfscAfcUfUfccagGfgCfcCfgUfusUfsu	4622
D-3784	Formula XVI, k=3, n=1	5' end of sense strand	GfaCfgGfgAfcGfGfAfCfuaCfgAfgAfsusUf	4448	{Phos}usCfsuCfgUfAfguccGfuCfcCfgUfcsUfsu	4623
D-3785	Formula XVI, k=3, n=1	5' end of sense strand	AfcGfgGfaCfgGfAfCfUfacGfaGfaCfsusUf	4449	{Phos}gsUfscUfcGfUfagucCfgUfcCfcGfusUfsu	4624
D-3786	Formula XVI, k=3, n=1	5' end of sense strand	AfgCfaGfcCfgGfAfCfGfacUfgGfuAfsusUf	4450	{Phos}usAfscCfaGfUfcgucCfgGfcUfgCfusUfsu	4625
D-3787	Formula XVI, k=3, n=1	5' end of sense strand	CfcAfcUfuCfaCfCfGfAfcgAfcGfgCfsusUf	4451	{Phos}gsCfscGfuCfGfucggUfgAfaGfuGfgsUfsu	4626
D-3788	Formula XVI, k=3, n=1	5' end of sense strand	CfgAfcGfgCfcGfCfUfGfgaAfcGfaCfsusUf	4452	{Phos}gsUfscGfuUfCfcagcGfgCfcGfuCfgsUfsu	4627
D-3789	Formula XVI, k=3, n=1	5' end of sense strand	AfaAfcCfcGfuGfGfCfGfcuUfuCfuGfsusUf	4453	{Phos}csAfsgAfaAfGfcgccAfcGfgGfuUfusUfsu	4628
D-3790	Formula XVI, k=3, n=1	5' end of sense strand	CfcUfcUfuCfuGfCfUfUfucUfcGfgGfsusUf	4454	{Phos}csCfscGfaGfAfaagcAfgAfaGfaGfgsUfsu	4629
D-3791	Formula XVI, k=3, n=1	5' end of sense strand	GfaAfaCfcCfgUfGfGfCfgcUfuUfcUfsusUf	4455	{Phos}asGfsaAfaGfCfgccaCfgGfgUfuUfcsUfsu	4630

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3792	Formula XVI, k=3, n=1	5' end of sense strand	GfcAfgAfaAfuUfUfGfUfccAfgCfaCfsusUf	4456	{Phos}gsUfsgCfuGfGfacaaAfuUfuCfuGfcsUfsu	4631
D-3793	Formula XVI, k=3, n=1	5' end of sense strand	GfgAfcUfaCfgAfGfAfCfggGfcUfuCfsusUf	4457	{Phos}gsAfsaGfcCfCfgucuCfgUfaGfuCfcsUfsu	4632
D-3794	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfcCfcAfcUfUfCfAfccGfaCfgAfsusUf	4458	{Phos}usCfsgUfcGfGfugaaGfuGfgGfcAfcsUfsu	4633
D-3795	Formula XVI, k=3, n=1	5' end of sense strand	GfuUfgUfcUfgUfGfUfGfauCfgGfaUfsusUf	4459	{Phos}asUfscCfgAfUfcacaCfaGfaCfaAfcsUfsu	4634
D-3796	Formula XVI, k=3, n=1	5' end of sense strand	GfgUfcUfgCfgAfGfAfCfagAfgCfuGfsusUf	4460	{Phos}csAfsgCfuCfUfgucuCfgCfaGfaCfcsUfsu	4635
D-3797	Formula XVI, k=3, n=1	5' end of sense strand	AfgCfcAfcCfuCfUfCfCfuuUfaAfuUfsusUf	4461	{Phos}asAfsuUfaAfAfggagAfgGfuGfgCfusUfsu	4636
D-3798	Formula XVI, k=3, n=1	5' end of sense strand	GfcUfcCfaCfgUfGfAfAfgcAfgUfuCfsusUf	4462	{Phos}gsAfsaCfuGfCfuucaCfgUfgGfaGfcsUfsu	4637
D-3799	Formula XVI, k=3, n=1	5' end of sense strand	GfcGfcAfgCfuGfCfUfAfcuGfgUfuCfsusUf	4463	{Phos}gsAfsaCfcAfGfuagcAfgCfuGfcGfcsUfsu	4638
D-3800	Formula XVI, k=3, n=1	5' end of sense strand	GfcUfgCfuAfcUfGfGfUfucUfcUfcGfsusUf	4464	{Phos}csGfsaGfaGfAfaccaGfuAfgCfaGfcsUfsu	4639
D-3801	Formula XVI, k=3, n=1	5' end of sense strand	AfcUfgGfuUfcUfCfUfCfgcUfcCfgGfsusUf	4465	{Phos}csCfsgGfaGfCfgagaGfaAfcCfaGfusUfsu	4640
D-3802	Formula VIII	3' end of sense strand	{Phos}GfcAfgCfuGfcUfAfCfUfGfgUfuCfuCfuUf	4466	{Phos}gAfgAfaCfcaguaGfcAfgCfuGfcUfu	4641
D-3803	Formula VIII	3' end of sense strand	GfscsAfgCfuGfcUfAfCfUfGfgUfuCfuCfuUf	4467	gsAfsgAfaCfcaguaGfcAfgCfuGfcsUfsu	4642
D-3804	Formula XVI, k=3, n=1	5' end of sense strand	GfcAfGCfUGfcUfAfCfUfGfGUfUCfUCfUUf	4468	{Phos}GAfGAfACfcAGUAGfcAfGCfUGfcUfu	4643

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3805	Formula VIII	3' end of sense strand	{Phos}gsUfsgGfgAfaGfAfaAfgAfuGfaAfgUfuUf	4469	{Phos}asCfsuUfcAfuCfuUfucUfuCfcCfaCfsusUf	4644
D-3806	Formula XVI, k=3, n=1	5' end of sense strand	gUfgGfgAfaGfAfaAfgAfuGfaAfgUfsusUf	4470	{Phos}asCfsuUfcAfuCfuUfucUfuCfcCfaCfsusUf	4644
D-3807	Formula XVI, k=3, n=1	5' end of sense strand	gUfgGfgAfagAfaAfgAfuGfaAfgUfsusUf	4471	{Phos}asCfsuUfcAfuCfuUfuCfUfuCfcCfaCfsusUf	4645
D-3808	Formula XVI, k=3, n=1	5' end of sense strand	AfuGfgGfcCfuCfCfAfCfgaCfcAfaAfsusUf	4472	{Phos}usUfsuGfgUfCfguggAfgGfcCfcAfusUfsu	4646
D-3809	Formula XVI, k=3, n=1	5' end of sense strand	GfcAfcGfaGfcGfCfAfGfcuGfcUfaCfsusUf	4473	{Phos}gsUfsaGfcAfGfcugcGfcUfcGfuGfcsUfsu	4647
D-3810	Formula XVI, k=3, n=1	5' end of sense strand	UfuCfaCfcGfaCfGfAfCfggCfcGfcUfsusUf	4474	{Phos}asGfscGfgCfCfgucgUfcGfgUfgAfasUfsu	4648
D-3811	Formula XVI, k=3, n=1	5' end of sense strand	GfaAfgUfgGfgUfGfGfAfcgGfgAfcGfsusUf	4475	{Phos}csGfsuCfcCfGfuccaCfcCfaCfuUfcsUfsu	4649
D-3812	Formula XVI, k=3, n=1	5' end of sense strand	UfcAfcGfuCfcUfGfGfGfagGfaGfcAfsusUf	4476	{Phos}usGfscUfcCfUfcccaGfgAfcGfuGfasUfsu	4650
D-3813	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfuUfs{invAb}	4477	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3814	Formula XVI, k=3, n=1	5' end of sense strand	[invAb]GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4478	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3815	Formula XVI, k=3, n=1	5' end of sense strand	[invAb]GfuGfgGfaAfgAfAfAfGfauGfaAfgUfuUfs{invAb}	4479	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3816	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcUfus{invAb}	4651
D-3817	Formula XVI, k=3, n=1	5' end of sense strand	GfsusGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4480	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3818	Formula XVI, k=3, n=1	5' end of sense strand	GfsusGfsgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4481	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3819	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgsUfsusUf	4482	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3820	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfusUf	4483	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3821	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfsusUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4652
D-3822	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4653
D-3823	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfscsUfsu	4654
D-3824	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcUfsu	4655
D-3825	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfuUf	4484	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4597
D-3826	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}aCfuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4656
D-3827	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}asCfsuUfcAfUfcuuuCfuUfcCfcAfcUfu	4657
D-3828	Formula XVI, k=3, n=1	5' end of sense strand	CfcGfcUfgGfaAfCfGfAfcgAfcGfuCfsusUf	4485	{Phos}gsAfscGfuCfGfucguUfcCfaGfcGfgsUfsu	4658
D-3829	Formula XVI, k=3, n=1	5' end of sense strand	GfaUfgCfcAfcGfUfUfUfggCfgUfgCfsusUf	4486	{Phos}gsCfsaCfgCfCfaaacGfuGfgCfaUfcsUfsu	4659
D-3830	Formula XVI, k=3, n=1	5' end of sense strand	GfaGfcAfcCfcAfGfGfGfagGfcAfaUfsusUf	4487	{Phos}asUfsuGfcCfUfcccuGfgGfuGfcUfcsUfsu	4660

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3831	Formula XVI, k=3, n=1	5' end of sense strand	GfgCfuUfgAfgCfAfCfCfcaGfgGfaGfsusUf	4488	{Phos}csUfscCfcUfGfggugCfuCfaAfgCfcsUfsu	4661
D-3832	Formula XVI, k=3, n=1	5' end of sense strand	GfaAfgAfaAfgAfUfGfAfagUfcGfcUfsusUf	4489	{Phos}asGfscGfaCfUfucauCfuUfuCfuUfcsUfsu	4662
D-3833	Formula XVI, k=3, n=1	5' end of sense strand	GfaGfaUfgCfcAfCfGfUfuuGfgCfgUfsusUf	4490	{Phos}asCfsgCfcAfAfacguGfgCfaUfcUfcsUfsu	4663
D-3834	Formula XVI, k=3, n=1	5' end of sense strand	CfgGfgAfcGfgAfCfUfAfcgAfgAfcGfsusUf	4491	{Phos}csGfsuCfuCfGfuaguCfcGfuCfcCfgsUfsu	4664
D-3835	Formula XVI, k=3, n=1	5' end of sense strand	CfuAfcGfaGfaCfGfGfGfcuUfcAfaGfsusUf	4492	{Phos}csUfsuGfaAfGfcccgUfcUfcGfuAfgsUfsu	4665
D-3836	Formula XVI, k=3, n=1	5' end of sense strand	CfcCfgGfgCfaCfUfGfGfagAfuGfcCfsusUf	4493	{Phos}gsGfscAfuCfUfccagUfgCfcCfgGfgsUfsu	4666
D-3837	Formula XVI, k=3, n=1	5' end of sense strand	UfgAfaAfcCfcGfUfGfGfcgCfuUfuCfsusUf	4494	{Phos}gsAfsaAfgCfGfccacGfgGfuUfuCfasUfsu	4667
D-3838	Formula XVI, k=3, n=1	5' end of sense strand	GfgUfgGfuCfaCfGfUfCfcuGfgGfaGfsusUf	4495	{Phos}csUfscCfcAfGfgcsgUfgAfcCfaCfcsUfsu	4668
D-3839	Formula XVI, k=3, n=1	5' end of sense strand	CfaGfaAfaUfuUfGfUfCfcaGfcAfcCfsusUf	4496	{Phos}gsGfsuGfcUfGfgacaAfaUfuUfcUfgsUfsu	4669
D-3840	Formula XVI, k=3, n=1	5' end of sense strand	AfuGfcCfaCfgUfUfUfGfgcGfuGfcUfsusUf	4497	{Phos}asGfscAfcGfCfcaaaCfgUfgGfcAfusUfsu	4670
D-3841	Formula XVI, k=3, n=1	5' end of sense strand	AfgCfuGfcGfgGfGfCfCfugAfgAfgAfsusUf	4498	{Phos}usCfsuCfuCfAfggccCfcGfcAfgCfusUfsu	4671
D-3842	Formula XVI, k=3, n=1	5' end of sense strand	GfcCfcUfaUfcAfUfGfAfccAfaGfgAfsusUf	4499	{Phos}usCfscUfuGfGfucauGfaUfaGfgGfcsUfsu	4672
D-3843	Formula XVI, k=3, n=1	5' end of sense strand	AfgCfaAfcUfuCfAfCfAfgcGfaGfcAfsusUf	4500	{Phos}usGfscUfcGfCfugugAfaGfuUfgCfusUfsu	4673

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3844	Formula XVI, k=3, n=1	5' end of sense strand	AfgCfaGfaAfaUfUfUfGfucCfaGfcAfsusUf	4501	{Phos}usGfscUfgGfAfcaaaUfuUfcUfgCfusUfsu	4674
D-3845	Formula XVI, k=3, n=1	5' end of sense strand	AfaAfaCfgGfgCfCfCfUfggAfaGfuGfsusUf	4502	{Phos}csAfscUfuCfCfagggCfcCfgUfuUfusUfsu	4675
D-3846	Formula XVI, k=3, n=1	5' end of sense strand	GfcCfuGfaGfcUfGfUfCfagAfuGfgCfsusUf	4503	{Phos}gsCfscAfuCfUfgacaGfcUfcAfgGfcsUfsu	4676
D-3847	Formula XVI, k=3, n=1	5' end of sense strand	UfgGfaGfaUfgCfCfAfCfguUfuGfgCfsusUf	4504	{Phos}gsCfscAfaAfCfguggCfaUfcUfcCfasUfsu	4677
D-3848	Formula XVI, k=3, n=1	5' end of sense strand	AfcUfaCfgAfgAfCfGfGfgcUfuCfaAfsusUf	4505	{Phos}usUfsgAfaGfCfccguCfuCfgUfaGfusUfsu	4678
D-3849	Formula XVI, k=3, n=1	5' end of sense strand	AfaGfuGfgGfuGfGfAfCfggGfaCfgGfsusUf	4506	{Phos}csCfsgUfcCfCfguccAfcCfcAfcUfusUfsu	4679
D-3850	Formula XVI, k=3, n=1	5' end of sense strand	UfgCfaCfaGfcAfCfUfGfaaGfaAfcCfsusUf	4507	{Phos}gsGfsuUfcUfUfcaguGfcUfgUfgCfasUfsu	4680
D-3851	Formula XVI, k=3, n=1	5' end of sense strand	AfcGfgAfcUfaCfGfAfGfacGfgGfcUfsusUf	4508	{Phos}asGfscCfcGfUfcucgUfaGfuCfcGfusUfsu	4681
D-3852	Formula XVI, k=3, n=1	5' end of sense strand	GfgAfcGfaCfuGfGfUfAfcgGfcCfaCfsusUf	4509	{Phos}gsUfsgGfcCfGfuaccAfgUfcGfuCfcsUfsu	4682
D-3853	Formula XVI, k=3, n=1	5' end of sense strand	GfaGfcUfgCfgGfGfGfCfcuGfaGfaGfsusUf	4510	{Phos}csUfscUfcAfGfgcccCfgCfaGfcUfcsUfsu	4683
D-3854	Formula XVI, k=3, n=1	5' end of sense strand	CfaCfgUfuUfgGfCfGfUfgcUfuGfgAfsusUf	4511	{Phos}usCfscAfaGfCfacgcCfaAfaCfgUfgsUfsu	4684
D-3855	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}[invAbs]asCfsuUfcAfUfcuuuCfuUfcCfcAfcsUfsu	4685
D-3856	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaAfgAfAfAfGfauGfaAfgUfsusUf	4439	{Phos}[invAbs]asCfsuUfcAfUfcuuuCfuUfcCfcAfcUfus{invAb}	4686

Duplex No.	GalNAc Moiety	Site of GalNAc Moiety Conjug.	Sense Sequence (5'-3')	SEQ ID NO:	Antisense Sequence (5'-3')	SEQ ID NO:
D-3857	Formula XVI, k=3, n=1	5' end of sense strand	GfuGfgGfaaGfAfAfAfgAfuGfaAfgUfsusUf	4512	{Phos}asCfsuUfcAfuCfuuucUfUfcCfcAfcsUfsu	4687

[0262] The efficacy of the GalNAc-siRNA conjugates for inhibiting ASGR1 expression was tested in the Hep3B cell transfection immunoassay (described in Example 2) and/or the human ASGR1 CHO cell free uptake immunoassay (described in Example 7). The results of the assays are shown in Table 9 below.

