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(54) Title: COMPOUNDS AND METHODS FOR REDUCING IFNAR1 EXPRESSION

(57) Abstract: Provided are oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions for reducing the amount or activity of IFNAR1 RNA in a cell or an animal, and in certain instances, reducing the amount of IFNAR1 protein in a cell or animal. Such oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions are useful to treat diseases and conditions associated with neuroinflammation, including Aicardi-Goutieres Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia.



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COMPOUNDS AND METHODS FOR REDUCING IFNAR1 EXPRESSION**Sequence Listing**

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled BIOL0416WOSEQ_ST25.txt, created on June 8, 2022, which is 589 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

Field

Provided are oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions for reducing the amount or activity of IFNAR1 RNA in a cell or animal, and in certain instances reducing the amount of IFNAR1 protein in a cell or animal. Such oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions are useful to treat neurological diseases or conditions associated with neuroinflammation, including Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia.

Background

Aicardi-Goutières Syndrome (AGS) is a progressive inflammatory encephalopathy associated with several neuropathological manifestations, including seizures, difficulty feeding, dystonia, spasticity, delayed motor development, delayed language development, and delayed social skill development. Imaging of AGS patients reveals white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, and microencephaly; patients also have elevated levels of interferon alpha (IFNa) and lymphocytosis in cerebrospinal fluid. AGS has been associated with mutations in one of ten genes: TREX1 (DNA exonuclease), RNASEH2A, B or C (subunits of RNASEH2), SAMHD1 (dNTP hydrolase), ADAR1 (RNA editing enzyme), MDA5 (dsRNA sensor), USP18 (negative regulator of type I IFN signaling), LSM11 and RNU7-1 (components of the replication-dependent histone pre-mRNA-processing complex). Mutations in any one of these genes lead to aberrant activation of the antiviral response and high levels of IFNa (Adang, et al., 2020, J. Child Neurol., 35, 7016; Rodero, et al., 2016, J. Esp. Med., 213, 2527-2538).

Interferon Alpha and Beta Receptor Subunit 1 (IFNAR1) is one of two components of the interferon alpha receptor, involved in type I interferon signaling. Type I interferon signaling is elevated in AGS patients and is believed to be a key mediator of neuropathology. Elevated levels of type I interferon signaling are also associated with diseases or conditions such as neuroinflammation associated with stroke, brain injury, Alzheimer's disease, neuropsychiatric systemic lupus erythematosus, neuromyelitis optica, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, and ataxia telangiectasia (Wlodarczyk, et al., 2021, Glia 69, 943-953; Santer, et al., 2009, J. Immunol. 182,1192-1201; Zeng, et al., 2019, Arthritis Res. Ther. 21, 205.017; Karageorgas, et al., 2011, J Biomed Biotechnol 2011, 273907; Roy, et al., 2020, J Clin Invest. 130, 1912-1930; Witcher, 2021, J. Neurosci. JN-RM-2469-2420; Blank, et al., 2016, Immunity 44, 901-912; Härtlova, et al., 2015, Immunity 44, 901-912; McDonough, et al., 2017, J Neurosci. 37, 8292-8308). Over-expression of IFNa in transgenic mice leads to elevated levels of type I interferon signaling, resulting in neurodegenerative changes, T cell infiltration, B cell

infiltration, microglial cell activation, reactive astrocytosis, activation of endothelial cells, and calcification of the thalamus and cerebellum (Hofer, et al., 2013, Cytokine & Growth Factor Reviews 24, 257-267; Klok, et al., 2015, Ann. Clin. Transl. Neurol., 2, 774-779). Type I interferon signaling induces expression of hundreds of genes, including Interferon Induced Protein with Tetratricopeptide Repeats 1 (Ifit1), Interferon Induced Protein with Tetratricopeptide Repeats 3 (Ifit3), and Interferon Regulatory Factor 7 (Irf7) (Li, et al., 2018, J. Biol. Chem. 292, P5845-P5859). Crossing a mouse model of Alzheimer's disease with an IFNAR1 knockout mouse suppressed type I interferon signaling, resulted in a glial cell anti-inflammatory response, and reduced neuroinflammation (Minter, M.R., et al., 2016, Acta Neuropathologica Commun. 4:72).

Summary

Oligomeric agents, oligomeric compounds, methods, and pharmaceutical compositions of certain embodiments described herein are useful for reducing or inhibiting IFNAR1 expression in a cell or animal. In certain embodiments, IFNAR1 RNA or protein levels can be reduced in a cell or animal. In certain embodiments, the subject has Aicardi-Goutières Syndrome. In certain embodiments, the subject has a disease or disorder associated with a mutation in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, MDA5, USP18, LSM11, or RNU7-1.

Also provided are methods of treating a disease or disorder associated with elevated type I interferon signaling, in certain embodiments, the disease or disorder is AGS, stroke, epilepsy, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, or ataxia telangiectasia.

Detailed Description

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

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, and treatises, are hereby expressly incorporated-by-reference for the portions of the document discussed herein, as well as in their entirety.

DEFINITIONS

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

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

As used herein, “2′-deoxynucleoside” means a nucleoside comprising a 2′-H(H) deoxyfuranosyl sugar moiety. In certain embodiments, a 2′-deoxynucleoside is a 2′-β-D-deoxynucleoside and comprises a 2′-β-D-deoxyribose sugar moiety, which has the β-D ribosyl configuration as found in naturally occurring deoxyribonucleic acid (DNA). In certain
5 embodiments, a 2′-deoxynucleoside may comprise a modified nucleobase or may comprise an RNA nucleobase (uracil).

As used herein, “2′-MOE” means a 2′-O(CH₂)₂OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-MOE sugar moiety” or a “2′-O-methoxyethyl sugar moiety” means a sugar moiety with a 2′-O(CH₂)₂OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2′-MOE sugar moiety is in the β-D-ribose configuration. “MOE” means O-methoxyethyl.

10 As used herein, “2′-MOE nucleoside” means a nucleoside comprising a 2′-MOE sugar moiety.

As used herein, “2′-OMe” means a 2′-OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-O-methyl sugar moiety” or “2′-OMe sugar moiety” means a sugar moiety with a 2′-OCH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2′-OMe sugar moiety is in the β-D-ribose configuration.

15 As used herein, “2′-OMe nucleoside” means a nucleoside comprising a 2′-OMe sugar moiety.

As used herein, “2′-F” means a 2′-fluoro group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-F sugar moiety” means a sugar moiety with a 2′-F group in place of the 2′-OH group of a furanosyl sugar moiety. Unless otherwise indicated, a 2′-F sugar moiety is in the β-D ribosyl stereochemical configuration.

As used herein, “2′-F nucleoside” means a nucleoside comprising a 2′-F sugar moiety.

20 As used herein “2′-NMA” means a 2′-OCH₂C(=O)-N(H)CH₃ group in place of the 2′-OH group of a furanosyl sugar moiety. A “2′-NMA sugar moiety” or “2′-O-[2-(methylamino)-2-oxoethyl] sugar moiety” means a sugar moiety with a 2′-OCH₂C(=O)-N(H)CH₃ group in place of the 2′-OH group of a furanosyl sugar moiety.

“2′-NMA sugar moiety” means the sugar moiety of a 2′-NMA nucleoside.

As used herein, “2′-substituted nucleoside” means a nucleoside comprising a 2′-substituted furanosyl sugar
25 moiety. As used herein, “2′-substituted” in reference to a sugar moiety means a sugar moiety comprising at least one 2′-substituent group other than H or OH.

As used herein, “3′ target site” refers to the 3′-most nucleotide of a target nucleic acid which is complementary to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

As used herein, “5′ target site” refers to the 5′-most nucleotide of a target nucleic acid which is complementary
30 to an antisense oligonucleotide, when the antisense oligonucleotide is hybridized to the target nucleic acid.

As used herein, “5-methylcytosine” means a cytosine modified with a methyl group attached to the 5 position. A 5-methylcytosine is a modified nucleobase.

As used herein, “abasic sugar moiety” means a sugar moiety of a nucleoside that is not attached to a nucleobase. Such abasic sugar moieties are sometimes referred to in the art as “abasic nucleosides.”

35 As used herein, “ameliorate” in reference to a treatment means improvement in at least one symptom or hallmark relative to the same symptom or hallmark in the absence of the treatment. In certain embodiments, amelioration is the reduction in the severity or frequency of a symptom or hallmark or the delayed onset or slowing of progression in the severity or frequency of a symptom or hallmark. In certain embodiments, the symptom or hallmark is one or more of seizures, difficulty feeding, dystonia, spasticity, delayed motor development, delayed language

development, delayed social skill development, white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, and microencephaly. In certain embodiments, the hallmark is the level of IFNa or lymphocytosis in cerebrospinal fluid in the subject.

As used herein, “bicyclic sugar” or “bicyclic sugar moiety” means a modified sugar moiety comprising two rings, wherein the second ring is formed via a bridge connecting two of the atoms in the first ring thereby forming a bicyclic structure. In certain embodiments, the first ring of the bicyclic sugar moiety is a furanosyl moiety. In certain embodiments, the bicyclic sugar moiety does not comprise a furanosyl moiety. Examples of bicyclic sugar moieties include LNA (locked nucleic acid) sugar moiety and cEt sugar moiety as defined herein. A “bicyclic nucleoside” is a nucleoside comprising a bicyclic sugar moiety.

As used herein, “chirally enriched” in reference to a population means a plurality of molecules of identical molecular formula, wherein the number or percentage of molecules within the population that contain a particular stereochemical configuration at a particular chiral center is greater than the number or percentage of molecules expected to contain the same particular stereochemical configuration at the same particular chiral center within the population if the particular chiral center were stereorandom as defined herein. Chirally enriched populations of molecules having multiple chiral centers within each molecule may contain one or more stereorandom chiral centers. In certain embodiments, the molecules are modified oligonucleotides. In certain embodiments, the molecules are oligomeric compounds comprising modified oligonucleotides. In certain embodiments, the chiral center is at the phosphorous atom of a phosphorothioate internucleoside linkage. In certain embodiments, the chiral center is at the phosphorous atom of a mesyl phosphoramidate internucleoside linkage.

As used herein, “cerebrospinal fluid” or “CSF” means the fluid filling the space around the brain and spinal cord. “Artificial cerebrospinal fluid” or “aCSF” means a prepared or manufactured fluid that has certain properties (e.g., osmolarity, pH, and/or electrolytes) similar to cerebrospinal fluid and is biocompatible with CSF.

As used herein, “cleavable moiety” means a bond or group of atoms that is cleaved under physiological conditions, for example, inside a cell, an animal, or a human.

As used herein, “complementary” in reference to an oligonucleotide means that at least 70% of the nucleobases of the oligonucleotide and the nucleobases of another nucleic acid or one or more regions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. “Complementary region” in reference to a region of an oligonucleotide means that at least 70% of the nucleobases of that region and the nucleobases of another nucleic acid or one or more regions thereof are capable of hydrogen bonding with one another when the nucleobase sequence of the oligonucleotide and the other nucleic acid are aligned in opposing directions. Complementary nucleobases mean nucleobases that are capable of forming hydrogen bonds with one another. Complementary nucleobase pairs include adenine (A) and thymine (T), adenine (A) and uracil (U), cytosine (C) and guanine (G), 5-methyl cytosine (mC) and guanine (G). Certain modified nucleobases that pair with natural nucleobases or with other modified nucleobases are known in the art and are not considered complementary nucleobases as defined herein unless indicated otherwise. For example, inosine can pair, but is not considered complementary, with adenosine, cytosine, or uracil. Complementary oligonucleotides and/or nucleic acids need not have nucleobase complementarity at each nucleoside. Rather, some mismatches are tolerated. As used herein, “fully complementary” or “100% complementary” in reference to oligonucleotides means that oligonucleotides are complementary to another oligonucleotide or nucleic acid at each nucleoside of the oligonucleotide.

As used herein, “conjugate group” means a group of atoms that is directly attached to an oligonucleotide. Conjugate groups include a conjugate moiety and a conjugate linker that attaches the conjugate moiety to the oligonucleotide.

As used herein, “conjugate linker” means a single bond or a group of atoms comprising at least one bond that connects a conjugate moiety to an oligonucleotide.

As used herein, “conjugate moiety” means a covalently bound group of atoms that modifies one or more properties of a molecule compared to the identical molecule lacking the conjugate moiety, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge, and clearance.

As used herein, “constrained ethyl” or “cEt” or “cEt modified sugar moiety” means a β -D ribosyl bicyclic sugar moiety wherein the second ring of the bicyclic sugar is formed via a bridge connecting the 4'-carbon and the 2'-carbon of the β -D ribosyl sugar moiety, wherein the bridge has the formula 4'-CH(CH₃)-O-2', and wherein the methyl group of the bridge is in the *S* configuration.

As used herein, “cEt nucleoside” means a nucleoside comprising a cEt modified sugar moiety.

As used herein, “deoxy region” means a region of 5-12 contiguous nucleotides, wherein at least 70% of the nucleosides comprise a β -D-2'-deoxyribose sugar moiety. In certain embodiments, a deoxy region is the gap of a gapmer.

As used herein, “hotspot region” is a range of nucleobases on a target nucleic acid that is amenable to reduction of the amount or activity of the target nucleic acid by the action of an oligomeric agent, oligomeric compound, antisense compound, or antisense agent.

As used herein, “internucleoside linkage” is the covalent linkage between adjacent nucleosides in an oligonucleotide. As used herein “modified internucleoside linkage” means any internucleoside linkage other than a phosphodiester internucleoside linkage.

As used herein, “linked nucleosides” are nucleosides that are connected in a contiguous sequence (i.e., no additional nucleosides are presented between those that are linked).

As used herein, “linker-nucleoside” means a nucleoside that links, either directly or indirectly, an oligonucleotide to a conjugate moiety. Linker-nucleosides are located within the conjugate linker of an oligomeric compound. Linker-nucleosides are not considered part of the oligonucleotide portion of an oligomeric compound even if they are contiguous with the oligonucleotide.

As used herein, “mismatch” or “non-complementary” means a nucleobase of a first nucleic acid sequence that is not complementary with the corresponding nucleobase of a second nucleic acid sequence or target nucleic acid when the first and second nucleic acid sequences are aligned.

As used herein, “motif” means the pattern of unmodified and/or modified sugar moieties, nucleobases, and/or internucleoside linkages, in an oligonucleotide.

As used herein, “modified nucleoside” means a nucleoside comprising a modified nucleobase and/or a modified sugar moiety.

As used herein, “non-bicyclic modified sugar moiety” means a modified sugar moiety that comprises a modification, such as a substituent, that does not form a bridge between two atoms of the sugar to form a second ring.

As used herein, “nucleobase” means an unmodified nucleobase or a modified nucleobase. A nucleobase is a heterocyclic moiety. As used herein an “unmodified nucleobase” is adenine (A), thymine (T), cytosine (C), uracil (U), or guanine (G). As used herein, a “modified nucleobase” is a group of atoms other than unmodified A, T, C, U, or G capable of pairing with at least one other nucleobase. A “5-methyl cytosine” is a modified nucleobase. A universal base is a modified nucleobase that can pair with any one of the five unmodified nucleobases.

As used herein, “nucleobase sequence” means the order of contiguous nucleobases in a nucleic acid or oligonucleotide independent of any sugar or internucleoside linkage modification.

As used herein, “nucleoside” means a compound or fragment of a compound comprising a nucleobase and a sugar moiety. The nucleobase and sugar moiety are each, independently, unmodified or modified.

As used herein, “oligomeric agent” means an oligomeric compound and optionally one or more additional features, such as a second oligomeric compound. An oligomeric agent may be a single-stranded oligomeric compound or may be an oligomeric duplex formed by two complementary oligomeric compounds.

As used herein, “oligomeric compound” means an oligonucleotide and optionally one or more additional features, such as a conjugate group or terminal group. An oligomeric compound may be paired with a second oligomeric compound that is complementary to the first oligomeric compound or may be unpaired. A “singled-stranded oligomeric compound” is an unpaired oligomeric compound.

The term “oligomeric duplex” means a duplex formed by two oligomeric compounds having complementary nucleobase sequences.

As used herein, “oligonucleotide” means a strand of linked nucleosides connected via internucleoside linkages, wherein each nucleoside and internucleoside linkage may be modified or unmodified. Unless otherwise indicated, oligonucleotides consist of 8-50 linked nucleosides. As used herein, “modified oligonucleotide” means an oligonucleotide, wherein at least one nucleoside or internucleoside linkage is modified. As used herein, “unmodified oligonucleotide” means an oligonucleotide that does not comprise any nucleoside modifications or internucleoside modifications.

As used herein, “pharmaceutically acceptable carrier or diluent” means any substance suitable for use in administering to an animal. Certain such carriers enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and lozenges for the oral ingestion by a subject. In certain embodiments, a pharmaceutically acceptable carrier or diluent is sterile water, sterile saline, sterile buffer solution or sterile artificial cerebrospinal fluid.

As used herein “pharmaceutically acceptable salts” means physiologically and pharmaceutically acceptable salts of compounds. Pharmaceutically acceptable salts retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein “pharmaceutical composition” means a mixture of substances suitable for administering to a subject. For example, a pharmaceutical composition may comprise an oligomeric compound and a sterile aqueous solution. In certain embodiments, a pharmaceutical composition shows activity in free uptake assay in certain cell lines.

As used herein “prodrug” means a therapeutic agent in a first form outside the body that is converted to a second form within an animal or cells thereof. Typically, conversion of a prodrug within the animal is facilitated by the action of an enzymes (e.g., endogenous or viral enzyme) or chemicals present in cells or tissues and/or by physiologic conditions. In certain embodiments, the first form of the prodrug is less active than the second form.

As used herein, “stabilized phosphate group” refers to a 5'-chemical moiety that results in stabilization of a 5'-phosphate moiety of the 5'-terminal nucleoside of an oligonucleotide, relative to the stability of an unmodified 5'-phosphate of an unmodified nucleoside under biologic conditions. Such stabilization of a 5'-phosphate group includes but is not limited to resistance to removal by phosphatases. Stabilized phosphate groups include, but are not limited to, 5'-vinyl phosphonates and 5'-cyclopropyl phosphonate.

As used herein, “standard cell assay” means the assays described in Examples 1 and 2 and reasonable variations thereof.

As used herein, “stereorandom” or “stereorandom chiral center” in the context of a population of molecules of identical molecular formula means a chiral center that is not controlled during synthesis, or enriched following synthesis, for a particular absolute stereochemical configuration. The stereochemical configuration of a chiral center is considered random when it is the result of a synthetic method that is not designed to control the stereochemical configuration. For example, in a population of molecules comprising a stereorandom chiral center, the number of molecules having the (S) configuration of the stereorandom chiral center may be but is not necessarily the same as the number of molecules having the (R) configuration of the stereorandom chiral center (“racemic”). In certain embodiments, the stereorandom chiral center is not racemic because one absolute configuration predominates following synthesis, e.g., due to the action of non-chiral reagents near the enriched stereochemistry of an adjacent sugar moiety. In certain embodiments, a stereorandom chiral center is at the phosphorous atom of a stereorandom phosphorothioate or mesyl phosphoroamidate internucleoside linkage.

As used herein, “sugar moiety” means an unmodified sugar moiety or a modified sugar moiety. As used herein, “unmodified sugar moiety” means a 2'-OH(H) ribosyl moiety, as found in RNA (an “unmodified RNA sugar moiety”), or a 2'-H(H) deoxyribosyl sugar moiety, as found in DNA (an “unmodified DNA sugar moiety”). Unmodified sugar moieties have one hydrogen at each of the 1', 3', and 4' positions, an oxygen at the 3' position, and two hydrogens at the 5' position. As used herein, “modified sugar moiety” or “modified sugar” means a modified furanosyl sugar moiety or a sugar surrogate.

As used herein, “sugar surrogate” means a modified sugar moiety that can link a nucleobase to another group, such as an internucleoside linkage, conjugate group, or terminal group in an oligonucleotide, but which is not a furanosyl sugar moiety or a bicyclic sugar moiety. Modified nucleosides comprising sugar surrogates can be incorporated into one or more positions within an oligonucleotide and such oligonucleotides are capable of hybridizing to complementary oligomeric compounds or target nucleic acids. Examples of sugar surrogates include GNA (glycol nucleic acid), FHNA (fluoro hexitol nucleic acid), morpholino, and other structures described herein and known in the art.

As used herein, “symptom or hallmark” means any physical feature or test result that indicates the existence or extent of a disease or disorder. In certain embodiments, a symptom is apparent to a subject or to a medical professional examining or testing said subject. In certain embodiments, a hallmark is apparent upon invasive diagnostic testing, including, but not limited to, post-mortem tests. In certain embodiments, a hallmark is apparent on a brain MRI scan.

As used herein, “target nucleic acid” and “target RNA” mean a nucleic acid that an oligomeric compound is designed to affect. Target RNA means an RNA transcript and includes pre-mRNA and mature mRNA unless otherwise specified.

As used herein, “target region” means a portion of a target nucleic acid to which an oligomeric compound is designed to hybridize.

As used herein, “terminal group” means a chemical group or group of atoms that is covalently linked to a terminus of an oligonucleotide.

As used herein, “antisense activity” means any detectable and/or measurable change attributable to the hybridization of an antisense compound to its target nucleic acid. In certain embodiments, antisense activity is a decrease in the amount or expression of a target nucleic acid or protein encoded by such target nucleic acid compared to target nucleic acid levels or target protein levels in the absence of the antisense compound. In certain embodiments, antisense activity is the modulation of splicing of a target pre-mRNA.

As used herein, “antisense agent” means an antisense compound and optionally one or more additional features, such as a sense compound.

As used herein, “antisense compound” means an antisense oligonucleotide and optionally one or more additional features, such as a conjugate group.

As used herein, “sense compound” means a sense oligonucleotide and optionally one or more additional features, such as a conjugate group.

As used herein, “antisense oligonucleotide” means an oligonucleotide, including the oligonucleotide portion of an antisense compound, that is capable of hybridizing to a target nucleic acid and is capable of at least one antisense activity. Antisense oligonucleotides include but are not limited to antisense RNAi oligonucleotides and antisense RNase H oligonucleotides.

As used herein, “sense oligonucleotide” means an oligonucleotide, including the oligonucleotide portion of a sense compound, that is capable of hybridizing to an antisense oligonucleotide.

As used herein, “gapmer” means a modified oligonucleotide comprising an internal region positioned between external regions having one or more nucleosides, wherein the nucleosides comprising the internal region are chemically distinct from the nucleoside or nucleosides comprising the external regions, and wherein the modified oligonucleotide supports RNase H cleavage. The internal region may be referred to as the “gap” and the external regions may be referred to as the “wings.” In certain embodiments, the internal region is a deoxy region. The positions of the internal region or gap refer to the order of the nucleosides of the internal region and are counted starting from the 5’-end of the internal region. Unless otherwise indicated, “gapmer” refers to a sugar motif. In certain embodiments, the internal region is a deoxy region. In certain embodiments, each nucleoside of the gap is a 2’-β-D-deoxynucleoside. In certain embodiments, the gap comprises one 2’-substituted nucleoside at position 1, 2, 3, 4, or 5 of the gap, and the remainder of the nucleosides of the gap are 2’-β-D-deoxynucleosides. As used herein, the term “MOE gapmer” indicates a gapmer having a gap comprising 2’-β-D-deoxynucleosides and wings comprising 2’-MOE nucleosides. As used herein, the term “mixed wing gapmer” indicates a gapmer having wings comprising modified nucleosides comprising at least two different sugar modifications. Unless otherwise indicated, a gapmer may comprise one or more modified internucleoside linkages and/or modified nucleobases and such modifications do not necessarily follow the gapmer pattern of the sugar modifications.

As used herein, “cell-targeting moiety” means a conjugate group or portion of a conjugate group that is capable of binding to a particular cell type or particular cell types.

As used herein, “hybridization” means the annealing of oligonucleotides and/or nucleic acids. While not limited to a particular mechanism, the most common mechanism of hybridization involves hydrogen bonding, which may be Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding, between complementary nucleobases. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a nucleic acid target. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an oligonucleotide and a nucleic acid target.

As used herein, “RNAi agent” means an antisense agent that acts, at least in part, through RISC or Ago2 to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. RNAi agents include, but are not limited to double-stranded siRNA, single-stranded RNAi (ssRNAi), and microRNA, including microRNA mimics. RNAi agents may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNAi agent modulates the amount and/or activity, of a target nucleic acid. The term RNAi agent excludes antisense agents that act through RNase H.

As used herein, “RNase H agent” means an antisense agent that acts through RNase H to modulate a target nucleic acid and/or protein encoded by a target nucleic acid. In certain embodiments, RNase H agents are single-stranded. In certain embodiments, RNase H agents are double-stranded. RNase H compounds may comprise conjugate groups and/or terminal groups. In certain embodiments, an RNase H agent modulates the amount and/or activity of a target nucleic acid. The term RNase H agent excludes antisense agents that act principally through RISC/Ago2.

As used herein, “treating” means improving a subject’s disease or condition by administering an oligomeric agent or oligomeric compound described herein. In certain embodiments, treating a subject improves a symptom relative to the same symptom in the absence of the treatment. In certain embodiments, treatment reduces in the severity or frequency of a symptom, or delays the onset of a symptom, slows the progression of a symptom, or slows the severity or frequency of a symptom.

As used herein, “therapeutically effective amount” means an amount of a pharmaceutical agent or composition that provides a therapeutic benefit to an animal. For example, a therapeutically effective amount improves a symptom of a disease.

CERTAIN EMBODIMENTS

Embodiment 1. An oligomeric compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an IFNAR1 nucleic acid, and wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 2. The oligomeric compound of embodiment 1, wherein the IFNAR1 nucleic acid has the nucleobase sequence of any of SEQ ID NO: 1 or SEQ ID NO: 2.

Embodiment 3. The oligomeric compound of embodiment 1 or embodiment 2, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 5085-5133, 19997-20061, 20076-20133, 20528-20616, 22294-22329, 22453-22476, 22595-22626, 25530-25565, 25606-25652, 25710-25767, 25768-25827, 28421-28468, 29924-29949, 29968-30021, 31072-31096, 31792-31837, 32353-32386, or 35016-35042 of SEQ ID NO: 1.

Embodiment 4. The oligomeric compound of any of embodiments 1-3, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 20003-20022, 20104-20123, 20591-20610, 22455-22474, 22456-22475, or 29981-30000 of SEQ ID NO: 1.

Embodiment 5. The oligomeric compound of any of embodiments 1-4, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of the IFNAR1 nucleic acid.

Embodiment 6. An oligomeric compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-2687, and wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

Embodiment 7. The oligomeric compound of embodiment 6, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 12-2687.

Embodiment 8. The oligomeric compound of embodiment 7, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of SEQ ID NOs: 12-2687.

Embodiment 9. The oligomeric compound of any of embodiments 6-8, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-89.

Embodiment 10. The oligomeric compound of any of embodiments 6-8, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 90-2687.

Embodiment 11. The oligomeric compound of any of embodiments 6-8, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

Embodiment 12. The oligomeric compound of embodiment 11, wherein the modified oligonucleotide consists of 20 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

Embodiment 13. The oligomeric compound of embodiment 12, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any one of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

Embodiment 14. The oligomeric compound of any of embodiments 6-12, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of an IFNAR1 nucleic acid, wherein the IFNAR1 nucleic acid has the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

Embodiment 15. The oligomeric compound of any of embodiments 1-14, wherein the modified oligonucleotide consists of 10 to 25, 10 to 30, 10 to 50, 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16

Embodiment 16. The oligomeric compound of any of embodiments 1-14, wherein the modified oligonucleotide consists of 20 linked nucleosides.

Embodiment 18. The oligomeric compound of embodiment 17, wherein the modified sugar moiety comprises a bicyclic sugar moiety.

Embodiment 20. The oligomeric compound of embodiment 17, wherein the modified sugar moiety comprises a non-bicyclic modified sugar moiety.

Embodiment 22. The oligomeric compound of any of embodiments 1-21, wherein at least one nucleoside of the modified oligonucleotide compound comprises a sugar surrogate.

Embodiment 24. The oligomeric compound of embodiment 23, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 26. The oligomeric compound of embodiment 25, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Embodiment 28. The oligomeric compound of any of embodiments 1-23, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

[illegible]

sssooosssssssssoss, and ssssoosssssssssoss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

Embodiment 31. The oligomeric compound of any of embodiments 1-30, wherein the modified oligonucleotide comprises at least one modified nucleobase.

5 Embodiment 32. The oligomeric compound of embodiment 31, wherein the modified nucleobase is 5-methyl cytosine.

Embodiment 33. The oligomeric compound of embodiment 32, wherein each cytosine is a 5-methyl cytosine.

Embodiment 34. The oligomeric compound of any of embodiments 1-33, wherein the modified oligonucleotide comprises a deoxy region.

10 Embodiment 35. The oligomeric compound of embodiment 34, wherein each nucleoside of the deoxy region is a 2'-β-D-deoxynucleoside.

Embodiment 36. The oligomeric compound of embodiment 34 or embodiment 35, wherein the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides.

15 Embodiment 37. The oligomeric compound of any of embodiments 34-36, wherein each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety.

Embodiment 38. The oligomeric compound of any of embodiments 34-37, wherein the deoxy region is flanked on the 5'-side by a 5'-external region consisting of 1-6 linked 5'-external region nucleosides and on the 3'-side by a 3'-external region consisting of 1-6 linked 3'-external region nucleosides; wherein

20 the 3'-most nucleoside of the 5' external region comprises a modified sugar moiety; and the 5'-most nucleoside of the 3' external region comprises a modified sugar moiety.

Embodiment 39. The oligomeric compound of embodiment 38, wherein each nucleoside of the 3' external region comprises a modified sugar moiety.

Embodiment 40. The oligomeric compound of embodiment 38 or embodiment 39, wherein each nucleoside of the 5' external region comprises a modified sugar moiety.

25 Embodiment 41. The oligomeric compound of embodiment 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 5 linked nucleosides;

a deoxy region consisting of 10 linked nucleosides; and

a 3' external region consisting of 5 linked nucleosides;

30 wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a 2'-MOE nucleoside.

Embodiment 42. The oligomeric compound of embodiment 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 6 linked nucleosides;

a deoxy region consisting of 10 linked nucleosides; and

a 3' external region consisting of 4 linked nucleosides;

35 wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a 2'-MOE nucleoside.

Embodiment 43. The oligomeric compound of embodiment 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 3 linked nucleosides;

a deoxy region consisting of 10 linked nucleosides; and

a 3' external region consisting of 3 linked nucleosides;
 wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a cEt nucleoside.

Embodiment 44. The oligomeric compound of embodiment 40, wherein the modified oligonucleotide has:
 a 5' external region consisting of 1-6 linked nucleosides;
 a deoxy region consisting of 6-10 linked nucleosides; and
 a 3' external region consisting of 1-6 linked nucleosides;
 wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a cEt nucleoside or a 2'-MOE nucleoside; and each of the deoxy region nucleosides is a 2'-β-D-deoxynucleoside.

Embodiment 45. The oligomeric compound of any of embodiments 38-39 or 41-44, wherein the modified oligonucleotide has a sugar motif comprising:

a 5' external region consisting of 3-6 linked nucleosides;
 a deoxy region consisting of 7-8 linked nucleosides; and
 a 3' external region consisting of 3-6 linked nucleosides;
 wherein each of the 3' external region nucleosides is selected from a 2'-MOE nucleoside and a cEt nucleoside, and the 5' external region has the following formula:
 $(Nk)_n(Nd)(Nx)$
 wherein each Nk is a bicyclic nucleoside, Nx 2'-OMe nucleoside and Nd is a 2'-β-D-deoxynucleoside;
 and n is from 1-4.

Embodiment 46. An oligomeric compound of any of embodiments 1-38, wherein the modified oligonucleotide has a sugar motif (5' to 3') selected from eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, and kkkkkkkkkkkkk, wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt modified sugar moiety.

Embodiment 47. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: ${}^mC_{es}T_{eo}T_{eo}T_{eo}T_{eo}T_{eo}{}^mC_{ds}T_{ds}G_{ds}{}^mC_{ds}T_{ds}{}^mC_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{eo}{}^mC_{es}G_{es}{}^mC_e$ (SEQ ID NO 2668), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribose sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

Embodiment 48. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: ${}^mC_{es}T_{eo}G_{eo}T_{eo}T_{eo}T_{eo}T_{ds}A_{ds}{}^mC_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{eo}T_{es}{}^mC_{es}{}^mC_e$ (SEQ ID NO 2040), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

5 Embodiment 49. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: T_{es}T_{eo}T_{eo}A_{eo}T_{es}^mC_{ds}^mC_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}^mC_{ds}^mC_{ds}A_{eo}T_{eo}^mC_{es}^mC_{es}^mC_e (SEQ ID NO 2670), wherein:

A = an adenine nucleobase,
^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

15 Embodiment 50. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: T_{es}^mC_{eo}G_{eo}^mC_{eo}^mC_{es}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{eo}T_{eo}^mC_{es}A_{es}^mC_e (SEQ ID NO 2679), wherein:

A = an adenine nucleobase,
^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

25 Embodiment 51. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: T_{es}T_{eo}T_{eo}^mC_{eo}A_{eo}T_{eo}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}^mC_{ds}T_{ds}T_{eo}^mC_{es}^mC_{es}T_e (SEQ ID NO 2625), wherein:

A = an adenine nucleobase,
^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

35 Embodiment 52. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: T_{es}T_{eo}^mC_{eo}G_{eo}^mC_{eo}^mC_{eo}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{eo}T_{es}^mC_{es}A_e (SEQ ID NO 1317), wherein:

A = an adenine nucleobase,
^mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,

T = a thymine nucleobase,
e = a 2'-MOE sugar moiety,
d = a 2'-β-D-deoxyribosyl sugar moiety,
s = a phosphorothioate internucleoside linkage, and
5 o = a phosphodiester internucleoside linkage.

Embodiment 53. The oligomeric compound of any of embodiments 1-52, consisting of the modified oligonucleotide.

Embodiment 54. The oligomeric compound of any of embodiments 1-52, wherein the oligomeric compound comprises a conjugate group.

10 Embodiment 55. The oligomeric compound of embodiment 54, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

Embodiment 56. The oligomeric compound of embodiment 54 or embodiment 55, wherein the conjugate linker consists of a single bond.

15 Embodiment 57. The oligomeric compound of any of embodiments 55 or 56, wherein the conjugate linker is cleavable.

Embodiment 58. The oligomeric compound of any of embodiments 55-57, wherein the conjugate linker comprises 1-3 linker-nucleosides.

Embodiment 59. The oligomeric compound of any of embodiments 55-57, wherein the conjugate linker does not comprise any linker nucleosides.

20 Embodiment 60. The oligomeric compound of any of embodiments 54-59, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

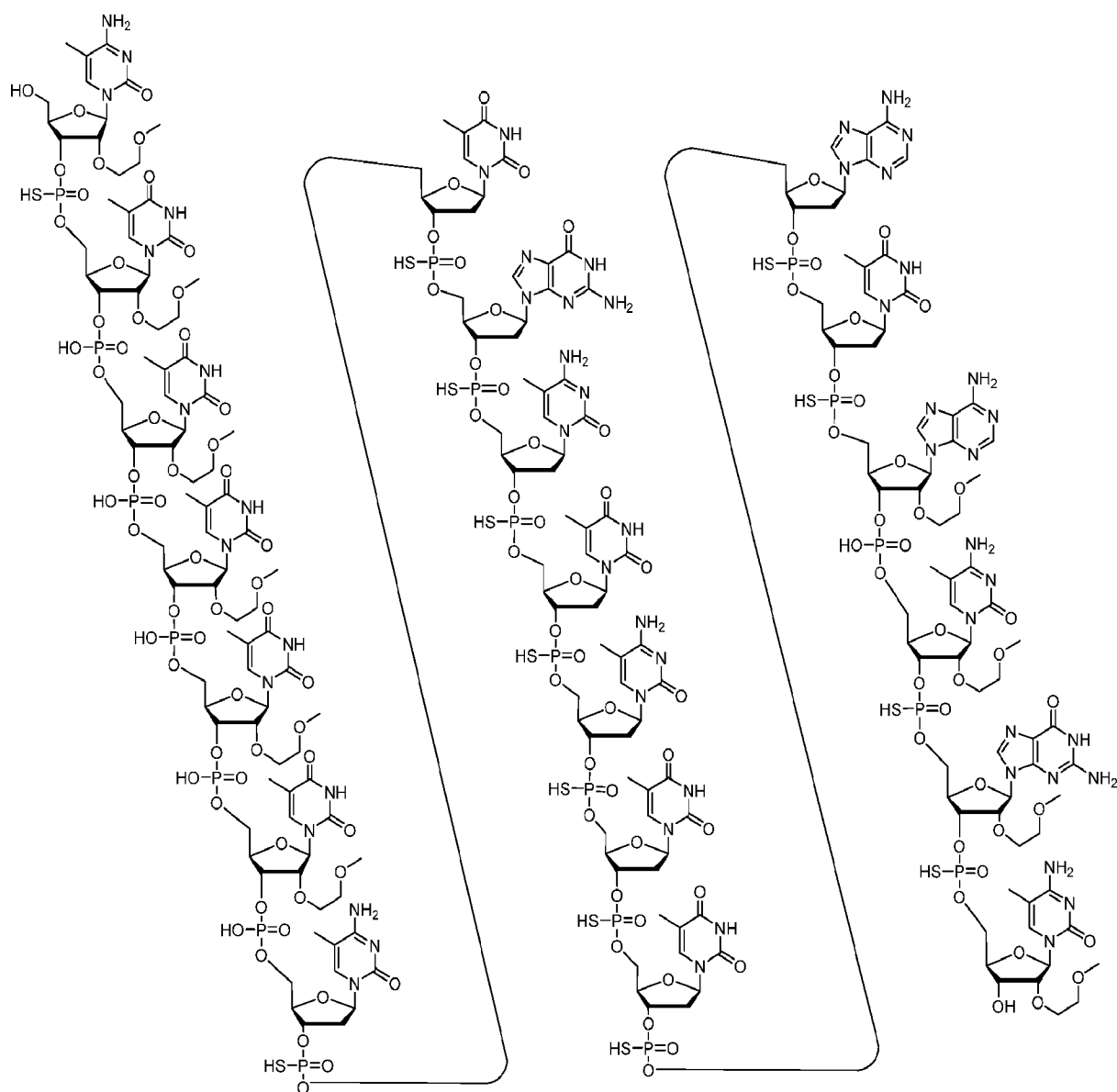
Embodiment 61. The oligomeric compound of any of embodiments 54-59, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

25 Embodiment 62. The oligomeric compound of any of embodiments 1 to 61, wherein the oligomeric compound comprises a terminal group.