Table 9. Efficacy of GalNAc-ASGR1 siRNA conjugates *in vitro*

Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 1197216.2	Duplex No.	Hep3B Transfected IC50 IP (μM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 IP (μM)	hASGR1 CHO Free Uptake Max Antagonist Activity
692-710	575-593	D-3651	0.00141	-0.90	> 0.5	-0.51
692-710	575-593	D-3652	0.00239	-0.97	> 0.5	-0.34
692-710	575-593	D-3653	0.00115	-0.84	> 0.5	-0.42
692-710	575-593	D-3654	0.00206	-0.89	> 0.5	-0.32
692-710	575-593	D-3655	0.00461	-0.77	> 0.5	-0.15
692-710	575-593	D-3656	0.00476	-0.97	> 0.5	-0.13
692-710	575-593	D-3657	0.00431	-0.83	> 0.5	-0.10
692-710	575-593	D-3658	0.00231	-0.96	> 0.5	-0.35
692-710	575-593	D-3659	0.00177	-0.90	> 0.5	-0.48
888-906	771-789	D-3660	0.00398	-0.62	> 0.5	-0.04
888-906	771-789	D-3661	> 12.5	-0.4	> 25.0	-0.30
888-906	771-789	D-3662	> 12.5	0.0	> 25.0	-0.10
888-906	771-789	D-3663	0.00309	-0.9	> 25.0	-0.20
888-906	771-789	D-3664	0.00229	-0.7	> 25.0	0.10
888-906	771-789	D-3665	0.000862	-0.7	> 25.0	0.00
888-906	771-789	D-3666	0.000545	-0.8	> 25.0	0.10
888-906	771-789	D-3667	0.000716	-0.8	> 25.0	0.10
888-906	771-789	D-3668	0.00358	-0.8	> 25.0	0.10
888-906	771-789	D-3669	> 12.5	-0.5	> 25.0	-0.10
888-906	771-789	D-3670	> 12.5	-0.3	> 25.0	0.10
888-906	771-789	D-3671	> 12.5	-0.1	> 25.0	-0.10
888-906	771-789	D-3672	0.00156	-0.7	> 25.0	0.10
888-906	771-789	D-3673	> 12.5	-0.2	> 25.0	-0.20

Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 1197216.2	Duplex No.	Hep3B Transfected IC50 IP (μM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 IP (μM)	hASGR1 CHO Free Uptake Max Antagonist Activity
691-709	574-592	D-3674	0.59834	-0.9	> 25.0	-0.10
691-709	574-592	D-3675	1	-0.5	> 25.0	-0.10
691-709	574-592	D-3676	0.24304	-0.7	> 25.0	-0.10
691-709	574-592	D-3677	1.99	-0.9	> 25.0	-0.30
692-710	575-593	D-3678	0.0085575	-1.0	1.26	-0.40
888-906	771-789	D-3679	0.33276	-0.8	0.00324	-0.20
691-709	574-592	D-3680	0.079157	-1.0	> 12.5	0.00
1158-1176	1041-1059	D-3681	0.02749	-0.8	> 12.5	-0.20
1088-1106	971-989	D-3682	0.0064167	-1.0	9.4	-0.30
884-902	767-785	D-3683	0.0057367	-0.9	> 12.5	-0.30
563-581	—	D-3684	0.18997	-1.0	5.48	-0.20
604-622	487-505	D-3685	0.070325	-0.9	0.306	-0.10
1185-1203	1068-1086	D-3686	0.25317	-0.9	> 12.5	-0.10
1221-1239	1104-1122	D-3687	0.012227	-0.9	> 12.5	0.10
1349-1367	1232-1250	D-3688	0.002845	-1.0	> 12.5	-0.20
547-565	—	D-3689	0.009105	-0.8	> 12.5	-0.20
396-414	396-414	D-3690	0.003015	-1.0	> 12.5	-0.10
978-996	861-879	D-3691	0.24201	-0.9	> 12.5	0.10
1334-1352	1217-1235	D-3692	0.10186	-0.9	> 12.5	-0.10
395-413	395-413	D-3693	0.081347	-0.9	> 12.5	-0.10
1393-1411	1276-1294	D-3694	0.58738	-1.0	> 12.5	0.10
1443-1461	1326-1344	D-3695	0.015662	-0.9	> 12.5	0.20
692-710	575-593	D-3696	> 12.5	0.1	> 25.0	-0.30
888-906	771-789	D-3697	0.00389	-0.7	> 25.0	0.00
691-709	574-592	D-3698	> 12.5	-0.2	> 25.0	-0.10
692-710	575-593	D-3699	0.00324	-0.9	0.638	-0.40
888-906	771-789	D-3700	> 12.5	-0.6	> 25.0	0.10
691-709	574-592	D-3701	> 12.5	-0.5	> 25.0	0.10
1073-1091	956-974	D-3702	0.009365	-0.8	> 12.5	-0.30
1260-1278	1143-1161	D-3703	> 0.195	-0.4	> 12.5	-0.20
796-814	679-697	D-3704	> 12.5	-0.3	> 12.5	-0.20
526-544	—	D-3705	> 12.5	-0.2	> 12.5	-0.10
523-541	—	D-3706	> 12.5	-0.2	> 12.5	-0.20
891-909	774-792	D-3707	0.00932	-0.6	> 12.5	-0.20
288-306	288-306	D-3708	2.22	-0.5	> 12.5	-0.20
897-915	780-798	D-3709	0.0129	-0.8	> 12.5	-0.20
1073-1091	956-974	D-3710	0.00656	-0.9	> 12.5	-0.20
1260-1278	1143-1161	D-3711	> 12.5	-0.2	> 12.5	-0.10
880-898	763-781	D-3712	0.00684	-0.6	> 12.5	-0.20
886-904	769-787	D-3713	0.0102	-0.7	> 12.5	-0.20

Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 1197216.2	Duplex No.	Hep3B Transfected IC50 IP (µM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 IP (µM)	hASGR1 CHO Free Uptake Max Antagonist Activity
1074-1092	957-975	D-3714	0.005445	-0.8	> 12.5	-0.30
772-790	655-673	D-3715	> 12.5	-0.2	> 12.5	-0.20
796-814	679-697	D-3716	> 12.5	-0.3	> 12.5	-0.40
607-625	490-508	D-3717	> 12.5	-0.3	> 12.5	-0.20
1172-1190	1055-1073	D-3718	> 12.5	0.0	> 12.5	-0.20
1042-1060	925-943	D-3719	> 0.0488	-0.6	> 12.5	-0.20
526-544	—	D-3720	> 12.5	-0.2	> 12.5	-0.10
523-541	—	D-3721	> 12.5	-0.2	> 12.5	-0.10
694-712	577-595	D-3722	0.0051033	-0.9	> 12.5	-0.20
1168-1186	1051-1069	D-3723	> 0.195	-0.5	> 12.5	-0.20
891-909	774-792	D-3724	0.00819	-0.9	> 12.5	-0.30
1052-1070	935-953	D-3725	> 12.5	-0.2	> 12.5	-0.20
1116-1134	99-1017	D-3726	0.00546	-0.5	> 12.5	-0.50
1228-1246	1111-1129	D-3727	0.006855	-0.9	> 12.5	-0.50
952-970	835-853	D-3728	> 12.5	-0.2	> 12.5	-0.30
975-993	858-876	D-3729	> 12.5	-0.1	> 12.5	-0.20
850-868	733-751	D-3730	> 12.5	-0.1	> 3.13	-0.20
288-306	288-306	D-3731	0.0106	-0.7	> 12.5	-0.10
1034-1052	917-935	D-3732	4.07	-0.5	> 12.5	0.20
1180-1198	1063-1081	D-3733	0.0311	-0.4	> 12.5	-0.20
897-915	780-798	D-3734	0.005955	-0.9	> 12.5	-0.20
1045-1063	928-946	D-3735	> 1.56	-0.6	> 12.5	-0.40
1225-1243	1108-1126	D-3736	> 0.0488	-0.6	> 12.5	-0.30
1073-1091	956-974	D-3737	0.086915	-0.7	> 12.5	-0.20
1260-1278	1143-1161	D-3738	0.68126	-0.9	> 12.5	-0.10
796-814	679-697	D-3739	0.024703	-0.9	> 12.5	-0.30
526-544	—	D-3740	> 12.5	-0.5	> 12.5	-0.10
523-541	—	D-3741	0.0982	-0.8	> 12.5	-0.10
891-909	774-792	D-3742	0.07107	-0.6	> 12.5	0.10
288-306	288-306	D-3743	0.025805	-0.6	> 12.5	-0.10
897-915	780-798	D-3744	0.03467	-0.8	> 12.5	0.10
888-906	771-789	D-3745	0.000851	-1.0	ND	ND
692-710	575-593	D-3746	0.00158	-0.9	ND	ND
692-710	575-593	D-3747	0.00289	-0.6	ND	ND
692-710	575-593	D-3748	0.0301	-0.6	ND	ND
692-710	575-593	D-3749	0.00133	-0.9	ND	ND
692-710	575-593	D-3750	0.00327	-0.6	ND	ND
692-710	575-593	D-3751	0.0043167	-1.0	0.0193	-0.70
692-710	575-593	D-3752	0.00545	-0.9	0.0507	-0.50
692-710	575-593	D-3753	0.00918	-1.0	> 25.0	0.10

Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 1197216.2	Duplex No.	Hep3B Transfected IC50 IP (µM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 IP (µM)	hASGR1 CHO Free Uptake Max Antagonist Activity
692-710	575-593	D-3754	0.0029367	-1.0	> 25.0	0.10
692-710	575-593	D-3755	0.00034033	-0.9	> 25.0	0.20
692-710	575-593	D-3756	0.0276	-0.5	> 25.0	0.10
692-710	575-593	D-3757	0.014369	-1.0	> 25.0	0.10
888-906	771-789	D-3758	0.0029492	-0.9	> 0.5	-0.20
691-709	574-592	D-3759	0.022895	-0.8	> 0.5	0.10
692-710	575-593	D-3760	0.0010037	-0.8	ND	ND
888-906	771-789	D-3761	> 0.0156	-0.3	ND	ND
692-710	575-593	D-3762	0.002224	-0.7	ND	ND
692-710	575-593	D-3763	0.001353	-0.8	ND	ND
692-710	575-593	D-3764	> 0.5	0.1	ND	ND
692-710	575-593	D-3765	0.0009435	-0.8	ND	ND
692-710	575-593	D-3766	0.000828	-0.7	ND	ND
692-710	575-593	D-3767	0.0037575	-0.9	0.01547	-0.80
692-710	575-593	D-3768	0.024725	-0.9	0.0662	-0.60
692-710	575-593	D-3769	0.00231	-0.4	0.0265	-0.20
692-710	575-593	D-3770	> 0.5	-0.5	ND	ND
692-710	575-593	D-3771	0.001805	-0.8	ND	ND
692-710	575-593	D-3772	0.001135	-0.9	ND	ND
888-906	771-789	D-3773	0.003285	-1.0	ND	ND
692-710	575-593	D-3774	0.004225	-1.0	0.0415	-0.60
692-710	575-593	D-3775	0.003205	-0.9	0.03335	-0.50
888-906	771-789	D-3776	0.25585	-0.7	> 12.5	-0.20
888-906	771-789	D-3777	0.12353	-1.0	> 12.5	-0.30
888-906	771-789	D-3778	0.00263	-0.76	ND	ND
1185-1203	1068-1086	D-3779	> 0.391	-0.58	ND	ND
1393-1411	1276-1294	D-3780	0.00496	-0.82	ND	ND
395-413	395-413	D-3781	> 0.195	-0.55	ND	ND
396-414	396-414	D-3782	0.00437	-0.79	ND	ND
1052-1070	935-953	D-3783	> 0.0977	-0.39	ND	ND
1073-1091	956-974	D-3784	0.00799	-0.69	ND	ND
1074-1092	957-975	D-3785	0.011	-0.66	ND	ND
1116-1134	99-1017	D-3786	> 12.5	-0.38	ND	ND
1168-1186	1051-1069	D-3787	> 12.5	-0.30	ND	ND
1180-1198	1063-1081	D-3788	0.00817	-0.70	ND	ND
1425-1444	1308-1327	D-3789	0.00365	-0.48	ND	ND
1341-1359	1224-1242	D-3790	> 6.25	-0.74	ND	ND
1424-1443	1307-1326	D-3791	0.00241	-0.74	ND	ND
991-1009	874-892	D-3792	> 12.5	-0.35	ND	ND
1081-1099	964-982	D-3793	> 12.5	-0.27	ND	ND
1164-1182	1047-1065	D-3794	> 12.5	-0.46	ND	ND

Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 1197216.2	Duplex No.	Hep3B Transfected IC50 IP (µM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 IP (µM)	hASGR1 CHO Free Uptake Max Antagonist Activity
563-581	—	D-3795	0.00349	-0.77	ND	ND
1225-1243	1108-1126	D-3796	> 0.781	-0.43	ND	ND
1260-1278	1143-1161	D-3797	> 0.781	-0.63	ND	ND
772-790	655-673	D-3798	> 0.781	-0.39	ND	ND
886-904	769-787	D-3799	0.0108	-0.76	ND	ND
891-909	774-792	D-3800	0.0039	-0.80	ND	ND
897-915	780-798	D-3801	0.00575	-0.76	ND	ND
888-906	771-789	D-3802	0.00406	-0.95	> 0.5	0.09
888-906	771-789	D-3803	0.01116	-0.91	> 0.5	-0.08
888-906	771-789	D-3804	0.00477	-0.97	> 0.5	-0.07
692-710	575-593	D-3805	> 0.5	0.07	> 0.5	-0.08
692-710	575-593	D-3806	> 0.5	0.13	> 0.5	0.04
692-710	575-593	D-3807	> 0.5	0.15	> 0.5	-0.18
692-710	575-593	D-3813	ND	ND	0.02753	-0.69
692-710	575-593	D-3814	ND	ND	0.00708	-0.70
692-710	575-593	D-3815	ND	ND	0.00987	-0.49
692-710	575-593	D-3816	ND	ND	No curve fit	0.074826181
692-710	575-593	D-3817	ND	ND	0.02035	-0.65
692-710	575-593	D-3818	ND	ND	0.02340	-0.68
692-710	575-593	D-3819	ND	ND	0.01316	-0.70
692-710	575-593	D-3820	ND	ND	0.02094	-0.75
692-710	575-593	D-3821	ND	ND	0.03345	-0.75
692-710	575-593	D-3822	ND	ND	0.03030	-0.65
692-710	575-593	D-3823	ND	ND	0.05948	-0.72
692-710	575-593	D-3824	ND	ND	0.01883	-0.43
692-710	575-593	D-3825	ND	ND	0.01320	-0.80
692-710	575-593	D-3826	ND	ND	0.07031	-0.76
692-710	575-593	D-3827	ND	ND	0.02455	-0.61
1186-1205	1069-1088	D-3828	ND	ND	No curve fit	0.07
170-189	170-189	D-3829	ND	ND	No curve fit	0.14
673-692	556-575	D-3830	ND	ND	No curve fit	0.18
668-687	551-570	D-3831	ND	ND	No curve fit	0.188
696-715	579-598	D-3832	ND	ND	0.01483	-0.78
168-187	168-187	D-3833	ND	ND	No curve fit	0.17
1075-1094	958-977	D-3834	ND	ND	No curve fit	0.13
1084-1103	967-986	D-3835	ND	ND	No curve fit	0.20
157-176	157-176	D-3836	ND	ND	No curve fit	-0.20
1423-1442	1306-1325	D-3837	ND	ND	No curve fit	0.13
970-989	853-872	D-3838	ND	ND	No curve fit	0.16
992-1011	875-894	D-3839	ND	ND	No curve fit	0.17

Target site of antisense sequence within NM_ 001671.4	Target site of antisense sequence within NM_ 1197216.2	Duplex No.	Hep3B Transfected IC50 IP (µM)	Hep3B Transfected Max Antagonist Activity	hASGR1 CHO Free Uptake IC50 IP (µM)	hASGR1 CHO Free Uptake Max Antagonist Activity
171-190	171-190	D-3840	ND	ND	No curve fit	-0.09
606-625	489-508	D-3841	ND	ND	No curve fit	0.06
393-412	393-412	D-3842	ND	ND	No curve fit	0.08
0632-0651	515-534	D-3843	ND	ND	No curve fit	0.17
0990-1009	873-892	D-3844	ND	ND	0.11508	-0.50
1050-1069	933-952	D-3845	ND	ND	No curve fit	-0.26
807-826	690-709	D-3846	ND	ND	No curve fit	-0.05
166-185	166-185	D-3847	ND	ND	No curve fit	0.19
1083-1102	966-985	D-3848	ND	ND	0.01367	-0.41
1064-1083	947-966	D-3849	ND	ND	No curve fit	0.17
328-347	328-347	D-3850	ND	ND	No curve fit	0.12
1079-1098	962-981	D-3851	ND	ND	No curve fit	0.09
1123-1142	1006-1025	D-3852	ND	ND	No curve fit	-0.04
605-624	488-507	D-3853	ND	ND	No curve fit	0.22
175-194	175-194	D-3854	ND	ND	No curve fit	0.29
692-710	575-593	D-3855	ND	ND	No curve fit	0.14
692-710	575-593	D-3856	ND	ND	No curve fit	0.11
692-710	575-593	D-3857	0.00532	-0.61	> 0.5	-0.44

[0263] Several of the GalNAc-ASGR1 siRNA conjugates were evaluated further for efficacy in knocking down ASGR1 mRNA levels in hepatocytes. Following the manufacturers protocol, human primary hepatocyte cells (Xenotech/Sekisui donor lot#HC3-38) were thawed in OptiThaw media (Xenotech cat#K8000). Cells were centrifuged and post media aspiration, resuspended in OptiPlate hepatocyte media (Xenotech cat#K8200) and plated into 96 well collagen coated plates (Greiner cat#655950). Following a 2-4 hour incubation period, media was removed and replaced with OptiCulture hepatocyte media (Xenotech cat#K8300). 2-4 hours following the addition of OptiCulture media, GalNAc-conjugated siRNAs were delivered to cells via free uptake (no transfection reagent). Cells were incubated 24-72 hours at 37°C and 5% CO_2. Cells were then lysed with Qiagen RLT buffer (79216) +1% 2-mercaptoethanol (Sigma, M-3148), and the lysates were stored at -20°C. RNA was purified using a Qiagen QIACube HT instrument (9001793) and a Qiagen RNeasy 96 QIACube HT Kit (74171) according to manufacturer's instructions. Samples were analyzed using a QIAxpert system (9002340).