Embodiment 63. The oligomeric compound of embodiment 62 wherein the terminal group is an abasic sugar moiety.

Embodiment 64. The oligomeric compound of any one of embodiments 1-62 wherein the oligomeric compound is a singled-stranded oligomeric compound.

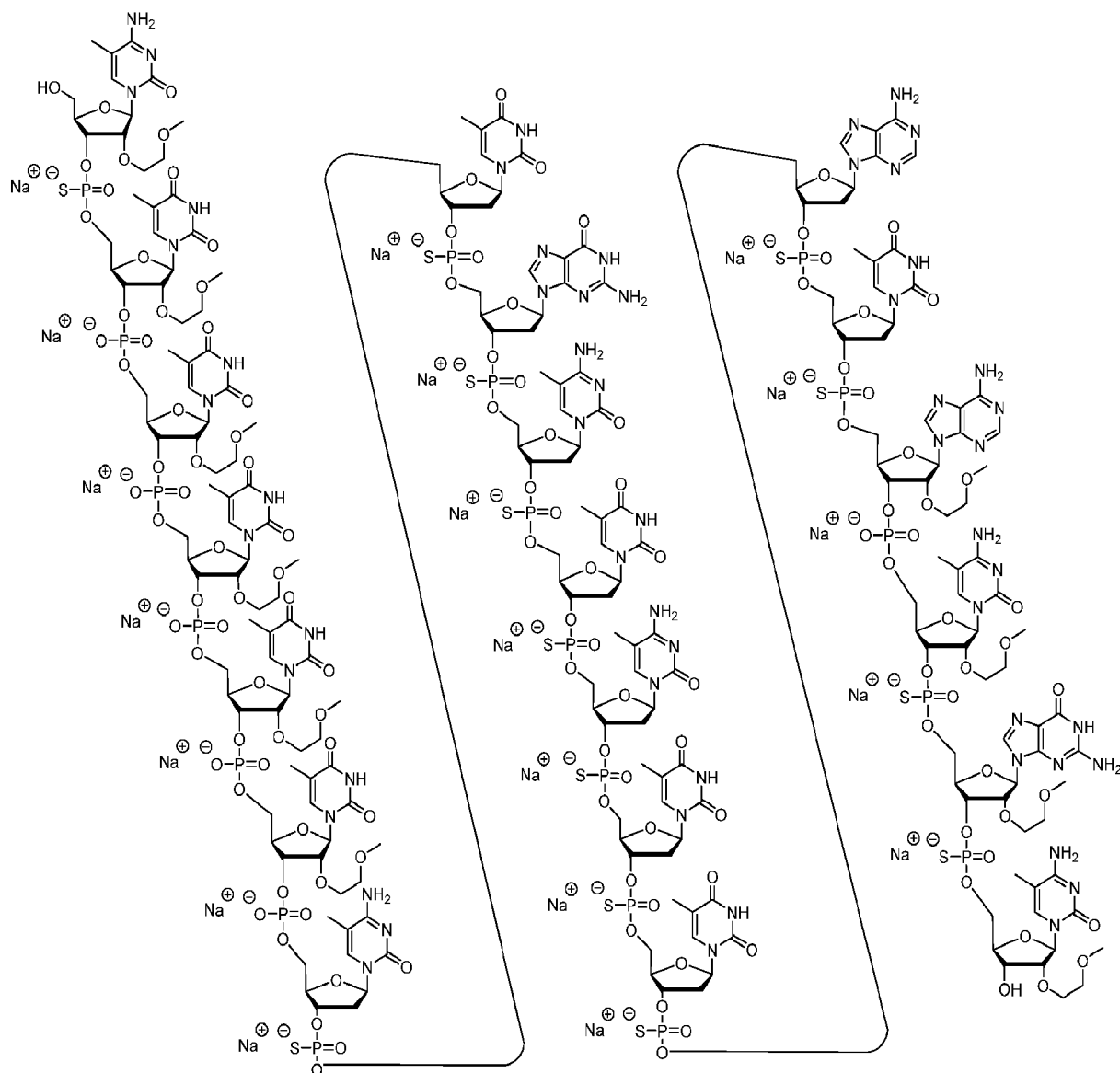
Embodiment 65. A modified oligonucleotide according to the following chemical structure:



5 (SEQ ID NO 2668), or a salt thereof.

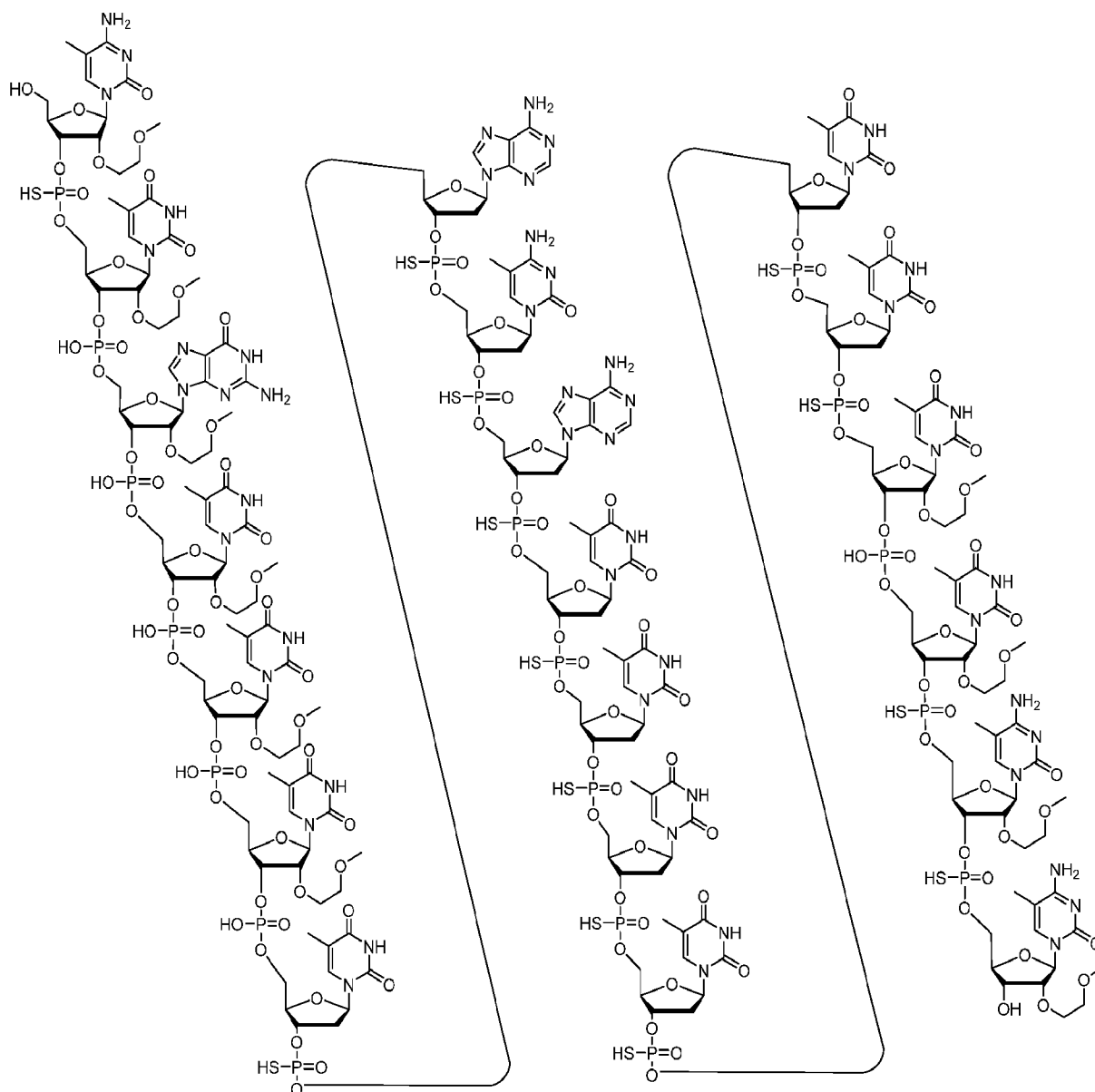
Embodiment 66. The modified oligonucleotide of embodiment 65, which is the sodium salt or the potassium salt.

Embodiment 67. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2668).

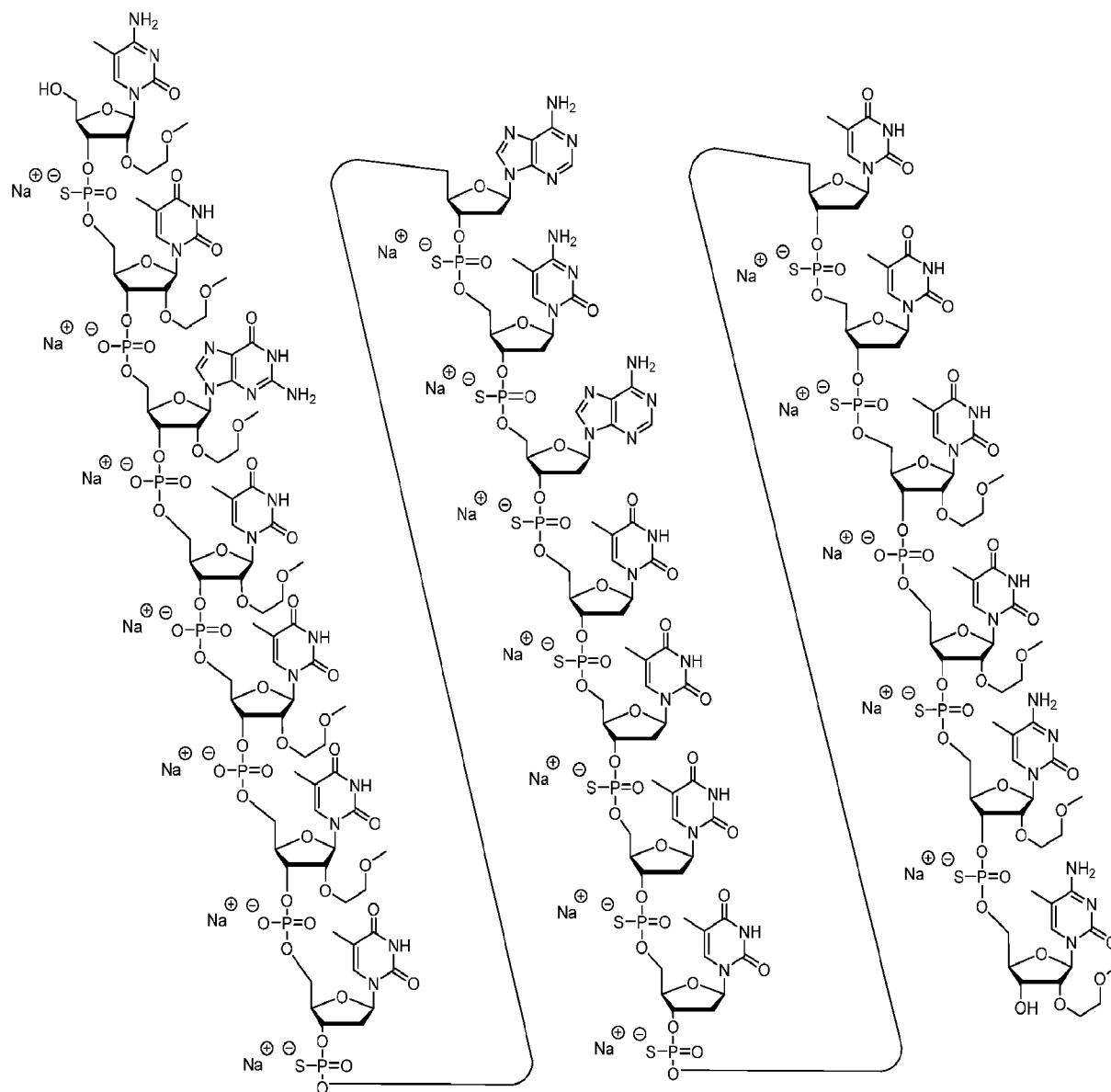
Embodiment 68. A modified oligonucleotide according to the following chemical structure:



5 (SEQ ID NO 2040), or a salt thereof.

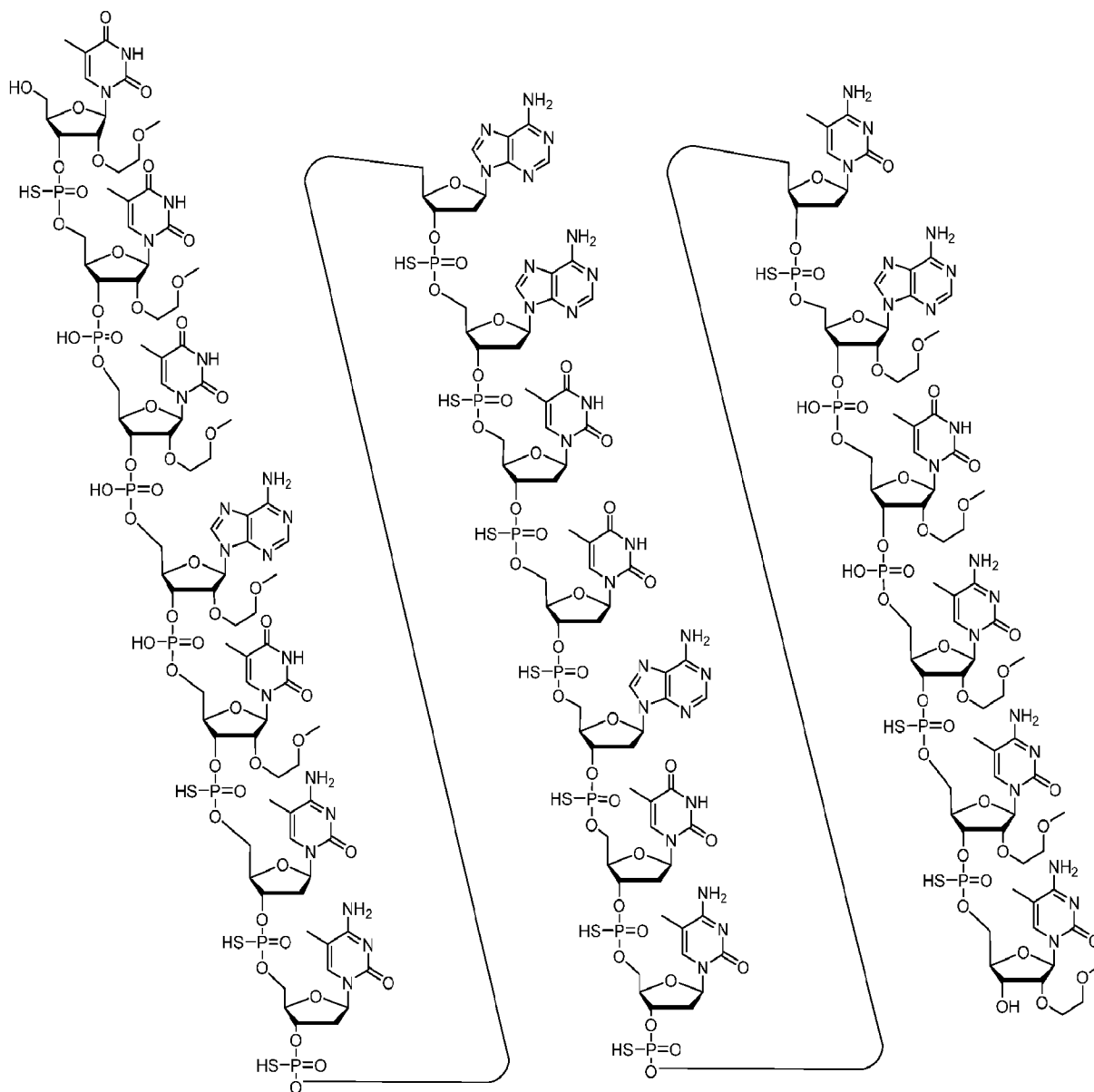
Embodiment 69. The modified oligonucleotide of embodiment 68, which is the sodium salt or the potassium salt.

Embodiment 70. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2040).

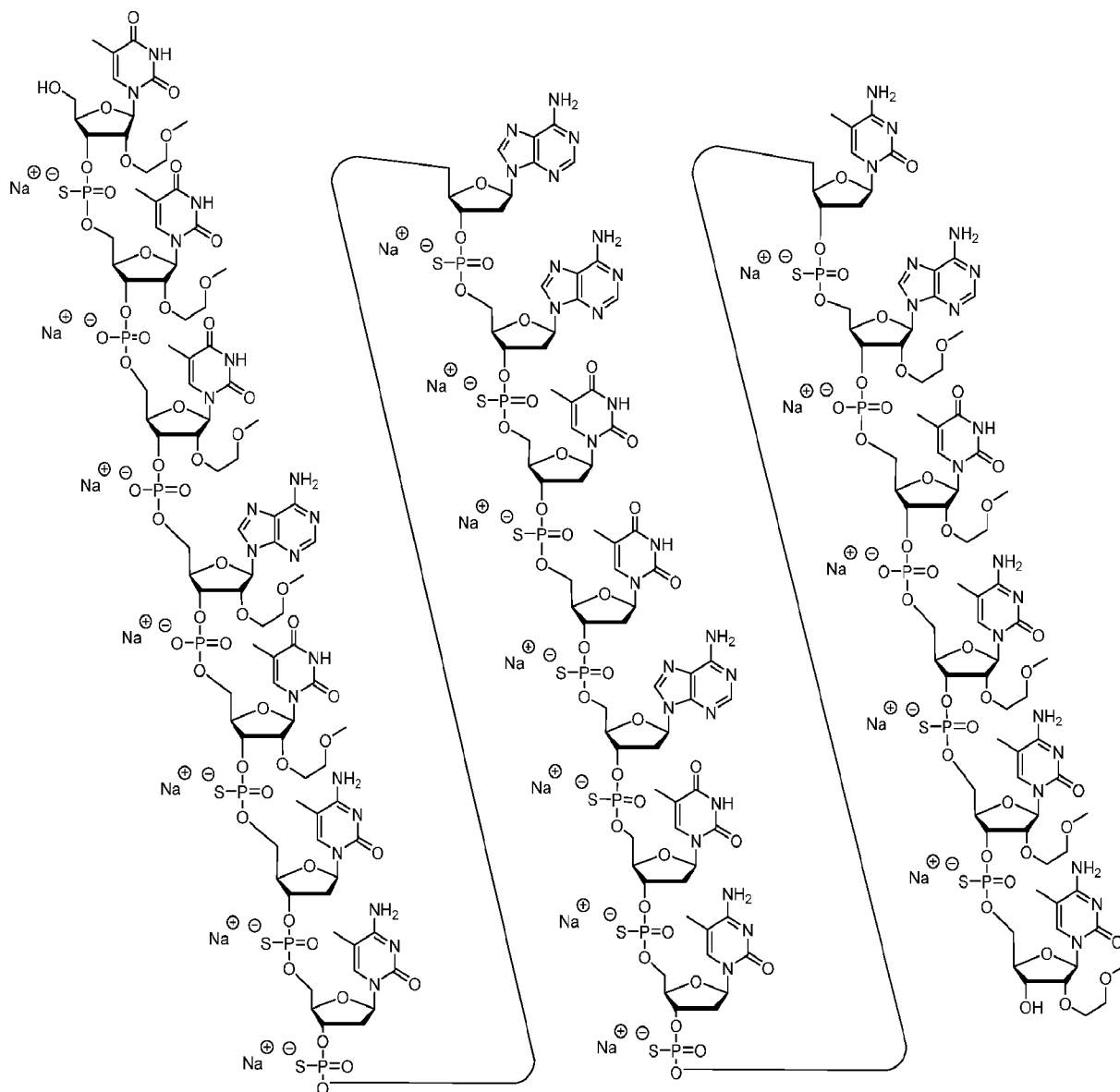
Embodiment 71. A modified oligonucleotide according to the following chemical structure:



5 (SEQ ID NO 2670), or a salt thereof.

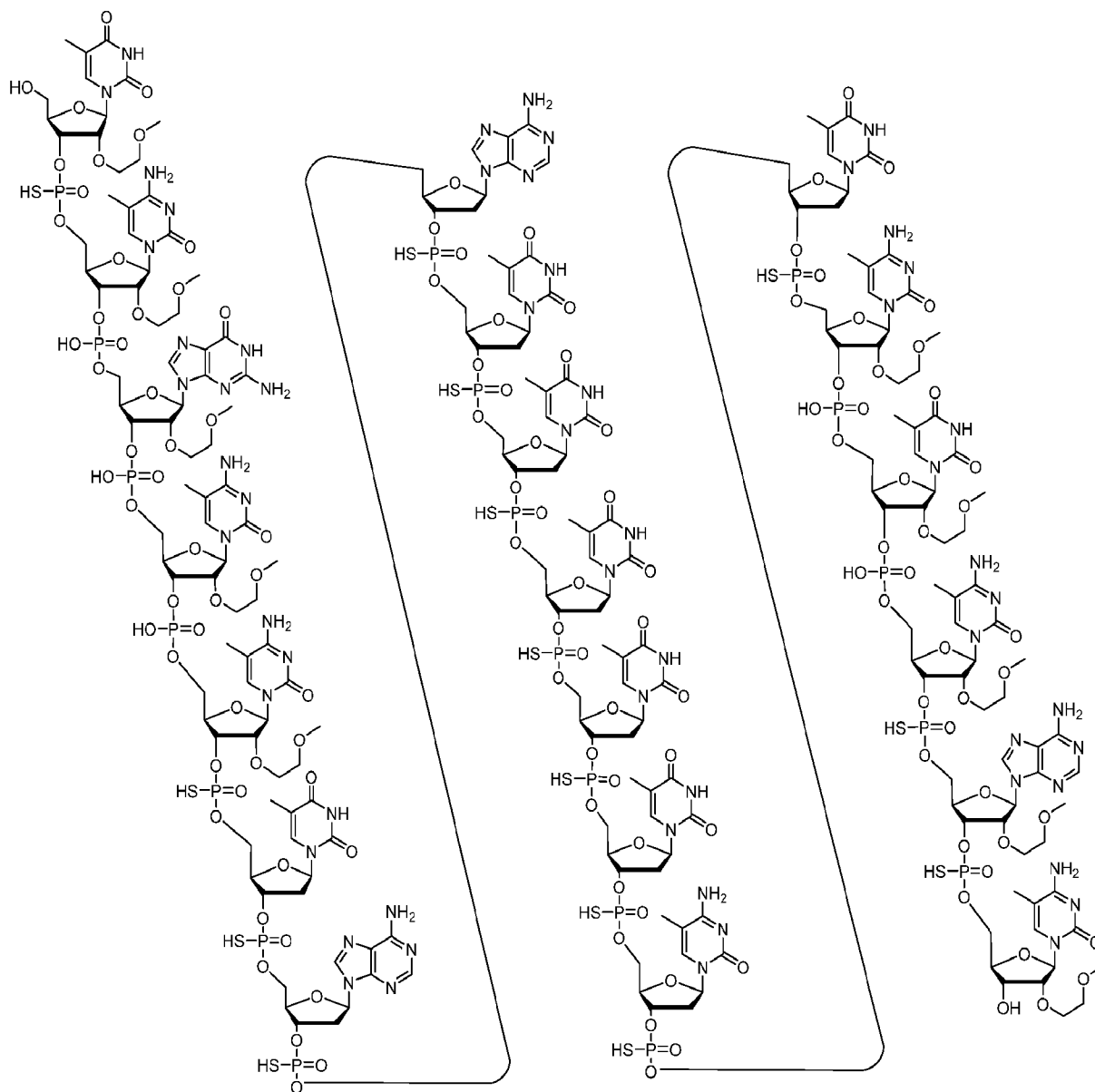
Embodiment 72. The modified oligonucleotide of embodiment 71, which is the sodium salt or the potassium salt.

Embodiment 73. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2670).

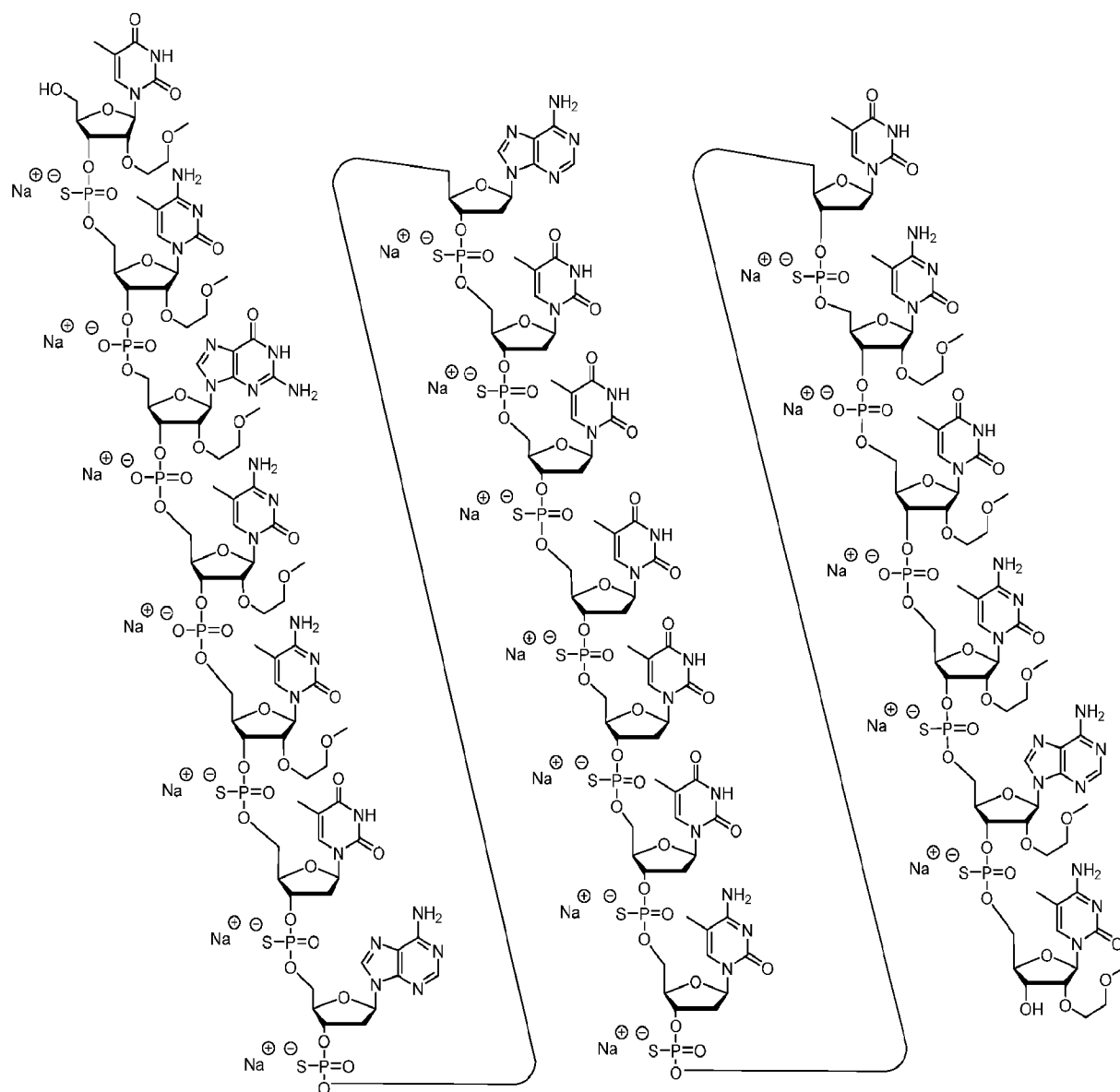
Embodiment 74. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2679), or a salt thereof.

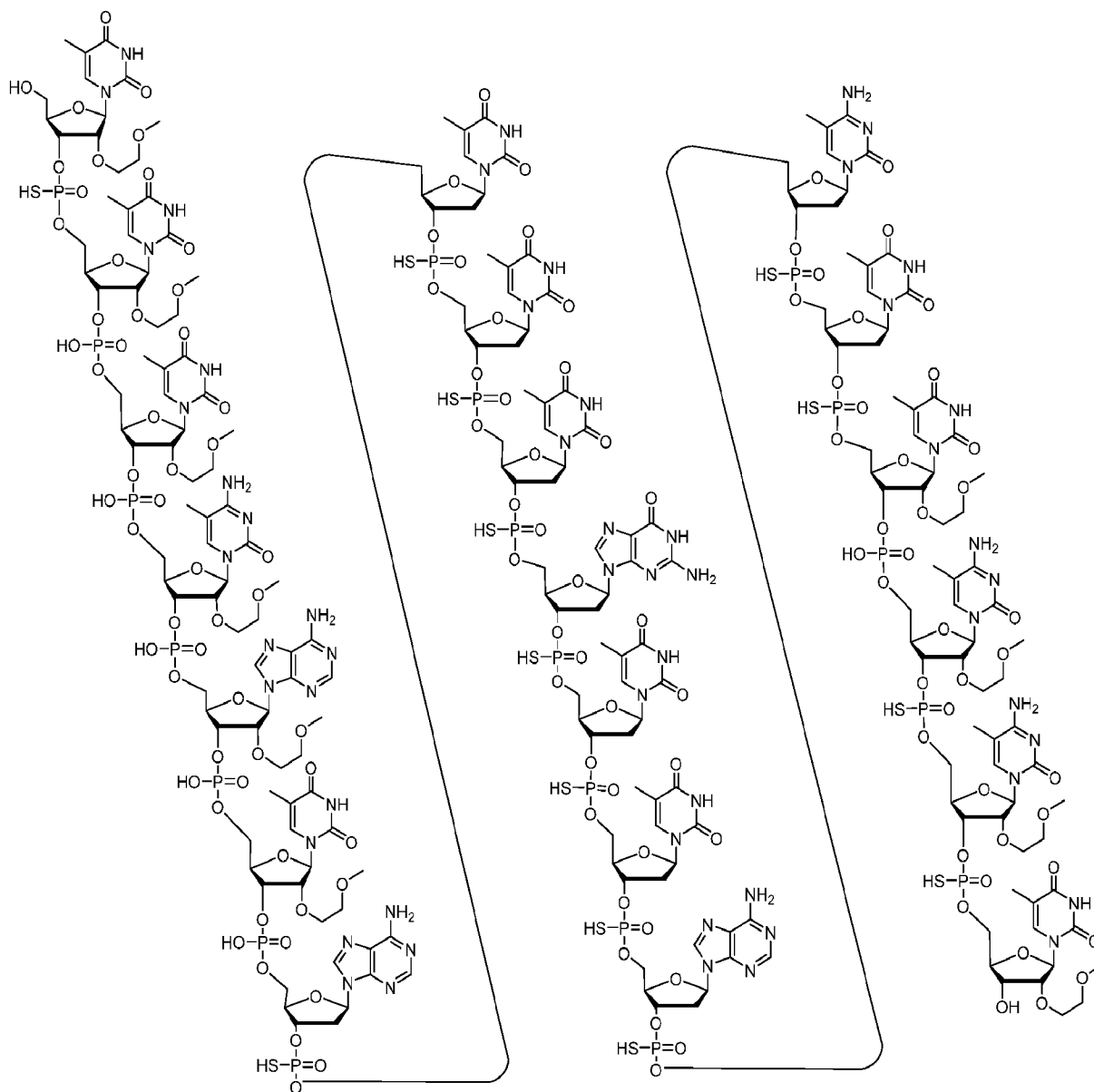
5 Embodiment 75. The modified oligonucleotide of embodiment 74, which is the sodium salt or the potassium salt.

Embodiment 76. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2679).

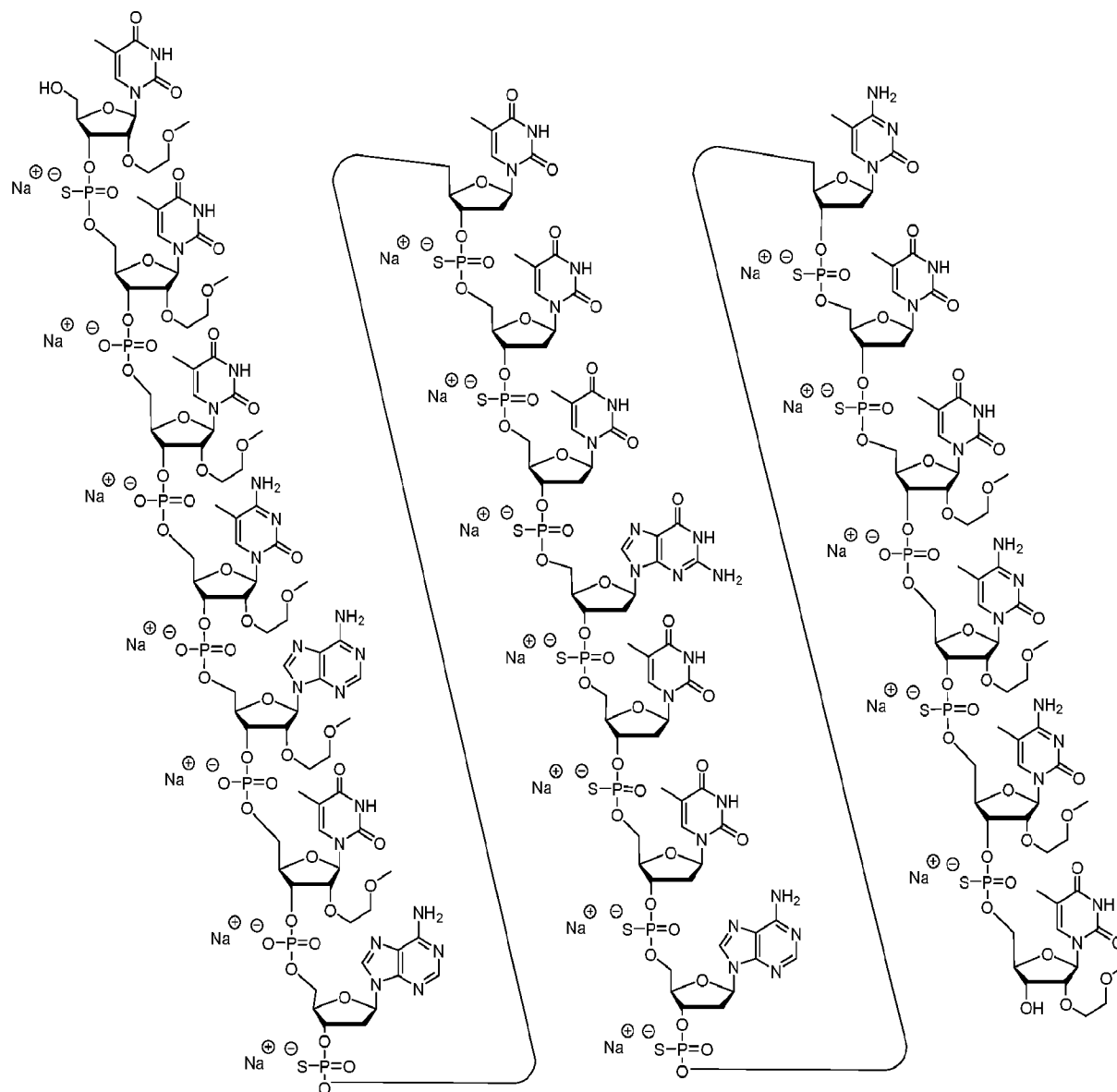
Embodiment 77. A modified oligonucleotide according to the following chemical structure:



5 (SEQ ID NO 2625), or a salt thereof.

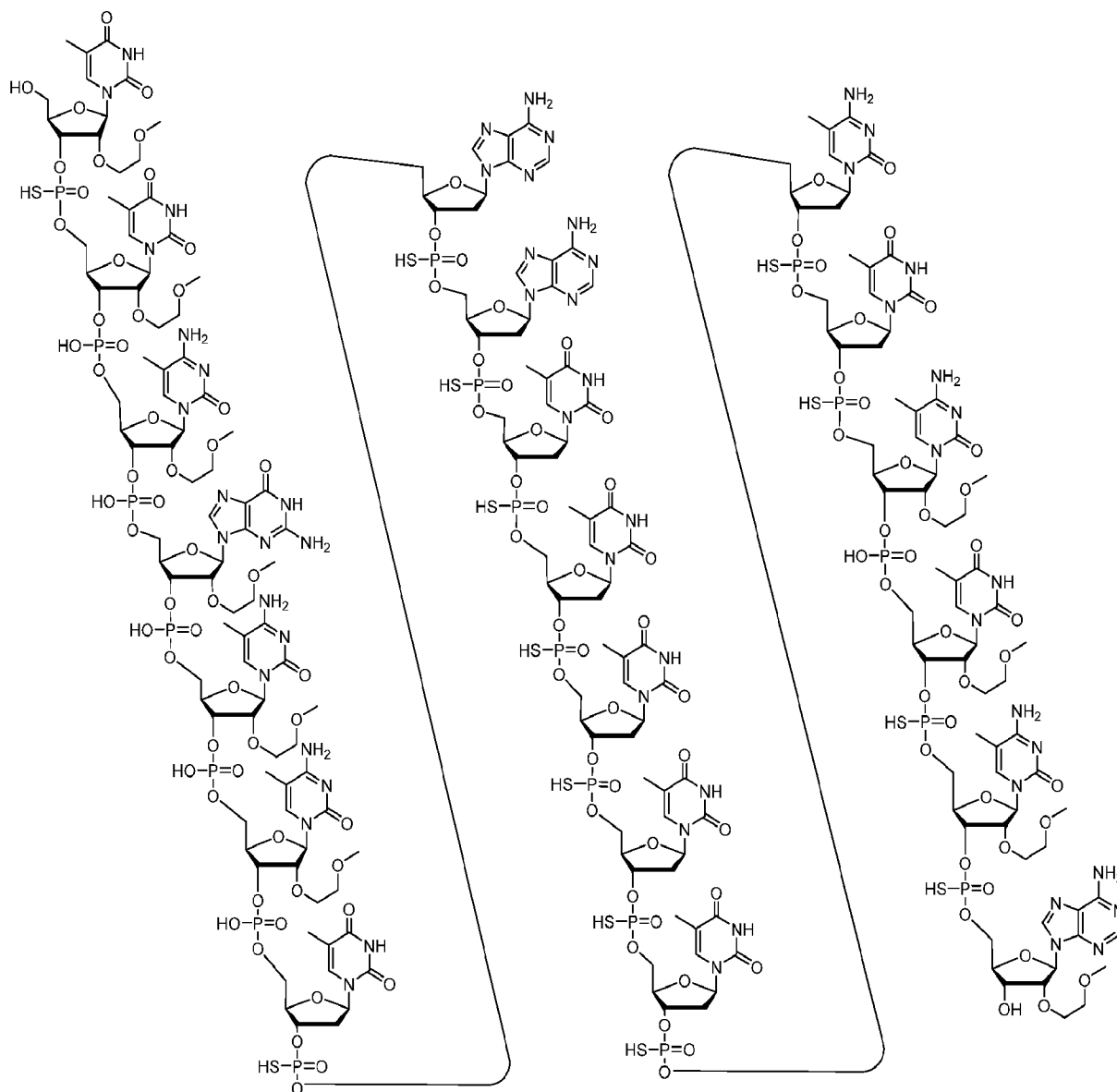
Embodiment 78. The modified oligonucleotide of embodiment 77, which is the sodium salt or the potassium salt.

Embodiment 79. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2625).

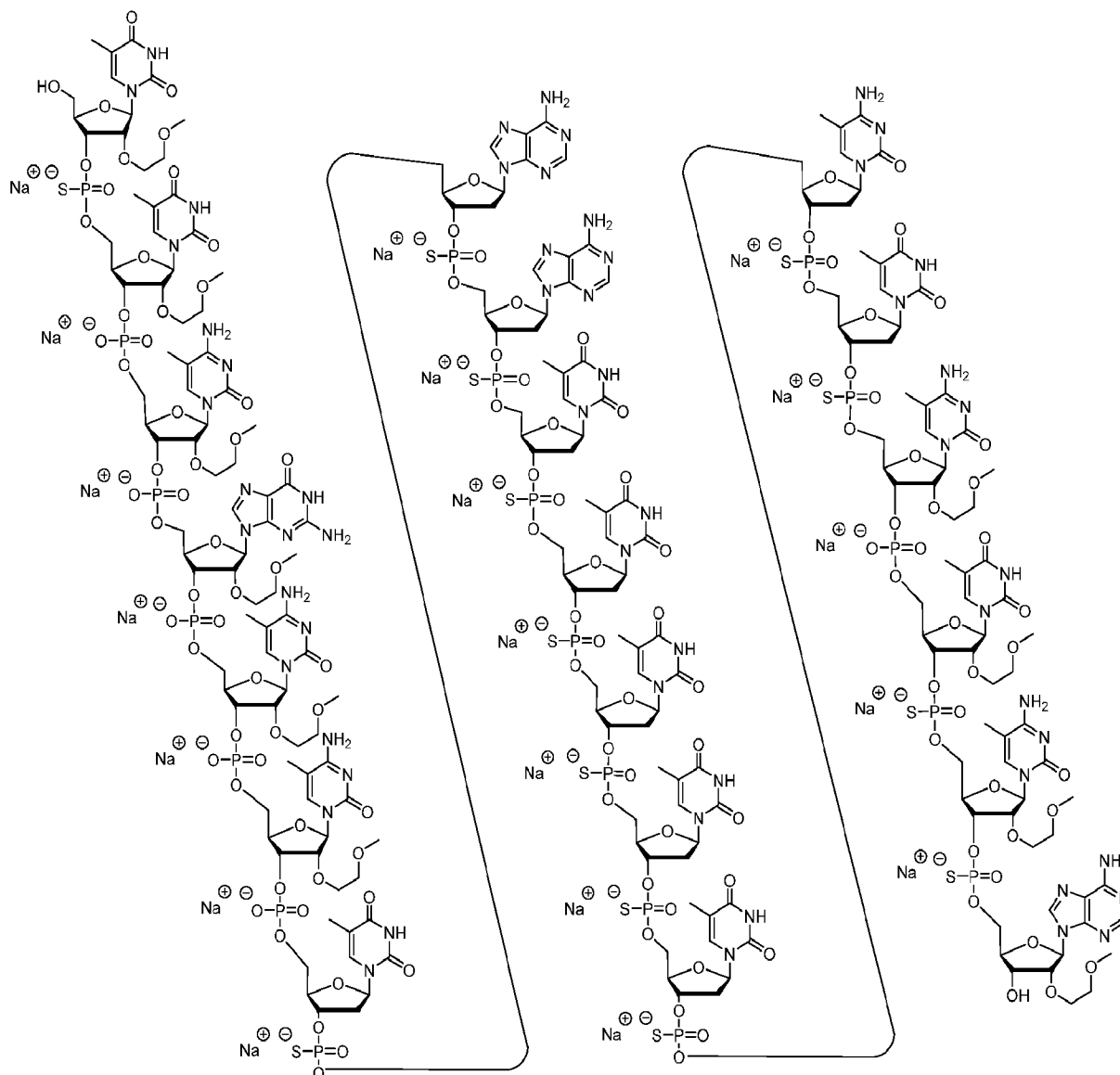
Embodiment 80. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 1317), or a salt thereof.

5 Embodiment 81. The modified oligonucleotide of embodiment 80, which is the sodium salt or the potassium salt.

Embodiment 82. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 1317).

Embodiment 83. A chirally enriched population of oligomeric compounds of any of embodiments 1-64 or a
 5 chirally enriched population of modified oligonucleotides of any of embodiments 65-82, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

Embodiment 84. The chirally enriched population of embodiment 83, wherein the population is enriched for
 10 modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) or (*Rp*) configuration.

Embodiment 85. The chirally enriched population of embodiment 83, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

Embodiment 86. The chirally enriched population of embodiment 83, wherein the population is enriched for
 15 modified oligonucleotides having the (*Rp*) configuration at one particular phosphorothioate internucleoside linkage and the (*Sp*) configuration at each of the remaining phosphorothioate internucleoside linkages.

Embodiment 87. The chirally enriched population of embodiment 83, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.

Embodiment 88. A population of oligomeric compounds of any of embodiments 1-64, or a population of modified oligonucleotides of any of embodiments 65-82, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

Embodiment 89. An oligomeric duplex, comprising a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of any of embodiments 1-64.

Embodiment 90. The oligomeric duplex of embodiment 89, wherein the second modified oligonucleotide consists of 8 to 80 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

Embodiment 91. The oligomeric duplex of embodiment 89 or embodiment 90, wherein the first modified oligonucleotide comprises a 5'-stabilized phosphate group.

Embodiment 92. The oligomeric duplex of embodiment 91, wherein the 5'-stabilized phosphate group comprises a cyclopropyl phosphonate or a vinyl phosphonate.

Embodiment 93. The oligomeric duplex of any of embodiments 89-92, wherein the first modified oligonucleotide comprises a glycol nucleic acid (GNA) sugar surrogate.

Embodiment 94. The oligomeric duplex of any of embodiments 89-92, wherein the first modified oligonucleotide comprises a 2'-NMA sugar moiety.

Embodiment 95. The oligomeric duplex of any of embodiments 89-94, wherein at least one nucleoside of the second modified oligonucleotide comprises a modified sugar moiety.

Embodiment 96. The oligomeric duplex of embodiment 95, wherein the modified sugar moiety of the second modified oligonucleotide comprises a bicyclic sugar moiety.

Embodiment 97. The oligomeric duplex of embodiment 96, wherein the bicyclic sugar moiety of the second modified oligonucleotide comprises a 2'-4' bridge selected from $-O-CH_2$ and $-O-CH(CH_3)-$.

Embodiment 98. The oligomeric duplex of embodiment 95, wherein the modified sugar moiety of the second modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

Embodiment 99. The oligomeric duplex of embodiment 98, wherein the non-bicyclic modified sugar moiety of the second modified oligonucleotide is a 2'-MOE sugar moiety, a 2'-F sugar moiety, or 2'-OMe sugar moiety.

Embodiment 100. The oligomeric duplex of any of embodiments 89-99, wherein at least one nucleoside of the second modified oligonucleotide comprises a sugar surrogate.

Embodiment 101. The oligomeric duplex of any of embodiments 89-100, wherein at least one internucleoside linkage of the second modified oligonucleotide is a modified internucleoside linkage.

Embodiment 102. The oligomeric duplex of embodiment 101, wherein at least one modified internucleoside linkage of the second modified oligonucleotide is a phosphorothioate internucleoside linkage.

Embodiment 103. The oligomeric duplex of any of embodiments 89-102, wherein at least one internucleoside linkage of the second modified oligonucleotide is a phosphodiester internucleoside linkage.

Embodiment 104. The oligomeric duplex of any of embodiments 89-101 or 103, wherein each internucleoside linkage of the second modified oligonucleotide is independently a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

Embodiment 105. The oligomeric duplex of any of embodiments 89-104, wherein the second modified oligonucleotide comprises at least one modified nucleobase.

Embodiment 106. The oligomeric duplex of embodiment 105, wherein the modified nucleobase of the second modified oligonucleotide is 5-methylcytosine.

Embodiment 107. The oligomeric duplex of any of embodiments 89-106, wherein the second modified oligonucleotide comprises a conjugate group.

Embodiment 108. The oligomeric duplex of embodiment 107, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

Embodiment 109. The oligomeric duplex of embodiment 107 or embodiment 108, wherein the conjugate group is attached to the second modified oligonucleotide at the 5'-end of the second modified oligonucleotide.

Embodiment 110. The oligomeric duplex of embodiment 107 or embodiment 108, wherein the conjugate group is attached to the second modified oligonucleotide at the 3'-end of the second modified oligonucleotide.

Embodiment 111. The oligomeric duplex of any of embodiments 107-110, wherein the conjugate group comprises a lipid.

Embodiment 112. The oligomeric duplex of any of embodiments 107-111, wherein the second modified oligonucleotide comprises a terminal group.

Embodiment 113. The oligomeric duplex of embodiment 112, wherein the terminal group is an abasic sugar moiety.

Embodiment 114. The oligomeric duplex of any of embodiments 89-113, wherein the second modified oligonucleotide consists of 10 to 25, 10 to 30, 10 to 50, 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 22, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

Embodiment 115. An antisense agent comprising an antisense compound, wherein the antisense compound is the oligomeric compound of any of embodiments 1-64 or the modified oligonucleotide of any of embodiments 65-82.

Embodiment 116. The antisense agent of embodiment 115, wherein the antisense agent is the oligomeric duplex of any of embodiments 89-114.

Embodiment 117. The antisense agent of embodiment 115 or embodiment 116, wherein the antisense agent is:

- i. an RNase H agent capable of reducing the amount of IFNAR1 nucleic acid through the activation of RNase H; or
- ii. an RNAi agent capable of reducing the amount of IFNAR1 nucleic acid through the activation of RISC/Ago2.

Embodiment 118. The antisense agent of any of embodiments 115-117, wherein the antisense agent comprises a conjugate group, wherein the conjugate group comprises a cell-targeting moiety.

Embodiment 119. A pharmaceutical composition comprising an oligomeric compound of any of embodiments 1-64, a modified oligonucleotide of any of embodiments 65-82, a population of any of embodiments 83-88, an oligomeric duplex of any of embodiments 89-114, or an antisense agent of any of embodiments 115-118, and a pharmaceutically acceptable diluent or carrier.

Embodiment 120. The pharmaceutical composition of embodiment 119, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline or artificial cerebrospinal fluid.

Embodiment 121. The pharmaceutical composition of embodiment 120, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent, and the phosphate-buffered saline or the artificial cerebrospinal fluid.

Embodiment 122. A method comprising administering to a subject an oligomeric compound of any of embodiments 1-64, a modified oligonucleotide of any of embodiments 65-82, a population of any of embodiments 83-88, an oligomeric duplex of any of embodiments 89-114, an antisense agent of any of embodiments 115-118, or a pharmaceutical composition of any of embodiments 119-121.

Embodiment 123. A method of treating a disease associated with type I interferon signaling comprising administering to a subject having a disease associated with type I interferon signaling a therapeutically effective amount of an oligomeric compound of any of embodiments 1-64, a modified oligonucleotide of any of embodiments 65-82, a population of any of embodiments 83-88, an oligomeric duplex of any of embodiments 89-114, an antisense agent of any of embodiments 115-118, or a pharmaceutical composition of any of embodiments 119-121 thereby treating the disease associated with type I interferon signaling.

Embodiment 124. The method of embodiment 123, wherein the disease associated with type I interferon signaling is Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, or ataxia telangiectasia.

Embodiment 125. The method of embodiment 123 or embodiment 124, wherein the disease is associated with an elevated level of interferon-alpha.

Embodiment 126. The method of any of embodiments 122-125, wherein the subject has a mutation in a gene selected from TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, MDA5, USP18, LSM11, and RNU7-1.

Embodiment 127. The method of any of embodiments 123-126, wherein administering the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition reduces seizures, dystonia, spasticity, white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, or microencephaly; or improves feeding, motor development, language development, or social skill development in the subject.

Embodiment 128. The method of any of embodiments 123-127, wherein administering the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition reduces interferon alpha and/or lymphocytosis in the cerebrospinal fluid of the subject.

Embodiment 129. The method of any of embodiments 122-128, wherein the subject is human.

Embodiment 130. A method of reducing expression of IFNAR1 in a cell comprising contacting the cell with an oligomeric compound of any of embodiments 1-64, a modified oligonucleotide of any of embodiments 65-82, a population of any of embodiments 83-88, an oligomeric duplex of any of embodiments 89-114, an antisense agent of any of embodiments 115-118, or a pharmaceutical composition of any of embodiments 119-121.

Embodiment 131. The method of embodiment 130, wherein the cell is a neuron or a glial cell, optionally wherein the cell is an astrocyte or microglial cell.

Embodiment 132. The method of embodiment 130 or embodiment 131, wherein the cell is a human cell.

Embodiment 133. Use of an oligomeric compound of any of embodiments 1-64, a modified oligonucleotide of any of embodiments 65-82, a population of any of embodiments 83-88, an oligomeric duplex of any of embodiments 89-114, an antisense agent of any of embodiments 115-118, or a pharmaceutical composition of any of embodiments 119-121 for treating a disease associated with type I interferon signaling.

Embodiment 134. Use of an oligomeric compound of any of embodiments 1-64, a modified oligonucleotide of any of embodiments 65-82, a population of any of embodiments 83-88, an oligomeric duplex of any of embodiments 89-114, an antisense agent of any of embodiments 115-118, or a pharmaceutical composition of any of embodiments 119-121 in the manufacture of a medicament for treating a disease associated with type I interferon signaling.

Embodiment 135. The use of embodiment 133 or embodiment 134, wherein the disease is associated with an elevated level of interferon alpha.

Embodiment 136. The use of any of embodiments 133-135, wherein the disease associated with type I interferon signaling is Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, or ataxia telangiectasia.

Certain Oligomeric Agents and Oligomeric Compounds

Certain embodiments provide oligomeric agents targeted to an IFNAR1 nucleic acid. In certain embodiments, the IFNAR1 nucleic acid has the sequence set forth in GENBANK Accession No. NC_000021.9, truncated from 33321001 to 33363000 (SEQ ID NO: 1) or GENBANK Accession No. NM_000629.2 (SEQ ID NO: 2), each of which is incorporated by reference in its entirety. In certain embodiments, the oligomeric agent is a single-stranded oligomeric compound. In certain embodiments, the oligomeric agent is an oligomeric duplex.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an IFNAR1 nucleic acid, and wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage. In certain embodiments, the IFNAR1 nucleic acid has the nucleobase sequence of SEQ ID NOs: 1 or 2. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of the IFNAR1 nucleic acid.

In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 80%

complementary to an equal length portion within nucleobases 3964-3983, 4050-4069, 4573-4592, 4574-4593, 4600-4619, 4601-4620, 4603-4622, 4606-4625, 4619-4638, 4620-4639, 4681-4700, 4716-4735, 4717-4736, 4724-4743, 4725-4744, 4731-4750, 4732-4751, 4733-4752, 4740-4759, 4744-4763, 4771-4790, 4772-4791, 4773-4792, 4786-4805, 4788-4807, 4797-4816, 4798-4817, 4801-4820, 4808-4827, 4812-4831, 4814-4833, 4815-4834, 4823-4838, 4825-4844, 4827-4846, 4841-4860, 4846-4865, 4847-4866, 4862-4881, 4875-4894, 4888-4907, 4889-4908, 4905-4924, 4906-4925, 4942-4961, 4952-4971, 4957-4976, 4958-4977, 5035-5054, 5036-5055, 5061-5080, 5082-5101, 5083-5102, 5084-5103, 5085-5104, 5086-5101, 5086-5105, 5087-5102, 5087-5106, 5089-5104, 5089-5108, 5090-5105, 5096-5115, 5113-5132, 5114-5133, 5137-5156, 5142-5161, 5147-5162, 5166-5185, 5179-5198, 5181-5200, 5182-5201, 5183-5202, 5519-5538, 5532-5551, 5533-5552, 5537-5556, 5546-5565, 5598-5617, 5599-5618, 5600-5619, 5637-5656, 5653-5672, 5657-5676, 5669-5688, 5673-5692, 5701-5720, 5702-5721, 5703-5722, 5709-5728, 5755-5774, 5757-5776, 5761-5780, 5850-5869, 5878-5897, 5901-5920, 5902-5921, 5904-5923, 5907-5926, 5910-5929, 5915-5934, 5916-5935, 5917-5936, 5920-5939, 5921-5940, 5922-5941, 5923-5942, 5924-5943, 5931-5950, 5934-5953, 5935-5954, 5955-5974, 5984-6003, 5985-6004, 6028-6047, 6033-6052, 6035-6054, 6051-6070, 6052-6071, 6090-6109, 6111-6130, 6112-6131, 6113-6132, 6145-6164, 6170-6189, 6171-6190, 6195-6214, 6203-6222, 6204-6223, 6206-6225, 6207-6226, 6237-6256, 6264-6283, 6279-6298, 6306-6325, 6357-6376, 6361-6380, 6407-6426, 6408-6427, 6409-6428, 6412-6431, 6420-6439, 6425-6444, 6481-6500, 6482-6501, 6512-6527, 6672-6691, 6674-6689, 6710-6729, 6734-6753, 6749-6768, 6759-6778, 6760-6779, 6831-6850, 6835-6854, 6838-6857, 6916-6935, 6919-6938, 6921-6940, 6926-6945, 6935-6954, 6936-6955, 6941-6960, 6945-6964, 7211-7230, 7230-7249, 7234-7253, 7237-7256, 7307-7326, 7310-7329, 7311-7330, 7312-7331, 7315-7334, 7331-7350, 7437-7456, 7438-7457, 7443-7462, 7458-7477, 7526-7545, 7528-7547, 7543-7562, 7545-7564, 7569-7588, 7570-7589, 7585-7604, 7588-7607, 7589-7608, 7590-7609, 7591-7610, 7592-7607, 7592-7611, 7593-7608, 7593-7612, 7595-7610, 7595-7614, 7596-7611, 7602-7621, 7614-7633, 7617-7636, 7618-7637, 7619-7638, 7639-7658, 7640-7659, 7644-7663, 7649-7664, 7661-7680, 7662-7681, 7663-7682, 7665-7684, 7667-7686, 7668-7687, 7681-7700, 7683-7702, 7684-7703, 7685-7704, 7747-7766, 7771-7790, 7772-7791, 7773-7792, 7774-7793, 7775-7794, 7777-7796, 7778-7797, 7781-7800, 7782-7801, 7784-7803, 7785-7804, 7787-7806, 7788-7807, 7790-7809, 7803-7822, 7805-7824, 7806-7825, 7831-7850, 7867-7882, 7931-7950, 7957-7976, 7978-7997, 7979-7998, 7980-7999, 8144-8163, 8196-8215, 8210-8229, 8211-8230, 8226-8245, 8227-8246, 8231-8250, 8232-8251, 8261-8280, 8271-8286, 8300-8319, 8301-8320, 8310-8329, 8324-8343, 8325-8344, 8339-8358, 8343-8362, 8347-8366, 8351-8370, 8356-8375, 8357-8376, 8359-8378, 8360-8379, 8361-8380, 8362-8381, 8364-8383, 8366-8385, 8368-8387, 8369-8388, 8383-8402, 8387-8406, 8388-8407, 8391-8410, 8392-8411, 8393-8412, 8394-8413, 8398-8417, 8408-8427, 8409-8428, 8421-8440, 8425-8444, 8428-8447, 8429-8448, 8433-8452, 8443-8462, 8444-8463, 8524-8543, 8549-8568, 8550-8569, 8551-8570, 8584-8603, 8624-8643, 8626-8645, 8627-8646, 8629-8648, 8630-8649, 8631-8650, 8632-8651, 8636-8655, 8637-8656, 8652-8671, 8653-8672, 8656-8675, 8657-8676, 8659-8678, 8660-8679, 8661-8680, 8682-8701, 8698-8717, 8716-8735, 8717-8736, 8721-8740, 8722-8741, 8724-8743, 8731-8750, 8733-8752, 8748-8767, 8761-8780, 8762-8781, 8763-8782, 8764-8783, 8765-8784, 8770-8789, 8776-8795, 8777-8796, 8778-8797, 8782-8801, 8791-8806, 8791-8810, 8792-8811, 8793-8808, 8793-8812, 8794-8809, 8794-8813, 8795-8810, 8795-8814, 8807-8826, 8808-8827, 8809-8828, 8822-8841, 8831-8850, 8834-8853, 8835-8854, 8836-8855, 8857-8876, 8938-8957, 8939-8958, 8957-8972, 8980-8999, 9021-9040, 9022-9041, 9025-9044, 9026-9041, 9026-9045, 9038-9057, 9156-9175, 9164-9183, 9204-9223, 9205-9224, 9252-9271, 9253-9272, 9254-9273, 9255-9274, 9257-9276, 9319-9338, 9329-9348, 9374-9393, 9375-9394, 9376-9395, 9377-9396, 9379-9398, 9388-9407, 9393-9412, 9394-9413, 9414-

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In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 216-235, 218-237, 220-239, 521-540, 670-689, 1119-1138, 1283-1302, 1284-1303, 1287-1306, 1288-1307, 1580-1599, 1581-1600 of SEQ ID NO: 2. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to the equal length portion of the IFNAR1 nucleic acid.

In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 5084-5133, 19997-20061, 20076-20133, 20528-20611, 20616, 22294-22329, 22453-22476, 22597-22595-22626, 25530-25565, 25606-25652, 25710-25767, 25768-25827, 28421-28468, 29924-29949, 29968-30021, 31072-31096, 31792-31837, 32353-32386, or 35016-35042 of SEQ ID NO: 1. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 20003-20022, 20104-20123, 20591-20610, 22455-22474, 22456-22475, 29981-30000, of SEQ ID NO: 1. In certain embodiments, the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to the equal length portion of the IFNAR1 nucleic acid.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-2687.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 16 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of nucleobase sequences of SEQ ID NOs: 12-89.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 16 linked nucleosides, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of the nucleobase sequences of SEQ ID NOs: 12-89.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 20 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of nucleobase sequences of SEQ ID NOs: 12-2687.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 20 linked nucleosides, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of the nucleobase sequences of SEQ ID NOs: 90-2687.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 16 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 20 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of the nucleobase sequences of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

Certain embodiments provide an oligomeric compound comprising a modified oligonucleotide consisting of 20 linked nucleosides, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of the nucleobase sequences of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

In any of the oligomeric compounds provided herein, the nucleobase sequence of the modified oligonucleotide can be at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of an IFNAR1 nucleic acid, wherein the IFNAR1 nucleic acid has the nucleobase sequence of SEQ ID NOs: 1 or 2.

In any of the oligomeric compounds provided herein, the modified oligonucleotide can consist of 10 to 25, 10 to 30, 10 to 50, 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 22, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

In any of the oligomeric compounds provided herein, at least one nucleoside of the modified oligonucleotide can comprise a modified sugar moiety. In certain embodiments, the modified sugar moiety comprises a bicyclic sugar moiety, such as a bicyclic sugar moiety comprising a 2'-4' bridge selected from -O-CH₂- and -O-CH(CH₃)-. In certain embodiments, the modified sugar moiety comprises a non-bicyclic modified sugar moiety, such as a 2'-MOE sugar moiety or 2'-OMe sugar moiety.

In any of the oligomeric compounds provided herein, at least one nucleoside of the modified oligonucleotide compound can comprise a sugar surrogate.

In any of the oligomeric compounds provided herein, at least one internucleoside linkage of the modified oligonucleotide can comprise a modified internucleoside linkage, such as a phosphorothioate internucleoside linkage. In certain embodiments, each internucleoside linkage of the modified oligonucleotide can be a modified internucleoside linkage or each internucleoside linkage of the modified oligonucleotide can be a phosphorothioate internucleoside linkage. In certain embodiments, at least one internucleoside linkage of the modified oligonucleotide can be a

phosphodiester internucleoside linkage. In certain embodiments, each internucleoside linkage of the modified oligonucleotide can be independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage. In certain embodiments, at least 2, at least 3, at least 4, at least 5, or at least 6 internucleoside linkages of the modified oligonucleotide can be phosphodiester internucleoside linkages. In certain embodiments, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 internucleoside linkages of the modified oligonucleotide can be phosphorothioate internucleoside linkages.

In any of the oligomeric compounds provided herein, at least one nucleobase of the modified oligonucleotide can be a modified nucleobase, such as 5-methyl cytosine. In certain embodiments, each cytosine is 5-methyl cytosine.

In any of the oligomeric compounds provided herein, the modified oligonucleotide can comprise a deoxy region consisting of 5-12 contiguous 2'-deoxynucleosides. In certain embodiments, each nucleoside of the deoxy region is a 2'-β-D-deoxynucleoside. In certain embodiments, the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides. In certain embodiments, each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety. In certain embodiments, the deoxy region is flanked on the 5'-side by a 5' external region consisting of 1-6 linked 5' external region nucleosides and on the 3'-side by a 3' external region consisting of 1-6 linked 3' external region nucleosides; wherein the 3'-most nucleoside of the 5' external region comprises a modified sugar moiety and the 5'-most nucleoside of the 3' external region comprises a modified sugar moiety. In certain embodiments, each nucleoside of the 3' external region comprises a modified sugar moiety. In certain embodiments, each nucleoside of the 5' external region comprises a modified sugar moiety.

1. Compound No. 1489477

In certain embodiments, Compound No. 1489477 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CTTTTCTGCTCTTATACGC (SEQ ID NO 2668), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1489477 is represented by the following chemical notation:

^mC_{es}T_{eo}T_{eo}T_{eo}T_{eo}T_{eo}^mC_{ds}T_{ds}G_{ds}^mC_{ds}T_{ds}^mC_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{eo}^mC_{es}G_{es}^mC_e (SEQ ID NO 2668), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

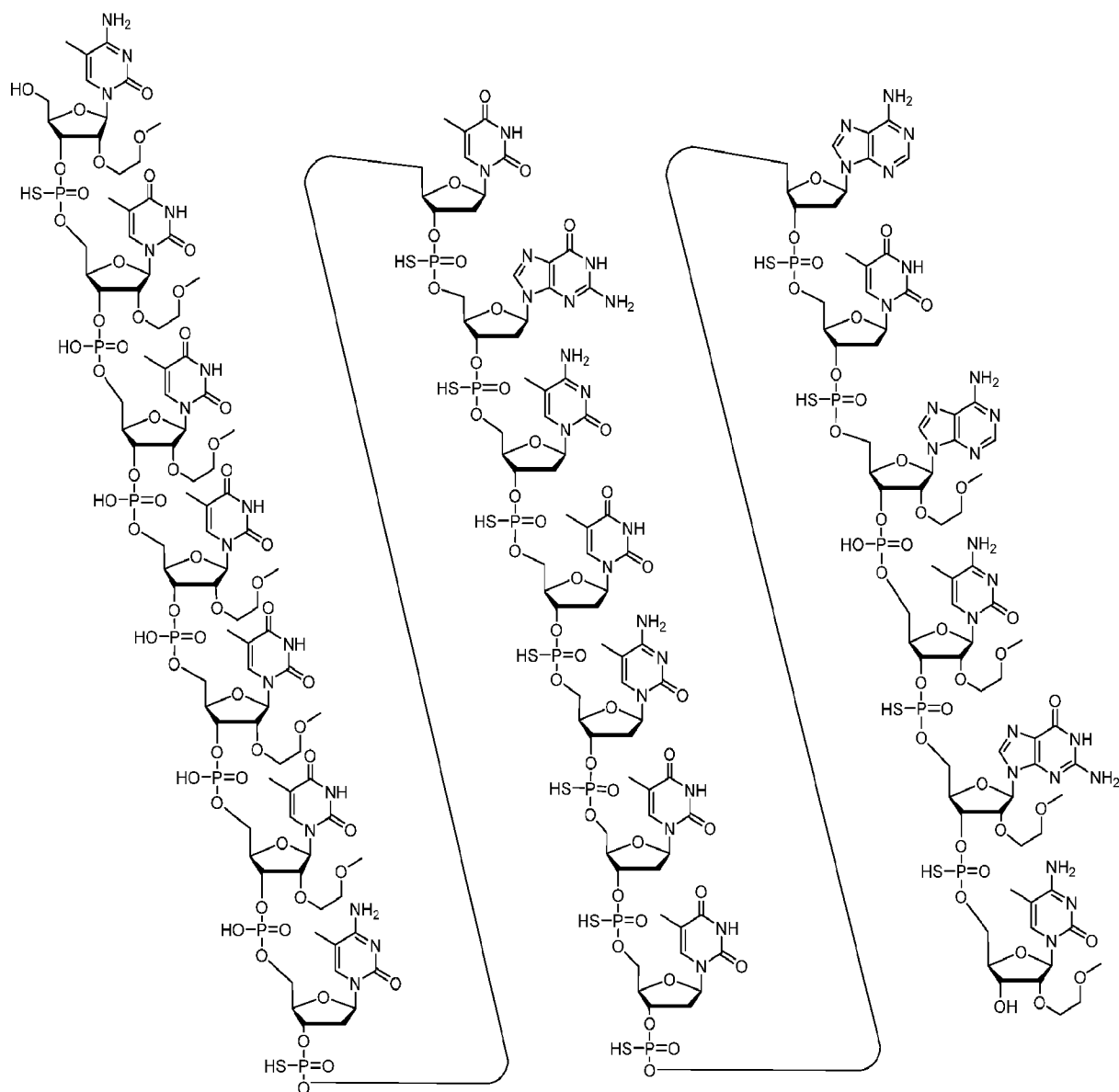
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments Compound No. 1489477 is represented by the following chemical structure:

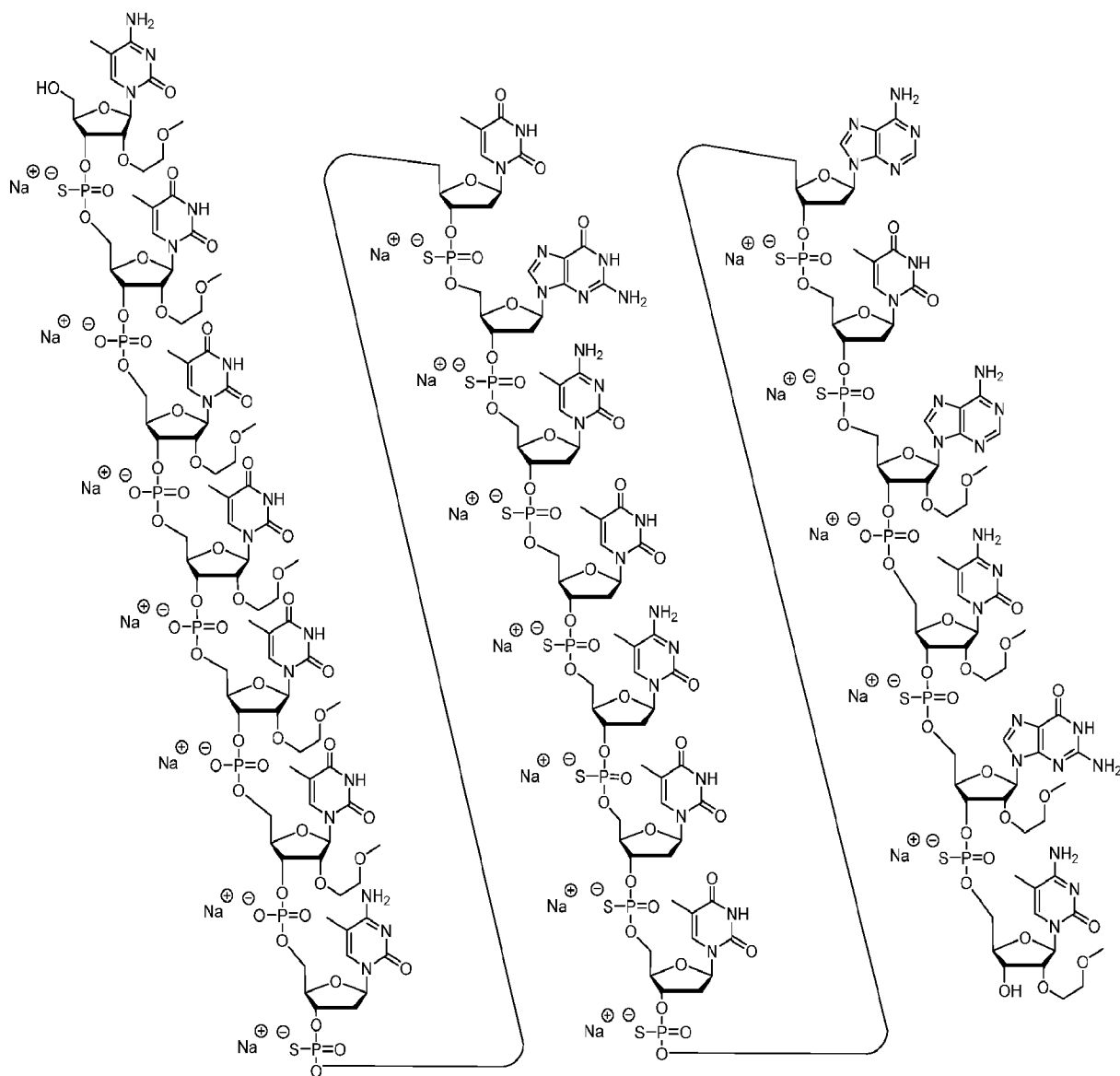


(SEQ ID NO 2668).

Structure 1. Compound No. 1489477

5 In certain embodiments, an oligomeric compound comprises the sodium salt or the potassium salt of the modified oligonucleotide represented by Structure 1.

In certain embodiments the sodium salt of Compound No. 1489477 is represented by the following chemical structure:



(SEQ ID NO 2668).