[0264] cDNA was synthesized from RNA samples using the Applied Biosystems High Capacity cDNA Reverse Transcription kit (4368813), reactions were assembled according to

manufacturer's instructions, input RNA concentration varied by sample. Reverse transcription was carried out on a BioRad tetrad thermal cycler (model# PTC-0240G) under the following conditions: 25°C 10 minutes, 37°C 120 minutes, 85°C 5 minutes followed by (an optional) 4°C infinite hold. Droplet digital PCR (ddPCR) was performed using BioRad's QX200 AutoDG droplet digital PCR system according to manufacturer's instructions. Reactions were assembled into an Eppendorf clear 96 well PCR plate (951020303) using BioRad ddPCR Supermix for Probes (1863010), fluorescently labeled qPCR assays for ASGR1 (IDT Hs.PT.56a.24725395, ordered with primer to probe ratio 3.6:1, 9 nanomoles each forward and reverse primer (sequences listed below), 2.5 nanomoles 6-FAM/ZEN/IBFQ labeled probe (sequence listed below)) and GUSB (IDT Hs.PT.58v.27737538, ordered with primer to probe ratio 3.6:1, 9 nanomoles each forward and reverse primer (sequences listed below), 2.5 nanomoles HEX/ZEN/IBFQ labeled probe (sequence listed below)) and RNase free water (Ambion, AM9937). Final primer/probe concentration was 900nM/250nM respectively, input cDNA concentration varied among wells.

[0265] Droplets were formed using a BioRad Auto DG droplet generator (1864101) set up with manufacturer recommended consumables (BioRad DG32 cartridges 1864108, BioRad tips 1864121, Eppendorf blue 96well PCR plate 951020362, BioRad droplet generation oil for probes 1864110 and a BioRad droplet plate assembly). Droplets were amplified on a BioRad C1000 touch thermal cycler (1851197) using the following conditions: enzyme activation 95°C 10 minutes, denaturation 94°C 30 seconds followed by annealing/extension 60°C for one minute, 40 cycles using a 2°C/second ramp rate, enzyme deactivation 98°C 10 minutes followed by (an optional) 4°C infinite hold. Samples were then read on a BioRad QX200 Droplet Reader measuring FAM/HEX signal that correlated to ASGR1 or GUSB concentration, respectively. Data was analyzed using BioRad's QuantaSoft software package. Samples were gated by channel (fluorescent label) to determine the concentration per sample. Each sample was then expressed as the ratio of the concentration of the gene of interest (ASGR1)/concentration of the housekeeping gene (GUSB) to control for differences in sample loading. Data was then imported into Genedata Screener, where each test siRNA was normalized to the median of the neutral control wells (buffer only) and was expressed as the POC (percent of control). IC50 and max activity are reported in Table 10 below.

ddPCR Assay Sequences

ASGR1:

Primer 1: CAGGCTGGAGTGATCTTCA (SEQ ID NO: 4688)

Primer 2: TTCAGCAACTTCACAGCGA (SEQ ID NO: 4689)

Probe: 56-FAM/TCTTTCTTC (SEQ ID NO: 4690) /ZEN/CCACATTGCCTCCCTG (SEQ ID NO: 4691)/3IABkFQ/

GUSB:

Primer 1: GTTTTTGATCCAGACCCAGATG (SEQ ID NO: 4692)

Primer 2: GCCCATTATTCAGAGCGAGTA (SEQ ID NO: 4693)

Probe: 5HEX/TGCAGGGTT (SEQ ID NO: 4694) /ZEN/TCACCAGGATCCAC (SEQ ID NO: 4695)/3IABkFQ/

Table 10. ASGR1 mRNA *in vitro* knockdown by select GalNAc-ASGR1 conjugates

Duplex No.	Primary Human Hepatocyte ddPCR IC50 (μM)	Primary Human Hepatocyte ddPCR Max Activity
D-3779	0.0302	-0.46
D-3780	0.0040	-0.80
D-3781	0.0158	-0.40
D-3782	0.0084	-0.79
D-3783	—	-0.19
D-3784	0.0281	-0.42
D-3785	0.0249	-0.40
D-3786	0.0267	-0.32
D-3787	—	0.03
D-3788	0.0127	-0.49
D-3789	—	-0.26
D-3790	0.0046	-0.34
D-3791	0.0041	-0.81
D-3792	—	-0.03
D-3793	—	-0.09
D-3794	—	-0.05
D-3795	0.0022	-0.66
D-3796	—	0.17
D-3797	0.0875	-0.45
D-3798	0.0114	-0.38

Duplex No.	Primary Human Hepatocyte ddPCR IC50 (μM)	Primary Human Hepatocyte ddPCR Max Activity
D-3799	0.0135	-0.36
D-3800	0.0094	-0.73
D-3801	0.0159	-0.57

[0266] The majority of the tested GalNAc-siRNA conjugates reduced ASGR1 mRNA levels in primary human hepatocytes indicating that the conjugates were effectively delivered to the cells and the siRNAs were active. Compounds D-3780, D-3782, D-3791, D-3795, and D-3800 were the most potent and had the highest maximum inhibitory activity of the conjugates evaluated in this assay.These compounds also exhibited potent inhibiton of ASGR1 protein expression when transfected into Hep3B cells. See Hep3B transfection assay data in Table 9.

Example 9. In Vivo Efficacy of GalNAc-ASGR1 siRNA Conjugates

[0267] To assess whether the GalNAc-ASGR1 siRNA conjugates could effectively silence ASGR1 expression *in vivo*, conjugates exhibiting the best *in vitro* inhibition as measured by ddPCR (Table 10) were administered to ASGR1 knockout mice expressing the human ASGR1 gene. 10-12 week old ASGR1 knockout mice (The Jackson Laboratory) were i.v. injected with an adeno-associated virus (AAV) encoding the human ASGR1 gene (AAV-hASGR1) at a dose of 1×10^{12} genome copies (GC) per animal. Two weeks following AAV-hASGR1 injection, mice received a s.c. injection of buffer or the indicated GalNAc-siRNA conjugate (compounds D-3752, D-3779, D-3780, D-3782, D-3784, D-3785, D-3788, D-3791, D-3795, D-3797, D-3799, D-3800, and D-3801) at 5 mg/kg body weight in 0.25 ml buffer (n=6 each group). At day 8 following compound administration, three animals in each treatment group were euthanized and harvested for further analysis. The remaining three animals in each treatment group were harvestred at day 15 following compound administration. Serum and livers were collected from all animals. Total RNA isolated from the livers of the animals was processed for qPCR analysis to assess human ASGR1 mRNA levels. Serum levels of alkaline phosphatase (ALP) were measured by a clinical analyzer (AU400 Chemistry Analyzer, Olympus). Elevated levels of ALP in the serum has been reported to correlate with reduced serum levels of non-HDL cholesterol and reduced risk of coronary artery disease (Nioi *et al.*, New England Journal of Medicine, Vol. 374(22):2131-2141, 2016), and thus serves as useful biomarker.

[0268] As shown in Figure 6A, several of the GalNAc-siRNA conjugates reduced human ASGR1 mRNA levels 8 days following administration. Compounds D-3752, D-3779, D-3782, D-3788, D-3799, and D-3800 were particularly effective. Suppression of hASGR1 mRNA levels 15 days following compound administration was observed for some of the compounds. Compounds D-3752 and D-3788 were especially effective at this time point. Figure 6B shows serum ALP levels at the same time points. Generally, elevation of serum ALP levels correlated with knockdown of hASGR1 mRNA. Some of the compounds (e.g. D-3752, D-3782) produced elevation of serum ALP to levels similar to those observed in ASGR1 knockout animals, which represent maximum inhibition of ASGR1 expression. The results of the *in vivo* experiments demonstrate that the GalNAc-ASGR1 siRNA conjugates, when administered subcutaneously, effectively suppress ASGR1 gene expression in the liver and modulate serum ALP, a biomarker of efficacy in treating coronary artery disease.

Example 10. ASGR1 Antibody as an Alternative Delivery Mechanism for siRNA Molecules

[0269] The purpose of the experiments described in this example was to determine whether a monoclonal antibody against ASGR1 could be used to deliver ASGR1 siRNA molecules to the liver. An anti-ASGR1 monoclonal antibody with an E272C mutation in its heavy chain according to the EU numbering scheme (anti-ASGR1 cys mAb, 200 mg) was incubated with 50 mL solution of 2.5 mM cystamine and 2.5 mM cysteamine in 40 mM HEPES buffer, pH 7.5-8.5 for 15-20 h at RT. The amino acid sequences of the heavy chain and light chain of the anti-ASGR1 antibody are provided below as SEQ ID NOs: 4696 and 4697, respectively. The reaction mixture was filtered using a 0.22 μm filter, and diluted to 250 mL with 100 mM sodium acetate buffer pH 5. Cation exchange chromatography was performed to purify the bis-cysteamine-capped anti-ASGR1 cys mAb from the reaction mixture. First, 250 mL of reaction mixture diluted in 100 mM sodium acetate buffer pH 5 was loaded onto 25 mL SP HP column (GE Healthcare Life Sciences) at 5 mL/min. The column was washed with 2 column volumes (CV) of 100 mM sodium acetate pH 5, followed by a 0-20% gradient of 100 mM sodium acetate with 1.2 M sodium chloride (NaCl) pH 5 over 10 CV. The main peak containing bis-cysteamine-capped anti-ASGR1 cys mAb was collected and buffer exchanged into 10 mM sodium acetate with 9% sucrose pH 5.2 via dialysis.

Anti-ASGR1 Cys mAb Heavy Chain

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDG SNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSSPYGMDVWGQ GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPCVKFNWYVDGVE VHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 4696)

Anti-ASGR1 Cys mAb Light Chain

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASSLQSGV PSRFSASGSGTDFTLTISSLQPEDFATYYCQQSDSFPRTFGQGTKVEIKRTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 4697)

[0270] A siRNA duplex containing a sense strand having a sequence (5′ to 3′) of GfsusGfgGfaAfgAfAfAfgAfuGfaAfgUfuUf (SEQ ID NO: 4698) and an antisense strand having a sequence (5′ to 3′) of asCfsuUfcAfuCfuuuCfuUfcCfcAfcsUfsu (SEQ ID NO: 4699) was used to generate the mAb-siRNA conjugate. The notations in the sense and antisense sequences are the same as those used for the nucleotide sequences in Tables 6 and 8 described above. The siRNA duplex had a 19 base pair duplex region with a 2 nucleotide overhang at the 3′ end of the sense and antisense strands. The sense strand of the siRNA duplex had a homoserine-aminohexanoic acid (hSer-Ahx) modification at its 3′ end. The siRNA duplex was formed in 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4 upon heating to 90 °C for 5 min and cooling to RT over 30 min. The 3′ hSer-Ahx siRNA duplex was further functionalized with a bromoacetyl group using succinimidyl bromoacetate (SBA) (Figure 7A). The 3′ hSer-Ahx siRNA duplex in 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4 was incubated with 10-20 equivalents of SBA at RT for 1 h. Then, an additional 10-20 equivalents of SBA were added, and the reaction mixture was incubated at RT for another hour. The reaction was

monitored using LC-TOF. Excess SBA was removed from the 3′-bromoacetyl-siRNA by buffer exchanging with 50 mM sodium phosphate, 2 mM ethylenediaminetetraacetic acid (EDTA), pH 7.5 using Amicon-15 3k spin concentrators.

[0271] Bis-cysteamine-capped anti-ASGR1 cys mAb (~5 mg/mL in 10 mM sodium acetate with 9% sucrose) was partially reduced using 3-4 equivalents of tris(2-carboxyethyl)phosphine (TCEP) or triphenylphosphine-3,3′,3′′-trisulfonic acid trisodium salt (TPPTS) at RT for 60-90 min (Figure 7B). The reaction was monitored using analytical cation exchange chromatography. TCEP or TPPTS was removed, and partially reduced cys mAb was buffer exchanged into 50 mM sodium phosphate buffer pH 7.5 containing 2 mM EDTA. To the partially reduced cys mAb was added 6-10 equivalents of dehydroascorbic acid (DHAA), and oxidation was carried out at RT until only trace amount of reduced mAb species were observed (30-180 min). Without removing DHAA, 6 equivalents of bromoacetyl-siRNA duplex were added to the reaction mixture, and the alkylation was carried out at RT for 15-48 h (Figure 7B). Excess siRNA duplex and small molecule reagents were removed by size exclusion chromatography (SEC) with isocratic flow of 0.17 M potassium phosphate, 0.21 M potassium chloride, 10% (v/v) isopropanol, pH 7. The anti-ASGR1 mAb-siRNA conjugates with RNA-to-antibody ratio (RAR) of 1 and 2 were separated using anion exchange chromatography. The SEC pool was diluted in 20 mM Tris-HCl pH 7, 100 mM NaCl and loaded onto Q HP column (GE Healthcare Life Sciences). The column was washed with 5 CV of 20 mM Tris-HCl pH 7, 100 mM NaCl, followed by a gradient elution with 20 mM Tris-HCl pH 7 containing 0.4 to 1 M NaCl over 20 CV. The purified RAR1 (compound 3549) and RAR2 (compound 3550) products were buffer exchanged into Dulbecco's phosphate-buffered saline (DPBS) using spin concentration.

[0272] The mAb-siRNA conjugates were evaluated for activity in a free uptake assay to determine whether the antibody could effectively deliver the siRNA to human primary hepatocytes to inhibit ASGR1 expression. Various concentrations (0.18 nM to 400 nM) of the anti-ASGR1 mAb conjugated to 1 or 2 ASGR1 siRNA molecules (compounds 3549 and 3550, respectively) were incubated with human primary hepatocytes for four days. RNA was isolated from the cells and processed for droplet digital PCR analysis to assess ASGR1 mRNA levels as described in Example 8. The results of the *in vitro* assay are shown in Figure 8. The anti-ASGR1 mAb conjugated to 1 or 2 ASGR1 siRNA molecules demonstrated 40-60% knockdown of ASGR1 mRNA. The unconjugated anti-ASGR1 cys mAb (PL-53515) was used as a control.

[0273] Next, the anti-ASGR1 mAb-siRNA conjugates were tested for *in vivo* efficacy. Nine-week old C57Bl/6 wild-type mice were injected subcutaneously or intravenously with compound 3550 (30 mg/kg or 60 mg/kg) or a GalNAc-conjugated siRNA control. The GalNAc-conjugated siRNA control had a sense strand having a sequence of SEQ ID NO: 4698 and an antisense strand having a sequence of SEQ ID NO: 4699 and was conjugated to a triantennary GalNAc moiety at the 3′ end of the sense strand. Serum and livers were collected from the animals at days 2, 4, 8, and 15 following compound administration. Total RNA isolated from the livers of the animals was processed for qPCR analysis to assess ASGR1 mRNA levels. ASGR1 protein expression in the liver was measured by ELISA. Serum levels of alkaline phosphatase (ALP) were measured by a clinical analyzer (AU400 Chemistry Analyzer, Olympus).