Structure 2. The sodium salt of Compound No. 1489477

5

2. Compound No. 1489494

In certain embodiments, Compound No. 1489494 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of CTGTTTACATTTTTTTTCC (SEQ ID NO 2040), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

10

In certain embodiments, Compound No. 1489494 is represented by the following chemical notation:

^mC_{es}T_{eo}G_{eo}T_{eo}T_{eo}T_{eo}T_{ds}A_{ds}^mC_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{eo}T_{es}^mC_{es}^mC_e (SEQ ID NO 2040), wherein:

15

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

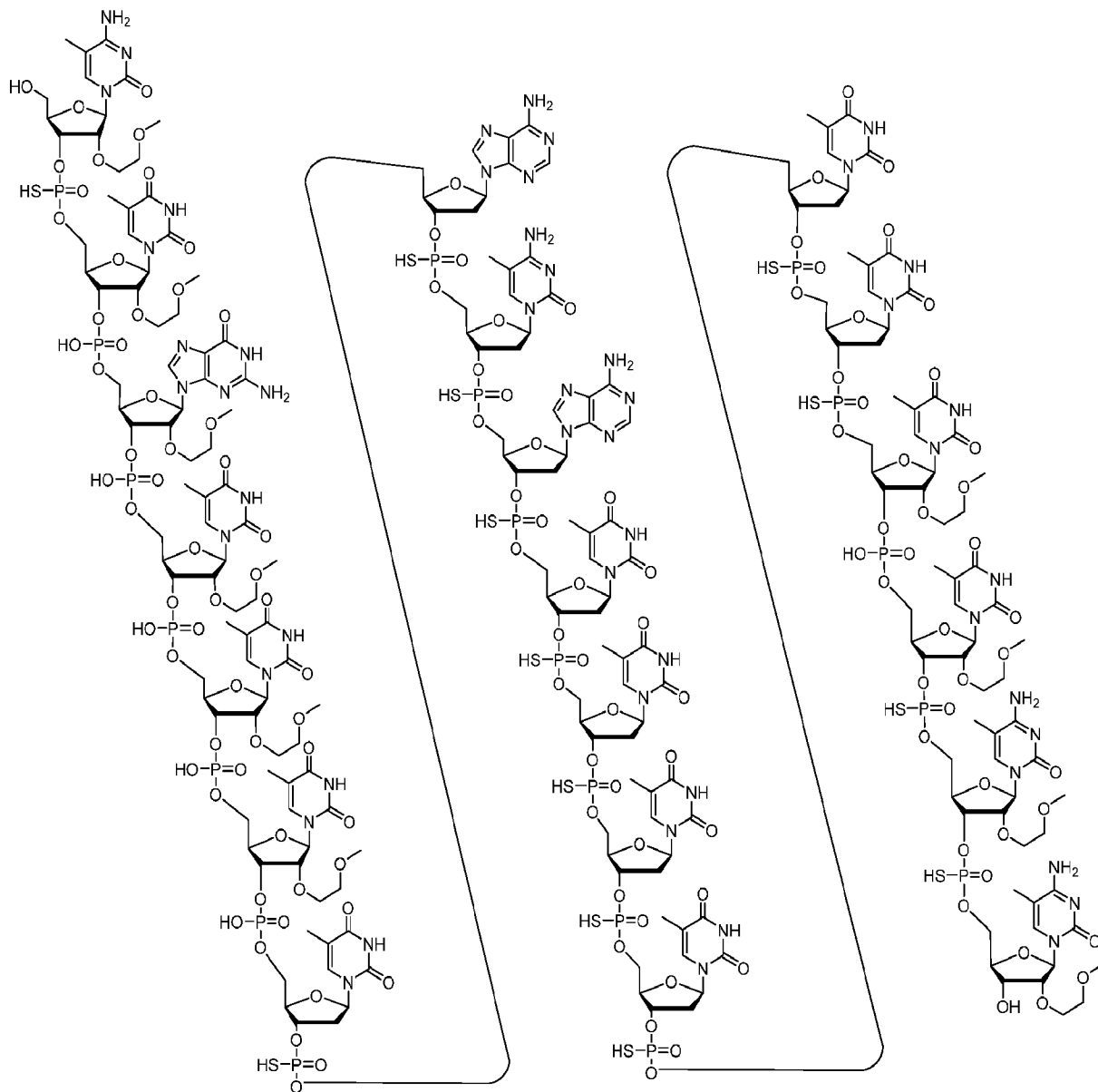
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments Compound No. 1489494 is represented by the following chemical structure:

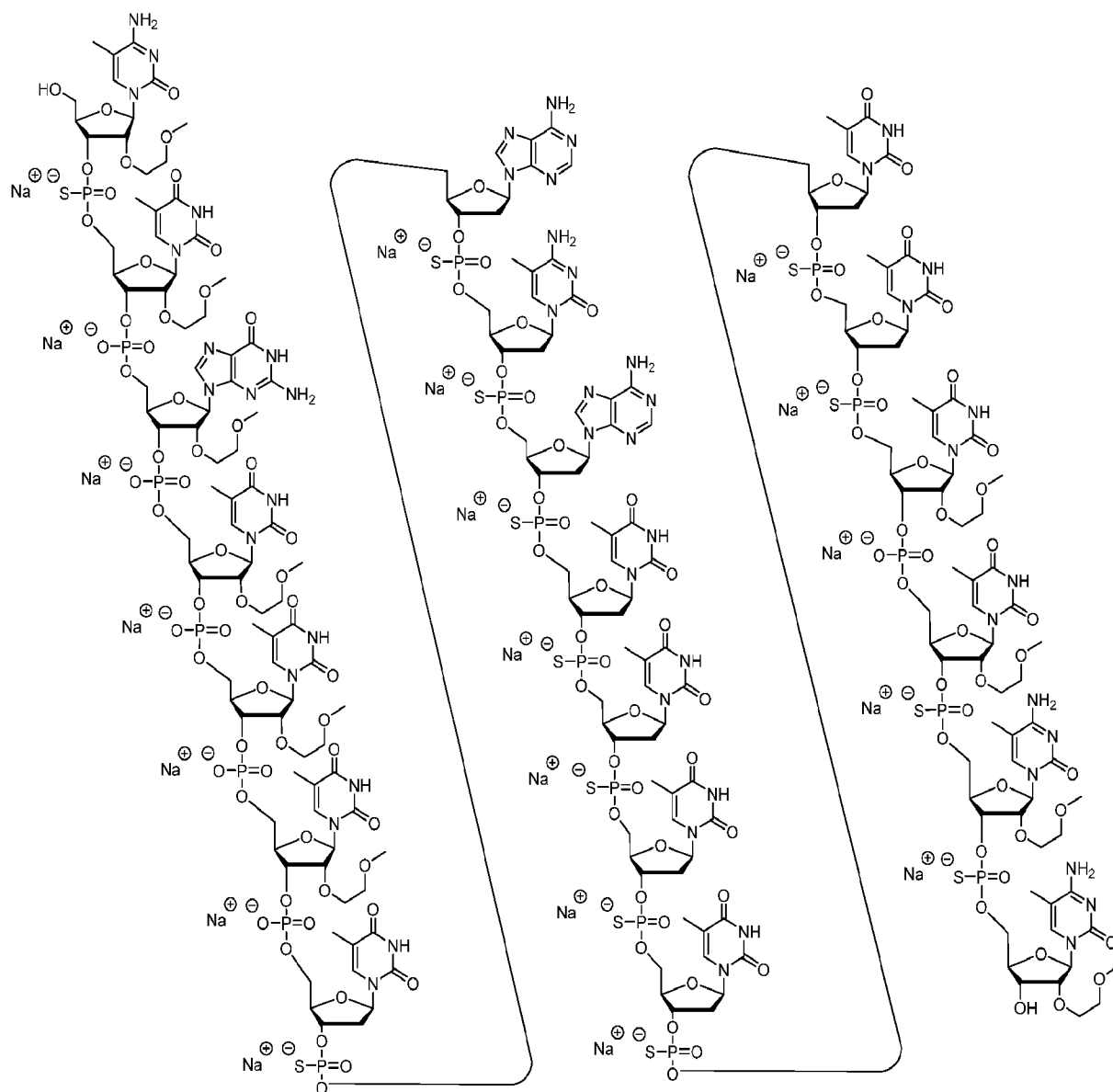


(SEQ ID NO 2040).

Structure 3. Compound No. 1489494

In certain embodiments, an oligomeric compound comprises the sodium salt or the potassium salt of the modified oligonucleotide represented by Structure 3.

In certain embodiments the sodium salt of Compound No. 1489494 is represented by the following chemical structure:



(SEQ ID NO 2040).

Structure 4. The sodium salt of Compound No. 1489494

5

3. Compound No. 1489525

In certain embodiments, Compound No. 1489525 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of TTTATCCAATTATCCATCCC (SEQ ID NO 2670), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1489525 is represented by the following chemical notation:

T_{es}T_{eo}T_{eo}A_{eo}T_{es}^mC_{ds}^mC_{ds}A_{ds}A_{ds}T_{ds}T_{ds}A_{ds}T_{ds}^mC_{ds}^mC_{ds}A_{eo}T_{eo}^mC_{es}^mC_{es}^mC_e (SEQ ID NO 2670), wherein:

15

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

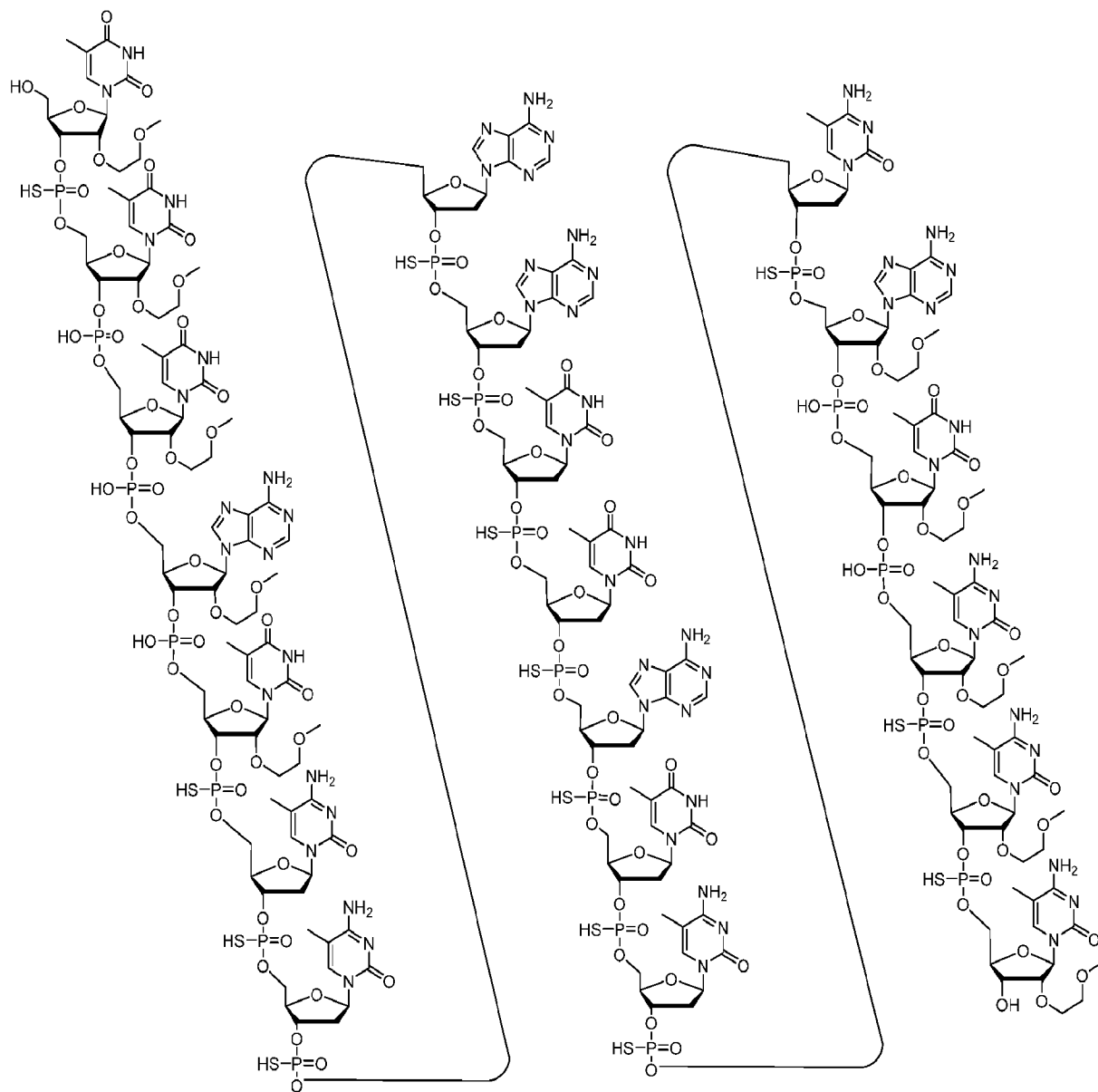
e = a 2'-MOE sugar moiety,

5 d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments Compound No. 1489525 is represented by the following chemical structure:



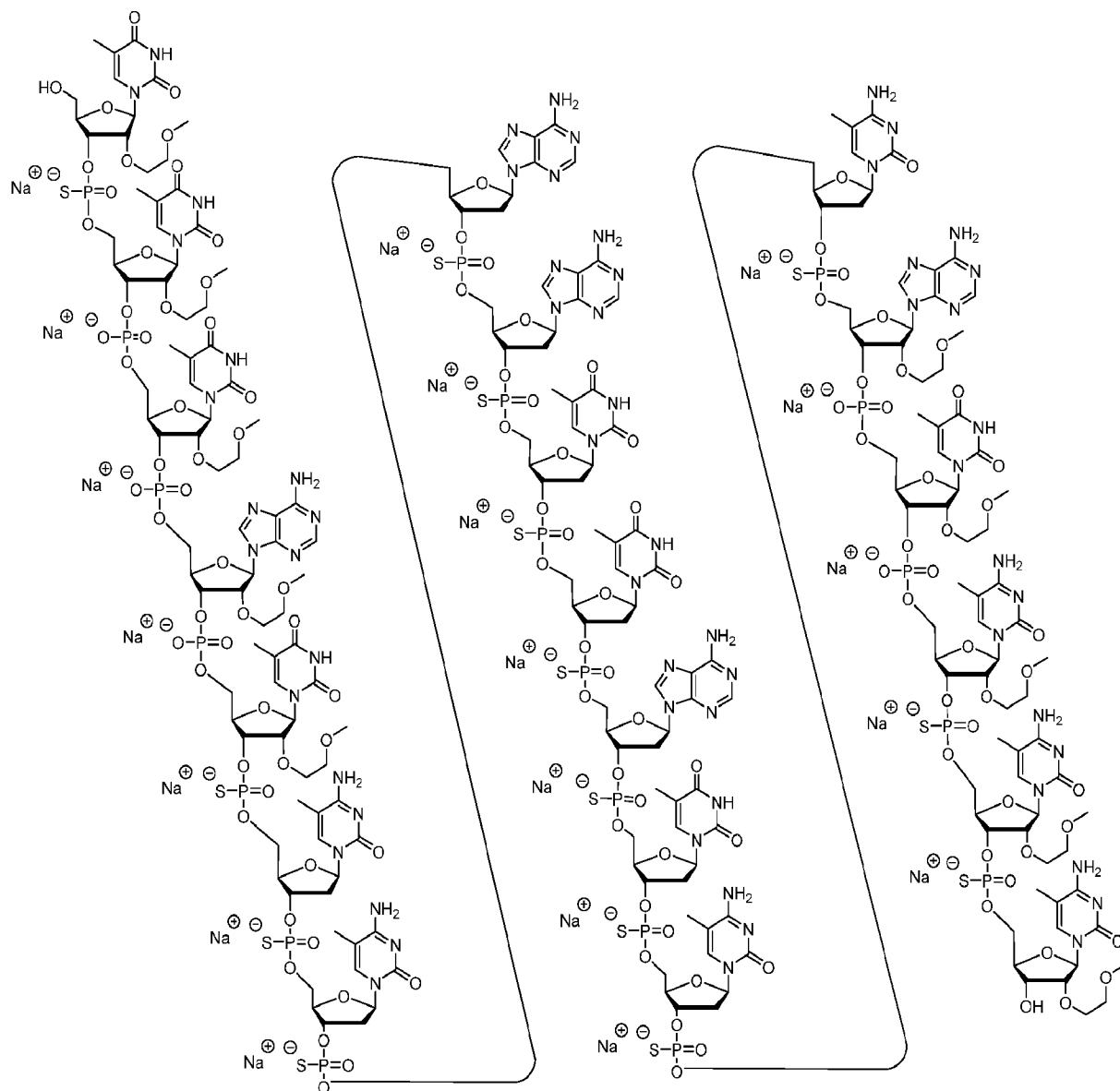
10 (SEQ ID NO 2670).

Structure 5. Compound No. 1489525

In certain embodiments, an oligomeric compound comprises the sodium salt or the potassium salt of the modified oligonucleotide represented by Structure 5.

15 In certain embodiments the sodium salt of Compound No. 1489525 is represented by the following chemical

structure:



(SEQ ID NO 2670).

Structure 6. The sodium salt of Compound No. 1489525

5

4. Compound No. 1492069

In certain embodiments, Compound No. 1492069 is characterized as a 5-10-5 MOE gapmer having a sequence (from 5' to 3') of TCGCCTAATTTTCTCTCAC (SEQ ID NO 2679), wherein each of nucleosides 1-5 and 16-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 6-15 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 16 to 17, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 5 to 6, 6 to 7, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1492069 is represented by the following chemical notation:

15 T_{es}^mC_{eo}^mG_{eo}^mC_{eo}^mC_{es}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}T_{ds}^mC_{ds}T_{ds}^mC_{eo}T_{eo}^mC_{es}A_{es}^mC_e (SEQ ID NO 2679), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

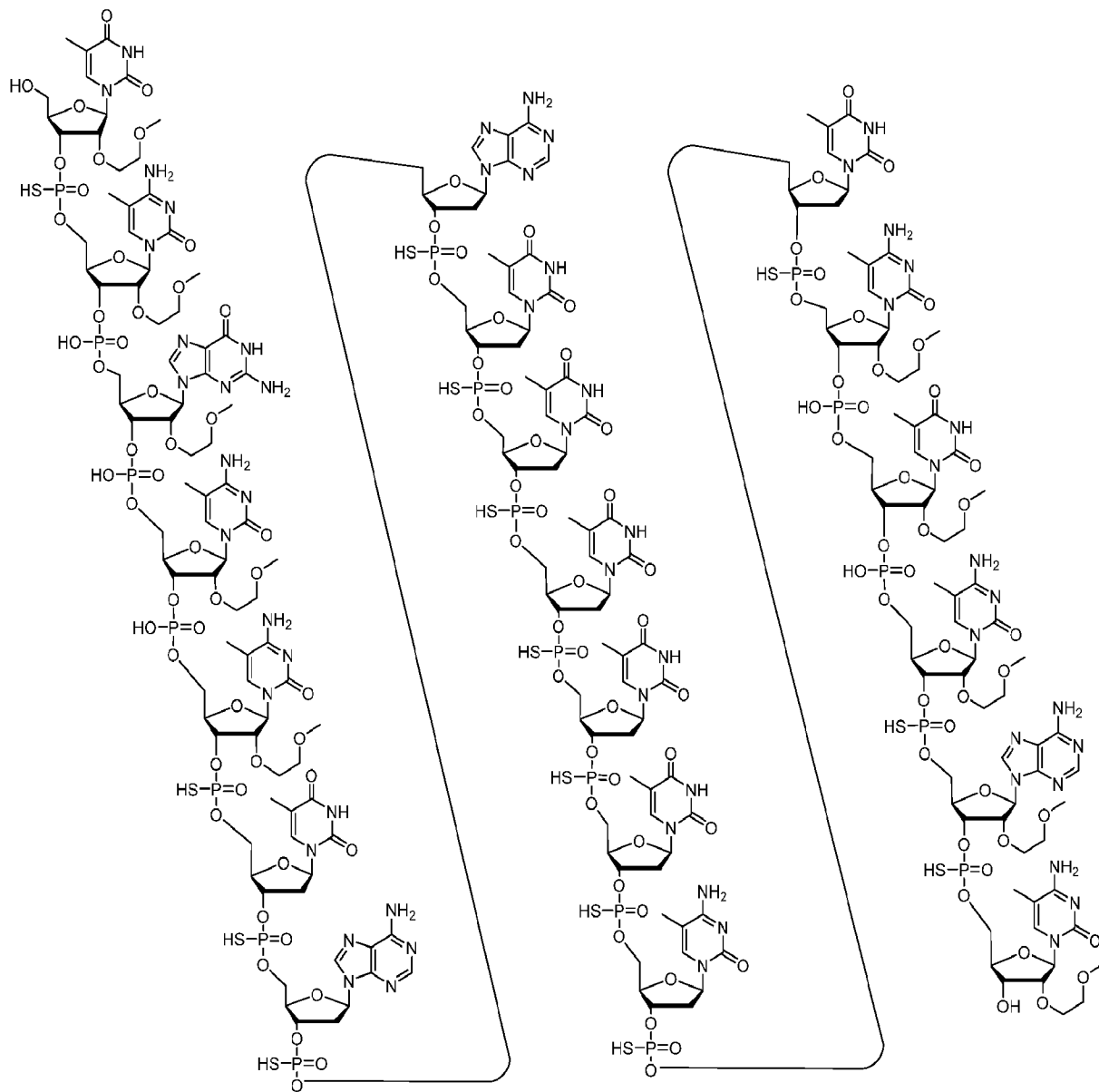
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments Compound No. 1492069 is represented by the following chemical structure:



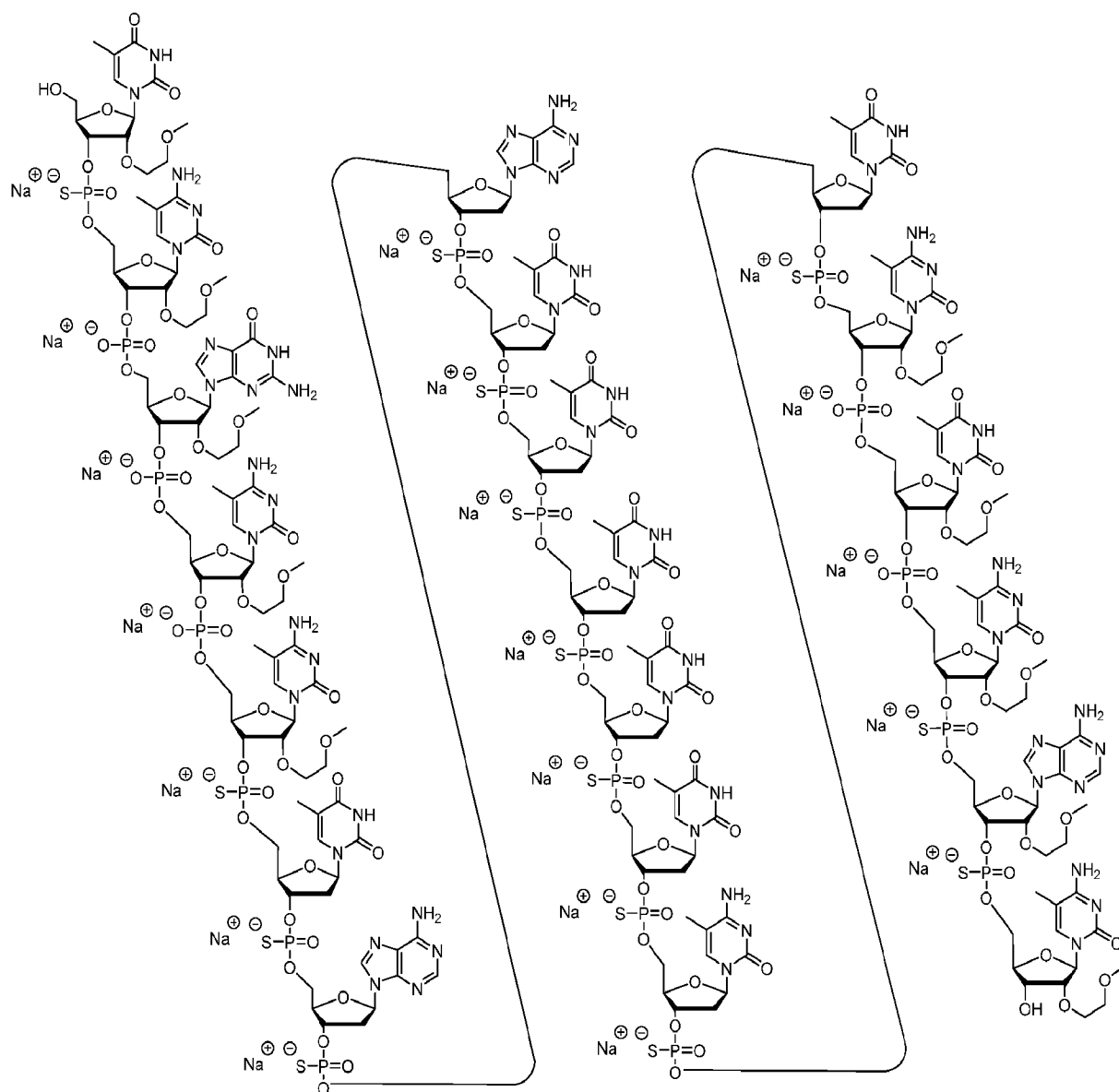
(SEQ ID NO 2679).

Structure 7. Compound No. 1492069

In certain embodiments, an oligomeric compound comprises the sodium salt or the potassium salt of the

modified oligonucleotide represented by Structure 7.

In certain embodiments the sodium salt of Compound No. 1492069 is represented by the following chemical structure:



5 (SEQ ID NO 2679).

Structure 8. The sodium salt of Compound No. 1492069

5. Compound No. 1492082

In certain embodiments, Compound No. 1492082 is characterized as a 6-10-4 MOE gapmer having a sequence
 10 (from 5' to 3') of TTTTCATATTGTTACTTCCT (SEQ ID NO 2625), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to 12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages,

and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1492082 is represented by the following chemical notation:

T_{es}T_{eo}T_{eo}^mC_{eo}A_{eo}T_{eo}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}T_{ds}A_{ds}^mC_{ds}T_{ds}T_{eo}^mC_{es}^mC_{es}T_e (SEQ ID NO 2625), wherein:

A = an adenine nucleobase,

^mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

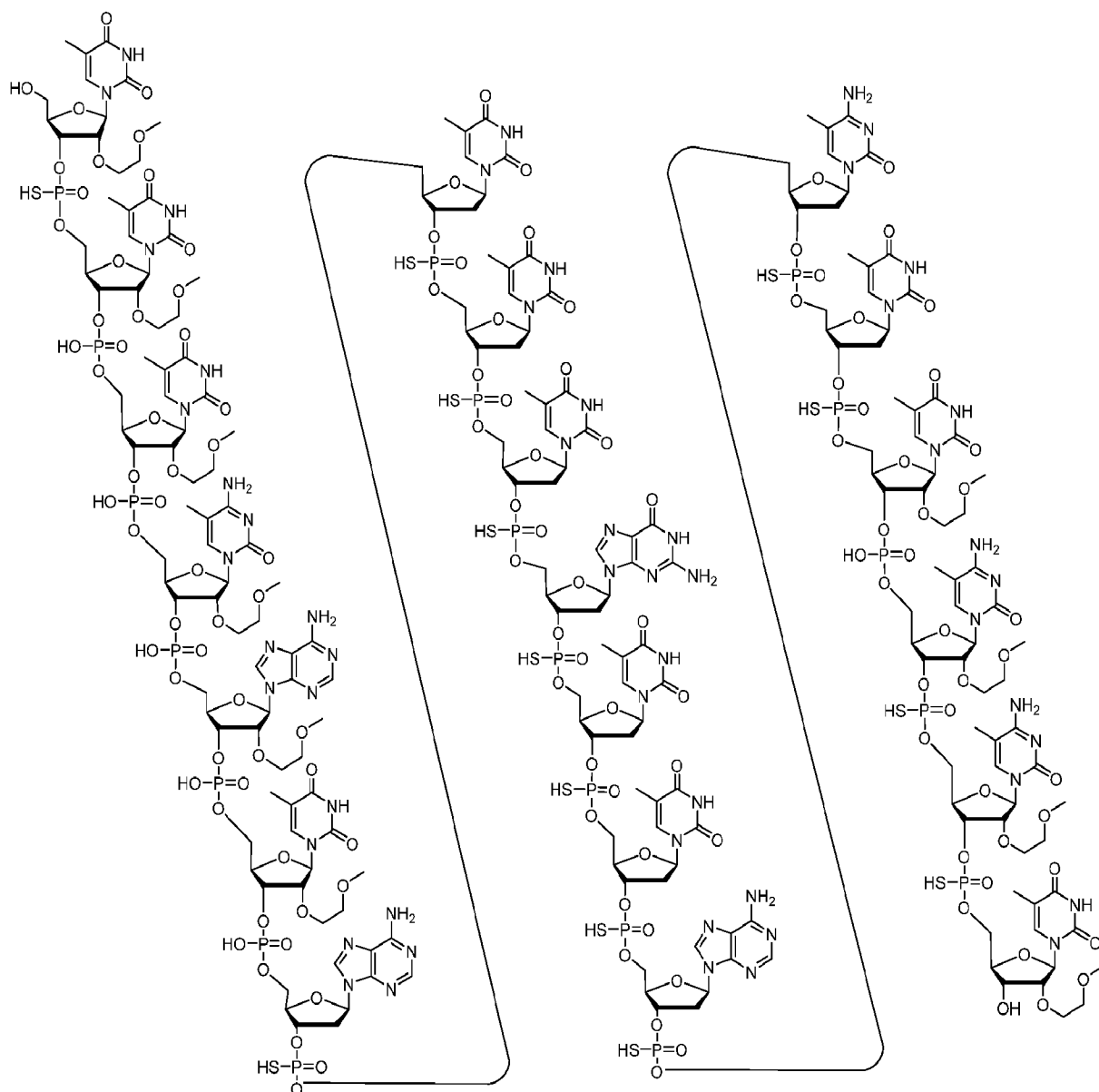
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments Compound No. 1492082 is represented by the following chemical structure:

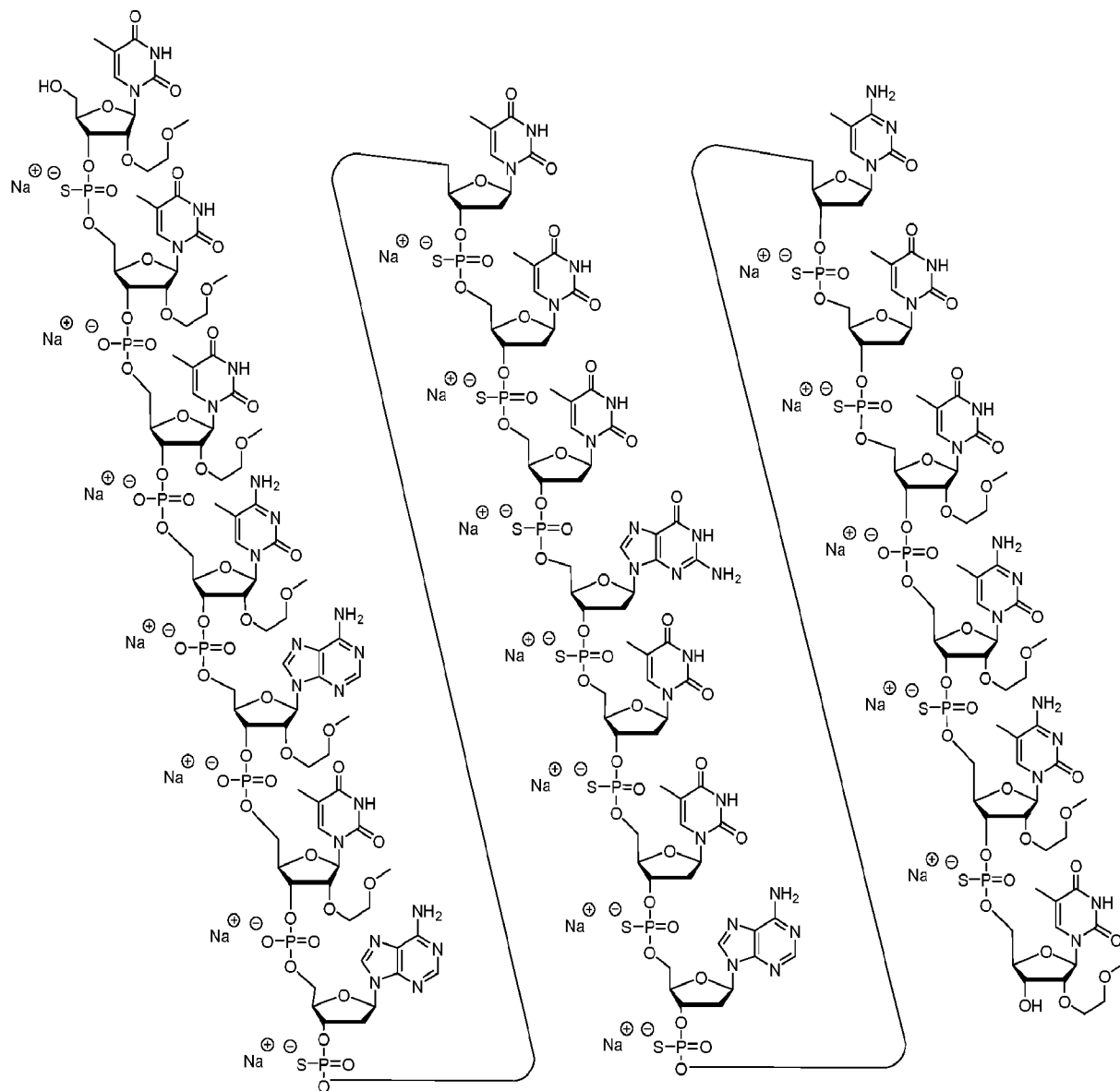


(SEQ ID NO 2625).

Structure 9. Compound No. 1492082

In certain embodiments, an oligomeric compound comprises the sodium salt or the potassium salt of the modified oligonucleotide represented by Structure 9.

In certain embodiments the sodium salt of Compound No. 1492082 is represented by the following chemical structure:



(SEQ ID NO 2625).

Structure 10. The sodium salt of Compound No. 1492082

6. Compound No. 1492131

In certain embodiments, Compound No. 1492131 is characterized as a 6-10-4 MOE gapmer having a sequence (from 5' to 3') of TTCGCCTAATTTTCTCTCA (SEQ ID NO 1317), wherein each of nucleosides 1-6 and 17-20 (from 5' to 3') are 2'-MOE nucleosides and each of nucleosides 7-16 are 2'-β-D-deoxynucleosides, wherein the internucleoside linkages between nucleosides 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 17 to 18 are phosphodiester internucleoside linkages, the internucleoside linkages between nucleosides 1 to 2, 7 to 8, 8 to 9, 9 to 10, 10 to 11, 11 to

12, 12 to 13, 13 to 14, 14 to 15, 15 to 16, 16 to 17, 18 to 19, and 19 to 20 are phosphorothioate internucleoside linkages, and wherein each cytosine is a 5-methyl cytosine.

In certain embodiments, Compound No. 1492131 is represented by the following chemical notation:

$T_{es}T_{eo}{}^mC_{eo}G_{eo}{}^mC_{eo}{}^mC_{eo}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}{}^mC_{ds}T_{ds}{}^mC_{eo}T_{es}{}^mC_{es}A_e$ (SEQ ID NO 1317), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

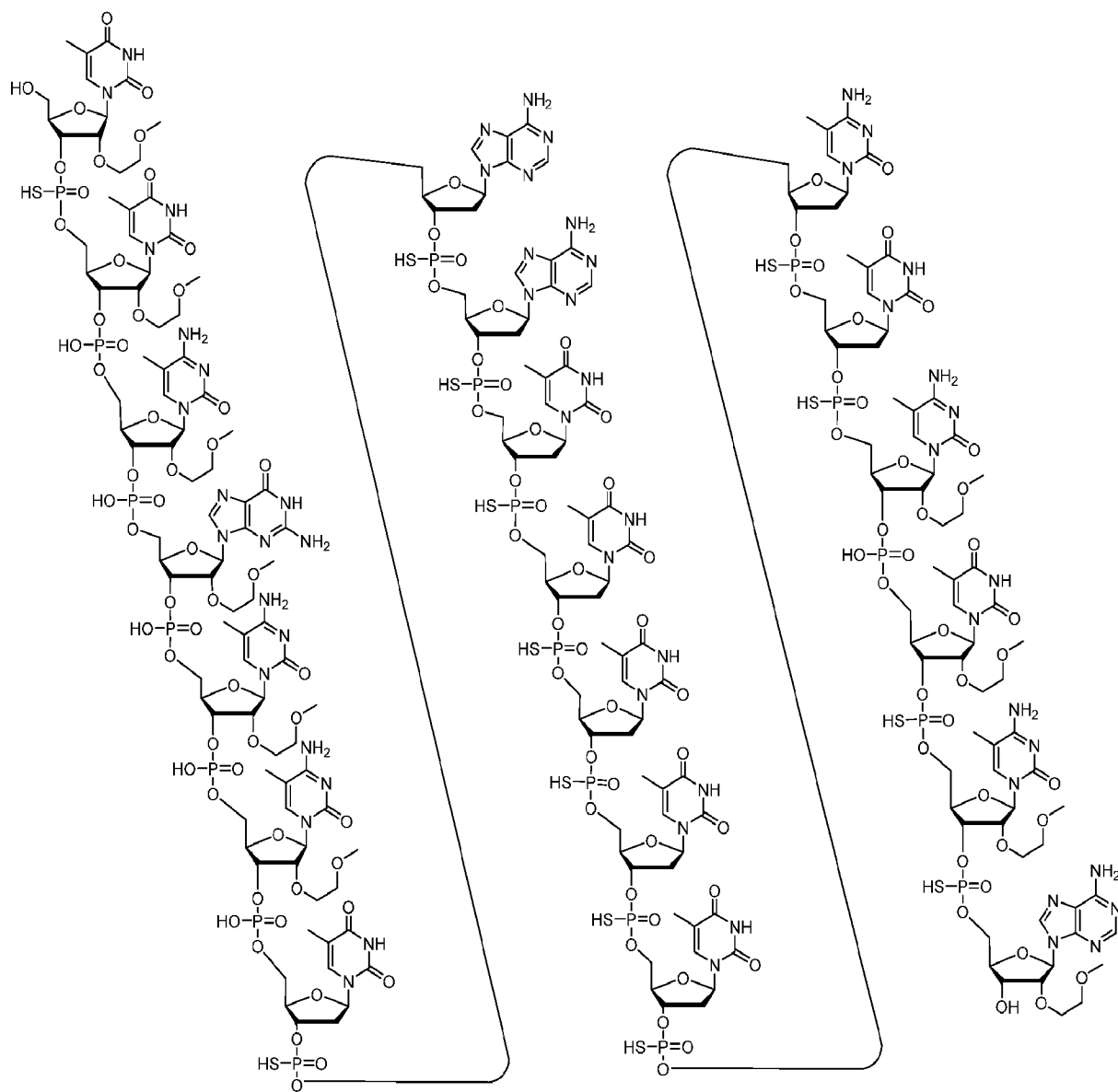
e = a 2'-MOE sugar moiety,

d = a 2'-β-D-deoxyribsyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

In certain embodiments Compound No. 1492131 is represented by the following chemical structure:

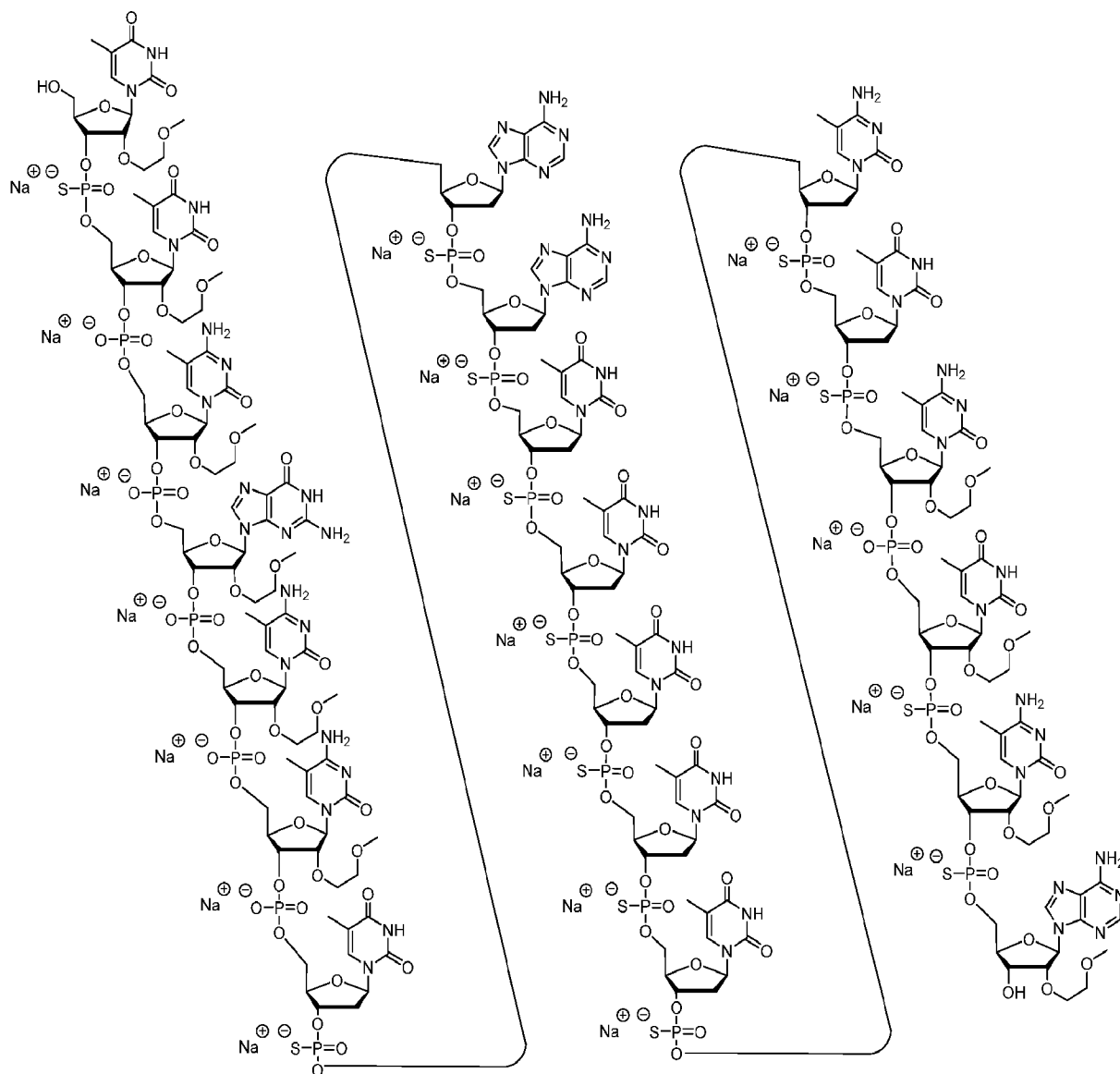


(SEQ ID NO 1317).

Structure 11. Compound No. 1492131

In certain embodiments, an oligomeric compound comprises the sodium salt or the potassium salt of the modified oligonucleotide represented by Structure 11.

5 In certain embodiments the sodium salt of Compound No. 1492131 is represented by the following chemical structure:



(SEQ ID NO 1317).

Structure 12. The sodium salt of Compound No. 1492131

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Certain Oligomeric Duplexes

Certain embodiments are directed to oligomeric duplexes comprising a first oligomeric compound and a second oligomeric compound.

In certain embodiments, an oligomeric duplex comprises:

15

a first oligomeric compound comprising a first modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the first modified oligonucleotide is at least 80% complementary to an

equal length portion within nucleobases 3964-3983, 4050-4069, 4573-4592, 4574-4593, 4600-4619, 4601-4620, 4603-4622, 4606-4625, 4619-4638, 4620-4639, 4681-4700, 4716-4735, 4717-4736, 4724-4743, 4725-4744, 4731-4750, 4732-4751, 4733-4752, 4740-4759, 4744-4763, 4771-4790, 4772-4791, 4773-4792, 4786-4805, 4788-4807, 4797-4816, 4798-4817, 4801-4820, 4808-4827, 4812-4831, 4814-4833, 4815-4834, 4823-4838, 4825-4844, 4827-4846, 4841-4860, 4846-4865, 4847-4866, 4862-4881, 4875-4894, 4888-4907, 4889-4908, 4905-4924, 4906-4925, 4942-4961, 4952-4971, 4957-4976, 4958-4977, 5035-5054, 5036-5055, 5061-5080, 5082-5101, 5083-5102, 5084-5103, 5085-5104, 5086-5101, 5086-5105, 5087-5102, 5087-5106, 5089-5104, 5089-5108, 5090-5105, 5096-5115, 5113-5132, 5114-5133, 5137-5156, 5142-5161, 5147-5162, 5166-5185, 5179-5198, 5181-5200, 5182-5201, 5183-5202, 5519-5538, 5532-5551, 5533-5552, 5537-5556, 5546-5565, 5598-5617, 5599-5618, 5600-5619, 5637-5656, 5653-5672, 5657-5676, 5669-5688, 5673-5692, 5701-5720, 5702-5721, 5703-5722, 5709-5728, 5755-5774, 5757-5776, 5761-5780, 5850-5869, 5878-5897, 5901-5920, 5902-5921, 5904-5923, 5907-5926, 5910-5929, 5915-5934, 5916-5935, 5917-5936, 5920-5939, 5921-5940, 5922-5941, 5923-5942, 5924-5943, 5931-5950, 5934-5953, 5935-5954, 5955-5974, 5984-6003, 5985-6004, 6028-6047, 6033-6052, 6035-6054, 6051-6070, 6052-6071, 6090-6109, 6111-6130, 6112-6131, 6113-6132, 6145-6164, 6170-6189, 6171-6190, 6195-6214, 6203-6222, 6204-6223, 6206-6225, 6207-6226, 6237-6256, 6264-6283, 6279-6298, 6306-6325, 6357-6376, 6361-6380, 6407-6426, 6408-6427, 6409-6428, 6412-6431, 6420-6439, 6425-6444, 6481-6500, 6482-6501, 6512-6527, 6672-6691, 6674-6689, 6710-6729, 6734-6753, 6749-6768, 6759-6778, 6760-6779, 6831-6850, 6835-6854, 6838-6857, 6916-6935, 6919-6938, 6921-6940, 6926-6945, 6935-6954, 6936-6955, 6941-6960, 6945-6964, 7211-7230, 7230-7249, 7234-7253, 7237-7256, 7307-7326, 7310-7329, 7311-7330, 7312-7331, 7315-7334, 7331-7350, 7437-7456, 7438-7457, 7443-7462, 7458-7477, 7526-7545, 7528-7547, 7543-7562, 7545-7564, 7569-7588, 7570-7589, 7585-7604, 7588-7607, 7589-7608, 7590-7609, 7591-7610, 7592-7607, 7592-7611, 7593-7608, 7593-7612, 7595-7610, 7595-7614, 7596-7611, 7602-7621, 7614-7633, 7617-7636, 7618-7637, 7619-7638, 7639-7658, 7640-7659, 7644-7663, 7649-7664, 7661-7680, 7662-7681, 7663-7682, 7665-7684, 7667-7686, 7668-7687, 7681-7700, 7683-7702, 7684-7703, 7685-7704, 7747-7766, 7771-7790, 7772-7791, 7773-7792, 7774-7793, 7775-7794, 7777-7796, 7778-7797, 7781-7800, 7782-7801, 7784-7803, 7785-7804, 7787-7806, 7788-7807, 7790-7809, 7803-7822, 7805-7824, 7806-7825, 7831-7850, 7867-7882, 7931-7950, 7957-7976, 7978-7997, 7979-7998, 7980-7999, 8144-8163, 8196-8215, 8210-8229, 8211-8230, 8226-8245, 8227-8246, 8231-8250, 8232-8251, 8261-8280, 8271-8286, 8300-8319, 8301-8320, 8310-8329, 8324-8343, 8325-8344, 8339-8358, 8343-8362, 8347-8366, 8351-8370, 8356-8375, 8357-8376, 8359-8378, 8360-8379, 8361-8380, 8362-8381, 8364-8383, 8366-8385, 8368-8387, 8369-8388, 8383-8402, 8387-8406, 8388-8407, 8391-8410, 8392-8411, 8393-8412, 8394-8413, 8398-8417, 8408-8427, 8409-8428, 8421-8440, 8425-8444, 8428-8447, 8429-8448, 8433-8452, 8443-8462, 8444-8463, 8524-8543, 8549-8568, 8550-8569, 8551-8570, 8584-8603, 8624-8643, 8626-8645, 8627-8646, 8629-8648, 8630-8649, 8631-8650, 8632-8651, 8636-8655, 8637-8656, 8652-8671, 8653-8672, 8656-8675, 8657-8676, 8659-8678, 8660-8679, 8661-8680, 8682-8701, 8698-8717, 8716-8735, 8717-8736, 8721-8740, 8722-8741, 8724-8743, 8731-8750, 8733-8752, 8748-8767, 8761-8780, 8762-8781, 8763-8782, 8764-8783, 8765-8784, 8770-8789, 8776-8795, 8777-8796, 8778-8797, 8782-8801, 8791-8806, 8791-8810, 8792-8811, 8793-8808, 8793-8812, 8794-8809, 8794-8813, 8795-8810, 8795-8814, 8807-8826, 8808-8827, 8809-8828, 8822-8841, 8831-8850, 8834-8853, 8835-8854, 8836-8855, 8857-8876, 8938-8957, 8939-8958, 8957-8972, 8980-8999, 9021-9040, 9022-9041, 9025-9044, 9026-9041, 9026-9045, 9038-9057, 9156-9175, 9164-9183, 9204-9223, 9205-9224, 9252-9271, 9253-9272, 9254-9273, 9255-9274, 9257-9276, 9319-9338, 9329-9348, 9374-9393, 9375-9394, 9376-9395, 9377-9396, 9379-9398, 9388-9407, 9393-9412, 9394-9413, 9414-9433, 9416-9435, 9419-9438, 9421-9440, 9422-9441, 9423-9442, 9425-9444, 9446-9465, 9467-9486, 9469-9488, 9499-9518, 9557-9576, 9560-

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a second oligomeric compound comprising a second modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide. In certain embodiments, the nucleobase sequence of the first modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of the IFNAR1 nucleic acid.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the first modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 5084-5133, 19997-20061, 20076-20133, 20528-20611, 20616, 22294-22329, 22453-22476, 22597-22595-22626, 25530-25565, 25606-25652, 25710-25767, 25768-25827, 28421-28468, 29924-29949, 29968-30021, 31072-31096, 31792-31837, 32353-32386, or 35016-35042 of SEQ ID NO: 1; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide. In certain embodiments, the nucleobase sequence of the first modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of the IFNAR1 nucleic acid.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 8 to 80 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of the nucleobase sequence of any of SEQ ID NOs 12-2687, wherein each thymine is replaced by uracil; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 8 to 80 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region

of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide. In certain embodiments, the nucleobase sequence of the first modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of the IFNAR1 nucleic acid.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In certain embodiments, an oligomeric duplex comprises:

a first oligomeric compound comprising a first modified oligonucleotide consisting of 16 to 80 linked nucleosides wherein the nucleobase sequence of the first modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs 12-89, wherein each thymine is replaced by uracil; and

a second oligomeric compound comprising a second modified oligonucleotide consisting of 16 to 80 linked nucleosides wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 16 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

In certain embodiments, the first oligomeric compound is an antisense compound. In certain embodiments, the first modified oligonucleotide is an antisense oligonucleotide. In certain embodiments, the second oligomeric compound is a sense compound. In certain embodiments, the second modified oligonucleotide is a sense oligonucleotide.

In any of the oligomeric duplexes described herein, at least one nucleoside of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a modified sugar moiety. Examples of suitable modified sugar moieties include, but are not limited to, a bicyclic sugar moiety, such as a bicyclic sugar moiety comprising a 2'-4' bridge selected from -O-CH₂- and -O-CH(CH₃)-, and a non-bicyclic sugar moiety, such as a 2'-MOE sugar moiety, a 2'-F sugar moiety, a 2'-OMe sugar moiety, or a 2'-NMA sugar moiety. In certain embodiments, at least 80%, at least 90%, or 100% of the nucleosides of the first modified oligonucleotide and/or the second modified oligonucleotide comprises a modified sugar moiety selected from 2'-F sugar moiety and 2'-OMe sugar moiety.

In any of the oligomeric duplexes described herein, at least one nucleoside of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a sugar surrogate. Examples of suitable sugar surrogates include, but are not limited to, morpholino, peptide nucleic acid (PNA), glycol nucleic acid (GNA), and unlocked nucleic acid (UNA). In certain embodiments, at least one nucleoside of the first modified oligonucleotide comprises a sugar surrogate, which can be a GNA.

In any of the oligomeric duplexes described herein, at least one internucleoside linkage of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a modified internucleoside linkage. In certain embodiments, the modified internucleoside linkage is a phosphorothioate internucleoside linkage. In certain embodiments, at least one of the first, second, or third internucleoside linkages from the 5' end and/or the 3' end of the first modified oligonucleotide comprises a phosphorothioate linkage. In certain embodiments, at least one of the first, second, or third internucleoside linkages from the 5' end and/or the 3' end of the second modified oligonucleotide comprises a phosphorothioate linkage.

In any of the oligomeric duplexes described herein, at least one internucleoside linkage of the first modified oligonucleotide and/or the second modified oligonucleotide can comprise a phosphodiester internucleoside linkage.

In any of the oligomeric duplexes described herein, each internucleoside linkage of the first modified oligonucleotide and/or the second modified oligonucleotide can be independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

In any of the oligomeric duplexes described herein, at least one nucleobase of the first modified oligonucleotide and/or the second modified oligonucleotide can be a modified nucleobase. In certain embodiments, the modified nucleobase is 5-methyl cytosine.

In any of the oligomeric duplexes described herein, the first modified oligonucleotide can comprise a stabilized phosphate group attached to the 5' position of the 5'-most nucleoside. In certain embodiments, the stabilized 5'-phosphate group comprises a cyclopropyl phosphonate or an (*E*)-vinyl phosphonate.

In any of the oligomeric duplexes described herein, the first modified oligonucleotide can comprise a conjugate group. In certain embodiments, the conjugate group comprises a conjugate linker and a conjugate moiety. In certain embodiments, the conjugate group is attached to the first modified oligonucleotide at the 5'-end of the first modified oligonucleotide. In certain embodiments, the conjugate group is attached to the first modified oligonucleotide at the 3'-end of the modified oligonucleotide. In certain embodiments, the conjugate group comprises N-acetyl galactosamine. In certain embodiments, the conjugate group comprises a cell-targeting moiety having an affinity for transferrin receptor (TfR), also known as TfR1 and CD71. In certain embodiments, the conjugate group comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C17 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C17 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl. In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C17 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, or C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In any of the oligomeric duplexes described herein, the second modified oligonucleotide can comprise a conjugate group. In certain embodiments, the conjugate group comprises a conjugate linker and a conjugate moiety. In certain embodiments, the conjugate group is attached to the second modified oligonucleotide at the 5'-end of the second modified oligonucleotide. In certain embodiments, the conjugate group is attached to the second modified oligonucleotide at the 3'-end of the modified oligonucleotide. In certain embodiments, the conjugate group comprises N-acetyl galactosamine. In certain embodiments, the conjugate group comprises a cell-targeting moiety having an affinity for transferrin receptor (TfR), also known as TfR1 and CD71. In certain embodiments, the conjugate group comprises an anti-TfR1 antibody or fragment thereof. In certain embodiments, the conjugate group comprises a protein or peptide capable of binding TfR1. In certain embodiments, the conjugate group comprises an aptamer capable of binding TfR1. In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C17 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C17 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9

alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl. In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C17 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, or C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

5 In certain embodiments, an antisense agent comprises an antisense compound comprising an oligomeric compound or an oligomeric duplex described herein. In certain embodiments, an antisense agent, which can comprise an oligomeric compound or an oligomeric duplex described herein, is an RNAi agent capable of reducing the amount of IFNAR1 nucleic acid through the activation of RISC/Ago2.

Certain embodiments provide an oligomeric agent comprising two or more oligomeric duplexes. In certain
10 embodiments, an oligomeric agent comprises two or more of any of the oligomeric duplexes described herein. In certain embodiments, an oligomeric agent comprises two or more of the same oligomeric duplex, which can be any of the oligomeric duplexes described herein. In certain embodiments, the two or more oligomeric duplexes are linked together. In certain embodiments, the two or more oligomeric duplexes are covalently linked together. In certain embodiments, the second modified oligonucleotides of two or more oligomeric duplexes are covalently linked together. In certain
15 embodiments, the second modified oligonucleotides of two or more oligomeric duplexes are covalently linked together at their 3' ends. In certain embodiments, the two or more oligomeric duplexes are covalently linked together by a glycol linker, such as a tetraethylene glycol linker. Certain such compounds are described in, e.g., Alterman, et al., *Nature Biotech.*, 37:844-894, 2019.

20 I. Certain Oligonucleotides

In certain embodiments, provided herein are oligomeric compounds comprising oligonucleotides, which consist of linked nucleosides. Oligonucleotides may be unmodified oligonucleotides (RNA or DNA) or may be modified oligonucleotides. Modified oligonucleotides comprise at least one modification relative to unmodified RNA or DNA. That is, modified oligonucleotides comprise at least one modified nucleoside (comprising a modified sugar moiety
25 and/or a modified nucleobase) and/or at least one modified internucleoside linkage. Certain modified nucleosides and modified internucleoside linkages suitable for use in modified oligonucleotides are described below.

A. Certain Modified Nucleosides

Modified nucleosides comprise a modified sugar moiety or a modified nucleobase or both a modified sugar moiety and a modified nucleobase. In certain embodiments, modified nucleosides comprising the following modified
30 sugar moieties and/or the following modified nucleobases may be incorporated into modified oligonucleotides.

1. Certain Sugar Moieties

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties. In certain
embodiments, modified sugar moieties are bicyclic or tricyclic sugar moieties. In certain embodiments, modified sugar moieties are sugar surrogates. Such sugar surrogates may comprise one or more substitutions corresponding to those of
35 other types of modified sugar moieties.

In certain embodiments, modified sugar moieties are non-bicyclic modified sugar moieties comprising a furanosyl ring with one or more substituent groups none of which bridges two atoms of the furanosyl ring to form a bicyclic structure. Such non bridging substituents may be at any position of the furanosyl, including but not limited to substituents at the 2', 3', 4', and/or 5' positions. In certain embodiments one or more non-bridging substituent of non-

bicyclic modified sugar moieties is branched. Examples of 2'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 2'-F, 2'-OCH₃ ("OMe" or "O-methyl"), and 2'-O(CH₂)₂OCH₃ ("MOE" or "O-methoxyethyl"). In certain embodiments, 2'-substituent groups are selected from among: halo, allyl, amino, azido, SH, CN, OCN, CF₃, OCF₃, O-C₁-C₁₀ alkoxy, O-C₁-C₁₀ substituted alkoxy, O-C₁-C₁₀ alkyl, O-C₁-C₁₀ substituted alkyl, S-alkyl, N(R_m)-alkyl, O-alkenyl, S-alkenyl, N(R_m)-alkenyl, O-alkynyl, S-alkynyl, N(R_m)-alkynyl, O-alkylenyl-O-alkyl, alkynyl, alkaryl, aralkyl, O-alkaryl, O-aralkyl, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n) or OCH₂C(=O)-N(R_m)(R_n), where each R_m and R_n is, independently, H, an amino protecting group, or substituted or unsubstituted C₁-C₁₀ alkyl, -O(CH₂)₂ON(CH₃)₂ ("DMAOE"), 2'-O(CH₂)₂O(CH₂)₂N(CH₃)₂ ("DMAEOE"), and the 2'-substituent groups described in Cook et al., U.S. 6,531,584; Cook et al., U.S. 5,859,221; and Cook et al., U.S. 6,005,087. Certain embodiments of these 2'-substituent groups can be further substituted with one or more substituent groups independently selected from among: hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro (NO₂), thiol, thioalkoxy, thioalkyl, halogen, alkyl, aryl, alkenyl and alkynyl. In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 3'-position. Examples of substituent groups suitable for the 3'-position of modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl (e.g., methyl, ethyl). In certain embodiments, non-bicyclic modified sugar moieties comprise a substituent group at the 4'-position. Examples of 4'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to alkoxy (e.g., methoxy), alkyl, and those described in Manoharan et al., WO 2015/106128. Examples of 5'-substituent groups suitable for non-bicyclic modified sugar moieties include but are not limited to: 5'-methyl (R or S), 5'-vinyl, ethyl, and 5'-methoxy. In certain embodiments, non-bicyclic modified sugar moieties comprise more than one non-bridging sugar substituent, for example, 2'-F-5'-methyl sugar moieties and the modified sugar moieties and modified nucleosides described in Migawa et al., WO 2008/101157 and Rajeev et al., US2013/0203836).

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, NH₂, N₃, OCF₃, OCH₃, O(CH₂)₃NH₂, CH₂CH=CH₂, OCH₂CH=CH₂, O(CH₂)₂OCH₃, O(CH₂)₂SCH₃, O(CH₂)₂ON(R_m)(R_n), O(CH₂)₂O(CH₂)₂N(CH₃)₂, and N-substituted acetamide (OCH₂C(=O)-N(R_m)(R_n)), where each R_m and R_n is, independently, H, an amino protecting group, or a substituted or unsubstituted C₁-C₁₀ alkyl.

In certain embodiments, a 2'-substituted nucleoside non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCF₃, OCH₃, O(CH₂)₂OCH₃ (MOE), O(CH₂)₂SCH₃, O(CH₂)₂ON(CH₃)₂, O(CH₂)₂O(CH₂)₂N(CH₃)₂, O(CH₂)₂ON(CH₃)₂ ("DMAOE"), OCH₂OCH₂N(CH₃)₂ ("DMAEOE"), and OCH₂C(=O)-N(H)CH₃ ("NMA").

In certain embodiments, a 2'-substituted non-bicyclic modified nucleoside comprises a sugar moiety comprising a non-bridging 2'-substituent group selected from: F, OCH₃, and O(CH₂)₂OCH₃.

In certain embodiments, modified furanosyl sugar moieties and nucleosides incorporating such modified furanosyl sugar moieties are further defined by isomeric configuration. For example, a 2'-deoxyfuranosyl sugar moiety may be in seven isomeric configurations other than the naturally occurring β-D-deoxyribose configuration. Such modified sugar moieties are described in, e.g., WO 2019/157531, incorporated by reference herein. A 2'-modified sugar moiety has an additional stereocenter at the 2'-position relative to a 2'-deoxyfuranosyl sugar moiety; therefore, such sugar moieties have a total of sixteen possible isomeric configurations. 2'-modified sugar moieties described herein are in the β-D-ribose isomeric configuration unless otherwise specified.

In naturally occurring nucleic acids, sugars are linked to one another 3' to 5'. In certain embodiments, oligonucleotides include one or more nucleoside or sugar moiety linked at an alternative position, for example at the 2' position or inverted 5' to 3'. For example, where the linkage is at the 2' position, the 2'-substituent groups may instead be at the 3'-position.

Certain modified sugar moieties comprise a substituent that bridges two atoms of the furanosyl ring to form a second ring, resulting in a bicyclic sugar moiety. Nucleosides comprising such bicyclic sugar moieties have been referred to as bicyclic nucleosides (BNAs), locked nucleosides, or conformationally restricted nucleotides (CRN). Certain such compounds are described in US Patent Publication No. 2013/0190383; and PCT publication WO 2013/036868. In certain such embodiments, the bicyclic sugar moiety comprises a bridge between the 4' and the 2' furanose ring atoms. In certain such embodiments, the furanose ring is a ribose ring. Examples of such 4' to 2' bridging sugar substituents include but are not limited to: 4'-CH₂-2', 4'-(CH₂)₂-2', 4'-(CH₂)₃-2', 4'-CH₂-O-2' ("LNA"), 4'-CH₂-S-2', 4'-(CH₂)₂-O-2' ("ENA"), 4'-CH(CH₃)-O-2' (referred to as "constrained ethyl" or "cEt" when in the *S* configuration), 4'-CH₂-O-CH₂-2', 4'-CH₂-N(R)-2', 4'-CH(CH₂OCH₃)-O-2' ("constrained MOE" or "cMOE") and analogs thereof (*see, e.g.*, Seth et al., U.S. 7,399,845, Bhat et al., U.S. 7,569,686, Swayze et al., U.S. 7,741,457, and Swayze et al., U.S. 8,022,193), 4'-C(CH₃)(CH₃)-O-2' and analogs thereof (*see, e.g.*, Seth et al., U.S. 8,278,283), 4'-CH₂-N(OCH₃)-2' and analogs thereof (*see, e.g.*, Prakash et al., U.S. 8,278,425), 4'-CH₂-O-N(CH₃)-2' (*see, e.g.*, Allerson et al., U.S. 7,696,345 and Allerson et al., U.S. 8,124,745), 4'-CH₂-C(H)(CH₃)-2' (*see, e.g.*, Zhou, *et al.*, *J. Org. Chem.*, 2009, 74, 118-134), 4'-CH₂-C(=CH₂)-2' and analogs thereof (*see e.g.*, Seth et al., U.S. 8,278,426), 4'-C(R_aR_b)-N(R)-O-2', 4'-C(R_aR_b)-O-N(R)-2', 4'-CH₂-O-N(R)-2', and 4'-CH₂-N(R)-O-2', wherein each R, R_a, and R_b is, independently, H, a protecting group, or C₁-C₁₂ alkyl (*see, e.g.* Imanishi et al., U.S. 7,427,672).

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

wherein:

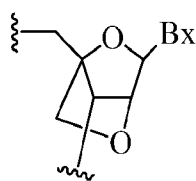
x is 0, 1, or 2;

n is 1, 2, 3, or 4;

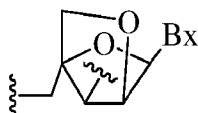
each R_a and R_b is, independently, H, a protecting group, hydroxyl, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, heterocycle radical, substituted heterocycle radical, heteroaryl, substituted heteroaryl, C₅-C₇ alicyclic radical, substituted C₅-C₇ alicyclic radical, halogen, OJ₁, NJ₁J₂, SJ₁, N₃, COOJ₁, acyl (C(=O)-H), substituted acyl, CN, sulfonyl (S(=O)₂-J₁), or sulfoxyl (S(=O)-J₁); and each J₁ and J₂ is, independently, H, C₁-C₁₂ alkyl, substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, substituted C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, substituted C₂-C₁₂ alkynyl, C₅-C₂₀ aryl, substituted C₅-C₂₀ aryl, acyl (C(=O)-H), substituted acyl, a heterocycle radical, a substituted heterocycle radical, C₁-C₁₂ aminoalkyl, substituted C₁-C₁₂ aminoalkyl, or a protecting group.

Additional bicyclic sugar moieties are known in the art, *see, for example*: Freier et al., *Nucleic Acids Research*, 1997, 25(22), 4429-4443; Albaek et al., *J. Org. Chem.*, 2006, 71, 7731-7740; Singh et al., *Chem. Commun.*, 1998, 4, 455-456; Koshkin et al., *Tetrahedron*, 1998, 54, 3607-3630; Wahlestedt et al., *Proc. Natl. Acad. Sci. U. S. A.*, 2000, 97, 5633-5638; Kumar et al., *Bioorg. Med. Chem. Lett.*, 1998, 8, 2219-2222; Singh et al., *J. Org. Chem.*, 1998, 63, 10035-10039; Srivastava et al., *J. Am. Chem. Soc.*, 2007, 129, 8362-8379; Elayadi et al., *Curr. Opin. Inven. Drugs*, 2001, 2,

558-561; Braasch et al., Chem. Biol., 2001, 8, 1-7; Orum et al., Curr. Opinion Mol. Ther., 2001, 3, 239-243; Wengel et al., U.S. 7,053,207, Imanishi et al., U.S. 6,268,490, Imanishi et al. U.S. 6,770,748, Imanishi et al., U.S. RE44,779; Wengel et al., U.S. 6,794,499, Wengel et al., U.S. 6,670,461; Wengel et al., U.S. 7,034,133, Wengel et al., U.S. 8,080,644; Wengel et al., U.S. 8,034,909; Wengel et al., U.S. 8,153,365; Wengel et al., U.S. 7,572,582; and Ramasamy et al., U.S. 6,525,191, Torsten et al., WO 2004/106356, Wengel et al., WO 1999/014226; Seth et al., WO 2007/134181; Seth et al., U.S. 7,547,684; Seth et al., U.S. 7,666,854; Seth et al., U.S. 8,088,746; Seth et al., U.S. 7,750,131; Seth et al., U.S. 8,030,467; Seth et al., U.S. 8,268,980; Seth et al., U.S. 8,546,556; Seth et al., U.S. 8,530,640; Migawa et al., U.S. 9,012,421; Seth et al., U.S. 8,501,805; Allerson et al., US2008/0039618; and Migawa et al., US2015/0191727. In certain embodiments, bicyclic sugar moieties and nucleosides incorporating such bicyclic sugar moieties are further defined by isomeric configuration. For example, an LNA nucleoside (described herein) may be in the α -L configuration or in the β -D configuration.



LNA (β -D-configuration)
bridge = 4'-CH₂-O-2'



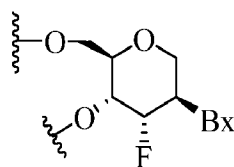
α -L-LNA (α -L-configuration)
bridge = 4'-CH₂-O-2'

α -L-methyleneoxy (4'-CH₂-O-2') or α -L-LNA bicyclic nucleosides have been incorporated into oligonucleotides that showed antisense activity (Frieden et al., *Nucleic Acids Research*, 2003, 21, 6365-6372). The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) *Nucleic Acids Research* 33(1):439-447; Mook, OR. et al., (2007) *Mal Cane Ther* 6(3):833-843; Grunweller, A. et al., (2003) *Nucleic Acids Research* 31(12):3185-3193). Herein, general descriptions of bicyclic nucleosides include both isomeric configurations. When the positions of specific bicyclic nucleosides (*e.g.*, LNA or cEt) are identified in exemplified embodiments herein, they are in the β -D configuration, unless otherwise specified.

In certain embodiments, modified sugar moieties comprise one or more non-bridging sugar substituent and one or more bridging sugar substituent (*e.g.*, 5'-substituted and 4'-2' bridged sugars).

In certain embodiments, modified sugar moieties are sugar surrogates. In certain such embodiments, the oxygen atom of the sugar moiety is replaced, *e.g.*, with a sulfur, carbon, or nitrogen atom. In certain such embodiments, such modified sugar moieties also comprise bridging and/or non-bridging substituents as described herein. For example, certain sugar surrogates comprise a 4'-sulfur atom and a substitution at the 2'-position (*see, e.g.*, Bhat et al., U.S. 7,875,733 and Bhat et al., U.S. 7,939,677) and/or the 5' position.

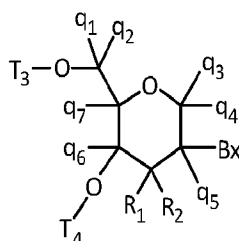
In certain embodiments, sugar surrogates comprise rings having other than 5 atoms. For example, in certain embodiments, a sugar surrogate comprises a six-membered tetrahydropyran ("THP"). Such tetrahydropyrans may be further modified or substituted. Nucleosides comprising such modified tetrahydropyrans include but are not limited to hexitol nucleic acid ("HNA"), anitol nucleic acid ("ANA"), manitol nucleic acid ("MNA") (*see, e.g.*, Leumann, CJ. *Bioorg. & Med. Chem.* 2002, 10, 841-854), fluoro HNA:



F-HNA

(“F-HNA”, *see e.g.* Swayze et al., U.S. 8,088,904; Swayze et al., U.S. 8,440,803; Swayze et al., U.S. 8,796,437; and Swayze et al., U.S. 9,005,906; F-HNA can also be referred to as a F-THP or 3'-fluoro tetrahydropyran), and nucleosides comprising additional modified THP compounds having the formula:

5



wherein, independently, for each of said modified THP nucleoside:

Bx is a nucleobase moiety;

T₃ and T₄ are each, independently, an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide or one of T₃ and T₄ is an internucleoside linking group linking the modified THP nucleoside to the remainder of an oligonucleotide and the other of T₃ and T₄ is H, a hydroxyl protecting group, a conjugate group or a 5' or 3'-terminal group;

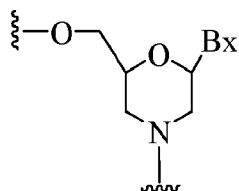
q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each, independently, H, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₆ alkynyl, or substituted C₂-C₆ alkynyl; and

each of R₁ and R₂ is independently selected from among: hydrogen, halogen, substituted or unsubstituted alkoxy, NJ₁J₂, SJ₁, N₃, OC(=X)J₁, OC(=X)NJ₁J₂, NJ₃C(=X)NJ₁J₂, and CN, wherein X is O, S or NJ₁, and each J₁, J₂, and J₃ is, independently, H or C₁-C₆ alkyl.

In certain embodiments, modified THP nucleosides are provided wherein q₁, q₂, q₃, q₄, q₅, q₆ and q₇ are each H.

In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is other than H. In certain embodiments, at least one of q₁, q₂, q₃, q₄, q₅, q₆ and q₇ is methyl. In certain embodiments, modified THP nucleosides are provided wherein one of R₁ and R₂ is F. In certain embodiments, R₁ is F and R₂ is H, in certain embodiments, R₁ is methoxy and R₂ is H, and in certain embodiments, R₁ is methoxyethoxy and R₂ is H.

In certain embodiments, sugar surrogates comprise rings having more than 5 atoms and more than one heteroatom. For example, nucleosides comprising morpholino sugar moieties and their use in oligonucleotides have been reported (*see, e.g.*, Braasch et al., *Biochemistry*, 2002, 41, 4503-4510 and Summerton et al., U.S. 5,698,685; Summerton et al., U.S. 5,166,315; Summerton et al., U.S. 5,185,444; and Summerton et al., U.S. 5,034,506). As used here, the term “morpholino” means a sugar surrogate having the following structure:



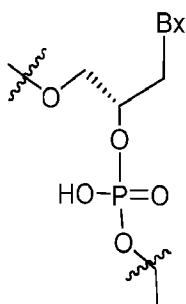
In certain embodiments, morpholinos may be modified, for example by adding or altering various substituent groups from the above morpholino structure. Such sugar surrogates are referred to herein as “modified morpholinos.”

In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include but are not limited to peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (*see, e.g.*, Kumar et al., *Org. Biomol. Chem.*, 2013, 11, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., WO2011/133876. In certain embodiments, sugar surrogates comprise acyclic moieties. Examples of nucleosides and oligonucleotides comprising such acyclic sugar surrogates include, but are not limited to, peptide nucleic acid (“PNA”), acyclic butyl nucleic acid (*see, e.g.*, Kumar et al., *Org. Biomol. Chem.*, 2013, 11, 5853-5865), and nucleosides and oligonucleotides described in Manoharan et al., US 2013/130378. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262. Additional PNA compounds suitable for use in the oligonucleotides of the invention are described in, for example, in Nielsen *et al.*, *Science*, 1991, 254, 1497-1500.

In certain embodiments, sugar surrogates are the “unlocked” sugar structure of UNA (unlocked nucleic acid) nucleosides. UNA is an unlocked acyclic nucleic acid, wherein any of the bonds of the sugar has been removed, forming an unlocked sugar surrogate. Representative U.S. publications that teach the preparation of UNA include, but are not limited to, US Patent No. 8,314,227; and US Patent Publication Nos. 2013/0096289; 2013/0011922; and 2011/0313020, the entire contents of each of which are hereby incorporated herein by reference.

In certain embodiments, sugar surrogates are the glycerol as found in GNA (glycol nucleic acid) nucleosides as depicted below:

(S)-GNA



where Bx represents any nucleobase.

Many other bicyclic and tricyclic sugar and sugar surrogates are known in the art that can be used in modified nucleosides.

2. Certain Modified Nucleobases

In certain embodiments, modified oligonucleotides comprise one or more nucleosides comprising an unmodified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides

comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more nucleosides that does not comprise a nucleobase, referred to as an abasic nucleoside. In certain embodiments, modified oligonucleotides comprise one or more inosine nucleosides (i.e., nucleosides comprising a hypoxanthine nucleobase).

In certain embodiments, modified nucleobases are selected from: 5-substituted pyrimidines, 6-azapyrimidines, alkyl or alkynyl substituted pyrimidines, alkyl substituted purines, and N-2, N-6 and O-6 substituted purines. In certain embodiments, modified nucleobases are selected from: 5-methylcytosine, 2-aminopropyladenine, 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-N-methylguanine, 6-N-methyladenine, 2-propyladenine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl ($-C\equiv C-CH_3$) uracil, 5-propynylcytosine, 6-azouracil, 6-azocytosine, 6-azothymine, 5-ribosyluracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, 8-aza and other 8-substituted purines, 5-halo, particularly 5-bromo, 5-trifluoromethyl, 5-halouracil, and 5-halocytosine, 7-methylguanine, 7-methyladenine, 2-F-adenine, 2-aminoadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine, 3-deazaadenine, 6-N-benzoyladenine, 2-N-isobutyrylguanine, 4-N-benzoylcytosine, 4-N-benzoyluracil, 5-methyl 4-N-benzoylcytosine, 5-methyl 4-N-benzoyluracil, universal bases, hydrophobic bases, promiscuous bases, size-expanded bases, and fluorinated bases. Further modified nucleobases include tricyclic pyrimidines, such as 1,3-diazaphenoxazine-2-one, 1,3-diazaphenothiazine-2-one and 9-(2-aminoethoxy)-1,3-diazaphenoxazine-2-one (G-clamp). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in Merigan et al., U.S. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, Kroschwitz, J.I., Ed., John Wiley & Sons, 1990, 858-859; Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613; Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993, 273-288; and those disclosed in Chapters 6 and 15, *Antisense Drug Technology*, Crooke S.T., Ed., CRC Press, 2008, 163-166 and 442-443.

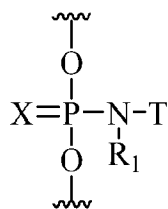
Publications that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include without limitation, Manoharan et al., US2003/0158403; Manoharan et al., US2003/0175906; Dinh et al., U.S. 4,845,205; Spielvogel et al., U.S. 5,130,302; Rogers et al., U.S. 5,134,066; Bischofberger et al., U.S. 5,175,273; Urdea et al., U.S. 5,367,066; Benner et al., U.S. 5,432,272; Matteucci et al., U.S. 5,434,257; Gmeiner et al., U.S. 5,457,187; Cook et al., U.S. 5,459,255; Froehler et al., U.S. 5,484,908; Matteucci et al., U.S. 5,502,177; Hawkins et al., U.S. 5,525,711; Haralambidis et al., U.S. 5,552,540; Cook et al., U.S. 5,587,469; Froehler et al., U.S. 5,594,121; Switzer et al., U.S. 5,596,091; Cook et al., U.S. 5,614,617; Froehler et al., U.S. 5,645,985; Cook et al., U.S. 5,681,941; Cook et al., U.S. 5,811,534; Cook et al., U.S. 5,750,692; Cook et al., U.S. 5,948,903; Cook et al., U.S. 5,587,470; Cook et al., U.S. 5,457,191; Matteucci et al., U.S. 5,763,588; Froehler et al., U.S. 5,830,653; Cook et al., U.S. 5,808,027; Cook et al., U.S. 6,166,199; and Matteucci et al., U.S. 6,005,096.

3. Certain Modified Internucleoside Linkages

The naturally occurring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. In certain embodiments, nucleosides of modified oligonucleotides may be linked together using one or more modified internucleoside linkages. The two main classes of internucleoside linking groups are defined by the presence or absence of a phosphorus atom. Representative phosphorus-containing internucleoside linkages include but are not limited to phosphates, which contain a phosphodiester bond ("P=O") (also referred to as unmodified or naturally occurring

linkages), phosphotriesters, methylphosphonates, phosphoramidates, phosphorothioates ("P=S"), and phosphorodithioates ("HS-P=S"). Representative non-phosphorus containing internucleoside linking groups include but are not limited to methylenemethylimino (-CH₂-N(CH₃)-O-CH₂-), thiodiester, thionocarbamate (-O-C(=O)(NH)-S-), siloxane (-O-SiH₂-O-), and N,N'-dimethylhydrazine (-CH₂-N(CH₃)-N(CH₃)-). Modified internucleoside linkages, compared to naturally occurring phosphate linkages, can be used to alter, typically increase, nuclease resistance of the oligonucleotide. In certain embodiments, internucleoside linkages having a chiral atom can be prepared as a racemic mixture, or as separate enantiomers. Methods of preparation of phosphorous-containing and non-phosphorous-containing internucleoside linkages are well known to those skilled in the art.