[0274] The mAb-siRNA conjugate 3550 effectively delivered siRNA to its mRNA target *in vivo*. The highest knockdown level (~80%) resulted from 30 mpk i.v. administration of 3550 in wild-type mice measured on day 8 (Figure 9A). The ASGR1 protein expression in liver was also measured, and >80% reduction in ASGR1 protein was achieved in the 30 mpk i.v. group, consistent with the level of mRNA knockdown (Figure 9B). Nadir of protein knockdown was day 8 for the anti-ASGR1 mAb-siRNA conjugate, dosed either i.v. or s.c., and day 4 for the GalNAc-siRNA conjugate. The mAb-siRNA conjugate 3550 resulted in 2-4 fold increase in ALP on day 8, corresponding to decreased ASGR1 mRNA level and protein expression (Figure 10). The anti-ASGR1 antibody alone did not induce any increase in ALP even at 100 mg/kg (data not shown).

[0275] Taken together, the results of these experiments demonstrate that siRNA duplexes can be effectively delivered to the liver using an anti-ASGR1 antibody in lieu of a GalNAc moiety. The mAb-siRNA conjugates exhibited comparable efficacy to a GalNAc-siRNA conjugate in terms of inhibition of liver ASGR1 expression and elevation of serum ALP levels, a biomarker of target inhibition.

[0276] All publications, patents, and patent applications discussed and cited herein are hereby incorporated by reference in their entireties. It is understood that the disclosed invention is not limited to the particular methodology, protocols and materials described as these can vary. It is also understood that the terminology used herein is for the purposes of describing particular embodiments only and is not intended to limit the scope of the appended claims.

[0277] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

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CLAIMS

1. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is complementary to an ASGR1 mRNA sequence, and wherein said region comprises (i) the sequence of nucleotides 1-19 of SEQ ID NO: 2651, (ii) the sequence of nucleotides 2-19 of SEQ ID NO: 2651, or (iii) the sequence of SEQ ID NO: 2651.

2. The RNAi construct of claim 1, wherein the sense strand comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length.

3. The RNAi construct of claim 2, wherein the duplex region is about 19 to about 21 base pairs in length.

4. The RNAi construct of claim 1, wherein the sense strand and the antisense strand are each about 19 to about 27 nucleotides in length.

5. The RNAi construct of claim 1, wherein the sense strand and the antisense strand are each about 21 to about 25 nucleotides in length.

6. The RNAi construct of any one of claims 1 to 5, wherein the RNAi construct comprises at least one blunt end.

7. The RNAi construct of any one of claims 1 to 5, wherein the RNAi construct comprises at least one nucleotide overhang of 1 to 4 unpaired nucleotides.

8. The RNAi construct of claim 7, wherein the nucleotide overhang has 2 unpaired nucleotides.

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9. The RNAi construct of claim 7 or 8, wherein the RNAi construct comprises a nucleotide overhang at the 3′ end of the sense strand, the 3′ end of the antisense strand, or the 3′ end of both the sense strand and the antisense strand.

10. The RNAi construct of any one of claims 1 to 9, wherein the RNAi construct comprises at least one modified nucleotide.

11. The RNAi construct of claim 10, wherein the modified nucleotide is a 2′-modified nucleotide.

12. The RNAi construct of claim 10, wherein the modified nucleotide is a 2′-fluoro modified nucleotide, a 2′-O-methyl modified nucleotide, a 2′-O-methoxyethyl modified nucleotide, a 2′-O-allyl modified nucleotide, a bicyclic nucleic acid (BNA), or combinations thereof.

13. The RNAi construct of claim 10, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.

14. The RNAi construct of claim 13, wherein the modified nucleotides are 2′-O-methyl modified nucleotides, 2′-fluoro modified nucleotides, or combinations thereof.

15. The RNAi construct of any one of claims 1 to 14, wherein the RNAi construct comprises at least one phosphorothioate internucleotide linkage.

16. The RNAi construct of claim 15, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at the 3′ end of the antisense strand.

17. The RNAi construct of claim 15, wherein the RNAi construct comprises two consecutive phosphorothioate internucleotide linkages at both the 3′ and 5′ ends of the antisense strand and two consecutive phosphorothioate internucleotide linkages at the 5′ end of the sense strand.

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18. The RNAi construct of any one of claims 1 to 17, wherein the sense strand comprises (i) the sequence of nucleotides 1-19 of SEQ ID NO: 1148, (ii) the sequence of nucleotides 2-19 of SEQ ID NO: 1148, or (iii) the sequence of SEQ ID NO: 1148.

19. The RNAi construct of any one of claims 1 to 18, wherein:

(a) the sense strand comprises the sequence of SEQ ID NO: 1148 and the antisense strand comprises the sequence of SEQ ID NO: 2651; or

(b) the sense strand comprises the sequence of SEQ ID NO: 1147 and the antisense strand comprises the sequence of SEQ ID NO: 2650.

20. The RNAi construct of claim 19, wherein:

(a) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3050 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3701;

(b) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3051 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3702;

(c) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3065 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3716;

(d) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3067 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3718;

(e) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3071 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 3722;

(f) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 4420 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 4600; or

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(g) the sense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 4698 and the antisense strand comprises the sequence of modified nucleotides according to SEQ ID NO: 4699.

21. The RNAi construct of any one of claims 1 to 20, wherein the RNAi construct further comprises a ligand.

22. The RNAi construct of claim 21, wherein the ligand comprises a cholesterol moiety, a vitamin, a steroid, a bile acid, a folate moiety, a fatty acid, a carbohydrate, a glycoside, or antibody or antigen-binding fragment thereof.

23. The RNAi construct of claim 21, wherein the ligand comprises galactose, galactosamine, N-acetyl-galactosamine, a multivalent galactose moiety, or a multivalent N-acetyl-galactosamine moiety.

24. The RNAi construct of any one of claims 21 to 23, wherein the ligand is covalently attached to the sense strand optionally through a linker.

25. The RNAi construct of claim 24, wherein the ligand is covalently attached to the 3′ end or 5′ end of the sense strand.

26. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to 25 and a pharmaceutically acceptable carrier, excipient, or diluent.

27. A method for reducing the expression of ASGR1 in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 25.

28. The method of claim 27, wherein the patient is diagnosed with or at risk for coronary artery disease or has a history of myocardial infarction.

29. The method of claim 27, wherein the patient has elevated levels of non-HDL cholesterol.

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30. A method for reducing non-HDL cholesterol in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 25.

31. A method for treating or preventing cardiovascular disease in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 25.

32. The method of claim 31, wherein the cardiovascular disease is coronary artery disease or myocardial infarction.

33. A method for reducing the risk of myocardial infarction in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 25.

34. The method of any one of claims 27 to 33, wherein the RNAi construct is administered to the patient via a parenteral route of administration.

35. The method of claim 34, wherein the parenteral route of administration is intravenous or subcutaneous.

36. Use of the RNAi construct of any one of claims 1 to 25 in the manufacture of a medicament for reducing the expression of ASGR1 in a patient.

37. Use of the RNAi construct of any one of claims 1 to 25 in the manufacture of a medicament for reducing non-HDL cholesterol in a patient.

38. Use of the RNAi construct of any one of claims 1 to 25 in the manufacture of a medicament for treating or preventing cardiovascular disease in a patient.

39. Use of the RNAi construct of any one of claims 1 to 25 in the manufacture of a medicament for reducing the risk of myocardial infarction in a patient.