In certain embodiments, a modified internucleoside linkage is any of those described in WO 2021/030778, incorporated by reference herein. In certain embodiments, a modified internucleoside linkage comprises the formula:



wherein independently for each internucleoside linking group of the modified oligonucleotide:

X is selected from O or S;

R₁ is selected from H, a C₁-C₆ alkyl, and a substituted C₁-C₆ alkyl; and

T is selected from SO₂R₂, C(=O)R₃, and P(=O)R₄R₅, wherein:

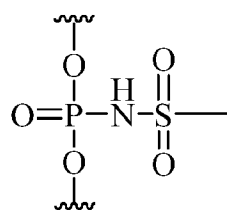
R₂ is selected from an aryl, a substituted aryl, a heterocycle, a substituted heterocycle, an aromatic heterocycle, a substituted aromatic heterocycle, a diazole, a substituted diazole, a C₁-C₆ alkoxy, a C₁-C₆ alkyl, a C₁-C₆ alkenyl, a C₁-C₆ alkynyl, a substituted C₁-C₆ alkyl, a substituted C₁-C₆ alkenyl, a substituted C₁-C₆ alkynyl, and a conjugate group;

R₃ is selected from an aryl, a substituted aryl, CH₃, N(CH₃)₂, OCH₃, and a conjugate group;

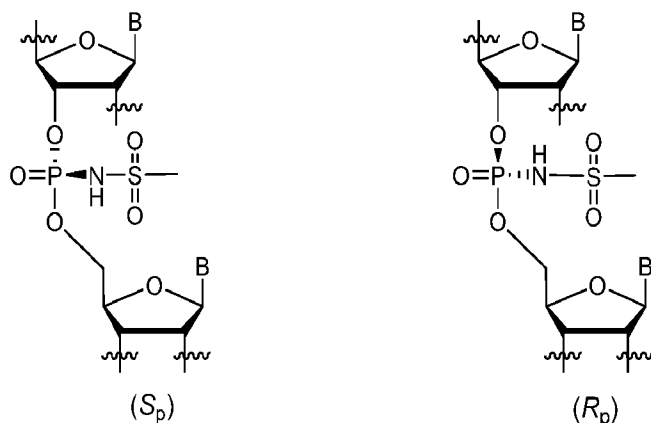
R₄ is selected from OCH₃, OH, a C₁-C₆ alkyl, a substituted C₁-C₆ alkyl, and a conjugate group; and

R₅ is selected from OCH₃, OH, a C₁-C₆ alkyl, and a substituted C₁-C₆ alkyl.

In certain embodiments, a modified internucleoside linkage comprises a mesyl phosphoramidate linking group having a formula:



In certain embodiments, a mesyl phosphoramidate internucleoside linkage may comprise a chiral center. In certain embodiments, modified oligonucleotides comprising (Rp) and/or (Sp) mesyl phosphoramidates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



Representative internucleoside linkages having a chiral center include but are not limited to alkylphosphonates, mesyl phosphoramidates, and phosphorothioates. Modified oligonucleotides comprising internucleoside linkages having a chiral center can be prepared as populations of modified oligonucleotides comprising stereorandom internucleoside

5 linkages, or as populations of modified oligonucleotides comprising phosphorothioate or other linkages containing chiral centers in particular stereochemical configurations. In certain embodiments, populations of modified oligonucleotides comprise phosphorothioate internucleoside linkages wherein all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, populations of modified oligonucleotides comprise mesyl phosphoramidate internucleoside linkages wherein all of the mesyl phosphoramidate internucleoside linkages are stereorandom. Such

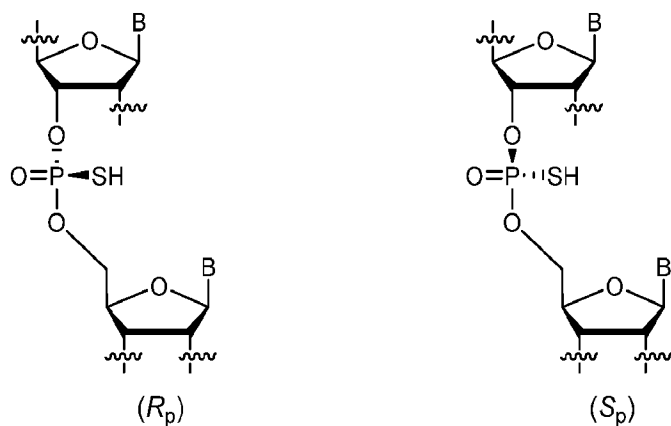
10 modified oligonucleotides can be generated using synthetic methods that result in random selection of the stereochemical configuration of each phosphorothioate or mesyl phosphoramidate linkage. Nonetheless, each individual phosphorothioate or mesyl phosphoramidate of each individual oligonucleotide molecule has a defined stereoconfiguration. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising one or more particular phosphorothioate or mesyl phosphoramidate internucleoside

15 linkages in a particular, independently selected stereochemical configuration. In certain embodiments, the particular configuration of the particular phosphorothioate or mesyl phosphoramidate linkage is present in at least 65% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate or mesyl phosphoramidate linkage is present in at least 70% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate or mesyl phosphoramidate linkage is present in at least

20 80% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate or mesyl phosphoramidate linkage is present in at least 90% of the molecules in the population. In certain embodiments, the particular configuration of the particular phosphorothioate or mesyl phosphoramidate linkage is present in at least 99% of the molecules in the population. Such chirally enriched populations of modified oligonucleotides can be generated using synthetic methods known in the art, *e.g.*, methods described in Oka et al., *JACS*

25 125, 8307 (2003), Wan et al. *Nuc. Acid. Res.* 42, 13456 (2014), and WO 2017/015555. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one indicated phosphorothioate or mesyl phosphoramidate in the (*S_p*) configuration. In certain embodiments, a population of modified oligonucleotides is enriched for modified oligonucleotides having at least one phosphorothioate or mesyl phosphoramidate in the (*R_p*) configuration. In certain embodiments, modified oligonucleotides comprising (*R_p*) and/or

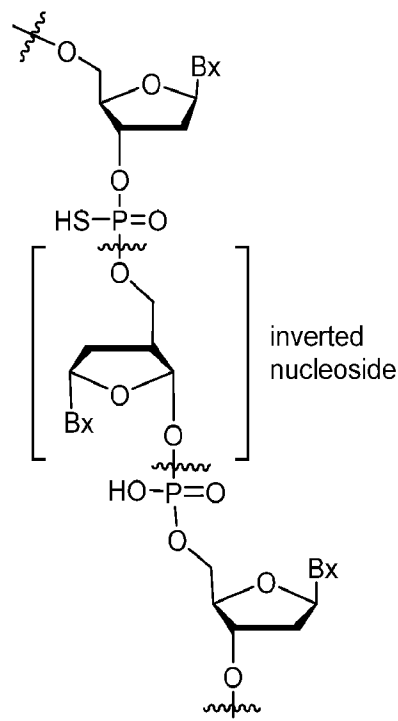
30 (*S_p*) phosphorothioates comprise one or more of the following formulas, respectively, wherein "B" indicates a nucleobase:



Unless otherwise indicated, chiral internucleoside linkages of modified oligonucleotides described herein can be stereorandom or in a particular stereochemical configuration.

Neutral internucleoside linkages include, without limitation, phosphotriesters, methylphosphonates, MMI (3'-CH₂-N(CH₃)-O-5'), amide-3 (3'-CH₂-C(=O)-N(H)-5'), amide-4 (3'-CH₂-N(H)-C(=O)-5'), formacetal (3'-O-CH₂-O-5'), methoxypropyl (MOP), and thioformacetal (3'-S-CH₂-O-5'). Further neutral internucleoside linkages include nonionic linkages comprising siloxane (dialkylsiloxane), carboxylate ester, carboxamide, sulfide, sulfonate ester and amides (See for example: *Carbohydrate Modifications in Antisense Research*; Y.S. Sanghvi and P.D. Cook, Eds., ACS Symposium Series 580; Chapters 3 and 4, 40-65). Further neutral internucleoside linkages include nonionic linkages comprising mixed N, O, S and CH₂ component parts.

In certain embodiments, modified oligonucleotides comprise one or more inverted nucleoside, as shown below:



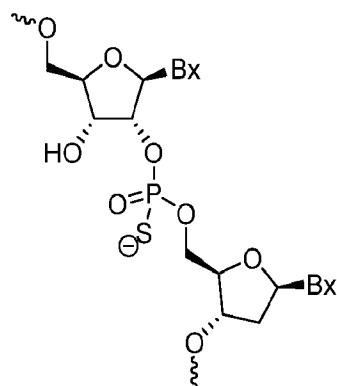
wherein each Bx independently represents any nucleobase.

In certain embodiments, an inverted nucleoside is terminal (i.e., the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage depicted above will be present. In certain such embodiments,

additional features (such as a conjugate group) may be attached to the inverted nucleoside. Such terminal inverted nucleosides can be attached to either or both ends of an oligonucleotide.

In certain embodiments, such groups lack a nucleobase and are referred to herein as inverted sugar moieties. In certain embodiments, an inverted sugar moiety is terminal (i.e., attached to the last nucleoside on one end of an oligonucleotide) and so only one internucleoside linkage described above will be present. In certain such embodiments, additional features (such as a conjugate group) may be attached to the inverted sugar moiety. Such terminal inverted sugar moieties can be attached to either or both ends of an oligonucleotide.

In certain embodiments, nucleic acids can be linked 2' to 5' rather than the standard 3' to 5' linkage. Such a linkage is illustrated below.



wherein each Bx represents any nucleobase.

B. Certain Motifs

In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified sugar moiety. In certain embodiments, modified oligonucleotides comprise one or more modified nucleosides comprising a modified nucleobase. In certain embodiments, modified oligonucleotides comprise one or more modified internucleoside linkage. In such embodiments, the modified, unmodified, and differently modified sugar moieties, nucleobases, and/or internucleoside linkages of a modified oligonucleotide define a pattern or motif. In certain embodiments, the patterns of sugar moieties, nucleobases, and internucleoside linkages are each independent of one another. Thus, a modified oligonucleotide may be described by its sugar motif, nucleobase motif and/or internucleoside linkage motif (as used herein, nucleobase motif describes the modifications to the nucleobases independent of the sequence of nucleobases).

1. Certain Sugar Motifs

In certain embodiments, oligonucleotides comprise one or more type of modified sugar and/or unmodified sugar moiety arranged along the oligonucleotide or region thereof in a defined pattern or sugar motif. In certain instances, such sugar motifs include but are not limited to any of the sugar modifications discussed herein.

Gapmer Oligonucleotides

In certain embodiments, modified oligonucleotides comprise or consist of a region having a gapmer motif, which is defined by two external regions or “wings” and a central or internal region or “gap.” The three regions of a gapmer motif (the 5'-wing, the gap, and the 3'-wing) form a contiguous sequence of nucleosides wherein at least some

of the sugar moieties of the nucleosides of each of the wings differ from at least some of the sugar moieties of the nucleosides of the gap. Specifically, at least the sugar moieties of the nucleosides of each wing that are closest to the gap (the 3'-most nucleoside of the 5'-wing and the 5'-most nucleoside of the 3'-wing) differ from the sugar moiety of the neighboring gap nucleosides, thus defining the boundary between the wings and the gap (i.e., the wing/gap junction). In certain embodiments, the sugar moieties within the gap are the same as one another. In certain embodiments, the gap includes one or more nucleoside having a sugar moiety that differs from the sugar moiety of one or more other nucleosides of the gap. In certain embodiments, the sugar motifs of the two wings are the same as one another (symmetric gapmer). In certain embodiments, the sugar motif of the 5'-wing differs from the sugar motif of the 3'-wing (asymmetric gapmer).

In certain embodiments, the wings of a gapmer comprise 1-6 nucleosides. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least two nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least three nucleosides of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least four nucleosides of each wing of a gapmer comprises a modified sugar moiety.

In certain embodiments, the gap of a gapmer comprises 7-12 nucleosides. In certain embodiments, each nucleoside of the gap of a gapmer comprises a 2'- β -D-deoxyribose sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety.

In certain embodiments, the gapmer is a deoxy gapmer. In certain embodiments, the nucleosides on the gap side of each wing/gap junction comprise 2'-deoxyribose sugar moieties and the nucleosides on the wing sides of each wing/gap junction comprise modified sugar moieties. In certain embodiments, each nucleoside of the gap comprises a 2'- β -D-deoxyribose sugar moiety. In certain embodiments, each nucleoside of each wing of a gapmer comprises a modified sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a modified sugar moiety. In certain embodiments, one nucleoside of the gap comprises a modified sugar moiety and each remaining nucleoside of the gap comprises a 2'-deoxyribose sugar moiety. In certain embodiments, at least one nucleoside of the gap of a gapmer comprises a 2'-OMe sugar moiety.

Herein, the lengths (number of nucleosides) of the three regions of a gapmer may be provided using the notation [# of nucleosides in the 5'-wing] – [# of nucleosides in the gap] – [# of nucleosides in the 3'-wing]. Thus, a 3-10-3 gapmer consists of 3 linked nucleosides in each wing and 10 linked nucleosides in the gap. Where such nomenclature is followed by a specific modification, that modification is the modification in each sugar moiety of each wing and the gap nucleosides comprise 2'- β -D-deoxyribose sugar moieties. Thus, a 5-10-5 MOE gapmer consists of 5 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'- β -D-deoxynucleosides in the gap, and 5 linked 2'-MOE nucleosides in the 3'-wing. A 6-10-4 MOE gapmer consists of 6 linked 2'-MOE nucleosides in the 5'-wing, 10 linked 2'- β -D-deoxynucleosides in the gap, and 4 linked 2'-MOE nucleosides in the 3'-wing. A 3-10-3 cEt gapmer consists of 3 linked cEt nucleosides in the 5'-wing, 10 linked 2'- β -D-deoxynucleosides in the gap, and 3 linked cEt nucleosides in the 3'-wing.

In certain embodiments, modified oligonucleotides have a sugar motif selected from 5' to 3': eeeeeeeeeeeeeee; wherein each "d" represents a 2'- β -D-deoxyribose sugar moiety, and each "e" represents a 2'-MOE sugar moiety.

In certain embodiments, modified oligonucleotides have a sugar motif selected from 5' to 3': eeeeeeddddddddeeee; wherein each "d" represents a 2'- β -D-deoxyribsyl sugar moiety, and each "e" represents a 2'-MOE sugar moiety.

In certain embodiments, modified oligonucleotides have the sugar motif from 5' to 3': kkkdddddskkk; wherein each "d" represents a 2'- β -D-deoxyribsyl sugar moiety, and each "k" represents a cEt modified sugar moiety.

In certain embodiments, modified oligonucleotides have the sugar motif from 5' to 3': eeeedyddddddeeee; wherein each "d" represents a 2'- β -D-deoxyribsyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "y" represents a 2'-OMe sugar moiety.

In certain embodiments, modified oligonucleotides have the sugar motif from 5' to 3': eeeedyddddddeeee; wherein each "d" represents a 2'- β -D-deoxyribsyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "y" represents a 2'-OMe sugar moiety.

In certain embodiments, modified oligonucleotides have the sugar motif from 5' to 3': kkkdydddddskkk; wherein each "d" represents a 2'- β -D-deoxyribsyl sugar moiety, each "k" represents a cEt modified sugar moiety, and each "y" represents a 2'-OMe sugar moiety.

2. Certain Nucleobase Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified nucleobases arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each nucleobase is modified. In certain embodiments, none of the nucleobases are modified. In certain embodiments, each purine or each pyrimidine is modified. In certain embodiments, each adenine is modified. In certain embodiments, each guanine is modified. In certain embodiments, each thymine is modified. In certain embodiments, each uracil is modified. In certain embodiments, each cytosine is modified. In certain embodiments, some or all of the cytosine nucleobases in a modified oligonucleotide are 5-methyl cytosines. In certain embodiments, all of the cytosine nucleobases are 5-methyl cytosines and all of the other nucleobases of the modified oligonucleotide are unmodified nucleobases.

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

In certain embodiments, oligonucleotides having a gapmer motif comprise a nucleoside comprising a modified nucleobase. In certain such embodiments, one nucleoside comprising a modified nucleobase is in the central gap of an oligonucleotide having a gapmer motif. In certain such embodiments, the sugar moiety of said nucleoside is a 2'-deoxyribsyl sugar moiety. In certain embodiments, the modified nucleobase is selected from: a 2-thiopyrimidine and a 5-propynepyrimidine.

3. Certain Internucleoside Linkage Motifs

In certain embodiments, oligonucleotides comprise modified and/or unmodified internucleoside linkages arranged along the oligonucleotide or region thereof in a defined pattern or motif. In certain embodiments, each internucleoside linking group is a phosphodiester internucleoside linkage (P=O). In certain embodiments, each internucleoside linking group of a modified oligonucleotide is a phosphorothioate internucleoside linkage (P=S). In

certain embodiments, each internucleoside linkage of a modified oligonucleotide is independently selected from a phosphorothioate internucleoside linkage and phosphodiester internucleoside linkage. In certain embodiments, each phosphorothioate internucleoside linkage is independently selected from a stereorandom phosphorothioate, a (Sp) phosphorothioate, and a (Rp) phosphorothioate.

5 In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer and the internucleoside linkages within the gap are all modified. In certain such embodiments, some or all of the internucleoside linkages in the wings are unmodified phosphodiester internucleoside linkages. In certain embodiments, the terminal internucleoside linkages are modified. In certain embodiments, the sugar motif of a modified oligonucleotide is a gapmer, and the internucleoside linkage motif comprises at least one phosphodiester internucleoside linkage in at least one wing, wherein
10 the at least one phosphodiester linkage is not a terminal internucleoside linkage, and the remaining internucleoside linkages are phosphorothioate internucleoside linkages. In certain such embodiments, all of the phosphorothioate linkages are stereorandom. In certain embodiments, all of the phosphorothioate linkages in the wings are (Sp) phosphorothioates, and the gap comprises at least one Sp, Sp, Rp motif. In certain embodiments, populations of modified oligonucleotides are enriched for modified oligonucleotides comprising such internucleoside linkage motifs.

15 In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sssssssssssss, wherein each "s" represents a phosphorothioate internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sosoossssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):

20 sosoosssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sossossssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sossossssssssooss, wherein each "s" represents a phosphorothioate
25 internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sosoosssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):

30 sossosssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soossssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soososssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):
35 soossssssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):

linkage motif of (5' to 3'): soooooossssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soooooossssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soosoooooooooooooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):

soossssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soossoossssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soossoossssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): soossssssssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'):

sssooooooooooooo, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sssooooooooooooo, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): ssssooooooooooooo, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): sssooooooooooooo, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): ssssoosssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage. In certain embodiments, modified oligonucleotides have an internucleoside linkage motif of (5' to 3'): ssssoosssssssssoss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

In certain embodiments, modified oligonucleotides have an internucleoside linkage motif comprising one or more mesyl phosphoramidate linking groups. In certain embodiments, one or more phosphorothioate internucleoside linkages or one or more phosphodiester internucleoside linkages of the internucleoside linkage motifs herein is substituted with a mesyl phosphoramidate linking group.

C. Certain Lengths

It is possible to increase or decrease the length of an oligonucleotide without eliminating activity. For example, in Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), a series of oligonucleotides 13-25 nucleobases in length were tested for their ability to induce cleavage of a target RNA in an oocyte injection model. Oligonucleotides 25 nucleobases in length with 8 or 11 mismatch bases near the ends of the oligonucleotides were able to direct specific

cleavage of the target RNA, albeit to a lesser extent than the oligonucleotides that contained no mismatches. Similarly, target specific cleavage was achieved using 13 nucleobase oligonucleotides, including those with 1 or 3 mismatches.

In certain embodiments, oligonucleotides (including modified oligonucleotides) can have any of a variety of ranges of lengths. In certain embodiments, oligonucleotides consist of X to Y linked nucleosides, where X represents the fewest number of nucleosides in the range and Y represents the largest number nucleosides in the range. In certain such embodiments, X and Y are each independently selected from 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, and 50; provided that $X \leq Y$. For example, in certain embodiments, oligonucleotides consist of 12 to 13, 12 to 14, 12 to 15, 12 to 16, 12 to 17, 12 to 18, 12 to 19, 12 to 20, 12 to 21, 12 to 22, 12 to 23, 12 to 24, 12 to 25, 12 to 26, 12 to 27, 12 to 28, 12 to 29, 12 to 30, 13 to 14, 13 to 15, 13 to 16, 13 to 17, 13 to 18, 13 to 19, 13 to 20, 13 to 21, 13 to 22, 13 to 23, 13 to 24, 13 to 25, 13 to 26, 13 to 27, 13 to 28, 13 to 29, 13 to 30, 14 to 15, 14 to 16, 14 to 17, 14 to 18, 14 to 19, 14 to 20, 14 to 21, 14 to 22, 14 to 23, 14 to 24, 14 to 25, 14 to 26, 14 to 27, 14 to 28, 14 to 29, 14 to 30, 15 to 16, 15 to 17, 15 to 18, 15 to 19, 15 to 20, 15 to 21, 15 to 22, 15 to 23, 15 to 24, 15 to 25, 15 to 26, 15 to 27, 15 to 28, 15 to 29, 15 to 30, 16 to 17, 16 to 18, 16 to 19, 16 to 20, 16 to 21, 16 to 22, 16 to 23, 16 to 24, 16 to 25, 16 to 26, 16 to 27, 16 to 28, 16 to 29, 16 to 30, 17 to 18, 17 to 19, 17 to 20, 17 to 21, 17 to 22, 17 to 23, 17 to 24, 17 to 25, 17 to 26, 17 to 27, 17 to 28, 17 to 29, 17 to 30, 18 to 19, 18 to 20, 18 to 21, 18 to 22, 18 to 23, 18 to 24, 18 to 25, 18 to 26, 18 to 27, 18 to 28, 18 to 29, 18 to 30, 19 to 20, 19 to 21, 19 to 22, 19 to 23, 19 to 24, 19 to 25, 19 to 26, 19 to 27, 19 to 28, 19 to 29, 19 to 30, 20 to 21, 20 to 22, 20 to 23, 20 to 24, 20 to 25, 20 to 26, 20 to 27, 20 to 28, 20 to 29, 20 to 30, 21 to 22, 21 to 23, 21 to 24, 21 to 25, 21 to 26, 21 to 27, 21 to 28, 21 to 29, 21 to 30, 22 to 23, 22 to 24, 22 to 25, 22 to 26, 22 to 27, 22 to 28, 22 to 29, 22 to 30, 23 to 24, 23 to 25, 23 to 26, 23 to 27, 23 to 28, 23 to 29, 23 to 30, 24 to 25, 24 to 26, 24 to 27, 24 to 28, 24 to 29, 24 to 30, 25 to 26, 25 to 27, 25 to 28, 25 to 29, 25 to 30, 26 to 27, 26 to 28, 26 to 29, 26 to 30, 27 to 28, 27 to 29, 27 to 30, 28 to 29, 28 to 30, or 29 to 30 linked nucleosides.

D. Certain Modified Oligonucleotides

In certain embodiments, the above modifications (sugar, nucleobase, internucleoside linkage) are incorporated into a modified oligonucleotide. In certain embodiments, modified oligonucleotides are characterized by their modification motifs and overall lengths. In certain embodiments, such parameters are each independent of one another. Thus, unless otherwise indicated, each internucleoside linkage of an oligonucleotide having a gapmer sugar motif may be modified or unmodified and may or may not follow the gapmer modification pattern of the sugar modifications. For example, the internucleoside linkages within the wing regions of a sugar gapmer may be the same or different from one another and may be the same or different from the internucleoside linkages of the gap region of the sugar motif. Likewise, such sugar gapmer oligonucleotides may comprise one or more modified nucleobase independent of the gapmer pattern of the sugar modifications. Unless otherwise indicated, all modifications are independent of nucleobase sequence.

E. Certain Populations of Modified Oligonucleotides

Populations of modified oligonucleotides in which all of the modified oligonucleotides of the population have the same molecular formula can be stereorandom populations or chirally enriched populations. All of the chiral centers of all of the modified oligonucleotides are stereorandom in a stereorandom population. In a chirally enriched population,

at least one particular chiral center is not stereorandom in the modified oligonucleotides of the population. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for β -D ribosyl sugar moieties, and all of the phosphorothioate internucleoside linkages are stereorandom. In certain embodiments, the modified oligonucleotides of a chirally enriched population are enriched for both β -D ribosyl sugar moieties and at least one particular phosphorothioate internucleoside linkage in a particular stereochemical configuration.

F. Nucleobase Sequence

In certain embodiments, oligonucleotides (unmodified or modified oligonucleotides) are further described by their nucleobase sequence. In certain embodiments oligonucleotides have a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain such embodiments, a region of an oligonucleotide has a nucleobase sequence that is complementary to a second oligonucleotide or an identified reference nucleic acid, such as a target nucleic acid. In certain embodiments, the nucleobase sequence of a region or entire length of an oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to the second oligonucleotide or nucleic acid, such as a target nucleic acid.

II. Certain Oligomeric Compounds

In certain embodiments, provided herein are oligomeric compounds, which consist of an oligonucleotide (modified or unmodified) and optionally one or more conjugate groups and/or terminal groups. Conjugate groups consist of one or more conjugate moiety and a conjugate linker which links the conjugate moiety to the oligonucleotide. Conjugate groups may be attached to either or both ends of an oligonucleotide and/or at any internal position. In certain embodiments, conjugate groups are attached to the 2'-position of a nucleoside of a modified oligonucleotide. In certain embodiments, conjugate groups that are attached to either or both ends of an oligonucleotide are terminal groups. In certain such embodiments, conjugate groups or terminal groups are attached at the 3' and/or 5'-end of oligonucleotides. In certain such embodiments, conjugate groups (or terminal groups) are attached at the 3'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 3'-end of oligonucleotides. In certain embodiments, conjugate groups (or terminal groups) are attached at the 5'-end of oligonucleotides. In certain embodiments, conjugate groups are attached near the 5'-end of oligonucleotides.

Examples of terminal groups include but are not limited to conjugate groups, capping groups, phosphate moieties, protecting groups, modified or unmodified nucleosides, and two or more nucleosides that are independently modified or unmodified.

A. Certain Conjugate Groups

In certain embodiments, oligonucleotides are covalently attached to one or more conjugate groups. In certain embodiments, conjugate groups modify one or more properties of the attached oligonucleotide, including but not limited to pharmacodynamics, pharmacokinetics, stability, binding, absorption, tissue distribution, cellular distribution, cellular uptake, charge and clearance.

In certain embodiments, conjugation of one or more carbohydrate moieties to a modified oligonucleotide can optimize one or more properties of the modified oligonucleotide. In certain embodiments, the carbohydrate moiety is

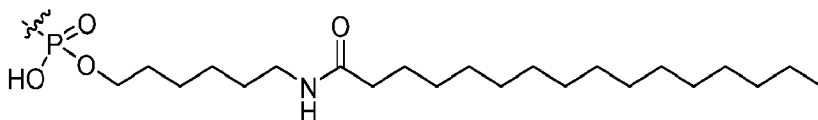
attached to a modified subunit of the modified oligonucleotide. For example, the ribose sugar of one or more ribonucleotide subunits of a modified oligonucleotide can be replaced with another moiety, e.g. a non-carbohydrate (preferably cyclic) carrier to which is attached a carbohydrate ligand. A ribonucleotide subunit in which the ribose sugar of the subunit has been so replaced is referred to herein as a ribose replacement modification subunit (RRMS), which is a modified sugar moiety. A cyclic carrier may be a carbocyclic ring system, i.e., one or more ring atoms may be a heteroatom, e.g., nitrogen, oxygen, sulphur. The cyclic carrier may be a monocyclic ring system, or may contain two or more rings, e.g. fused rings. The cyclic carrier may be a fully saturated ring system, or it may contain one or more double bonds. In certain embodiments, the modified oligonucleotide is a gapmer.

In certain embodiments, conjugate groups impart a new property on the attached oligonucleotide, e.g., fluorophores or reporter groups that enable detection of the oligonucleotide. Certain conjugate groups and conjugate moieties have been described previously, for example: cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660, 306-309; Manoharan et al., *Bioorg. Med. Chem. Lett.*, 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, 20, 533-538), an aliphatic chain, e.g., do-decan-diol or undecyl residues (Saison-Behmoaras et al., *EMBO J.*, 1991, 10, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk et al., *Biochimie*, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic acid a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, 277, 923-937), a tocopherol group (Nishina et al., *Molecular Therapy Nucleic Acids*, 2015, 4, e220; and Nishina et al., *Molecular Therapy*, 2008, 16, 734-740), or a GalNAc cluster (e.g., WO2014/179620).

In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, C5 alkyl, C22 alkenyl, C20 alkenyl, C16 alkenyl, C10 alkenyl, C21 alkenyl, C19 alkenyl, C18 alkenyl, C15 alkenyl, C14 alkenyl, C13 alkenyl, C12 alkenyl, C11 alkenyl, C9 alkenyl, C8 alkenyl, C7 alkenyl, C6 alkenyl, or C5 alkenyl.

In certain embodiments, the conjugate group may comprise a conjugate moiety selected from any of a C22 alkyl, C20 alkyl, C16 alkyl, C10 alkyl, C21 alkyl, C19 alkyl, C18 alkyl, C15 alkyl, C14 alkyl, C13 alkyl, C12 alkyl, C11 alkyl, C9 alkyl, C8 alkyl, C7 alkyl, C6 alkyl, or C5 alkyl, where the alkyl chain has one or more unsaturated bonds.

In certain embodiments, a conjugate group is a lipid having the following structure:



1. Conjugate Moieties

Conjugate moieties include, without limitation, intercalators, reporter molecules, polyamines, polyamides, peptides, carbohydrates (e.g., GalNAc), vitamin moieties, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, fluorophores, and dyes.

In certain embodiments, a conjugate moiety comprises an active drug substance, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triodobenzoic acid, fingolimod, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethacin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

2. Conjugate Linkers

Conjugate moieties are attached to oligonucleotides through conjugate linkers. In certain oligomeric compounds, the conjugate linker is a single chemical bond (i.e., the conjugate moiety is attached directly to an oligonucleotide through a single bond). In certain embodiments, the conjugate linker comprises a chain structure, such as a hydrocarbyl chain, or an oligomer of repeating units such as ethylene glycol, nucleosides, or amino acid units.

In certain embodiments, a conjugate linker comprises pyrrolidine.

In certain embodiments, a conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, disulfide, polyethylene glycol, ether, thioether, and hydroxylamino groups. In certain such embodiments, the conjugate linker comprises one or more groups selected from alkyl, amino, oxo, amide, and ether groups. In certain embodiments, the conjugate linker comprises one or more groups selected from alkyl and amide groups. In certain embodiments, the conjugate linker comprises one or more groups selected from alkyl and ether groups. In certain embodiments, the conjugate linker comprises at least one phosphorus moiety. In certain embodiments, the conjugate linker comprises at least one phosphate group. In certain embodiments, the conjugate linker includes at least one neutral linking group.

In certain embodiments, conjugate linkers, including the conjugate linkers described above, are bifunctional linking moieties, e.g., those known in the art to be useful for attaching conjugate moieties to compounds, such as the oligonucleotides provided herein. In general, a bifunctional linking moiety comprises at least two functional groups. One of the functional groups is selected to react with a particular site on a compound and the other is selected to react with a conjugate moiety. Examples of functional groups used 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 certain embodiments, bifunctional linking moieties comprise one or more groups selected from amino, hydroxyl, carboxylic acid, thiol, alkyl, alkenyl, and alkynyl.

Examples of conjugate linkers include but are not limited to pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), and 6-aminohexanoic acid (AHX or AHA). Other conjugate linkers include but are not limited to a substituted or unsubstituted C₁-C₁₀ alkyl, a substituted or unsubstituted C₂-C₁₀ alkenyl or a substituted or unsubstituted C₂-C₁₀ alkynyl, wherein a nonlimiting list of preferred substituent groups includes hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl, and alkynyl.

In certain embodiments, conjugate linkers comprise 1-10 linker-nucleosides. In certain embodiments, conjugate linkers comprise 2-5 linker-nucleosides. In certain embodiments, conjugate linkers comprise exactly 3 linker-

nucleosides. In certain embodiments, conjugate linkers comprise the TCA motif. In certain embodiments, such linker-nucleosides are modified nucleosides. In certain embodiments such linker-nucleosides comprise a modified sugar moiety. In certain embodiments, linker-nucleosides are unmodified. In certain embodiments, linker-nucleosides comprise an optionally protected heterocyclic base selected from a purine, a substituted purine, a pyrimidine or substituted pyrimidine. In certain embodiments, a cleavable moiety is a nucleoside selected from uracil, thymine, cytosine, 4-N-benzoylcytosine, 5-methyl cytosine, 4-N-benzoyl-5-methyl cytosine, adenine, 6-N-benzoyladenine, guanine and 2-N-isobutyrylguanine. It is typically desirable for linker-nucleosides to be cleaved from the oligomeric compound after it reaches a target tissue. Accordingly, linker-nucleosides are typically linked to one another and to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are phosphodiester bonds.

Herein, linker-nucleosides are not considered to be part of the oligonucleotide. Accordingly, in embodiments in which an oligomeric compound comprises an oligonucleotide consisting of a specified number or range of linked nucleosides and/or a specified percent complementarity to a reference nucleic acid, and the oligomeric compound also comprises a conjugate group comprising a conjugate linker comprising linker-nucleosides, those linker-nucleosides are not counted toward the length of the oligonucleotide and are not used in determining the percent complementarity of the oligonucleotide for the reference nucleic acid. For example, an oligomeric compound may comprise (1) a modified oligonucleotide consisting of 8-30 nucleosides and (2) a conjugate group comprising 1-10 linker-nucleosides that are contiguous with the nucleosides of the modified oligonucleotide. The total number of contiguous linked nucleosides in such an oligomeric compound is more than 30. Alternatively, an oligomeric compound may comprise a modified oligonucleotide consisting of 8-30 nucleosides and no conjugate group. The total number of contiguous linked nucleosides in such an oligomeric compound is no more than 30. Unless otherwise indicated conjugate linkers comprise no more than 10 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 5 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 3 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 2 linker-nucleosides. In certain embodiments, conjugate linkers comprise no more than 1 linker-nucleoside.

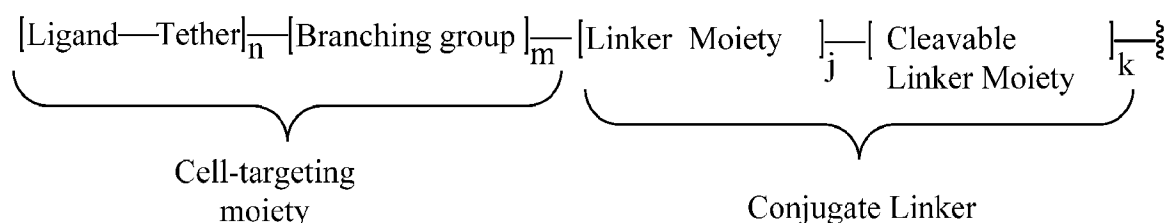
In certain embodiments, it is desirable for a conjugate group to be cleaved from the oligonucleotide. For example, in certain circumstances oligomeric compounds comprising a particular conjugate moiety are better taken up by a particular cell type, but once the oligomeric compound has been taken up, it is desirable that the conjugate group be cleaved to release the unconjugated or parent oligonucleotide. Thus, certain conjugate linkers may comprise one or more cleavable moieties. In certain embodiments, a cleavable moiety is a cleavable bond. In certain embodiments, a cleavable moiety is a group of atoms comprising at least one cleavable bond. In certain embodiments, a cleavable moiety comprises a group of atoms having one, two, three, four, or more than four cleavable bonds. In certain embodiments, a cleavable moiety is selectively cleaved inside a cell or subcellular compartment, such as a lysosome. In certain embodiments, a cleavable moiety is selectively cleaved by endogenous enzymes, such as nucleases.

In certain embodiments, a cleavable bond is selected from among an amide, an ester, an ether, one or both esters of a phosphodiester, a phosphate ester, a carbamate, or a disulfide. In certain embodiments, a cleavable bond is one or both of the esters of a phosphodiester. In certain embodiments, a cleavable moiety comprises a phosphate or phosphodiester. In certain embodiments, the cleavable moiety is a phosphate linkage between an oligonucleotide and a conjugate moiety or conjugate group.

In certain embodiments, a cleavable moiety comprises or consists of one or more linker-nucleosides. In certain such embodiments, the one or more linker-nucleosides are linked to one another and/or to the remainder of the oligomeric compound through cleavable bonds. In certain embodiments, such cleavable bonds are unmodified phosphodiester bonds. In certain embodiments, a cleavable moiety is a 2'-deoxynucleoside that is attached to either the 3' or 5'-terminal nucleoside of an oligonucleotide by a phosphate internucleoside linkage and covalently attached to the remainder of the conjugate linker or conjugate moiety by a phosphate or phosphorothioate linkage. In certain such embodiments, the cleavable moiety is 2'-deoxyadenosine.

3. Cell-Targeting Moieties

In certain embodiments, a conjugate group comprises a cell-targeting moiety. In certain embodiments, a conjugate group has the general formula:



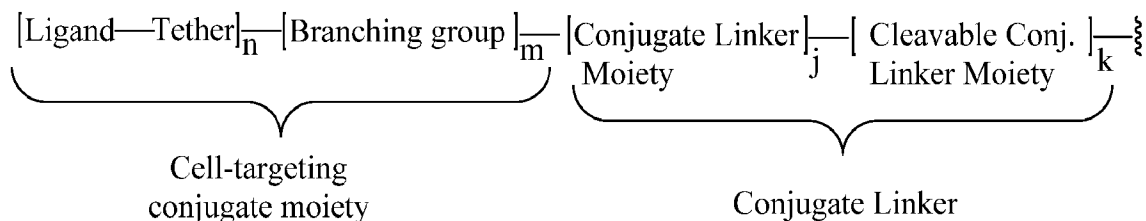
wherein n is from 1 to about 3, m is 0 when n is 1, m is 1 when n is 2 or greater, j is 1 or 0, and k is 1 or 0.