1 CCCAAACGGT GCACGGAAGA GTGAGGTGAC TGGCATGTGT GGGGGCAACA CGATTCTCCT

61 CCCTGGGGAG CAGAGCAGAG GCAACCCATC CCCCACTCCC ACCCCCACAC TCCCCTAAGT

121 TCCAATCCAT TTCCACCTCT GTTTACTGTC CAAAGTCCCG GGCACTGGAG ATGCCACGTT

181 TGGCGTGCTT GGACACACAG ACACGCAGAC ACAGAGACAC CGGGGCCCAG GGCCCTCCTA

241 TGGACCCTGC CCGCTCCCCT CCCATTGTCC ACGGCTGTCC GCCCACCCCC ATTCTCCAAG

301 CTTCAGCCCC CTCCTTAGTT CGGCATCTGC ACAGCACTGA AGAACCTGGG AATCAGACCC

361 TGAGACCCTG AGCAATCCCA GGTCCAGCGC CAGCCCTATC ATGACCAAGG AGTATCAAGA

421 CCTTCAGCAT CTGGACAATG AGGAGAGTGA CCACCATCAG CTCAGAAAAG GGCCACCTCC

481 TCCCCAGCCC CTCCTGCAGC GTCTCTGCTC CGGACCTCGC CTCCTCCTGC TCTCCCTGGG

541 CCTCAGCCTC CTGCTGCTTG TGGTTGTCTG TGTGATCGGA TCCCAAAACT CCCAGCTGCA

601 GGAGGAGCTG CGGGGCCTGA GAGAGACGTT CAGCAACTTC ACAGCGAGCA CGGAGGCCCA

661 GGTCAAGGGC TTGAGCACCC AGGGAGGCAA TGTGGGAAGA AAGATGAAGT CGCTAGAGTC

721 CCAGCTGGAG AAACAGCAGA AGGACCTGAG TGAAGATCAC TCCAGCCTGC TGCTCCACGT

781 GAAGCAGTTC GTGTCTGACC TGCGGAGCCT GAGCTGTCAG ATGGCGGCGC TCCAGGGCAA

841 TGGCTCAGAA AGGACCTGCT GCCCGGTCAA CTGGGTGGAG CACGAGCGCA GCTGCTACTG

901 GTTCTCTCGC TCCGGGAAGG CCTGGGCTGA CGCCGACAAC TACTGCCGGC TGGAGGACGC

961 GCACCTGGTG GTGGTCACGT CCTGGGAGGA GCAGAAATTT GTCCAGCACC ACATAGGCCC

1021 TGTGAACACC TGGATGGGCC TCCACGACCA AAACGGGCCC TGGAAGTGGG TGGACGGGAC

1081 GGACTACGAG ACGGGCTTCA AGAACTGGAG GCCGGAGCAG CCGGACGACT GGTACGGCCA

1141 CGGGCTCGGA GGAGGCGAGG ACTGTGCCCA CTTCACCGAC GACGGCCGCT GGAACGACGA

1201 CGTCTGCCAG AGGCCCTACC GCTGGGTCTG CGAGACAGAG CTGGACAAGG CCAGCCAGGA

1261 GCCACCTCTC CTTTAATTTA TTTCTTCAAT GCCTCGACCT GCCGCAGGGG TCCGGGATTG

1321 GGAATCCGCC CATCTGGGGG CCTCTTCTGC TTTCTCGGGA ATTTTCATCT AGGATTTTAA

1381 GGGAAGGGGA AGGATAGGGT GATGTTCCGA AGGTGAGGAG CTTGAAACCC GTGGCGCTTT

1441 CTGCAGTTTG CAGGTTATCA TTGTGAACTT TTTTTTTTTA AGAGTAAAAA GAAATATACC

1501 TAAAAAAAAA AAAAAAAAA (SEQ ID NO: 1)

FIG. 1A

1 CCCAAACGGT GCACGGAAGA GTGAGGTGAC TGGCATGTGT GGGGGCAACA CGATTCTCCT

61 CCCTGGGGAG CAGAGCAGAG GCAACCCATC CCCCACTCCC ACCCCCACAC TCCCCTAAGT

121 TCCAATCCAT TTCCACCTCT GTTTACTGTC CAAAGTCCCG GGCACTGGAG ATGCCACGTT

181 TGGCGTGCTT GGACACACAG ACACGCAGAC ACAGAGACAC CGGGGCCCAG GGCCCTCCTA

241 TGGACCCTGC CCGCTCCCCT CCCATTGTCC ACGGCTGTCC GCCCACCCCC ATTCTCCAAG

301 CTTCAGCCCC CTCCTTAGTT CGGCATCTGC ACAGCACTGA AGAACCTGGG AATCAGACCC

361 TGAGACCCTG AGCAATCCCA GGTCCAGCGC CAGCCCTATC ATGACCAAGG AGTATCAAGA

421 CCTTCAGCAT CTGGACAATG AGGAGAGTGA CCACCATCAG CTCAGAAAAG ACTCCCAGCT

481 GCAGGAGGAG CTGCGGGGCC TGAGAGAGAC GTTCAGCAAC TTCACAGCGA GCACGGAGGC

541 CCAGGTCAAG GGCTTGAGCA CCCAGGGAGG CAATGTGGGA AGAAAGATGA AGTCGCTAGA

601 GTCCCAGCTG GAGAAACAGC AGAAGGACCT GAGTGAAGAT CACTCCAGCC TGCTGCTCCA

661 CGTGAAGCAG TTCGTGTCTG ACCTGCGGAG CCTGAGCTGT CAGATGGCGG CGCTCCAGGG

721 CAATGGCTCA GAAAGGACCT GCTGCCCGGT CAACTGGGTG GAGCACGAGC GCAGCTGCTA

781 CTGGTTCTCT CGCTCCGGGA AGGCCTGGGC TGACGCCGAC AACTACTGCC GGCTGGAGGA

841 CGCGCACCTG GTGGTGGTCA CGTCCTGGGA GGAGCAGAAA TTTGTCCAGC ACCACATAGG

901 CCCTGTGAAC ACCTGGATGG GCCTCCACGA CCAAAACGGG CCCTGGAAGT GGGTGGACGG

961 GACGGACTAC GAGACGGGCT TCAAGAACTG GAGGCCGGAG CAGCCGGACG ACTGGTACGG

1021 CCACGGGCTC GGAGGAGGCG AGGACTGTGC CCACTTCACC GACGACGGCC GCTGGAACGA

1081 CGACGTCTGC CAGAGGCCCT ACCGCTGGGT CTGCGAGACA GAGCTGGACA AGGCCAGCCA

1141 GGAGCCACCT CTCCTTTAAT TTATTTCTTC AATGCCTCGA CCTGCCGCAG GGGTCCGGGA

1201 TTGGGAATCC GCCCATCTGG GGGCCTCTTC TGCTTTCTCG GGAATTTTCA TCTAGGATTT

1261 TAAGGGAAGG GGAAGGATAG GGTGATGTTC CGAAGGTGAG GAGCTTGAAA CCCGTGGCGC

1321 TTTCTGCAGT TTGCAGGTTA TCATTGTGAA CTTTTTTTTT TTAAGAGTAA AAAGAAATAT

1381 ACCTAAAAAA AAAAAAAAAA AA (SEQ ID NO: 2)

FIG. 1B

1 CACATGGGCC CTGGATGGAC CCTGTCCCCT CCCCTCCCAT TGCCCAGGGC TCTTCACCTG

61 GTTCTTCAGG CTTCAGCCCC CTCCTTAGCC TGGGCTCTTC GTGGTGCTGA GGGACCTTCA

121 GTCCGGATCC AGTGCCATCA TGACAAAGGA TTATCAAGAT TTCCAGCACC TGGACAATGA

181 TAATGACCAT CATCAACTCC GGAGAGGGCC GCCTCCCACT CCACGGCTCT TGCAGCGACT

241 CTGCTCTGGA TCCCGCCTCC TCCTGCTCTC CTCGAGCCTC AGCATTCTGT TGCTGGTGGT

301 TGTCTGTGTG ATCACATCCC AAAATTCCCA ACTCCGGGAA GATCTGCTGG CTCTAAGGCA

361 GAATTTCAGC AACCTCACTG TGAGCACTGA GGACCAGGTC AAGGCCCTGA GCACCCAGGG

421 AAGTAGTGTG GGAAGAAAGA TGAAGTTAGT GGAGTCGAAG CTGGAAAAAC AGCAGAAGGA

481 TCTGACTGAA GATCACTCCA GTTTGCTACT GCACGTGAAG CAGTTAGTGT CTGACGTGCG

541 AAGCTTGAGC TGCCAGATGG CTGCATTTCG GGGCAATGGC TCTGAAAGGA CCTGCTGCCC

601 CATCAACTGG GTGGAGTATG AAGGCAGCTG CTACTGGTTC TCCAGCTCTG TGAGGCCTTG

661 GACTGAAGCT GACAAGTACT GCCAGCTGGA AAATGCCCAT CTGGTGGTGG TGACCTCCAG

721 GGATGAGCAG AACTTCCTCC AGCGCCACAT GGGCCCCTTA AACACTTGGA TTGGCCTAAC

781 TGACCAGAAC GGGCCCTGGA AATGGGTGGA TGGAACAGAC TACGAGACAG GCTTCCAGAA

841 TTGGAGACCA GAGCAGCCAG ATAACTGGTA CGGACATGGG CTTGGAGGAG GCGAGGACTG

901 TGCCCACTTC ACGACGGATG GCCGCTGGAA TGACGACGTC TGCAGGAGGC CCTACCGCTG

961 GGTCTGTGAG ACAAAGTTGG ATAAGGCTAA TTAGGAACCT TCCTTCCCCT CATTTATATC

1021 CTTAATTCCT TGAGCTGCTG AGGTTTAGAA CTGGTAGAGC CTACCTAAGG GTCTCCCCAT

1081 CTCCAGGAAC TCTCATGTAG GATTTTTAAA GGACCGGTAA AGAATGGTGT TTGAGAAATG

1141 GTGTATGATG CCTGGTGGTG GTAGGGGTGC GTATTGAAAC CCAGCGCGCA GTTCTCTTCT

1201 GTCAGCTTGT TTTTTTTAGA GTAAAAGGAA GAGAAATAAA AGTTC (SEQ ID NO: 3011)

FIG. 2

1 CTGTCCACCT GGTTCTTCAG GCTTCAGCCC CCTCCTTAGC CTGGGCTCTT CGTGGTGCTG

61 AGGGACCTTC AGTCCTGCCC CAGTGCTATC ATGACAAAGG ATTATCAAGA TTTCCAGCAC

121 TTGGACAATG AGAACGACCA CCATCAACTC CAGAGAGGGC CACCTCCCGC TCCAAGGCTC

181 TTGCAGCGAC TCTGCTCTGG ATTCCGTCTC TTCCTGCTTT CCCTGGGCCT CAGCATCCTG

241 CTGCTGGTGG TTGTCTGTGT GATCACATCC CAAAATTCCC AACTCCGGGA AGATCTGCGG

301 GTTCTAAGGC AGAATTTCAG CAACTTTACC GTGAGCACTG AGGACCAGGT CAAGGCCCTG

361 ACCACCCAGG GAGAGAGAGT GGGAAGAAAG ATGAAGTTAG TCGAGTCACA GCTGGAAAAA

421 CATCAGGAGG ATCTGAGGGA AGACCACTCT AGATTGCTAC TGCATGTAAA GCAGTTAGTG

481 TCTGACGTGC GAAGCTTGAG CTGCCAGATG GCCGCACTTC GGGGCAATGG CTCTGAAAGG

541 ATCTGCTGCC CCATCAACTG GGTGGAGTAT GAAGGCAGCT GCTACTGGTT CTCCAGCTCT

601 GTGAAGCCTT GGACGGAAGC TGACAAGTAC TGCCAGCTGG AGAACGCCCA CCTGGTGGTG

661 GTGACTTCCT GGGAGGAGCA GAGATTCGTC CAGCAACACA TGGGCCCCTT AAATACTTGG

721 ATTGGCCTAA CTGACCAGAA CGGACCCTGG AAATGGGTGG ATGGGACAGA CTATGAGACA

781 GGCTTCAAGA ACTGGAGACC AGGGCAGCCA GATGACTGGT ACGGACATGG GCTTGGAGGG

841 GGTGAAGACT GTGCCCACTT CACCACCGAT GGCCACTGGA ATGATGACGT CTGCAGGAGG

901 CCCTACCGCT GGGTCTGTGA GACAGAGTTG GGCAAGGCCA ATTAGGAGCC TCCATTCCCC

961 TGATTTATTT CCTGAGTGCC TTGAGCTGTG AGGCTTAGAG TTGGGAGGTC CTACTCAAGG

1021 GTCTCCCCAT CTTTGGGAAC TTTCATCTAG GATTTTAAGG GGCTGGTAAA GAATGGTGTT

1081 TGAGGAATGT GGTATGATGC CTGGTGGTGG TGGTGGTGGT GGTTATTGGA ACCCATGACA

1141 CTTTGTGCAG TGTGCAGCTT ACTACTGCCA ACTTGTTTTT GAGAGTAAAA GAAGGAAGAT

1201 AAAC (SEQ ID NO: 3012)

FIG. 3

1 TTACTGTCCA AAGTCCCGGG CACTGGAGAT GCCACGTTTG GCGTGCTTGG ACACACAGAC

61 ACGCAGACAC AGAGACACCG GGGCCCAGGG CCCTCCTATG GACCCTGCCC GCTCCCACTC

121 CATCGTCCAC GGCTGTCCAC CCACCCCCAT TCTCCAAGCT TCAGCCCCCC TCCTTAGTCC

181 GGCATCTGCA CAGCACTGAA GAACCTGGGA GTCAGACCCT GAGACCCCGA GCAACTCTAG

241 TCCTCGTGAG CCCCCACCTC AGCCCCAGCC TCAGCCTTGA CTCAGTCCCA GCTCCAGCAC

301 CAGCCCTATC ATGACCAAGG AGTATCAGGA CCTGCAGCAT CTGGACAATG AGGAGAGTGA

361 CCACCATCAG CTCGGAAAAG GGCCACCTCC TCCGCAGTCC CTCCTGCGGC GTCTCTGCTC

421 CGGCCCTCGC CTCCTCCTGC TCTCCCTGGG CCTCAGCCTC CTGCTGCTGG TGGTTGTCTG

481 TGTGATCGGA TCCCAAAACG CCCAGCTGCA GCGGGAGCTG CGGGGCCTGA GAGAGACGCT

541 CAGCAACTTC ACAGCGAGCA CCGAGGCCCA GGTCAAGGGC TTGAGCACCC AGGGAGGCAA

601 TGTGGGAAGA AAGATGAAGT CGCTGGAGTC CCAGCTGGAG AAACAGCAGA AGGACTTGAG

661 TGAAGATCAC TCCAGCCTGC TGCTCCACGT GAAGCAGTTC GTGTCTGACC TGCGGAGCCT

721 GAGCTGTCAG ATGGCGGCGC TCCAGGGCAA TGGCTCGGAA AGGGCCTGCT GCCCAGTCAA

781 CTGGGTGGAG CACGAGCGCA GCTGCTACTG GTTCTCTCGC TCCGGGAAGG CCTGGGCCGA

841 CGCCGACAAC TACTGCCGGC TGGAGGACGC GCACCTGGTG GTGGTCACGT CCTGGGAGGA

901 GCAGAAATTT GTCCAGCACC ACATAGGTCC TGTGAACACC TGGATGGGCC TCCACGACCA

961 AAACGGGCCC TGGAAGTGGG TGGACGGGAC GGACTACGAG ACGGGCTTCA AGAACTGGAG

1021 ACCGGAGCAG CCGGACGACT GGTACGGCCA CGGGCTCGGG GGAGGGGAGG ACTGTGCCCA

1081 CTTCACCGAC GACGGCCGCT GGAACGACGA CGTCTGCCAG AGGCCCTACC GCTGGGTCTG

1141 CGAGACAGAG CTGGACAAGG CCAGTCAGGA GCCACCTCTC CTTTAATTTA TTTCTTCAGT

1201 GCCTCGACCT GCCGCAGGGG TCCGGGGTTG GGAATCCGCC CGTCTGGGGG CCTCTTCTGC

1261 TTTCTCGGGG ATTTTCATGT AGGATTTTAA GGGAAGGGGA AGGATAGGAT GATGTTGGGA

1321 AGGTGGGGGA CTTGAAACCC GTGGCGCTTT CTGTAGTTTG CACGTTATCA TTGTCAACTT

1381 TTTTTTTTTT TTAGAGTAAA AAGAAATATA CCTAAAC (SEQ ID NO: 3013)

FIG. 4

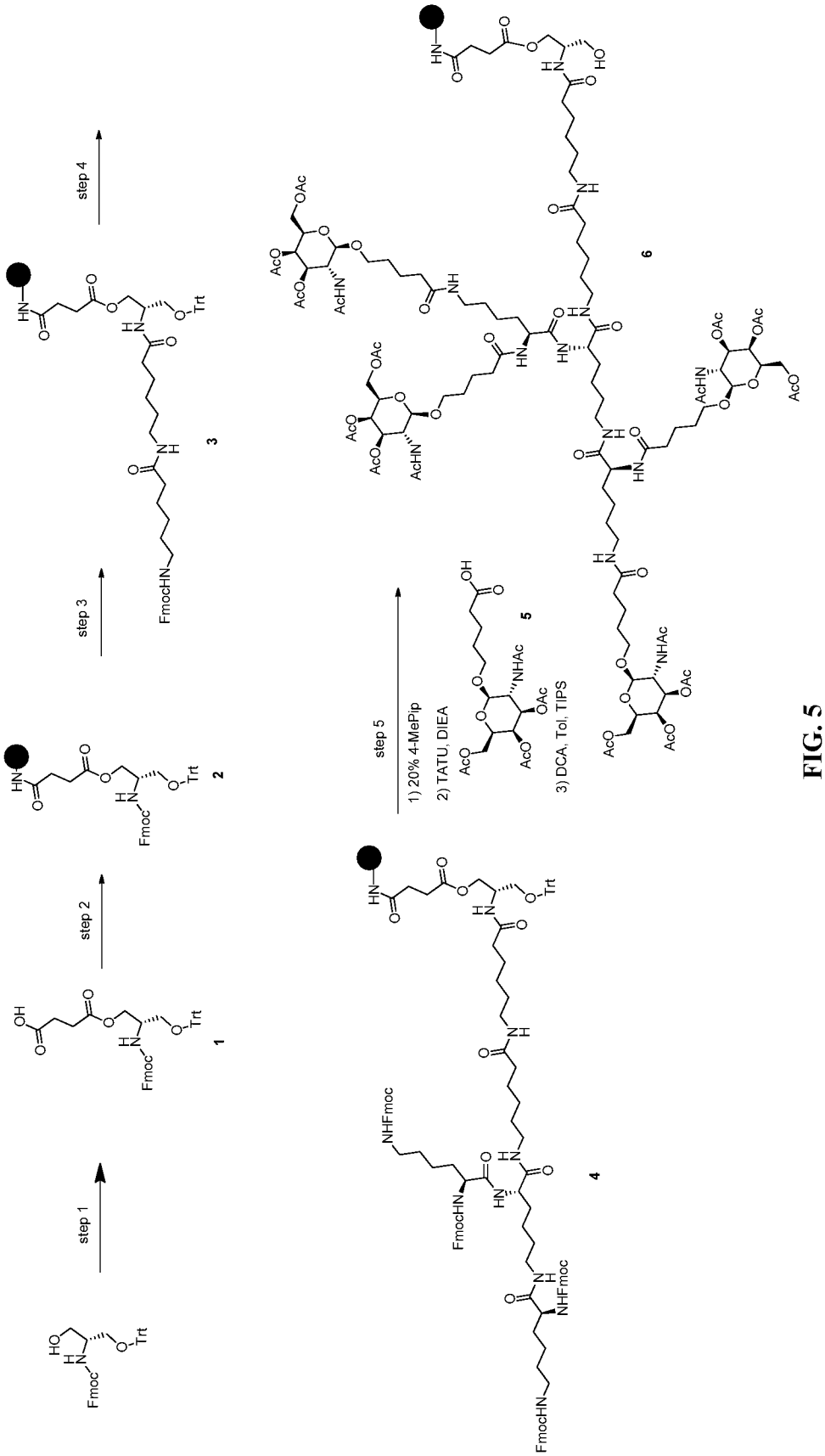

step 1
step 2
step 3
step 4
step 5
1) 20% 4-MePip
2) TATU, DIEA
3) DCA, Tol, TIPS
Fmoc
Trt
FmocHN
NHFmoc
AcO
AcHN
NHAc
OAc
1
2
3
4
5
6

FIG. 5

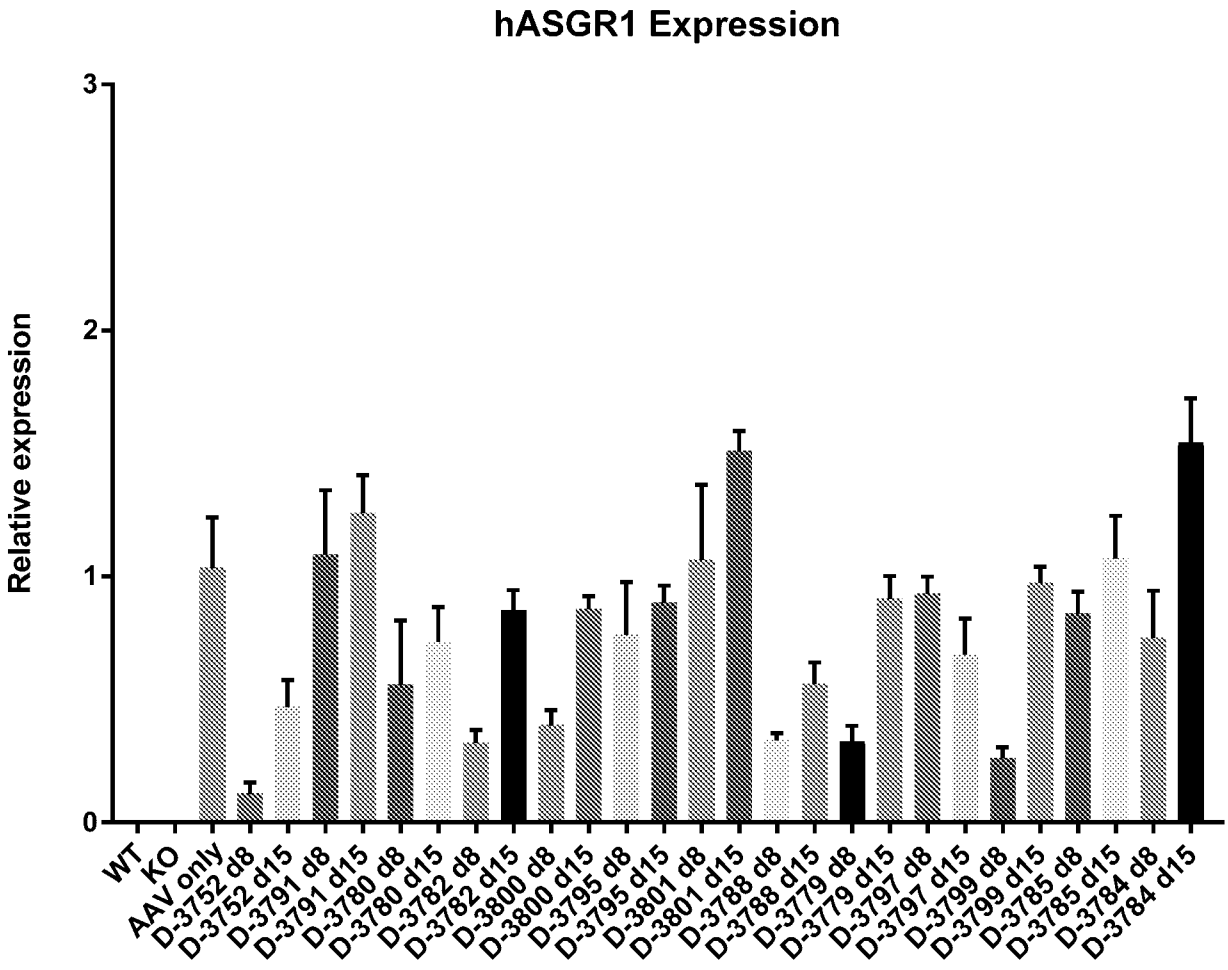

hASGR1 Expression
Relative expression
3
2
1
0
WT
KO
AAV only
D-3752 d8
D-3752 d15
D-3791 d8
D-3791 d15
D-3780 d8
D-3780 d15
D-3782 d8
D-3782 d15
D-3800 d8
D-3800 d15
D-3795 d8
D-3795 d15
D-3801 d8
D-3801 d15
D-3788 d8
D-3788 d15
D-3779 d8
D-3779 d15
D-3797 d8
D-3797 d15
D-3799 d8
D-3799 d15
D-3785 d8
D-3785 d15
D-3784 d8
D-3784 d15