In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain embodiments, n is 2, j is 0 and k is 1. In certain embodiments, n is 2, j is 1 and k is 1. In certain embodiments, n is 3, j is 1 and k is 0. In certain embodiments, n is 3, j is 0 and k is 1. In certain embodiments, n is 3, j is 1 and k is 1.

In certain embodiments, conjugate groups comprise cell-targeting moieties that have at least one tethered ligand. In certain embodiments, cell-targeting moieties comprise two tethered ligands covalently attached to a branching group.

In certain embodiments, each ligand of a cell-targeting moiety has an affinity for at least one type of receptor on a target cell. In certain embodiments, each ligand has an affinity for at least one type of receptor on the surface of a mammalian liver cell. In certain embodiments, each ligand has an affinity for the hepatic asialoglycoprotein receptor (ASGP-R). In certain embodiments, each ligand is a carbohydrate.

In certain embodiments, a conjugate group comprises a cell-targeting conjugate moiety. In certain embodiments, a conjugate group has the general formula:



wherein n is from 1 to about 3, m is 0 when n is 1, m is 1 when n is 2 or greater, j is 1 or 0, and k is 1 or 0.

In certain embodiments, n is 1, j is 1 and k is 0. In certain embodiments, n is 1, j is 0 and k is 1. In certain embodiments, n is 1, j is 1 and k is 1. In certain embodiments, n is 2, j is 1 and k is 0. In certain embodiments, n is 2, j is 0 and k is 1. In certain embodiments, n is 2, j is 1 and k is 1. In certain embodiments, n is 3, j is 1 and k is 0. In certain embodiments, n is 3, j is 0 and k is 1. In certain embodiments, n is 3, j is 1 and k is 1.

In certain embodiments, conjugate groups comprise cell-targeting moieties that have at least one tethered ligand. In certain embodiments, cell-targeting moieties comprise two tethered ligands covalently attached to a branching group. In certain embodiments, cell-targeting moieties comprise three tethered ligands covalently attached to a branching group.

B. Certain Terminal Groups

In certain embodiments, oligomeric compounds comprise one or more terminal groups. In certain such embodiments, oligomeric compounds comprise a stabilized 5'-phosphate. Stabilized 5'-phosphates include, but are not limited to 5'-phosphonates, including, but not limited to 5'-vinylphosphonates. In certain embodiments, terminal groups comprise one or more abasic sugar moieties and/or inverted nucleosides. In certain embodiments, terminal groups comprise one or more 2'-linked nucleosides or sugar moieties. In certain such embodiments, the 2'-linked group is an abasic sugar moiety.

III. Antisense Activity

In certain embodiments, oligomeric compounds and oligomeric duplexes are capable of hybridizing to a target nucleic acid, resulting in at least one antisense activity; such oligomeric compounds and oligomeric duplexes are antisense compounds. In certain embodiments, antisense compounds have antisense activity when they reduce or inhibit the amount or activity of a target nucleic acid by 25% or more in the standard cell assay. In certain embodiments, antisense compounds selectively affect one or more target nucleic acid. Such antisense compounds comprise a nucleobase sequence that hybridizes to one or more target nucleic acid, resulting in one or more desired antisense activity and does not hybridize to one or more non-target nucleic acid or does not hybridize to one or more non-target nucleic acid in such a way that results in significant undesired antisense activity.

In certain antisense activities, hybridization of an antisense compound to a target nucleic acid results in recruitment of a protein that cleaves the target nucleic acid. For example, certain antisense compounds result in RNase H mediated cleavage of the target nucleic acid. RNase H is a cellular endonuclease that cleaves the RNA strand of an RNA:DNA duplex. The DNA in such an RNA:DNA duplex need not be unmodified DNA. In certain embodiments, described herein are antisense compounds that are sufficiently "DNA-like" to elicit RNase H activity. In certain embodiments, one or more non-DNA-like nucleoside in the gap of a gapmer is tolerated.

In certain antisense activities, an antisense compound or a portion of an antisense compound is loaded into an RNA-induced silencing complex (RISC), ultimately resulting in cleavage of the target nucleic acid. For example, certain antisense compounds result in cleavage of the target nucleic acid by Argonaute. Antisense compounds that are loaded into RISC are RNAi compounds. RNAi compounds may be double-stranded (siRNA or dsRNAi) or single-stranded (ssRNA).

In certain embodiments, hybridization of an antisense compound to a target nucleic acid does not result in recruitment of a protein that cleaves that target nucleic acid. In certain embodiments, hybridization of the antisense

compound to the target nucleic acid results in alteration of splicing of the target nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in inhibition of a binding interaction between the target nucleic acid and a protein or other nucleic acid. In certain embodiments, hybridization of an antisense compound to a target nucleic acid results in alteration of translation of the target nucleic acid.

Antisense activities may be observed directly or indirectly. In certain embodiments, observation or detection of an antisense activity involves observation or detection of a change in an amount of a target nucleic acid or protein encoded by such target nucleic acid, a change in the ratio of splice variants of a nucleic acid or protein and/or a phenotypic change in a cell or animal.

IV. Certain Target Nucleic Acids

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid. In certain embodiments, the target nucleic acid is an endogenous RNA molecule. In certain embodiments, the target nucleic acid encodes a protein. In certain such embodiments, the target nucleic acid is selected from: a mature mRNA and a pre-mRNA, including intronic, exonic and untranslated regions. In certain embodiments, the target RNA is a mature mRNA. In certain embodiments, the target nucleic acid is a pre-mRNA. In certain embodiments, the target region is entirely within an intron. In certain embodiments, the target region spans an intron/exon junction. In certain embodiments, the target region is at least 50% within an intron.

A. Complementarity/Mismatches to the Target Nucleic Acid and Duplex Complementarity

In certain embodiments, oligonucleotides are complementary to the target nucleic acid over the entire length of the oligonucleotide. In certain embodiments, oligonucleotides are 99%, 95%, 90%, 85%, or 80% complementary to the target nucleic acid. In certain embodiments, oligonucleotides are at least 80% complementary to the target nucleic acid over the entire length of the oligonucleotide and comprise a region that is 100% or fully complementary to a target nucleic acid. In certain embodiments, the region of full complementarity is from 6 to 20, 10 to 18, or 18 to 20 nucleobases in length.

It is possible to introduce mismatch bases without eliminating activity. For example, Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL in vitro and in vivo. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity in vivo. Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358, 1988) tested a series of tandem 14 nucleobase oligonucleotides, and 28 and 42 nucleobase oligonucleotides comprised of the sequence of two or three of the tandem oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase oligonucleotides.

In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, antisense activity against the target is reduced by such mismatch, but activity against a non-target is reduced by a greater amount. Thus, in certain embodiments selectivity of the oligonucleotide is improved. In certain embodiments, the mismatch is specifically positioned within an oligonucleotide having a gapmer

motif. In certain embodiments, the mismatch is at position 1, 2, 3, 4, 5, 6, 7, or 8 from the 5'-end of the gap region. In certain embodiments, the mismatch is at position 9, 8, 7, 6, 5, 4, 3, 2, 1 from the 3'-end of the gap region. In certain embodiments, the mismatch is at position 1, 2, 3, or 4 from the 5'-end of the wing region. In certain embodiments, the mismatch is at position 4, 3, 2, or 1 from the 3'-end of the wing region.

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B. IFNAR1

In certain embodiments, oligomeric agents or oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is an IFNAR1 nucleic acid. In certain embodiments, an IFNAR1 nucleic acid has the sequence set forth in SEQ ID NO: 1 (GENBANK
 10 Accession No. NC_000021.9, truncated from nucleosides 33321001 to 33363000) or SEQ ID NO: 2 (GENBANK Accession No. NM_000629.2). In certain embodiments, contacting a cell with an oligomeric compound complementary to SEQ ID NO: 1 or SEQ ID NO: 2 reduces the amount of IFNAR1 RNA, and in certain embodiments reduces the amount of IFNAR1 protein. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide. In certain embodiments, the oligomeric compound consists of a modified oligonucleotide and a conjugate group.

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C. Certain Target Nucleic Acids in Certain Tissues

In certain embodiments, oligomeric compounds comprise or consist of an oligonucleotide comprising a region that is complementary to a target nucleic acid, wherein the target nucleic acid is expressed in a pharmacologically relevant tissue. In certain embodiments, the pharmacologically relevant tissues are the brain and spinal cord. In certain
 20 embodiments, the target nucleic acid is expressed in a pharmacologically relevant cell. In certain embodiments the pharmacologically relevant cell is a neuron or a glial cell. In certain embodiments, the pharmacologically relevant cell is an astrocyte or a microglial cell. In certain embodiments, the pharmacologically relevant cell is a vascular smooth muscle cell, a vascular endothelial cell, or a pericyte.

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V. Certain Methods and Uses

Certain embodiments provided herein relate to methods of inhibiting IFNAR1 expression, which can be useful
 25 for treating a disease associated with neuroinflammation, for example, a disease associated with elevated type I interferon signaling, or with over-expression of a type I interferons in a subject, by administration of an oligomeric agent, oligomeric compound, modified oligonucleotide, or oligomeric duplex, any of which comprising a modified oligonucleotide having a nucleobase sequence complementary to an IFNAR1 nucleic acid.

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30 Examples of diseases treatable with the oligomeric agents, oligomeric compounds, modified oligonucleotides, oligomeric duplexes, and methods provided herein include neurological diseases or conditions associated with neuroinflammation, for example, a disease associated with elevated type I interferon signaling, or with over-expression of type I interferons, selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative
 35 delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, a method comprises administering to a subject an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex, any of which have a

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nucleobase sequence complementary to an IFNAR1 nucleic acid. In certain embodiments, the subject has a neurological disease or condition associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, a method of treating neurological diseases or conditions associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia in a subject comprises administering to the subject a therapeutically effective amount of an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex, any of which having a nucleobase sequence complementary to an IFNAR1 nucleic acid, thereby treating the subject. In certain embodiments, administering the therapeutically effective amount of the oligomeric agent, oligomeric compound, or modified oligonucleotide improves a symptom or hallmark of a disease or condition associated with neuroinflammation. In certain embodiments, the symptom or hallmark is selected from seizures, difficulty feeding, dystonia, spasticity, delayed motor development, delayed language development, delayed social skill development, white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, and microencephaly. In certain embodiments, administering the therapeutically effective amount of the oligomeric agent, oligomeric compound, or modified oligonucleotide reduces type I IFN signaling or lymphocytosis in cerebrospinal fluid in the subject.

In certain embodiments, a method of inhibiting expression of IFNAR1 nucleic acid, such as RNA, in a subject having a disease associated with neuroinflammation, for example, a disease associated with elevated type I interferon signaling, or with over-expression of type I interferons, comprises administering to the subject an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex, any of which having a nucleobase sequence complementary to an IFNAR1 nucleic acid, thereby inhibiting expression of IFNAR1 nucleic acid in the subject. In certain embodiments, administering the oligomeric agent, the oligomeric compound, the modified oligonucleotide, or the oligomeric duplex inhibits expression of IFNAR1 in the brain or the spinal cord. In certain embodiments, the subject has a neurological disease or condition associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, a method of inhibiting expression of IFNAR1 nucleic acid in a cell comprises contacting the cell with an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex, any of which having a nucleobase sequence complementary to an IFNAR1 nucleic acid, thereby inhibiting expression of IFNAR1 nucleic acid in the cell. In certain embodiments, the cell is glial cell, for example, an astrocyte or a microglial cell. In certain embodiments, the cell is in a subject having a neurological disease or condition associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia.

Certain embodiments are drawn to an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex, any of which having a nucleobase sequence complementary to an IFNAR1 nucleic acid, for use in treating a disease associated with neuroinflammation associated with neuroinflammation, for example, a disease associated with elevated type I interferon signaling, or with over-expression of IFN α . In certain embodiments, the disease is a neurological disease or condition associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex is for use in improving a symptom or hallmark of a disease or condition associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, the symptom or hallmark is selected from seizures, difficulty feeding, dystonia, spasticity, delayed motor development, delayed language development, delayed social skill development, white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, and microencephaly. In certain embodiments, an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex is for use in reducing type I IFN signaling or lymphocytosis in the cerebrospinal fluid in a subject.

Certain embodiments are drawn to an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex, any of which comprising a modified oligonucleotide having a nucleobase sequence complementary to an IFNAR1 nucleic acid, for the manufacture or preparation of a medicament for treating a disease associated with neuroinflammation, for example, a disease associated with elevated type I interferon signaling, or with over-expression of IFN α . In certain embodiments, the disease is a neurological disease or condition associated with neuroinflammation selected from Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, an oligomeric agent, oligomeric compound, modified oligonucleotide, or oligomeric duplex is for the manufacture or preparation of a medicament for improving symptoms or hallmarks associated with Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, and ataxia telangiectasia. In certain embodiments, the symptom or hallmark is selected from seizures, difficulty feeding, dystonia, spasticity, delayed motor development, delayed language development, delayed social skill development, white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, and microencephaly. In certain embodiments, an oligomeric agent, an oligomeric compound, a modified oligonucleotide, or an oligomeric duplex is for the manufacture or preparation of a medicament for use in reducing type I IFN signaling or lymphocytosis in the cerebrospinal fluid in a subject.

In any of the methods or uses described herein, the oligomeric agent, oligomeric compound, modified oligonucleotide, or oligomeric duplex can be any described herein.

VI. Certain Pharmaceutical Compositions

5 In certain embodiments, described herein are pharmaceutical compositions comprising one or more oligomeric compounds. In certain embodiments, the one or more oligomeric compounds each consists of a modified oligonucleotide. In certain embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable diluent or carrier. In certain embodiments, a pharmaceutical composition comprises or consists of a sterile saline solution and one or more oligomeric compound. In certain embodiments, the sterile saline is pharmaceutical grade
10 saline. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and sterile water. In certain embodiments, the sterile water is pharmaceutical grade water. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and phosphate-buffered saline (PBS). In certain embodiments, the sterile PBS is pharmaceutical grade PBS. In certain embodiments, a pharmaceutical composition comprises or consists of one or more oligomeric compound and artificial cerebrospinal
15 fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade artificial cerebrospinal fluid.

In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and PBS. In certain embodiments, a pharmaceutical composition consists of a modified oligonucleotide and PBS. In certain embodiments, a pharmaceutical composition consists essentially of a modified oligonucleotide and PBS. In certain embodiments, the PBS is pharmaceutical grade.

20 In certain embodiments, a pharmaceutical composition comprises a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, a pharmaceutical composition consists essentially of a modified oligonucleotide and artificial cerebrospinal fluid. In certain embodiments, the artificial cerebrospinal fluid is pharmaceutical grade.

25 In certain embodiments, pharmaceutical compositions comprise one or more oligomeric compound and one or more excipients. In certain embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, and polyvinylpyrrolidone.

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

In certain embodiments, pharmaceutical compositions comprising an oligomeric compound encompass any pharmaceutically acceptable salts of the oligomeric compound, esters of the oligomeric compound, or salts of such
35 esters. In certain embodiments, pharmaceutical compositions comprising oligomeric compounds comprising one or more oligonucleotide, upon administration to an animal, including a human, are capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of oligomeric compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium

and potassium salts. In certain embodiments, prodrugs comprise one or more conjugate group attached to an oligonucleotide, wherein the conjugate group is cleaved by endogenous nucleases within the body.

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

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

In certain embodiments, pharmaceutical compositions comprise one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present invention to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

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

In certain embodiments, pharmaceutical compositions are prepared for oral administration. In certain embodiments, pharmaceutical compositions are prepared for buccal administration. In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, intrathecal (IT), intracerebroventricular (ICV), etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in

pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Under certain conditions, certain compounds disclosed herein act as acids. Although such compounds may be drawn or described in protonated (free acid) form, or ionized and in association with a cation (salt) form, aqueous solutions of such compounds exist in equilibrium among such forms. For example, a phosphate linkage of an oligonucleotide in aqueous solution exists in equilibrium among free acid, anion, and salt forms. Unless otherwise indicated, compounds described herein are intended to include all such forms. Moreover, certain oligonucleotides have several such linkages, each of which is in equilibrium. Thus, oligonucleotides in solution exist in an ensemble of forms at multiple positions all at equilibrium. The term "oligonucleotide" is intended to include all such forms. Drawn structures necessarily depict a single form. Nevertheless, unless otherwise indicated, such drawings are likewise intended to include corresponding forms. Herein, a structure depicting the free acid of a compound followed by the term "or a salt thereof" expressly includes all such forms that may be fully or partially protonated/de-protonated/in association with a cation. In certain instances, one or more specific cation is identified.

In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with sodium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in aqueous solution with potassium. In certain embodiments, modified oligonucleotides or oligomeric compounds are in PBS. In certain embodiments, modified oligonucleotides or oligomeric compounds are in water. In certain such embodiments, the pH of the solution is adjusted with NaOH and/or HCl to achieve a desired pH.

Herein, certain specific doses are described. A dose may be in the form of a dosage unit. For clarity, a dose (or dosage unit) of a modified oligonucleotide or an oligomeric compound in milligrams indicates the mass of the free acid form of the modified oligonucleotide or oligomeric compound. As described above, in aqueous solution, the free acid is in equilibrium with anionic and salt forms. However, for the purpose of calculating dose, it is assumed that the modified oligonucleotide or oligomeric compound exists as a solvent-free, sodium-acetate free, anhydrous, free acid. For example, where a modified oligonucleotide or an oligomeric compound is in solution comprising sodium (e.g., saline), the modified oligonucleotide or oligomeric compound may be partially or fully de-protonated and in association with Na⁺ ions. However, the mass of the protons are nevertheless counted toward the weight of the dose, and the mass of the Na⁺ ions are not counted toward the weight of the dose. Thus, for example, a dose, or dosage unit, of 10 mg of Compound No. 1492069, equals the number of fully protonated molecules that weighs 10 mg. This would be equivalent to 10.76 mg of solvent-free, sodium acetate-free, anhydrous sodiated Compound No. 1492069. When an oligomeric compound comprises a conjugate group, the mass of the conjugate group is included in calculating the dose of such oligomeric compound. If the conjugate group also has an acid, the conjugate group is likewise assumed to be fully protonated for the purpose of calculating dose.

VII. Certain Hotspot Regions

1. Nucleobases 5085-5133 of SEQ ID NO: 1

In certain embodiments, nucleobases 5085-5133 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 5085-5133 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified

The nucleobase sequences of SEQ ID Nos: 31, 33, 37, 69, 376, 411, 528, 616, 709, 766, 838, and 945 are complementary to an equal length portion within nucleobases 5085-5133 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1273156, 1273157, 1273160, 1273190, 1321435, 1322469, 1322618, 1322678, 1322794, 1322801, 1323239, and 1323343 are complementary to an equal length portion within nucleobases 5085-5133 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 5085-5133 of SEQ ID NO: 1 achieve at least 38% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 5085-5133 of SEQ ID NO: 1 achieve an average of 61% reduction of IFNAR1 RNA in vitro in the standard cell assay.

2. Nucleobases 19997-20061 of SEQ ID NO: 1

SSOOSSSSSSSSSSOOSS, SOOSSSSSSSSSSSOOSS, SOOSOOSSSSSSSSSOSS, SOOSSSSSSSSSSSSSOSS, SOOSSSSSSSSSSSSSOSS, SSOOOSSSSSSSSSSSOOSS, SSSOOSSSSSSSSSSSOOSS, SSSSOSSSSSSSSSSSOOSS, SSOOOSSSSSSSSSSSOOSS, SSSOOSSSSSSSSSSSOSS, and SSSSOSSSSSSSSSSSOOSS, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

5 The nucleobase sequences of SEQ ID Nos: 13, 15, 18, 116, 187, 1604, 1657, 1779, 1809, 1868, 1955, 2079, 2156, 2231, 2304, 2334, 2434, 2531, 2669, 2670, and 2669 are complementary to an equal length portion within nucleobases 19997-20061 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1273127, 1273129, 1273132, 1321102, 1321374, 1321458, 1321651, 1321671, 1321717, 1321779, 1321943, 1322460, 1322611, 1322887, 1322962, 1323010, 1323056, 1323090, 1489524, 1489525, 1489527, 1489531, 1489532, 1489533, 1489534, 1489535, 1489536, 1521445, 1521446, 1521447, 1521448, 1521449, 1521593, 1521594, 1521595, 1521596, 1521597, 1521598, 1521599, 1521600, 1521601, 1521602, 1521603, 1521604, 1521608, 1521609, 1521610, 1521611, 1521612, 1521613, 1521614, 1521615, 1521616, 1521617, and 1521618 are complementary to an equal length portion within nucleobases 19997-20061 of SEQ ID NO: 1.

15 In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 19997-20061 of SEQ ID NO: 1 achieve at least 28% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 19997-20061 of SEQ ID NO: 1 achieve an average of 65% reduction of IFNAR1 RNA in vitro in the standard cell assay.

3. Nucleobases 20076-20133 of SEQ ID NO: 1

1 In certain embodiments, nucleobases 20076-20133 of SEQ ID NO: 1 comprise a hotspot region. In certain
embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 20076-20133
of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain
embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified
oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the
25 gapmers are cEt gapmers. In certain embodiments, the sugar motif for the gapmers are selected from (from 5' to 3'):
eeeeeddddddddeeeee, eeeeeeddddddddeeee, and kkkddddddekkk; wherein each "d" represents a 2'-β-D-
deoxyribsyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt modified sugar
moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by a combination of
phosphodiester and phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the modified
oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside
30 linkage motif for the gapmers is selected from (from 5' to 3'): sssssssssssss, sosossssssssooss, sososssssssssoss,
sossssssssssooss, sossssssssssooss, sossoosssssssoss, sossssssssssooss, sossoosssssssoss,
sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss,
sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss,
sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss,
35 sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, sossoossssssssooss, and
sssoossssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a
phosphodiester internucleoside linkage.

The nucleobase sequences of Compound Nos. 1320982, 1321049, 1321230, 1321330, 1321817, 1322707, 1322793, 1323059, 1323169, 1323314, 1410683, 1413523, 1413529, 1489455, 1489456, 1489457, 1489458, 1489459, 1489477, 1489478, 1489479, 1489480, 1489481, 1489482, 1489483, 1489484, 1489485, 1489486, and 1489487 are complementary to an equal length portion within nucleobases 20076-20133 of SEQ ID NO: 1.

4. Nucleobases 20528-20616 of SEQ ID NO: 1

The nucleobase sequences of SEQ ID Nos: 1952, 1980, 2040, 2069, 2164, 2195, 2272, 2299, 2388, 2641, 2642, 2643, 2644, 2645, 2646, 2683, and 2684 are complementary to an equal length portion within nucleobases 20528-20616 of SEQ ID NO: 1.

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In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 20528-20616 of SEQ ID NO: 1 achieve at least 60% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 20528-20616 of SEQ ID NO: 1 achieve an average of 71% reduction of IFNAR1 RNA in vitro in the standard cell assay.

[illegible]

The nucleobase sequences of Compound Nos. 1322270, 1322424, 1322428, 1322725, 1322905, and 1323347 are complementary to an equal length portion within nucleobases 22294-22329 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 22294-22329 of SEQ ID NO: 1 achieve at least 65% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 22294-22329 of SEQ ID NO: 1 achieve an average of 84% reduction of IFNAR1 RNA in vitro in the standard cell assay.

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7. Nucleobases 22595-22626 of SEQ ID NO: 1

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moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by a combination of phosphodiester and phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkage motif for the gapmers is selected from (from 5' to 3'): ssssssssssssss, sosossossssssooss, sossoossssssooss, sossoossssssooss, sosssossssssooss, soossssssssooss, soossssssssooss, soooossssssooss, soooooossssssooss, soossoossssssooss, soossssssssooss, soossoossssssooss, soooooossssssooss, soossoossssssooss, soossssssssooss, soossoossssssooss, soooooossssssooss, soooooossssssooss, soooooossssssooss, soooooossssssooss, soooooossssssooss, and ssssoossssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID Nos: 22, 1985, 2059, 2157, 2199, and 2574 are complementary to an equal length portion within nucleobases 22595-22626 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1273136, 1322165, 1322183, 1322197, 1323110, 1413580, and 1413741 are complementary to an equal length portion within nucleobases 22595-22626 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 22595-22626 of SEQ ID NO: 1 achieve at least 66% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 22595-22626 of SEQ ID NO: 1 achieve an average of 85% reduction of IFNAR1 RNA in vitro in the standard cell assay.

8. Nucleobases 25530-25565 of SEQ ID NO: 1

[illegible]

The nucleobase sequences of SEQ ID Nos: 67, 71, 1836, 1887, 1980, 2029, 2115, 2242, 2253, and 2394 are complementary to an equal length portion within nucleobases 25530-25565 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1273181, 1273185, 1321177, 1321321, 1321687, 1321737, 1322093, 1322468, 1322976, 1323187, and 1413682 are complementary to an equal length portion within nucleobases 25530-25565 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 25530-25565 of SEQ ID NO: 1 achieve at least 33% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 25530-25565 of SEQ ID NO: 1 achieve an average of 72% reduction of IFNAR1 RNA in vitro in the standard cell assay.

9. Nucleobases 25606-25652 of SEQ ID NO: 1

In certain embodiments, nucleobases 25606-25652 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 25606-25652 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are cEt gapmers. In certain embodiments, the sugar motif for the gapmers are selected from (from 5' to 3'): eeeeeeeeeeeeeee, eeeeeeeeeeeeeee, and kkkkkkkkkkkkk; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt modified sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by a combination of phosphodiester and phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside linkage motif for the gapmers is selected from (from 5' to 3'): sssssssssssss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, sosossssssssooss, and ssssoossssssssooss, wherein each "s" represents a phosphorothioate internucleoside linkage and each "o" represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID Nos: 201, 287, 341, 415, 547, 587, 676, 754, 2659, 2660, 2661, 2662, 2663, and 2687 are complementary to an equal length portion within nucleobases 25606-25652 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1321332, 1321475, 1322045, 1322057, 1322202, 1322364, 1322670, 1323172, 1413742, 1489461, 1489462, 1489463, 1489464, 1489467, 1489513, 1489514, 1489515, 1489516, 1489517, 1489518, 1489519, 1489520, 1492087, 1492088, 1492089, 1492090, 1492091, 1492092, 1492136, 1492137, 1492138, 1492139, 1492140, 1492141, 1492142, 1492143, 1521502, 1521503, 1521504, 1521505, 1521506, 1521507, 1521508, 1521509, 1521510, 1521511, and 1521512 are complementary to an equal length portion within nucleobases 25606-25652 of SEQ ID NO: 1.

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10. Nucleobases 25710-25767 of SEQ ID NO: 1

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In certain embodiments, nucleobases 25768-25827 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 25768-25827

5 eeeeeedddddddeeeeee, eeeeeedddddddeeeeee, and kkkdddddddkkk; wherein each “d” represents a 2’-β-D-deoxyribosyl sugar moiety, each “e” represents a 2’-MOE sugar moiety, and each “k” represents a cEt modified sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by a combination of phosphodiester and phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the modified
oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside
linkage motif for the gapmers is selected from (from 5’ to 3’): ssssssssssssss, sosossossssssooss, sossoossssssooss,
10 sossoossssssooss, sossssssssssooss, sosoooossssssooss, sosssossssssooss, soooooossssssooss,
sooossssssssooss, soooossssssssooss, soooooooooossssooss, soooooossssssssooss, soooooooooossssooss,
soossssssssssooss, soossssssssssooss, soosooooossssssooss, soossoossssssssooss, soossssssssssssooss,
soooooossssssssooss, sssoossssssssooss, ssssoossssssooss, sssoooooossssssooss, sssoooooooooossssooss, and
15 ssssoossssssooss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of Compound Nos. 1273194, 1320923, 1321145, 1321191, 1321349, 1322005, 1322080, 1322271, 1322466, 1322718, 1322758, 1322795, 1323037, 1323165, 1413692, and 1413738 are complementary to an equal length portion within nucleobases 25768-25827 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 25768-25827 of SEQ ID NO: 1 achieve at least 37% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 25768-25827 of SEQ ID NO: 1 achieve an average of 55% reduction of IFNAR1 RNA in vitro in the standard cell assay.

12. Nucleobases 28421-28468 of SEQ ID NO: 1

In certain embodiments, nucleobases 28421-28468 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 28421-28468 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are cEt gapmers. In certain embodiments, the sugar motif for the gapmers are selected from (from 5' to 3'): eeeeeeeeeeeeeeeeee, eeeeeeeeeeeeeeeeee, and kkkkkkkkkkkkkk; wherein each “d” represents a 2'-β-D-deoxyribsyl sugar moiety, each “e” represents a 2'-MOE sugar moiety, and each “k” represents a cEt modified sugar moiety. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by a combination of phosphodiester and phosphorothioate internucleoside linkages. In certain embodiments, the nucleosides of the modified oligonucleotides are linked by phosphorothioate internucleoside linkages. In certain embodiments, the internucleoside

[illegible]

The nucleobase sequences of SEQ ID Nos: 21, 30, 33, 449, 522, 617, and 660 are complementary to an equal length portion within nucleobases 28421-28468 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1273135, 1273144, 1273147, 1321713, 1322321, 1322724, and 1322933 are complementary to an equal length portion within nucleobases 28421-28468 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 28421-28468 of SEQ ID NO: 1 achieve at least 65% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 28421-28468 of SEQ ID NO: 1 achieve an average of 86% reduction of IFNAR1 RNA in vitro in the standard cell assay.

13. Nucleobases 29924-29949 of SEQ ID NO: 1

[illegible]

The nucleobase sequences of SEQ ID Nos: 78, 693, 759, 799, and 875 are complementary to an equal length portion within nucleobases 29924-29949 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 29924-29949 of SEQ ID NO: 1 achieve at least 69% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 29924-29949 of SEQ ID NO: 1 achieve an average of 81% reduction of IFNAR1 RNA in vitro in the standard cell assay.

[illegible]

The nucleobase sequences of SEQ ID Nos: 1500, 1625, 1677, 1733, 1790, 1896, 1981, 2036, 2106, 2217, 2620, 2625, 2636, 2654, 2655, 2656, 2657, 2658, and 2685 are complementary to an equal length portion within nucleobases 29968-30021 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1321074, 1321328, 1321462, 1321599, 1321700, 1321967, 1322094, 1322252, 1322697, 1323127, 1413685, 1413711, 1413736, 1492051, 1492052, 1492053, 1492054, 1492055, 1492056, 1492074, 1492075, 1492076, 1492077, 1492078, 1492080, 1492081, and 1492082 are complementary to an equal length portion within nucleobases 29968-30021 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 29968-30021 of SEQ ID NO: 1 achieve at least 24% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 29968-30021 of SEQ ID NO: 1 achieve an average of 68% reduction of IFNAR1 RNA in vitro in the standard cell assay.

15. Nucleobases 31072-31096 of SEQ ID NO: 1

[illegible]

The nucleobase sequences of SEQ ID Nos: 125, 210, 289, 335, 2509, and 2614 are complementary to an equal length portion within nucleobases 31072-31096 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1321187, 1321789, 1321877, 1322111, 1322246, 1413598, and 1413666 are complementary to an equal length portion within nucleobases 31072-31096 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 31072-31096 of SEQ ID NO: 1 achieve at least 48% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 31072-31096 of SEQ ID NO: 1 achieve an average of 77% reduction of IFNAR1 RNA in vitro in the standard cell assay.

16. Nucleobases 31792-31837 of SEQ ID NO: 1

In certain embodiments, nucleobases 31792-31837 of SEQ ID NO: 1 comprise a hotspot region. In certain embodiments, modified oligonucleotides are complementary to an equal length portion within nucleobases 31792-31837 of SEQ ID NO: 1. In certain embodiments, modified oligonucleotides are 16 nucleobases in length. In certain embodiments, modified oligonucleotides are 20 nucleobases in length. In certain embodiments, modified oligonucleotides are gapmers. In certain embodiments, the gapmers are MOE gapmers. In certain embodiments, the gapmers are cEt gapmers. In certain embodiments, the sugar motif for the gapmers are selected from (from 5' to 3'): eeeeeeeeeeeeeeeeeee, eeeeeeeeeeeeeeeeeee, and kkkkkkkkkkkkkkk; wherein each "d" represents a 2'-β-D-deoxyribosyl sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt modified sugar

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17. Nucleobases 32353-32386 of SEQ ID NO: 1

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sssoooosssssssssoss, and ssssoosssssssssoss, wherein each “s” represents a phosphorothioate internucleoside linkage and each “o” represents a phosphodiester internucleoside linkage.

The nucleobase sequences of SEQ ID Nos: 99, 2151, 2210, 2320, 2353, 2408, and 2483 are complementary to an equal length portion within nucleobases 32353-32386 of SEQ ID NO: 1.

5 The nucleobase sequences of Compound Nos. 1321068, 1321149, 1321172, 1321846, 1322543, 1322832, and 1323273 are complementary to an equal length portion within nucleobases 32353-32386 of SEQ ID NO: 1.

In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 32353-32386 of SEQ ID NO: 1 achieve at least 47% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 32353-32386 of SEQ ID NO: 1 achieve an average of 64% reduction of IFNAR1 RNA in vitro in the standard cell assay.

18. Nucleobases 35016-35042 of SEQ ID NO: 1

The nucleobase sequences of SEQ ID Nos: 1814, 1933, 1962, 2056, 2130, and 2237 are complementary to an equal length portion within nucleobases 35016-35042 of SEQ ID NO: 1.

The nucleobase sequences of Compound Nos. 1321729, 1321882, 1322128, 1322345, 1323017, 1323097, and 1413535 are complementary to an equal length portion within nucleobases 35016-35042 of SEQ ID NO: 1.

35 In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases 35016-35042 of SEQ ID NO: 1 achieve at least 72% reduction of IFNAR1 RNA in vitro in the standard cell assay. In certain embodiments, modified oligonucleotides complementary to an equal length portion within nucleobases

35016-35042 of SEQ ID NO: 1 achieve an average of 83% reduction of IFNAR1 RNA in vitro in the standard cell assay.

Nonlimiting disclosure and incorporation by reference

Each of the literature and patent publications listed herein is incorporated by reference in its entirety.

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

10 Although the sequence listing accompanying this filing identifies each sequence as either "RNA" or "DNA" as required, in reality, those sequences may be modified with any combination of chemical modifications. One of skill in the art will readily appreciate that such designation as "RNA" or "DNA" to describe modified oligonucleotides is, in certain instances, arbitrary. For example, an oligonucleotide comprising a nucleoside comprising a 2'-OH sugar moiety and a thymine base could be described as a DNA having a modified sugar (2'-OH in place of one 2'-H of DNA) or as an RNA having a modified base (thymine (methylated uracil) in place of an uracil of RNA). Accordingly, nucleic acid
15 sequences provided herein, including, but not limited to those in the sequence listing, are intended to encompass nucleic acids containing any combination of natural or modified RNA and/or DNA, including, but not limited to such nucleic acids having modified nucleobases. By way of further example and without limitation, an oligomeric compound having the nucleobase sequence "ATCGATCG" encompasses any oligomeric compounds having such nucleobase sequence, whether modified or unmodified, including, but not limited to, such compounds comprising RNA bases, such as those
20 having sequence "AUCGAUCG" and those having some DNA bases and some RNA bases such as "AUCGATCG" and oligomeric compounds having other modified nucleobases, such as "AT^mCGAUCG," wherein ^mC indicates a cytosine base comprising a methyl group at the 5-position.

Certain compounds described herein (e.g., modified oligonucleotides) have one or more asymmetric center and thus give rise to enantiomers, diastereomers, and other stereoisomeric configurations that may be defined, in terms of
25 absolute stereochemistry, as (*R*) or (*S*), as α or β such as for sugar anomers, or as (*D*) or (*L*), such as for amino acids, etc. Compounds provided herein that are drawn or described as having certain stereoisomeric configurations include only the indicated compounds. Compounds provided herein that are drawn or described with undefined stereochemistry include all such possible isomers, including their stereorandom and optically pure forms, unless specified otherwise. Likewise, tautomeric forms of the compounds herein are also included unless otherwise indicated. Unless otherwise indicated,
30 compounds described herein are intended to include corresponding salt forms.

The compounds described herein include variations in which one or more atoms are replaced with a non-radioactive isotope or radioactive isotope of the indicated element. For example, compounds herein that comprise hydrogen atoms encompass all possible deuterium substitutions for each of the ¹H hydrogen atoms. Isotopic substitutions encompassed by the compounds herein include but are not limited to: ²H or ³H in place of ¹H, ¹³C or ¹⁴C in
35 place of ¹²C, ¹⁵N in place of ¹⁴N, ¹⁷O or ¹⁸O in place of ¹⁶O, and ³³S, ³⁴S, ³⁵S, or ³⁶S in place of ³²S. In certain embodiments, non-radioactive isotopic substitutions may impart new properties on the oligomeric compound that are beneficial for use as a therapeutic or research tool. In certain embodiments, radioactive isotopic substitutions may make the compound suitable for research or diagnostic purposes such as imaging.

EXAMPLES

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

Example 1: Effect of 3-10-3 cEt full phosphorothioate modified oligonucleotides on human IFNAR1 RNA *in vitro*, single dose

Modified oligonucleotides complementary to human IFNAR1 nucleic acid were designed and tested for their single dose effects on IFNAR1 RNA *in vitro*.

The modified oligonucleotides in the table below are 3-10-3 cEt gapmers with full phosphorothioate internucleoside linkages. The gapmers are 16 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3') kkkkkkkkkkkkkk; wherein each "d" represents a 2'- β -D-deoxyribose sugar moiety, and each "k" represents a cEt sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3') ssssssssssssss; wherein each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO 1 (GENBANK Accession No. NC_000021.9, truncated from 33321001 to 33363000), to SEQ ID NO 2 (GENBANK Accession No. NM_000629.2), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured A431 cells were treated with modified oligonucleotide at a concentration of 2000 nM by free uptake at a density of 10,000 cells per well. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and IFNAR1 RNA levels were measured by quantitative real-time RTPCR. IFNAR1 RNA levels were measured by human IFNAR1 primer probe set RTS44352 (forward sequence CTTTCAAGTTCAGTGGCTCCA, designated herein as SEQ ID NO 6; reverse sequence CGTTTTGAGGAAAGACACACTG, designated herein as SEQ ID NO 7; probe sequence AGTTTTGACATTTTCACAGTCAGGTATTTGTTTCC, designated herein as SEQ ID NO 8). IFNAR1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of IFNAR1 RNA is presented in the tables below as percent IFNAR1 RNA relative to the amount in untreated control cells (% UTC). Each table represents results from an individual assay plate. The values marked with a "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region.