FIG. 6A

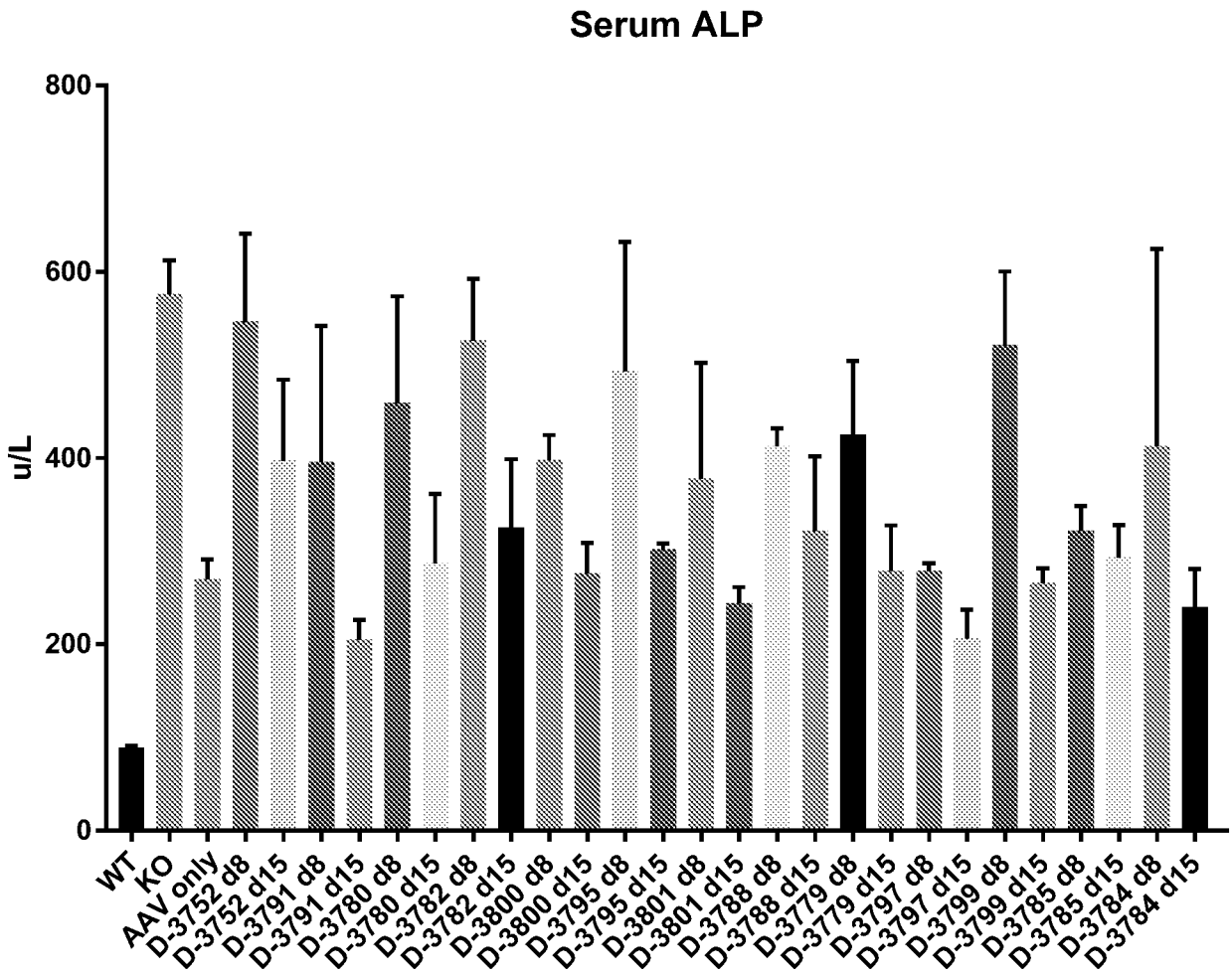

Serum ALP
u/L
800
600
400
200
0
WT
KO
AAV only
D-3752 d8
D-3752 d15
D-3791 d8
D-3791 d15
D-3780 d8
D-3780 d15
D-3782 d8
D-3782 d15
D-3800 d8
D-3800 d15
D-3795 d8
D-3795 d15
D-3801 d8
D-3801 d15
D-3788 d8
D-3788 d15
D-3779 d8
D-3779 d15
D-3797 d8
D-3797 d15
D-3799 d8
D-3799 d15
D-3785 d8
D-3785 d15
D-3784 d8
D-3784 d15

FIG. 6B

Modification of siRNA with linker and chemoselective functional group

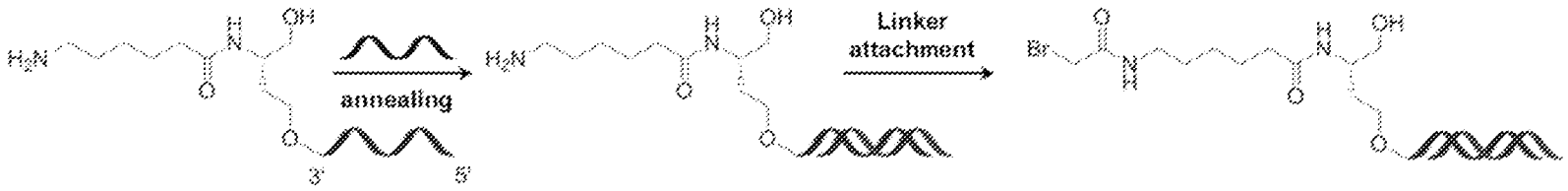


FIG. 7A

Uncapping and conjugation of cysteine-engineered mAb to siRNA

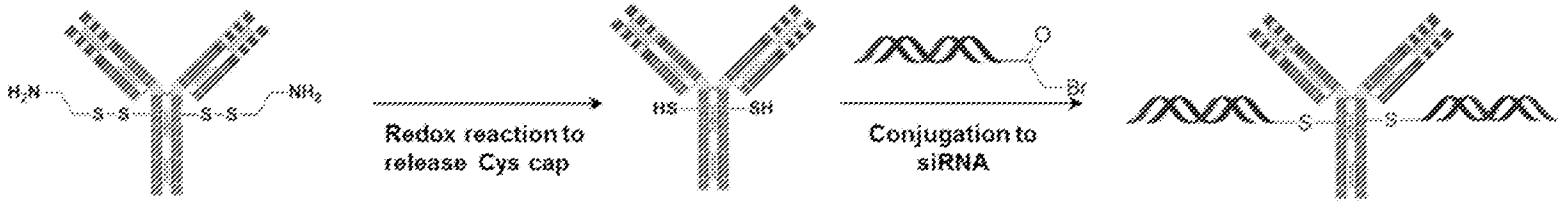


FIG. 7B

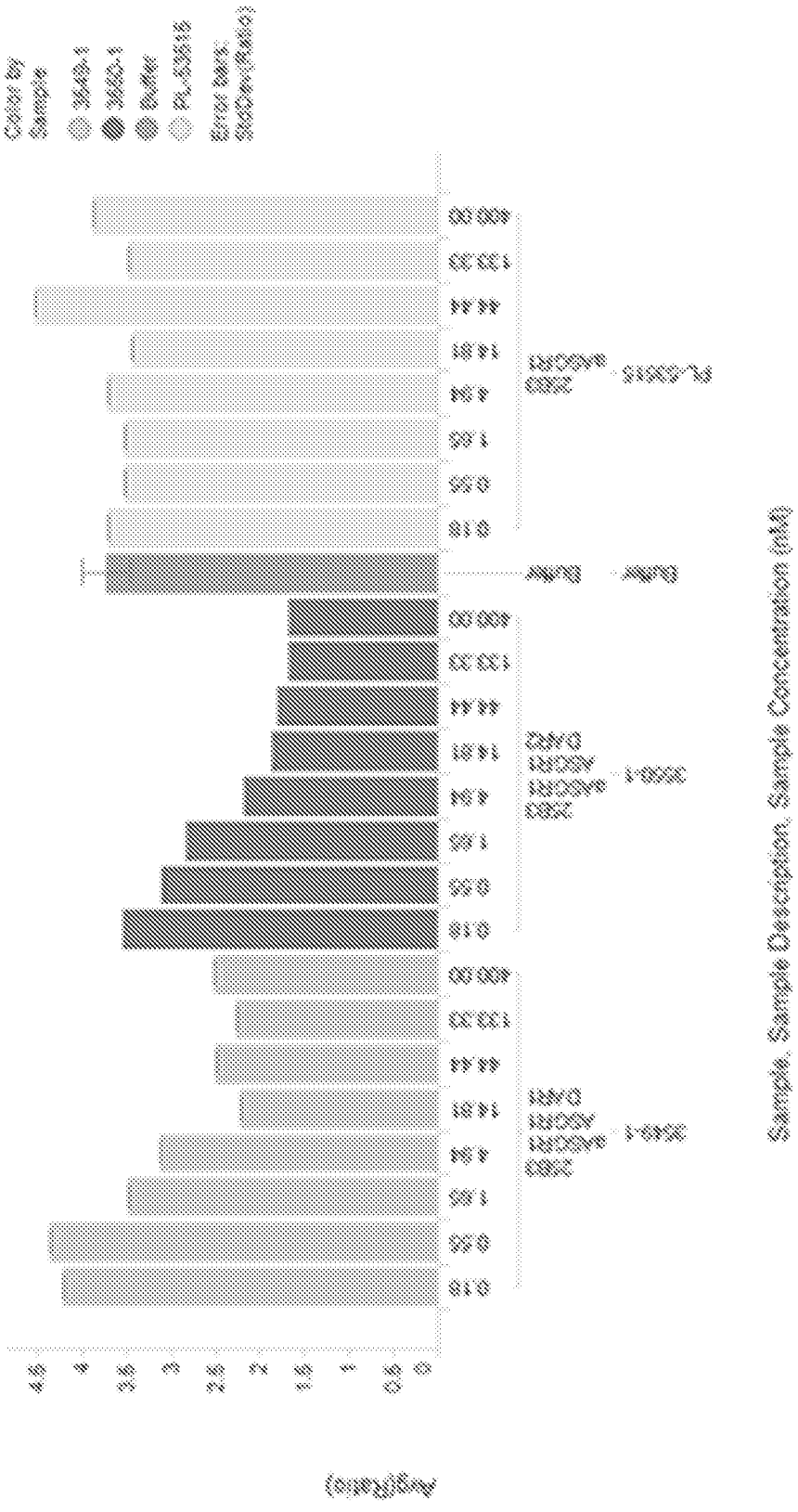

Color by Sample
3640-1
3662-1
Buffer
PL-3D816
Error bars: StdDev(Ratio)
Sample, Sample Description, Sample Concentration (nM)
Avg(Ratio)

FIG. 8

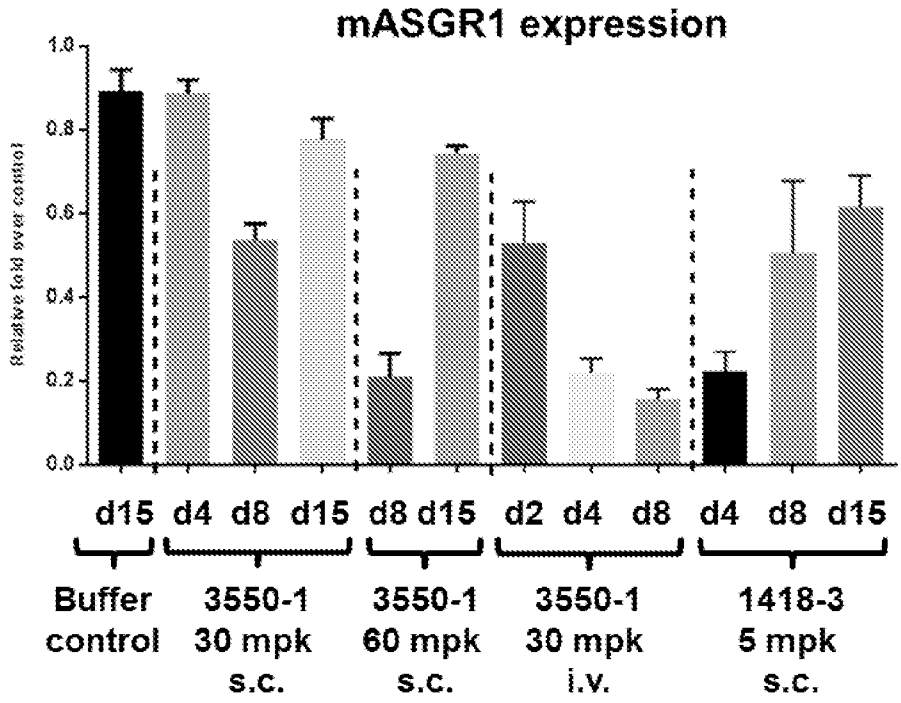

mASGR1 expression
Relative fold over control
1.0
0.8
0.6
0.4
0.2
0.0
d15 d4 d8 d15 d8 d15 d2 d4 d8 d4 d8 d15
Buffer control
3550-1 30 mpk s.c.
3550-1 60 mpk s.c.
3550-1 30 mpk i.v.
1418-3 5 mpk s.c.

FIG. 9A

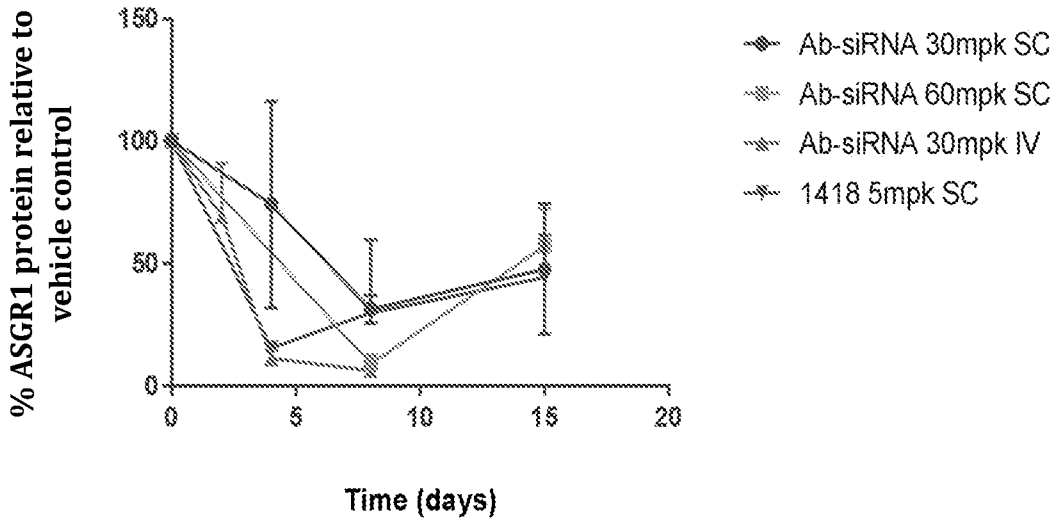

% ASGR1 protein relative to vehicle control
150
100
50
0
0
5
10
15
20
Time (days)
Ab-siRNA 30mpk SC
Ab-siRNA 60mpk SC
Ab-siRNA 30mpk IV
1418 5mpk SC

FIG. 9B

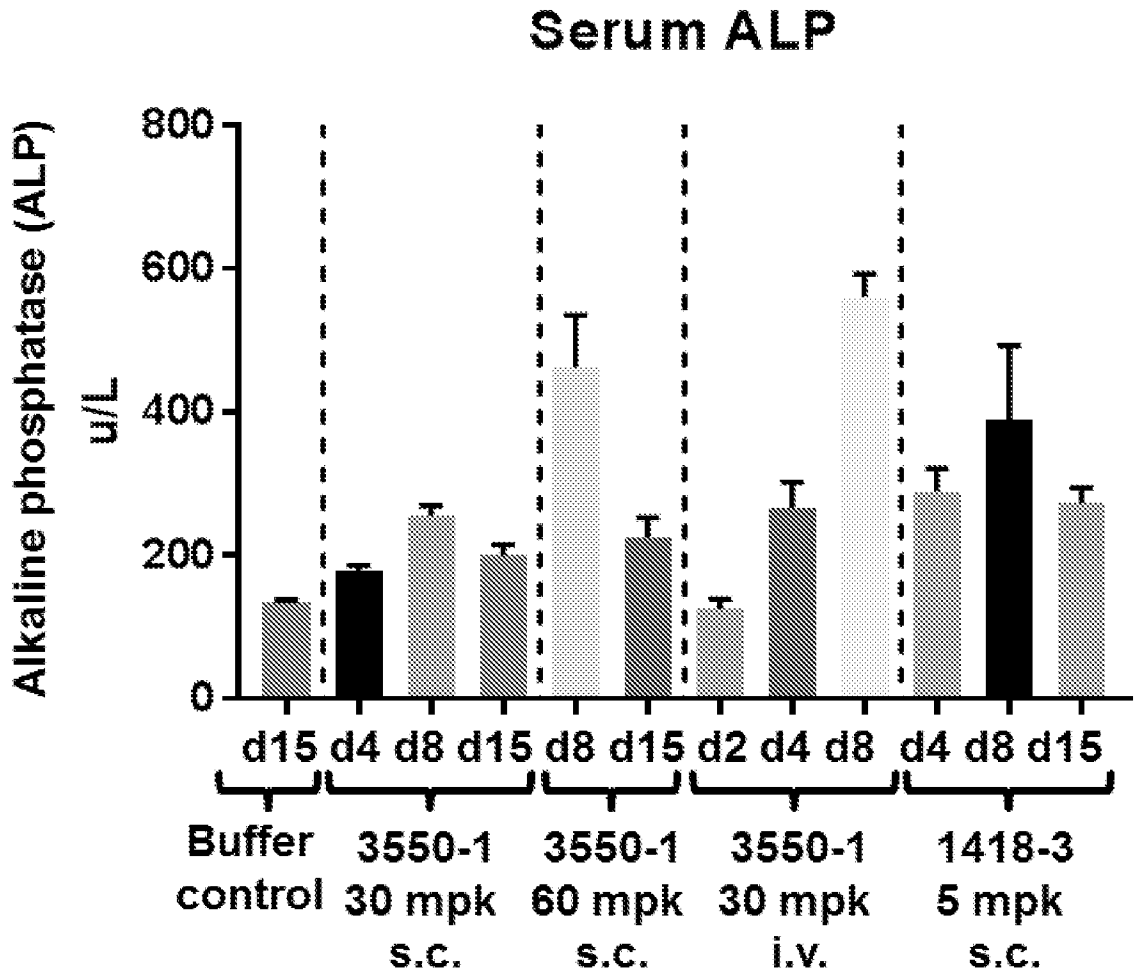

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Alkaline phosphatase (ALP)
u/L
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600
400
200
0
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FIG. 10

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<110> AMGEN INC.
OLLMANN, Michael
LI, Yang
ZHANG, Jun
BISWAS, Kaustav
HOMANN, Oliver
MIRANDA, Leslie P.
MURRAY, Justin K.
WU, Bin
YOON, Oh Kyu
ALLEN, John Gordon
NETIROJJANAKUL, Chawita

<120> RNAI CONSTRUCTS FOR INHIBITING ASGR1 EXPRESSION AND METHODS OF USE THEREOF

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<150> 62/380,216
<151> 2016-08-26

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35 40 45

Tyr Thr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Leu
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Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
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Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
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Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
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35 40 45

Ala Ile Ile Trp His Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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Leu Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Asp Leu Ser Met Gly Gly Met Asp Val Trp Gly Gln Gly Thr
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Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
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Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
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Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
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Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
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Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
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Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
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Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
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Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
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Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
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Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
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Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
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Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
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Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
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Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
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Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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gtccggatcc agtgccatca tgacaaagga ttatcaagat ttccagcacc tggacaatga 180

taatgaccat catcaactcc ggagagggcc gcctcccact ccacggctct tgcagcgact 240

ctgctctgga tcccgcctcc tcctgctctc ctcgagcctc agcattctgt tgctggtggt 300

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gaatttcagc aacctcactg tgagcactga ggaccaggtc aaggccctga gcacccaggg 420

aagtagtgtg ggaagaaaga tgaagttagt ggagtcgaag ctggaaaaac agcagaagga 480

tctgactgaa gatcactcca gtttgctact gcacgtgaag cagttagtgt ctgacgtgcg 540

aagcttgagc tgccagatgg ctgcatttcg gggcaatggc tctgaaagga cctgctgccc 600

catcaactgg gtggagtatg aaggcagctg ctactggttc tccagctctg tgaggccttg 660

gactgaagct gacaagtact gccagctgga aaatgcccat ctggtggtgg tgacctccag 720

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tgaccagaac gggccctgga aatgggtgga tggaacagac tacgagacag gcttccagaa 840

ttggagacca gagcagccag ataactggta cggacatggg cttggaggag gcgaggactg 900

tgcccacttc acgacggatg gccgctggaa tgacgacgtc tgcaggaggc cctaccgctg 960

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accacccagg gagagagagt gggaagaaag atgaagttag tcgagtcaca gctggaaaaa 420

catcaggagg atctgaggga agaccactct agattgctac tgcatgtaaa gcagttagtg 480

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cagccctatc atgaccaagg agtatcagga cctgcagcat ctggacaatg aggagagtga 360

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cggccctcgc ctcctcctgc tctccctggg cctcagcctc ctgctgctgg tggttgtctg 480

tgtgatcgga tcccaaaacg cccagctgca gcgggagctg cggggcctga gagagacgct 540

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3023
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<210> 3024
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3025
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3027
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 7-8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3028
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4-5, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3029
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 5-6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3030
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3031
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3032
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<223> Positions 2-3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3033
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1-2, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3034
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<223> Positions 1, 3, 5, 7, 9, 11, 14-15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12-13, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3035
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 15-16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3036
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14-15, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 17-18, 20

2'-O-methyl ribonucleotide

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<210> 3038
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16-17, 20

2'-O-methyl ribonucleotide

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<210> 3039
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 19-20

2'-O-methyl ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18-19

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

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<210> 3042
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1-2, 5-6, 9-10, 13-14, 17-18, 21

2'-O-methyl ribonucleotide

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<210> 3043
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<220>
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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

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<210> 3044
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

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<210> 3045

<211> 21
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<223> Positions 2, 14, 19

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 3045
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<210> 3046
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3047
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<221> modified_base
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<223> Positions 2, 4, 6, 9, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3048
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<223> Positions 1, 3, 5, 7, 10-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8-9, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3048
gugggaagaa agaugaaguu u 21

<210> 3049
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<212> DNA
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3050
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 11, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3051
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 11-12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3051
gugggaagaa agaugaaguu u 21

<210> 3052
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
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<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3052
gugggaagaa agaugaaguu u 21

<210> 3053
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<212> DNA
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<220>
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<220>
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3053
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<210> 3054
<211> 21
<212> DNA
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<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 3054
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<210> 3055
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3055
gugggaagaa agaugaaguu u 21

<210> 3056
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 3056
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<210> 3057
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3058
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<220>
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<223> Positions 1, 3, 5-6, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 7-8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3058
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<210> 3059
<211> 21
<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4-5, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3059
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 5-6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3060
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<210> 3061
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3061
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<210> 3062
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<220>
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<223> Positions 1-2, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3062
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<210> 3063
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3106
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<222> (1)..(21)
<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

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<210> 3107
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2'-O-methyl ribonucleotide

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<223> phosphorothioate linked nucleoside

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<210> 3108
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8-9, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 11-12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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gagcgcagcu gcuacugguu u 21

<210> 3114
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3116
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3117
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3117
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<210> 3118
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 7-8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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guugucugug ugaucggaut t 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3189
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3201
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-2, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12-13, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 15-16, 18, 20

2'-O-methyl ribonucleotide

<400> 3221
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14-15, 18, 20

2'-O-methyl ribonucleotide

<400> 3222
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 17-18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16-17, 20

2'-O-methyl ribonucleotide

<400> 3224
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 19-20

2'-O-methyl ribonucleotide

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<210> 3226
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18-19

2'-O-methyl ribonucleotide

<400> 3226
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<210> 3227

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3228
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<210> 3229
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3230
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3288
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3303
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<210> 3304
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12-13, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3315
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3363
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<400> 3368
cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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cuaucaugac caaggaguau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<210> 3380
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<210> 3381
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18-19

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

<400> 3387
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<210> 3388
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 9, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3389
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3389
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<210> 3390
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 11, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3391
cguccuggga ggagcagaau u 21

<210> 3392
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 11-12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3392
cguccuggga ggagcagaau u 21

<210> 3393
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3393
cguccuggga ggagcagaau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3394
cguccuggga ggagcagaau u 21

<210> 3395
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3395
cguccuggga ggagcagaau u 21

<210> 3396
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3396
cguccuggga ggagcagaau u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 7-8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 5-6, 8, 10, 12, 14, 16, 18, 20

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1-2, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3406
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<210> 3408
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3408
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<210> 3409
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 17-18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16-17, 20

2'-O-methyl ribonucleotide

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<210> 3411
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 19-20

2'-O-methyl ribonucleotide

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<210> 3412
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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18-19

2'-O-methyl ribonucleotide

<400> 3412
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1-2, 5-6, 9-10, 13-14, 17-18, 21

2'-O-methyl ribonucleotide

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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

<400> 3415
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<210> 3416
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

<400> 3416
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<223> Positions 1-2, 8-15, 17-19

2'-O-methyl ribonucleotide

<220>
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<400> 3417
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 9, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8-9, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3422
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 11, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 3423
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 11-12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<223> phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3429
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3430
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2-3, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3434
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3435
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1-2, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3436
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<223> Positions 1, 3, 5, 7, 9, 11, 14-15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12-13, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3437
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<210> 3438
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 15-16, 18, 20

2'-O-methyl ribonucleotide

<400> 3438
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

<400> 3439
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

<400> 3440
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<210> 3441
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

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<210> 3542
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3551
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 7-8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3560
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3562
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3562
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3563
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<210> 3564
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3564
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16-17, 20

2'-O-methyl ribonucleotide

<400> 3565
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<210> 3566

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 19-20

2'-O-methyl ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-2, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 3-4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 3651
cggacuacga gacgggcuuu u 21

<210> 3652
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3653
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<210> 3654
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3655
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 15-16, 18, 20

2'-O-methyl ribonucleotide

<400> 3655
cggacuacga gacgggcuuu u 21

<210> 3656
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14-15, 18, 20

2'-O-methyl ribonucleotide

<400> 3656
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<210> 3657
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3657
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<210> 3658
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3659
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 3659
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<210> 3660
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<210> 3661
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 3-4,7- 8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

<400> 3661
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<210> 3662
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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

<400> 3662
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

<400> 3663
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<210> 3664
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

<400> 3664
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<210> 3665
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<223> Positions 6, 12

2'-O-methyl ribonucleotide

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<223> phosphorothioate linked nucleoside

<400> 3665
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<210> 3666
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3667
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3668
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3670
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<210> 3671
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3672
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3673
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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3676
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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3679
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3681
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<210> 3682
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2'-O-methyl ribonucleotide

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<210> 3683
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2'-O-methyl ribonucleotide

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<400> 3683
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<210> 3684
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<400> 3684
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<210> 3685
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3685
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3687
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<210> 3688
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3689
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 3739
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3748
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

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<210> 3755
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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

<220>
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<400> 3755
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<210> 3756
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

<220>
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<400> 3756
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<210> 3757
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1-2, 5-6, 9-10, 13-14, 17-18, 21

2'-O-methyl ribonucleotide

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<400> 3757
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<223> Positions 3, 6, 9

2'-O-methyl ribonucleotide

<220>
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<400> 3758
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<210> 3759
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3761
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3761
accaguagca gcugcgcucu u 21

<210> 3762
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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<210> 3774
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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auccgaucac acagacaacu u 21

<210> 3797
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<222> (1)..(21)
<223> Positions 23, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

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<400> 3816
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

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<400> 3817
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

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<400> 3818
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3819
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2'-O-methyl ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-10, 12-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<400> 3822
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions1, 3, 5, 7, 9-10, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3824
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3825
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<210> 3826
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

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<400> 3826
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<210> 3827
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<221> modified_base
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 3829
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<400> 3830
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<210> 3831
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 3831
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<210> 3832
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

<220>
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<400> 3833
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<210> 3834
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13-14, 17, 19, 21

2'-O-methyl ribonucleotide

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<210> 3835
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 7, 9, 11, 13, 16-17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

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<210> 3836
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15-16, 19, 21

2'-O-methyl ribonucleotide

<220>
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<210> 3837
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 18-19, 21

2'-O-methyl ribonucleotide

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<210> 3838
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17-18, 21

2'-O-methyl ribonucleotide

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<223> phosphorothioate linked nucleoside

<400> 3838
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<210> 3839
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-O-methyl ribonucleotide

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<400> 3839
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<210> 3840
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<223> Positions 1, 3, 5-6, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<400> 3840
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<210> 3841
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2'-O-methyl ribonucleotide

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<400> 3841
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<210> 3842
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2'-O-methyl ribonucleotide

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<400> 3842
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<210> 3843
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 4-5, 7, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3843
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<210> 3844
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-2, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<400> 3844
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<210> 3845
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3845
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<210> 3846
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3846
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<210> 3847
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3848
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<210> 3849
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3852
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3853
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<210> 3854
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3854
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3855
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<210> 3856
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<223> Positions 1, 3, 5, 7-8, 10-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<400> 3856
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3859
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 3860
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<210> 3861
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<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<400> 3861
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<210> 3862
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 3862
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<210> 3863
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<400> 3863
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<210> 3864
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 7, 9, 11, 14-15, 17, 19, 21

2'-O-methyl ribonucleotide

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<400> 3864
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<210> 3865
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13-14, 17, 19, 21

2'-O-methyl ribonucleotide

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<400> 3865
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<210> 3866
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3866
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<210> 3867
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15-16, 19, 21

2'-O-methyl ribonucleotide

<220>
<221> modified_base
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<223> phosphorothioate linked nucleoside

<400> 3867
acgucgucgu uccagcggcu u 21

<210> 3868
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16-17, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 18-19, 21

2'-O-methyl ribonucleotide

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<400> 3868
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<210> 3869
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3869
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<210> 3870
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 3870
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3872
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3873
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 3891
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1-2, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3937
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2-3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3939
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

<220>
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<400> 3940
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<210> 3941
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 4-5, 8-9, 12-13, 16-17, 20-21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

<220>
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<400> 3942
ucugucucgc agacccagcu u 21

<210> 3943
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3944
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<210> 3955
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 3956
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3961
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17-18, 21

2'-O-methyl ribonucleotide

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<400> 3962
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<210> 3963
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-O-methyl ribonucleotide

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<400> 3963
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2'-O-methyl ribonucleotide

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<400> 3964
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 3966
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 3968
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2-3, 6-7, 10-11, 14-15, 18-19

2'-O-methyl ribonucleotide

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<400> 3971
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3-4, 7-8, 11-12, 15-16, 19-20

2'-O-methyl ribonucleotide

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<400> 3973
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<210> 3974
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-2, 5-6, 9-10, 13-14, 17-18, 21

2'-O-methyl ribonucleotide

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<400> 3974
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<210> 3975
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2'-O-methyl ribonucleotide

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<400> 3975
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3976
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<210> 3977
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 7, 9-10, 12-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3977
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<210> 3978
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>

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<223> Positions 1, 3, 5, 7, 9-10, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3978
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<210> 3979
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<400> 3979
aaccacaagc agcaggaggu u 21

<210> 3980
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4053

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4077
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4221
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4222
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4231
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4232
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 4233
augauaaccu gcaaacugcu u 21

<210> 4234
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<212> DNA
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3-4, 7, 9, 11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<210> 4308
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<223> Positions 1, 4-5, 7, 9, 11, 13, 15, 17, 19, 21

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<210> 4309
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2'-O-methyl ribonucleotide

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<210> 4310
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4315
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<223> Positions 1-2, 5-6, 9-10, 13-14, 17-18, 21

2'-O-methyl ribonucleotide

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<210> 4318
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4321
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<210> 4322
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2'-O-methyl ribonucleotide

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<400> 4323
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<210> 4324
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4325
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-6, 8, 10, 12-21

2'-O-methyl ribonucleotide

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<400> 4326
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<210> 4327
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4331
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4332
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<210> 4333
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<223> Positions 1, 3, 5, 7-10, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4333
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<210> 4334
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4334
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<210> 4335
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4335
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<210> 4336
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4336
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<210> 4337
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<212> DNA
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4337
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<210> 4338
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4338
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<210> 4339
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4339
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<210> 4340
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-6, 8, 10, 12-21

2'-O-methyl ribonucleotide

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<400> 4340
gcagcugcua cugguucucu u 21

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4341
gcagcugcua cugguucucu u 21

<210> 4342
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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4342
ugugggaaga aagaugaagu u 21

<210> 4343
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<220>
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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<223> phosphorothioate linked nucleoside

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<210> 4344
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-6, 8, 10, 12-21

2'-O-methyl ribonucleotide

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<223> phosphorothioate linked nucleoside

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<210> 4345
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<220>
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<223> Positions 5, 7-11, 13, 19

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1-4, 6, 12, 14-18, 20-21

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

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<210> 4346
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4346
gugggaagaa agaugaaguu u 21

<210> 4347
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4347
gcagcugcua cugguucucu u 21

<210> 4348
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 4349
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4349
aggacugugc ccacuucacu u 21

<210> 4350
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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 4350
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<210> 4351
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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gagcgcagcu gcuacugguu u 21

<210> 4352
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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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guugucugug ugaucggauu u 21

<210> 4353
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4353
ggagcugcgg ggccugagau u 21

<210> 4354
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4354
gccgcuggaa cgacgacguu u 21

<210> 4355
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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gcugggucug cgagacagau u 21

<210> 4356
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4356

gcuuucucgg gaauuuucau u 21

<210> 4357
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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4357
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<210> 4358
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4358
cuaucaugac caaggaguau u 21

<210> 4359

<211> 21
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4359
cguccuggga ggagcagaau u 21

<210> 4360
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<400> 4360
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<210> 4361
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4361
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<210> 4362
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4362
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<210> 4363
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4363
gcaguuugca gguuaucauu u 21

<210> 4364
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<212> DNA
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<223> Positions 1, 3, 5, 7, 9-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4364
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<210> 4365
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4365
gcagcugcua cugguucucu c 21

<210> 4366
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4366
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<210> 4367
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4367
augugggaag aaagaugaag u 21

<210> 4368
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4368
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<210> 4369
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4369
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<210> 4370
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4370
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<210> 4371
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (2)..(3)
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<400> 4371
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<210> 4372
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<222> (2)..(3)
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<400> 4372
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<210> 4373
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<223> 5'-monophosphate

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<222> (2)..(3)
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<400> 4373
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<210> 4374
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<223> 5'-monophosphate

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 4375
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<223> 5'-monophosphate

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4375
gcugcuacug guucucucgu u 21

<210> 4376
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<223> 5'-monophosphate

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4408
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<210> 4409
<211> 21
<212> DNA
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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4409
ccuccugcuc ucccugggcu u 21

<210> 4410
<211> 21
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6,12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4410
gcugcuacug guucucucgu u 21

<210> 4411
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4411
cccauucucc aagcuucagu u 21

<210> 4412
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<223> 5'-monophosphate

<220>
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<223> Positions 1, 3, 5, 7-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4412
acugguucuc ucgcuccggu u 21

<210> 4413
<211> 21
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4413
gcagcugcua cugguucucu u 21

<210> 4414
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<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<210> 4415
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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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gugggaagaa agaugaaguu u 21

<210> 4416
<211> 21

<212> DNA
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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4416
gugggaagaa agaugaaguu u 21

<210> 4417
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4417
gugggaagaa agaugaaguu u 21

<210> 4418
<211> 21
<212> DNA
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<220>

<223> Synthetic polynucleotide

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<222> (1)..(21)
<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4418
gugggaagaa agaugaaguu u 21

<210> 4419
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<223> Positions 1, 3, 5, 7, 9, 11-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
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<400> 4419
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<210> 4420
<211> 21
<212> DNA
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<223> Positions 1, 3, 5, 7, 9-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
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<400> 4420
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<210> 4421
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<212> DNA
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4421
gugggaagaa agaugaaguu u 21

<210> 4422
<211> 21
<212> DNA
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<223> 5'-monophosphate

<220>
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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20-21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18-19

2'-O-methyl ribonucleotide

<400> 4422
gugggaagaa agaugaaguu u 21

<210> 4423
<211> 21
<212> DNA
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<223> 5'-monophosphate

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<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4423
gugggaagaa agaugaaguu u 21

<210> 4424
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<220>
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<222> (1)..(21)
<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4424
gugggaagaa agaugaaguu u 21

<210> 4425
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<212> DNA
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<223> 5'-monophosphate

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<223> Positions 1, 3, 5, 7, 9-12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<400> 4425
gugggaagaa agaugaaguu u 21

<210> 4426
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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
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<223> phosphorothioate linked nucleoside

<400> 4426
gcagcugcua cugguucucu u 21

<210> 4427
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<212> DNA
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<223> 5'-monophosphate

<220>
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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4427
ugugggaaga aagaugaagu u 21

<210> 4428
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4428
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<210> 4429
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<223> Positions 1, 3, 5, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6-7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 4429
gcagcugcua cugguucucu u 21

<210> 4430
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<213> Artificial Sequence

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<223> 5'-monophosphate

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<223> Positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4430
gugggaagaa agaugaaguu u 21

<210> 4431
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<223> Positions 1, 3, 5, 7, 9-10, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 4431

gugggaagaa agaugaaguu u 21

<210> 4432
<211> 21
<212> DNA
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<223> Positions 1, 3, 6-7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4-5, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 4432
gugggaagaa agaugaaguu u 21

<210> 4433
<211> 21
<212> DNA
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<220>
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<222> (1)..(21)
<223> Positions 1, 4-5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2-3, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 4433
gugggaagaa agaugaaguu u 21

<210> 4434
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<223> Positions 2-3, 5, 7, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 4, 6, 8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4434
gugggaagaa agaugaaguu u 21

<210> 4435
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<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 9, 11, 13-14, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 12, 15-16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4435
gugggaagaa agaugaaguu u 21

<210> 4436
<211> 21
<212> DNA
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<220>
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<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 9, 11, 13, 15-16, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 12, 14, 17-18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4436
gugggaagaa agaugaaguu u 21

<210> 4437
<211> 21
<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 10, 12, 14, 16, 19-20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)

<223> phosphorothioate linked nucleoside

<400> 4437
gugggaagaa agaugaaguu u 21

<210> 4438
<211> 21
<212> DNA
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<220>
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<223> Positions 2, 4, 6, 8-11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions1, 3, 5, 7, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4438
gugggaagaa agaugaaguu u 21

<210> 4439
<211> 21
<212> DNA
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<220>
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<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4439
gugggaagaa agaugaaguu u 21

<210> 4440
<211> 21
<212> DNA
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<220>
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<220>
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<223> Positions 1, 3, 5, 7, 9-12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4440
gugggaagaa agaugaaguu u 21

<210> 4441
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4441
gcagcugcua cugguucucu u 21

<210> 4442
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<212> DNA
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<220>
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<223> 5'-monophosphate

<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 10, 12-13, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (2)..(3)
<223> phosphorothioate linked nucleoside

<400> 4442
gcagcugcua cugguucucu u 21

<210> 4443
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4443
gccgcuggaa cgacgacguu u 21

<210> 4444

<211> 21
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4444
gauaggguga uguuccgaau u 21

<210> 4445
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4445
ccuaucauga ccaaggaguu u 21

<210> 4446
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
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<223> phosphorothioate linked nucleoside

<400> 4446
cuaucaugac caaggaguau u 21

<210> 4447
<211> 21
<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4447
aacgggcccu ggaaagugggu u 21

<210> 4448
<211> 21
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2'-O-methyl ribonucleotide

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<400> 4448
gacgggacgg acuacgagau u 21

<210> 4449
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2'-O-methyl ribonucleotide

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<400> 4449
acgggacgga cuacgagacu u 21

<210> 4450
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2'-O-methyl ribonucleotide

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<400> 4450
agcagccgga cgacugguau u 21

<210> 4451
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4451
ccacuucacc gacgacggcu u 21

<210> 4452
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2'-O-methyl ribonucleotide

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<400> 4452
cgacggccgc uggaacgacu u 21

<210> 4453
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2'-O-methyl ribonucleotide

<220>
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<400> 4453
aaacccgugg cgcuuucugu u 21

<210> 4454
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2'-O-methyl ribonucleotide

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<400> 4454
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<210> 4455
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2'-O-methyl ribonucleotide

<220>
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<400> 4455
gaaacccgug gcgcuuucuu u 21

<210> 4456
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4456
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<210> 4457
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4457
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<210> 4458
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4458

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<210> 4459
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<400> 4459
guugucugug ugaucggauu u 21

<210> 4460
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<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4460
ggucugcgag acagagcugu u 21

<210> 4461

<211> 21
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4461
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<210> 4462
<211> 21
<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4462
gcuccacgug aagcaguucu u 21

<210> 4463
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<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4463
gcgcagcugc uacugguucu u 21

<210> 4464
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4464
gcugcuacug guucucucgu u 21

<210> 4465
<211> 21
<212> DNA
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<220>
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<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4465
acugguucuc ucgcuccggu u 21

<210> 4466
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<223> 5'-monophosphate

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4466
gcagcugcua cugguucucu u 21

<210> 4467
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<212> DNA
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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
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<400> 4467
gcagcugcua cugguucucu u 21

<210> 4468
<211> 21
<212> DNA
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<220>
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<220>
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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 8

2'-O-methyl ribonucleotide

<400> 4468
gcagcugcua cugguucucu u 21

<210> 4469
<211> 21
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<220>
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<223> 5'-monophosphate

<220>
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<223> Positions 2, 4, 6, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>

<221> modified_base
<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4469
gugggaagaa agaugaaguu u 21

<210> 4470
<211> 21
<212> DNA
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<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8-9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4470
gugggaagaa agaugaaguu u 21

<210> 4471
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<220>
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<220>
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<223> Positions 2, 4, 6, 9, 11, 13, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7-8, 10, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (20)..(21)
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<400> 4471
gugggaagaa agaugaaguu u 21

<210> 4472
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

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<400> 4472
augggccucc acgaccaaau u 21

<210> 4473
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4473
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<210> 4474
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4474
uucaccgacg acggccgcuu u 21

<210> 4475
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<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4475

gaagugggug gacgggacgu u 21

<210> 4476
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<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4476
ucacguccug ggaggagcau u 21

<210> 4477
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<220>
<221> misc_feature
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<223> n is a, c, g, t or u

<400> 4477
gugggaagaa agaugaaguu un 22

<210> 4478
<211> 22
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<220>
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<223> inverted abasic nucleotide attached by 3'-3' linkage

<220>
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<222> (1)..(22)
<223> Positions 2, 4, 6, 8, 10-13, 16, 18, 20, 22

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(22)
<223> Positions 3, 5, 7, 9, 14-15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
<221> misc_feature
<222> (1)..(1)
<223> n is a, c, g, t or u

<220>
<221> modified_base
<222> (21)..(22)
<223> phosphorothioate linked nucleoside

<400> 4478
ngugggaaga aagaugaagu uu 22

<210> 4479
<211> 23
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<220>
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<220>
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<223> Positions 1, 23

inverted abasic nucleotide attached by 3'-3' linkage

<220>

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<223> Positions 2, 4, 6, 8, 10-13, 16, 18, 20, 22

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 3, 5, 7, 9, 14-15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> n is a, c, g, t or u

<220>
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<220>
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<223> n is a, c, g, t or u

<400> 4479
ngugggaaga aagaugaagu uun 23

<210> 4480
<211> 21
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<220>
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<220>
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<222> (1)..(21)
<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4480
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<210> 4481
<211> 21

<212> DNA
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<220>
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<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2-4, 20-21

phosphorothioate linked nucleoside

<400> 4481
gugggaagaa agaugaaguu u 21

<210> 4482
<211> 21
<212> DNA
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4482
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<210> 4483
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4483
gugggaagaa agaugaaguu u 21

<210> 4484
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<400> 4484
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<210> 4485
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4485
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<210> 4486
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4486
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<210> 4487
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4487
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<210> 4488
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

<220>
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<400> 4488
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<210> 4489
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4489
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<210> 4490
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2'-O-methyl ribonucleotide

<220>
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<400> 4490
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<210> 4491
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2'-O-methyl ribonucleotide

<220>
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<400> 4491
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<210> 4492
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2'-O-methyl ribonucleotide

<220>
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<400> 4492
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<210> 4493
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2'-O-methyl ribonucleotide

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<400> 4493

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<210> 4494
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4494
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<210> 4495
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4497
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4497
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<210> 4498
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2'-O-methyl ribonucleotide

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<400> 4498
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<210> 4499
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<400> 4499
gcccuaucau gaccaaggau u 21

<210> 4500
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2'-O-methyl ribonucleotide

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<400> 4500
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<210> 4501
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4501
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<210> 4502
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4502
aaaacgggcc cuggaagugu u 21

<210> 4503
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleoside

<400> 4503
gccugagcug ucagauggcu u 21

<210> 4504
<211> 21
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>

<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<223> phosphorothioate linked nucleo

<400> 4504
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<210> 4505
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4505
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<210> 4506
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4506
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<210> 4507
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4507
ugcacagcac ugaagaaccu u 21

<210> 4508
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<220>
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
<223> phosphorothioate linked nucleoside

<400> 4508
acggacuacg agacgggcuu u 21

<210> 4509
<211> 21
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<220>
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<223> Positions 1, 3, 5, 7, 9-12, 15, 17, 19, 21

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
<221> modified_base
<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4509
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<210> 4510
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<222> (20)..(21)
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<400> 4510

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<210> 4511
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6, 8, 13-14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4511
cacguuuggc gugcuuggau u 21

<210> 4512
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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<400> 4512
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<210> 4513

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<220>
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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<222> (1)..(21)
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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4531
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2, 4, 6, 8, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4544
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<400> 4546
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<210> 4547
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 7, 9-13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<400> 4547

augauaaccu gcaaacugcu u 21

<210> 4548
<211> 23
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4549
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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 22-23

phosphorothioate linked nucleoside

<400> 4549
gagagaacca guagcagcug cuu 23

<210> 4550
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 22-23

phosphorothioate linked nucleoside

<400> 4550
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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 22-23

phosphorothioate linked nucleoside

<400> 4551
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<210> 4552
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4553
cuucaucuuu cuucccacau uuu 23

<210> 4554
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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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phosphorothioate linked nucleoside

<400> 4554
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<210> 4555
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4555
aauuaaagga gagguggcuu u 21

<210> 4556
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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4556
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<210> 4557
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4557
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<210> 4558
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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phosphorothioate linked nucleoside

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<210> 4559
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4560
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4560
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<210> 4561
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4562
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4562
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<210> 4563
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4563
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<210> 4564
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4564
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<210> 4565
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4566
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4568
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4568
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<210> 4569
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4571
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4574
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4577
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4578
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<210> 4579
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4585
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4586
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4587
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4587
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4589
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<210> 4591
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2'-O-methyl ribonucleotide

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2'-O-methyl ribonucleotide

<400> 4594
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<210> 4595
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2'-O-methyl ribonucleotide

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<210> 4596
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4597
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4599
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4606
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<223> Positions 2, 4, 7-8, 10, 12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4624
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4625
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4627
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4628
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4629
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4630
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4632
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4633
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4635
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4635
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<210> 4636
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5,8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4636
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<210> 4637
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<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4637
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<210> 4638
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4639
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4639
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<210> 4640
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4640

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<210> 4641
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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gagaaccagu agcagcugcu u 21

<210> 4642
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2'-O-methyl ribonucleotide

<220>
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phosphorothioate linked nucleoside

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<210> 4643
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<210> 4644
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2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4645
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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4646
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4646
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<210> 4647
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4647
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4648
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<210> 4649
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2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4649
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<210> 4650
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4650
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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<220>
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<223> n is a, c, g, t or u

<400> 4651
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<210> 4652
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-4, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 19-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 21

phosphorothioate linked nucleoside

<400> 4655
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3

phosphorothioate linked nucleoside

<400> 4657
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<210> 4658
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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phosphorothioate linked nucleoside

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<210> 4660
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4660
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<210> 4661
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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<210> 4662
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4662
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<210> 4663
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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

<400> 4663
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<210> 4664
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<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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phosphorothioate linked nucleoside

<400> 4664
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<210> 4665
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4665
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<210> 4666
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<223> 5'-monophosphate

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<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<222> (1)..(21)
<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4666
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<210> 4667
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<223> 5'-monophosphate

<220>
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<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

<220>
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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

<400> 4667
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<210> 4668
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<223> 5'-monophosphate

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 10, 19-20

phosphorothioate linked nucleoside

<400> 4668
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<210> 4669
<211> 21

<212> DNA
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<223> 5'-monophosphate

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<223> Positions 2, 4, 6-7, 12, 14, 16, 18, 20

2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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<223> Positions 1, 3, 5, 8-11, 13, 15, 17, 19, 21

2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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2'-O-methyl ribonucleotide

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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phosphorothioate linked nucleoside

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<210> 4696
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<220>
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<400> 4696

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Ser Ser Pro Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Cys Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
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Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
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Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
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Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  4697
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<400>  4697

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Ala
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asp Ser Phe Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
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Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
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Phe Asn Arg Gly Glu Cys
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2'-deoxy-2'-fluoro ("2'-fluoro") ribonucleotide

<220>
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<223> Positions 2, 4, 6, 8, 12, 14, 16, 18, 20

2'-O-methyl ribonucleotide

<220>
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phosphorothioate linked nucleoside

<400> 4698
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<210> 4699
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2'-O-methyl ribonucleotide

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<223> Positions 2-3, 20-21

phosphorothioate linked nucleoside

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