Table 1

Reduction of IFNAR1 RNA by 3-10-3 cEt gapmers with full PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1273126	22364	22379	620	635	AAGCTTAAACCATCCA	8	12
1273127	20044	20059	393	408	GCATTTGGTACTAGTA	8	13
1273128	35391	35406	2663	2678	GGGTAAGCTACTTTCC	67	14
1273129	20046	20061	395	410	TTGCATTTGGTACTAG	21	15
1273130	22386	22401	642	657	CCAGATAACTAAGCTA	78	16
1273131	22365	22380	621	636	AAAGCTTAAACCATCC	6	17
1273132	20037	20052	386	401	GTACTAGTAATATTCT	18	18
1273133	35396	35411	2668	2683	TTCTAGGGTAAGCTAC	47	19
1273134	35509	35524	2781	2796	TCCTAAACCATGTAAG	60	20
1273135	28448	28463	1195	1210	GTTTTGGAGCACCGAT	3	21
1273136	22611	22626	755	770	GTAAGTAGTGCTGCTT	3	22
1273137	35495	35510	2767	2782	AGGGTAGATACTGTGA	18	23
1273138	35844	35859	3116	3131	CTGATTAGGTGCTCAG	76	24
1273139	36997	37012	4269	4284	CTTTTTAGGCTATCCA	24	25
1273140	35520	35535	2792	2807	CCTGGCTTTAATCCTA	32	26
1273141	24315	24330	890	905	GCATATGTATAATCCC	3	27
1273142	35675	35690	2947	2962	AAACTTGTACACACTC	7	28
1273143	37341	37356	4613	4628	GTTAATTGGTACCCCC	17	29
1273144	28453	28468	1200	1215	AGACTGTTTTGGAGCA	4	30
1273145	37340	37355	4612	4627	TTAATTGGTACCCCCA	29	31
1273146	35502	35517	2774	2789	CCATGTAAGGGTAGAT	9	32
1273147	28443	28458	1190	1205	GGAGCACCGATATAGA	7	33
1273148	37343	37358	4615	4630	CGGTTAATTGGTACCC	71	34
1273149	37968	37983	5240	5255	GTTAGTAGTCACATGG	25	35
1273150	31765	31780	1298	1313	GTTTTTTCTCGATAA	6	36
1273151	37392	37407	4664	4679	TAGATTATATCTGGTC	45	37
1273152	38058	38073	5330	5345	TGAATAATAAGGTCCC	33	38
1273153	37355	37370	4627	4642	CTAATTTTCAGGCGGT	15	39
1273154	38181	38196	5453	5468	CGGTTATGTCCTTCTA	40	40
1273155	4823	4838	N/A	N/A	TGCATAACTGACTCCC	50	41
1273156	5089	5104	N/A	N/A	ACTGAGCAACATTACA	11	42
	7595	7610					
1273157	5090	5105	N/A	N/A	GACTGAGCAACATTAC	7	43
	7596	7611					
1273158	7867	7882	N/A	N/A	ACAATTAATTACCCCA	7	44
1273159	8271	8286	N/A	N/A	GGGTTTACAGAGTTTA	14	45
1273160	5086	5101	N/A	N/A	GAGCAACATTACAATC	14	46

	7592	7607					
1273161	8795	8810	N/A	N/A	GCAGAATTTATATCGC	28	47
1273162	5147	5162	N/A	N/A	GTCCTAGAATTGCATT	24	48
	7649	7664					
1273163	37634	37649	4906	4921	ACAATTCTAGGGAGCT	52	49
1273164	11882	11897	N/A	N/A	GTAAC TTACATAGTAT	56	50
1273165	11855	11870	N/A	N/A	CCTTTAATGATGTCCC	28	51
1273166	8791	8806	N/A	N/A	AATTTATATCGCTTCA	9	52
1273167	6512	6527	N/A	N/A	CAGGATTTGACTTCCC	33	53
1273168	12311	12326	N/A	N/A	TTCTCATAAGGCTGGT	39	54
1273169	12212	12227	N/A	N/A	GCATAGCATTCTTGGC	59	55
1273170	8793	8808	N/A	N/A	AGAATTTATATCGCTT	32	56
1273171	16543	16558	N/A	N/A	GTTTTAGTTACAAC TC	15	57
1273172	14804	14819	N/A	N/A	GTATTTGACTAAGTCT	13	58
1273173	20255	20270	N/A	N/A	GTTAGATTTTGCATCA	34	59
1273174	12310	12325	N/A	N/A	TCTCATAAGGCTGGTC	40	60
1273175	6674	6689	N/A	N/A	GTTGATTT CAGACCGG	16	61
1273176	19656	19671	N/A	N/A	TTAGTATGTTGGCTC	7	62
1273177	8794	8809	N/A	N/A	CAGAATTTATATCGCT	8	63
1273178	8957	8972	N/A	N/A	GTTACATCAGATTCTG	25	64
1273179	25821	25836	N/A	N/A	ACAATCAAGGCCTTGT	69	65
1273180	9026	9041	N/A	N/A	TGCAATTTACCATCTA	22	66
1273181	25542	25557	N/A	N/A	TCTATTTGGTGACCCT	4	67
1273182	22468	22483	N/A	N/A	AGGATTAATTCGCCTA	101	68
1273183	29536	29551	N/A	N/A	GGGTTTAGACCAGTGT	28	69
1273184	14454	14469	N/A	N/A	AATGTTATTCTATCCC	61	70
1273185	25543	25558	N/A	N/A	ATCTATTTGGTGACCC	9	71
1273186	11915	11930	N/A	N/A	TTGTATATGCCTCTTA	10	72
1273187	19829	19844	N/A	N/A	CTTGAGCTAATGTCCT	11	73
1273188	31243	31258	N/A	N/A	CATATGATCTATTCCT	29	74
1273189	22438	22453	N/A	N/A	TCGATTAAACAGAGGT	36	75
1273190	5087	5102	N/A	N/A	TGAGCAACATTACAAT	16	76
	7593	7608					
1273191	32424	32439	N/A	N/A	TGAAGTAAGAGATCCT	8	77
1273192	29928	29943	N/A	N/A	GTTATGATTACCACCA	5	78
1273193	39011	39026	N/A	N/A	ACTATCGAATTCTCCT	54	79
1273194	25768	25783	N/A	N/A	CTTTAGCCCCTATTCA	43	80
1273195	32813	32828	N/A	N/A	GTTCATTACCTAGCTG	55	81
1273196	19659	19674	N/A	N/A	GGATTTAGTATGTTGG	5	82
1273197	12309	12324	N/A	N/A	CTCATAAGGCTGGTCT	47	83
1273198	12189	12204	N/A	N/A	GTATATCATCCCATCC	40	84
1273199	33631	33646	N/A	N/A	ATGTTTAGGCCCTTCAC	11	85
1273200	38830	38845	N/A	N/A	GTTATTACTAAGTACC	46	86

1273201	34129	34144	N/A	N/A	GCATCATTAGTGAGGT	11	87
1273202	29464	29479	N/A	N/A	CCTAATCCTTCCCCCA	37	88
1273203	39014	39029	N/A	N/A	AGAACTATCGAATTCT	93	89

Example 2: Effect of 5-10-5 MOE mixed backbone modified oligonucleotides on human IFNAR1 RNA *in vitro*, single dose

Modified oligonucleotides complementary to human IFNAR1 nucleic acid were designed and tested for their single dose effects on IFNAR1 RNA *in vitro*. The modified oligonucleotides were tested in a series of experiments that had the same culture conditions.

The modified oligonucleotides in the tables below are 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeeeeeeeeeee; wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The internucleoside linkage motif for the gapmers is (from 5' to 3'): sooooooooooooo; wherein each "o" represents a phosphodiester internucleoside linkage, and each "s" represents a phosphorothioate internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

"Start site" indicates the 5'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. "Stop site" indicates the 3'-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO 1 (described herein above), to SEQ ID NO 2 (described herein above), or to both. 'N/A' indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

Cultured A431 cells were treated with modified oligonucleotide at a concentration of 4000 nM by free uptake at a density of 10,000 cells per well. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and IFNAR1 RNA levels were measured by quantitative real-time RTPCR. IFNAR1 RNA levels were measured by human primer probe set RTS44352 (described herein above). IFNAR1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of IFNAR1 RNA is presented in the tables below as percent IFNAR1 RNA relative to the amount in untreated control cells (% UTC). Each table represents results from an individual assay plate. The values marked with a "†" indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region. N.D. in the tables below refers to instances where the value was Not Defined.

Table 2

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320916	25341	25360	N/A	N/A	ACACTTCCCTTCTCCCTCAT	67	90
1320967	25230	25249	N/A	N/A	ATATCTTTCTTTCCATCTCT	46	91
1320971	35382	35401	2654	2673	AGTACTTTCCAGAAAACCA	38	92

1321005	24845	24864	N/A	N/A	TAGTTCCTTTCCAACCTTCTT	55	93
1321015	21116	21135	N/A	N/A	CACTCAGCTCCTTTACATTC	89	94
1321042	26875	26894	N/A	N/A	TTATTCAGCTTTCTTCCCAT	64	95
1321079	35810	35829	3082	3101	ATTCCTTCTCCTCTTGCACC	46	96
1321133	25182	25201	N/A	N/A	ACTTAATTTTCCTCTTCTCT	61	97
1321157	11964	11983	N/A	N/A	CTGTATCTCTCTCCAGACTT	60	98
1321172	32353	32372	N/A	N/A	GCACTTTTACACCATACAAC	26	99
1321186	27342	27361	N/A	N/A	ATGTTCCCAACTCCATATTC	55	100
1321193	8324	8343	N/A	N/A	TGGTTCTCATCCATTTGTTA	45	101
1321235	13727	13746	N/A	N/A	ACCTGGATCACCCCTGCGCAT	82	102
1321343	29325	29344	N/A	N/A	TAAGAACCAATTTTTGTCCC	94	103
1321392	14023	14042	N/A	N/A	GGTGACATCATCACAATAA	68	104
1321441	17236	17255	N/A	N/A	CAGCCTTTTTTAACTTTTAA	101	105
1321451	22358	22377	614	633	GCTTAAACCATCCAAAGCCC	82	106
1321456	11522	11541	N/A	N/A	TGATCTTCTTTTCATTGGGC	77	107
1321511	28145	28164	990	1009	TTTTGACATTTTCACAGTCA	54†	108
1321524	6264	6283	N/A	N/A	AATTAATTTCTTAATGCACA	85	109
1321555	29471	29490	N/A	N/A	GGCAATTTTTTCCTAATCCT	24	110
1321572	33884	33903	N/A	N/A	GTCTATTTTAAATAATAGCT	101	111
1321575	22541	22560	685	704	CTGGAATAAATATTTTCAAT	44	112
1321624	30254	30273	N/A	N/A	TGGGCTCCAGCATCTACGGT	69	113
1321650	29963	29982	N/A	N/A	CTTTTAAACCTTATAAACAT	96	114
1321669	5915	5934	N/A	N/A	CAAAATTACCTCTCACTCTC	79	115
1321671	19998	20017	N/A	N/A	CCAATTATCCATCCCAGTTC	40	116
1321725	30779	30798	N/A	N/A	ATTTCCAAAACAACCACCAC	88	117
1321773	9579	9598	N/A	N/A	CTAGTTGGCCATCTTGCTAA	81	118
1321782	35653	35672	2925	2944	AGATCTTAAATACAACAAT	79	119
1321801	16450	16469	N/A	N/A	TGCCTGCTTTTTCTTGGACA	59	120
1321803	20506	20525	N/A	N/A	TCAGTGACCATATCACCACA	59	121
1321805	28962	28981	N/A	N/A	GAAAAATGCTCATAATCTTC	39	122
1321834	13490	13509	N/A	N/A	TCTTAATTTCTTATGCTTT	74	123
1321847	37392	37411	4664	4683	TTCTTAGATTATATCTGGTC	43	124
1321877	31076	31095	N/A	N/A	GCAAGCATTATTTAATTCT	6	125
1321968	29730	29749	N/A	N/A	AGGGAAGCAGCCAAATCAAT	46	126
1321970	28595	28614	N/A	N/A	ATTCAGCTTTATTTACCCA	26	127
1321995	27811	27830	N/A	N/A	CTGGTTTATTTTTTTTGGCT	12	128
1322064	8791	8810	N/A	N/A	GCAGAATTTATATCGCTTCA	24	129
1322073	31292	31311	N/A	N/A	AGATACACCACTATAACCAA	33	130
1322129	24633	24652	N/A	N/A	CTAGTTACACTTCTTTTTT	64	131
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	6	132
1322203	9329	9348	N/A	N/A	CAGAGGGAGATTTCTAGCCC	59	133
1322215	36116	36135	3388	3407	ATTCCCAGACTTCCTGCCTA	46	134
1322250	24287	24306	862	881	ACATAGTTCTGATTTTGGAC	11	135

1322302	38831	38850	N/A	N/A	ATTTTGTATTACTAAGTAC	36	136
1322318	22856	22875	N/A	N/A	CCTGAACCTTTTAAGTAGAAT	87	137
1322320	16055	16074	N/A	N/A	ACAATATATTTACAAAGTGT	65	138
1322334	25748	25767	N/A	N/A	CCTTTACATTTTCAATTCT	43	139
1322340	38114	38133	5386	5405	TTAGATTTTCATTCAATCAAT	59	140
1322347	34407	34426	1679	1698	AGTTTCTTCTACTGTAGCAA	28	141
1322350	25527	25546	N/A	N/A	ACCCTATTATTTATTCACCTT	57	142
1322385	18473	18492	N/A	N/A	GACGATTTAGATATTAGAAA	71	143
1322391	25841	25860	N/A	N/A	TCTACTTAAAAAAATCTGA	95	144
1322441	7747	7766	N/A	N/A	GTTTACTATATCTTTAAGTC	58	145
1322494	7237	7256	N/A	N/A	TCTGCAGGCCTCATCTGCAT	112	146
1322560	27068	27087	N/A	N/A	CCCAGAACTCTAATAGCCTC	48	147
1322650	30079	30098	N/A	N/A	TCTATAGTAACAATTATTGA	93	148
1322694	25137	25156	N/A	N/A	TCCAATCAATATAAACTACA	60	149
1322704	26977	26996	N/A	N/A	CCTTCCTCAAATCCAGAGCT	61	150
1322777	31741	31760	N/A	N/A	TCTCTAGAAAATATAATTAA	96	151
1322802	8524	8543	N/A	N/A	TTGCTCTTTCCAGTTAGATC	26	152
1322807	37070	37089	4342	4361	ACCTAACAATTTCACTGGTG	81	153
1322827	20171	20190	N/A	N/A	AGCAACTTTTTCTTACCTTT	88	154
1322829	25660	25679	N/A	N/A	TGCTTTCAATTTTGAACCA	57	155
1322842	34656	34675	1928	1947	AGATGTTTTTTCTTTCCCTA	57	156
1322862	18165	18184	N/A	N/A	ATAATTTCAACCCAACCTCA	81	157
1322896	4814	4833	N/A	N/A	AACTGACTCCCTTTACTCTC	81	158
1322918	5166	5185	N/A	N/A	TTGGACAGTTTTCTTAGTCT	66	159
1322940	38363	38382	5635	5654	GATGAATACCTTTTAAAGGC	91	160
1323019	19587	19606	N/A	N/A	TCTTATCTTCCTTATTGAAA	64	161
1323025	26621	26640	N/A	N/A	ATCAGTTGAATCAAAATGAGA	59	162
1323236	32968	32987	N/A	N/A	AGGACAATCATTACTATCTC	41	163
1323270	12472	12491	N/A	N/A	TCCTCTCTTATTATTTATCA	96	164
1323282	10705	10724	N/A	N/A	AAGTCATGACTCTAAATCTT	77	165
1323293	28506	28525	1253	1272	TTCCCAAAAAATAATTTTCAT	119	166
1323337	33600	33619	N/A	N/A	TTCAATTAATATGCTAGCTT	70	167

Table 3

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320927	38113	38132	5385	5404	TAGATTTTCATTCAATA	64	168
1320929	9319	9338	N/A	N/A	TTTCTAGCCCTTTAAATCCA	77	169
1321082	27341	27360	N/A	N/A	TGTTCCCAACTCCATATTCA	65	170
1321121	7234	7253	N/A	N/A	GCAGGCCTCATCTGCATCAA	86	171

1321143	22533	22552	N/A	N/A	AATATTTTCAATCCTTTCCT	70	172
1321161	8444	8463	N/A	N/A	AATGTGGTACCCATCAGGTC	51	173
1321182	34386	34405	1658	1677	TGTGCTTATATTTTCAATTA	26	174
1321188	26976	26995	N/A	N/A	CTTCCTCAAATCCAGAGCTC	83	175
1321258	13461	13480	N/A	N/A	ATTTTGCCATATACAGGGTT	73	176
1321274	16408	16427	N/A	N/A	GGCCCCAACACATAATCGGA	93	177
1321281	38362	38381	5634	5653	ATGAATACCTTTTAAAGGCA	94	178
1321359	25338	25357	N/A	N/A	CTTCCCTTCTCCCTCATTTT	83	179
1321404	16046	16065	N/A	N/A	TTACAAAGTGTATCTAGGCC	55	180
1321476	21115	21134	N/A	N/A	ACTCAGCTCCTTTACATTCT	67	181
1321530	20169	20188	N/A	N/A	CAACTTTTTCTTACCTTTGC	96	182
1321564	29470	29489	N/A	N/A	GCAATTTTTTCTAATCCTT	63	183
1321594	26617	26636	N/A	N/A	GTTGAATCAAATGAGAGACT	43	184
1321610	25228	25247	N/A	N/A	ATCTTTCTTTCCATCTCTTT	55	185
1321639	29727	29746	N/A	N/A	GAAGCAGCCAAATCAATGGA	58	186
1321651	19997	20016	N/A	N/A	CAATTATCCATCCCAGTTCT	60	187
1321663	11960	11979	N/A	N/A	ATCTCTCTCCAGACTTGGGA	70	188
1321681	25181	25200	N/A	N/A	CTTAATTTTCTCTTCTCTT	65	189
1321689	20505	20524	N/A	N/A	CAGTGACCATATCACCACAT	68	190
1321707	31291	31310	N/A	N/A	GATACACCACTATAACCAAA	22	191
1321728	28594	28613	N/A	N/A	TTCAAGCTTTATTTACCCAA	26	192
1321754	8782	8801	N/A	N/A	ATATCGCTTCATACTTGATT	48	193
1321830	17195	17214	N/A	N/A	GGGAGACAATATCTCATGGC	40	194
1321856	29243	29262	N/A	N/A	GGAAGGAACACTACTGGCAT	24	195
1321870	28141	28160	986	1005	GACATTTTCACAGTCAGGTA	0†	196
1321941	36113	36132	3385	3404	CCCAGACTTCCTGCCTATTA	47	197
1322004	9578	9597	N/A	N/A	TAGTTGGCCATCTTGCTAAC	95	198
1322018	37391	37410	4663	4682	TCTTAGATTATATCTGGTCT	30	199
1322028	34655	34674	1927	1946	GATGTTTTTTCTTTCCCTAA	29	200
1322045	25633	25652	N/A	N/A	TTCTGCTGACTCTTTCCATT	26	201
1322103	30252	30271	N/A	N/A	GGCTCCAGCATCTACGGTCT	83	202
1322108	37036	37055	4308	4327	TGTCCGTATTTTCCCTTCTC	23	203
1322123	30076	30095	N/A	N/A	ATAGTAACAATTATTGATAT	94	204
1322146	27067	27086	N/A	N/A	CCAGAACTCTAATAGCCTCC	40	205
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	9	132
1322177	24630	24649	N/A	N/A	GTTACACTTTCTTTTTTTTC	27	206
1322181	28494	28513	1241	1260	AATTTTCATAAATCAGTGGAT	30	207
1322214	4812	4831	N/A	N/A	CTGACTCCCTTTACTCTCTT	79	208
1322241	35381	35400	2653	2672	GCTACTTTCCAGAAAACCAA	53	209
1322246	31075	31094	N/A	N/A	CAAGCATTATTTAATTTCTC	16	210
1322284	32259	32278	N/A	N/A	ACTAAACCAATCCCACATT	92	211
1322326	32967	32986	N/A	N/A	GGACAATCATTACTATCTCA	20	212
1322348	13725	13744	N/A	N/A	CTGGATCACCTGCGCATCA	74	213

1322413	22843	22862	N/A	N/A	GTAGAATTAATTTTCATTAC	60	214
1322425	29961	29980	N/A	N/A	TTTAAACCTTATAAACATCC	47	215
1322626	33883	33902	N/A	N/A	TCTATTTTAAATAATAGCTA	107	216
1322646	25136	25155	N/A	N/A	CCAATCAATATAAACTACAT	84	217
1322657	25526	25545	N/A	N/A	CCCTATTATTTATTCAC TTC	74	218
1322703	31740	31759	N/A	N/A	CTCTAGAAAATATAATTAAA	100	219
1322740	38829	38848	N/A	N/A	TTTGT TATTACTAAGTACCA	69	220
1322750	6237	6256	N/A	N/A	GGAATGTCAATTTTATATGA	61	221
1322751	12471	12490	N/A	N/A	CCTCTCTTATTATTTATCAT	86	222
1322812	5142	5161	N/A	N/A	TCCTAGAATTGCATTTACTA	53	223
	7644	7663					
1322840	35809	35828	3081	3100	TTCTTCTTCCTCTTGCACCA	37	224
1322885	5910	5929	N/A	N/A	TTACCTCTCACTCTCTATCA	95	225
1322915	18425	18444	N/A	N/A	GCTGAACCAAATACAAGTCT	41	226
1322920	8310	8329	N/A	N/A	TTGTTAGAATTTATAGATTC	90	227
1322973	28961	28980	N/A	N/A	AAAAATGCTCATAATCTTCA	50	228
1323021	25747	25766	N/A	N/A	CTTTACATTTTCAATTTCTG	60	229
1323035	26871	26890	N/A	N/A	TCAGCTTTCTTCCCAT TGCC	36	230
1323049	24269	24288	844	863	ACACTGACTTCTATATTTTC	37	231
1323068	27551	27570	N/A	N/A	CTCGGCCTCCTAAAATACAA	87	232
1323083	14021	14040	N/A	N/A	TGACATCATCACAAATAATT	86	233
1323108	22348	22367	604	623	TCCAAAGCCCACATAACACT	59	234
1323125	30777	30796	N/A	N/A	TTCCAAAACAACCACCACCA	87	235
1323134	7681	7700	N/A	N/A	GTCTTCCCATATTTTG GATA	49	236
1323142	19555	19574	N/A	N/A	GTCAACATAGCAAACCCTGT	67	237
1323148	35652	35671	2924	2943	GATCTTAAAATACAACAATT	100	238
1323195	33588	33607	N/A	N/A	GCTAGCTTCATAGAAGTGCC	95	239
1323222	18161	18180	N/A	N/A	TTTCAACCCAACCTCACTGT	72	240
1323233	10704	10723	N/A	N/A	AGTCATGACTCTAAATCTTG	85	241
1323257	25826	25845	N/A	N/A	TCTGAATTAACAATCAAGGC	23	242
1323277	11521	11540	N/A	N/A	GATCTTCTTTTCATTGGGCC	101	243
1323283	24844	24863	N/A	N/A	AGTTCTTTCCAAC TTTCTTT	31	244

Table 4

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320902	33587	33606	N/A	N/A	CTAGCTTCATAGAAGTGCCA	63	245
1320913	31289	31308	N/A	N/A	TACACCACTATAACCAAATC	89	246
1320934	11520	11539	N/A	N/A	ATCTTCTTTTCATTGGGCCA	90	247
1320943	4808	4827	N/A	N/A	CTCCCTTTACTCTCTTTTTC	87	248

1320964	8443	8462	N/A	N/A	ATGTGGTACCCATCAGGTCT	82	249
1321023	38095	38114	5367	5386	TAATTATTTTCTAAGTACTT	101	250
1321029	26586	26605	N/A	N/A	GCCTGACCTAATCAGATGAA	86	251
1321030	8301	8320	N/A	N/A	TTTATAGATTCTATGCAGCC	57	252
1321058	17137	17156	N/A	N/A	TGACCATTTTTTTCACATACT	31	253
1321067	24841	24860	N/A	N/A	TCTTTCCAACCTTTCTTTCCC	61	254
1321077	34652	34671	1924	1943	GTTTTTCTTTCCCTAAACA	83	255
1321093	25227	25246	N/A	N/A	TCTTTCTTTCCATCTCTTTT	55	256
1321112	28124	28143	969	988	GTATTTGTTTCCATTTATAC	60†	257
1321120	29960	29979	N/A	N/A	TTAAACCTTATAAACATCCT	76	258
1321129	19407	19426	N/A	N/A	TAGGCTATGATCATATCACT	94	259
1321164	5137	5156	N/A	N/A	GAATTGCATTTACTAGTTTA	73	260
1321166	8765	8784	N/A	N/A	ATTTGCATTTTTTCAGAGTA	48	261
1321201	25337	25356	N/A	N/A	TTCCCTTCTCCCTCATTTTT	89	262
1321229	22532	22551	N/A	N/A	ATATTTTCAATCCTTTTCTTA	91	263
1321233	32246	32265	N/A	N/A	CCACATTAAAAAACTCACAA	79	264
1321242	33869	33888	N/A	N/A	TAGCTATGAATATTACAGTA	58	265
1321277	28592	28611	N/A	N/A	CAAGCTTTATTTACCCAAAT	30	266
1321287	9571	9590	N/A	N/A	CCATCTTGCTAACATCACTC	73	267
1321305	26959	26978	N/A	N/A	CTCAGGTAACTATCACCCC	63	268
1321356	30604	30623	N/A	N/A	TGAGCTGACATCACATGAGT	83	269
1321389	16365	16384	N/A	N/A	TCTGTGTTCCCTTCTATATT	63	270
1321486	35802	35821	3074	3093	TCCTCTTGACCAAAGCCAG	68	271
1321507	22832	22851	N/A	N/A	TTTCATTACTATTTGAGACA	59	272
1321520	10702	10721	N/A	N/A	TCATGACTCTAAATCTTGGA	75	273
1321558	26870	26889	N/A	N/A	CAGCTTTCTTCCCATTGCCA	62	274
1321571	25746	25765	N/A	N/A	TTTACATTTTCAATTTCTGC	55	275
1321589	24268	24287	843	862	CACTGACTTCTATATTTTCT	43	276
1321638	30212	30231	N/A	N/A	ACCGTCCCAAGTATTTGCCA	53	277
1321666	37035	37054	4307	4326	GTCCGTATTTTCCCTTCTCC	32	278
1321796	7230	7249	N/A	N/A	GCCTCATCTGCATCAAGGGT	93	279
1321928	25133	25152	N/A	N/A	ATCAATATAAACTACATGCA	97	280
1321945	12433	12452	N/A	N/A	TAAGGTTTAATCTTTTCTC	98	281
1321957	25180	25199	N/A	N/A	TTAATTTTCTCTTCTCTTT	85	282
1322001	14020	14039	N/A	N/A	GACATCATCACAAATAATTG	73	283
1322013	34383	34402	1655	1674	GCTTATATTTTCAATTATGA	34	284
1322022	38792	38811	6064	6083	TAGGGATGATTTATTTATTA	78	285
1322030	7668	7687	N/A	N/A	TTGGATAGTTTTCTTAATCT	62	286
1322057	25630	25649	N/A	N/A	TGCTGACTCTTTCCATTCT	39	287
1322069	22347	22366	603	622	CCAAAGCCCACATAACACTA	49	288
1322111	31074	31093	N/A	N/A	AAGCATTATTTAATTTCTCT	52	289
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	9	132
1322185	29469	29488	N/A	N/A	CAATTTTTTCTAATCCCTC	100	290

1322259	30075	30094	N/A	N/A	TAGTAACAATTATTGATATA	91	291
1322265	15979	15998	N/A	N/A	TGAGCAGACCACCTGAGGTA	95	292
1322274	18160	18179	N/A	N/A	TTCAACCCAACCTCACTGTT	90	293
1322333	5907	5926	N/A	N/A	CCTCTCACTCTCTATCAACC	89	294
1322335	31738	31757	N/A	N/A	CTAGAAAATATAATTAAATC	107	295
1322409	37390	37409	4662	4681	CTTAGATTATATCTGGTCTC	70	296
1322411	27336	27355	N/A	N/A	CCAACTCCATATTCAGGGAC	51	297
1322416	35351	35370	2623	2642	GTTTCAGACTTTCCTAAATAA	31	298
1322583	38361	38380	5633	5652	TGAATACCTTTTAAAGGCAT	107	299
1322628	20167	20186	N/A	N/A	ACTTTTCTTACCTTTGCGA	96	300
1322690	18420	18439	N/A	N/A	ACCAAATACAAGTCTACCTT	69	301
1322692	13430	13449	N/A	N/A	GGTTTTGTTTTTTTTAGCAC	43	302
1322716	20503	20522	N/A	N/A	GTGACCATATCACCACATCA	64	303
1322717	11911	11930	N/A	N/A	TTGTATATGCCTCTTACCTT	60	304
1322734	36112	36131	3384	3403	CCAGACTTCCTGCCTATTAA	46	305
1322748	25825	25844	N/A	N/A	CTGAATTAACAATCAAGGCC	57	306
1322780	25522	25541	N/A	N/A	ATTATTTATTCACTTCTGAA	95	307
1322819	28960	28979	N/A	N/A	AAAATGCTCATAATCTTCAT	67	308
1322867	28493	28512	1240	1259	ATTTTCATAAATCAGTGGATA	70	309
1322955	29726	29745	N/A	N/A	AAGCAGCCAAATCAATGGAA	48	310
1322970	13718	13737	N/A	N/A	ACCCTGCGCATCACTTGACA	99	311
1323070	9257	9276	N/A	N/A	AAGGTGTAACAACAACAACC	100	312
1323092	27048	27067	N/A	N/A	CTGACTGGTTTCCTTATCTC	64	313
1323137	29177	29196	N/A	N/A	GGACAGCCCCCTCCCAAGGA	93	314
1323153	27549	27568	N/A	N/A	CGGCCTCCTAAAATACAAAC	91†	315
1323226	19922	19941	N/A	N/A	ATACTTTCTATTTACTGGTA	55	316
1323246	24623	24642	N/A	N/A	TTTCTTTTTTTTCTTAAGCC	41	317
1323247	6207	6226	N/A	N/A	AAAGCTTTTTTCACATCAAA	64	318
1323333	21113	21132	N/A	N/A	TCAGCTCCTTTACATTCTTA	57	319
1323344	35644	35663	2916	2935	AATACAACAATTATTTCTCT	60	320
1323346	32962	32981	N/A	N/A	ATCATTACTATCTCATGCTA	71	321

Table 5

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320888	27047	27066	N/A	N/A	TGACTGGTTTCCTTATCTCT	63	322
1320901	6206	6225	N/A	N/A	AAGCTTTTTTCACATCAAAC	63	323
1320919	34649	34668	1921	1940	TTTTCTTTCCCTAAACAGGG	96	324
1320981	32096	32115	N/A	N/A	GCATCCAACAACACCGACTT	57	325
1320994	28591	28610	N/A	N/A	AAGCTTTATTTACCCAAATC	51	326

1321002	19311	19330	N/A	N/A	TGATGATTCCCTTCTGACCT	49	327
1321035	9570	9589	N/A	N/A	CATCTTGCTAACATCACTCT	97	328
1321044	22819	22838	N/A	N/A	TGAGACAAAAATCCCAAGTA	59	329
1321056	17136	17155	N/A	N/A	GACCATTTTTTTCACATACTT	12	330
1321081	28120	28139	965	984	TTGTTTCCATTTATACAAAT	72†	331
1321106	11496	11515	N/A	N/A	TAGAGAGTTCTTACTTTCCT	99	332
1321159	35799	35818	3071	3090	TCTTGACCAAAGCCAGCGA	58	333
1321184	26576	26595	N/A	N/A	ATCAGATGAACCCCTTAAAA	62	334
1321187	31072	31091	N/A	N/A	GCATTATTTAATTTCTCTCT	13	335
1321203	21112	21131	N/A	N/A	CAGCTCCTTTACATTCTTAA	65	336
1321216	30602	30621	N/A	N/A	AGCTGACATCACATGAGTGC	95	337
1321250	25336	25355	N/A	N/A	TCCCTTCTCCCTCATTTTTT	91	338
1321271	29176	29195	N/A	N/A	GACAGCCCCCTCCCAAGGAA	77	339
1321304	33867	33886	N/A	N/A	GCTATGAATATTACAGTACA	44	340
1321332	25629	25648	N/A	N/A	GCTGACTCTTTCCATTTCTT	21	341
1321352	11910	11929	N/A	N/A	TGTATATGCCTCTTACCTTT	61	342
1321393	20501	20520	N/A	N/A	GACCATATCACCACATCACA	51	343
1321403	7667	7686	N/A	N/A	TGGATAGTTTTCTTAATCTA	72	344
1321468	29725	29744	N/A	N/A	AGCAGCCAAATCAATGGAAT	66	345
1321484	37034	37053	4306	4325	TCCGTATTTTCCCTTCTCCA	25	346
1321513	38791	38810	6063	6082	AGGGATGATTTATTTATTAT	62	347
1321531	31288	31307	N/A	N/A	ACACCACTATAACCAAATCA	61	348
1321537	30064	30083	N/A	N/A	ATTGATATATTATCCAGTAT	39	349
1321604	18405	18424	N/A	N/A	ACCTTGTTTTTCAAATGGA	85	350
1321642	36109	36128	3381	3400	GACTTCCTGCCTATTAAGGA	63	351
1321668	33571	33590	N/A	N/A	GCCAAACAAAAAAGTGTGAT	47	352
1321712	8433	8452	N/A	N/A	CATCAGGTCTCCCCATCCTC	91	353
1321775	35643	35662	2915	2934	ATACAACAATTATTTCTCTA	73	354
1321778	10700	10719	N/A	N/A	ATGACTCTAAATCTTGAAT	72	355
1321783	38060	38079	5332	5351	CAGTAATGAATAATAAGGTC	67	356
1321843	13663	13682	N/A	N/A	GGCAATAGCCCCACTGGCTG	90	357
1321887	25177	25196	N/A	N/A	ATTTTCTCTTCTCTTTTCT	105	358
1322000	27548	27567	N/A	N/A	GGCCTCCTAAAATACAAACT	93†	359
1322109	25226	25245	N/A	N/A	CTTTCTTTCCATCTCTTTTC	64	360
1322144	29468	29487	N/A	N/A	AATTTTTTCTTAATCCTTCC	87	361
1322151	12432	12451	N/A	N/A	AAGGTTTAATCTTTTCTCT	79	362
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	6	132
1322212	25500	25519	N/A	N/A	TGAGGTATACACAAAAGACT	86	363
1322220	4801	4820	N/A	N/A	TACTCTCTTTTTCTCTTCAA	86	364
1322254	22342	22361	598	617	GCCCACATAACACTATCTTT	51	365
1322256	24840	24859	N/A	N/A	CTTCCAACCTTTCTTTCCCA	45	366
1322374	38328	38347	5600	5619	TCTGTTGCATACAAATTCAC	88	367
1322387	5904	5923	N/A	N/A	CTCACTCTCTATCAACCTTG	39	368

1322395	25744	25763	N/A	N/A	TACATTTTCAATTTCTGCAA	56	369
1322461	22527	22546	N/A	N/A	TTCAATCCTTTCTATAACA	74	370
1322502	27290	27309	N/A	N/A	ATGGTGGGAATATTTATATC	21	371
1322537	15626	15645	N/A	N/A	GTACAATGCCATATCTTCAA	18	372
1322566	18159	18178	N/A	N/A	TCAACCCAACCTCACTGTTT	80	373
1322572	32961	32980	N/A	N/A	TCATTACTATCTCATGCTAT	63	374
1322593	28957	28976	N/A	N/A	ATGCTCATAATCTTCATTTT	51	375
1322616	35350	35369	2622	2641	TTCAGACTTTCCTAAATAAA	57	376
1322639	19900	19919	N/A	N/A	AGAGTTATTTCTTAACTCTT	103	377
1322678	5114	5133	N/A	N/A	AGTATGACTATTTTATGAC	57	378
1322683	31737	31756	N/A	N/A	TAGAAAATATAATTAAATCA	102	379
1322720	13414	13433	N/A	N/A	GCACCTTGAATACACTGGTC	44	380
1322746	20166	20185	N/A	N/A	CTTTTCTTACCTTTGCGAA	96	381
1322749	16363	16382	N/A	N/A	TGTGTTCCCTTCTATATTC	50	382
1322760	25119	25138	N/A	N/A	CATGCAGTTCTCTTTTATCA	31	383
1322763	37375	37394	4647	4666	GTCTCTCTAAGAACTATCAA	97	384
1322772	30205	30224	N/A	N/A	CAAGTATTTGCCAAACAGCA	56	385
1322839	26869	26888	N/A	N/A	AGCTTTCTTCCATTGCCAC	72	386
1322865	6945	6964	N/A	N/A	CCTTAGGACATCCCAGACAT	85	387
1322948	34369	34388	1641	1660	TTATGAAACATTTTTCGATT	87	388
1322949	29959	29978	N/A	N/A	TAAACCTTATAAACATCCTT	56	389
1323003	9255	9274	N/A	N/A	GGTGTAACAACAACAACCGC	87	390
1323053	8762	8781	N/A	N/A	TGCATTTTTTTCAGAGTATCC	21	391
1323103	24605	24624	N/A	N/A	CCAGTAAGAACCCAGATAT	60	392
1323149	8300	8319	N/A	N/A	TTATAGATTCTATGCAGCCA	18	393
1323180	26958	26977	N/A	N/A	TCAGGTAACTATCACCCCA	77	394
1323274	28482	28501	1229	1248	CAGTGGATAATCCTGGATCA	27	395
1323281	14019	14038	N/A	N/A	ACATCATCACAAATAATTGA	85	396
1323310	25824	25843	N/A	N/A	TGAATTAACAATCAAGGCCT	94	397
1323311	24243	24262	N/A	N/A	AGGTAGTTCATTTTCAACTA	29	398

Table 6

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320917	4798	4817	N/A	N/A	TCTCTTTTTCTCTTCAAGAC	92	399
1320948	18368	18387	N/A	N/A	ACCAAAAATATACACTAGCA	57	400
1320955	35349	35368	2621	2640	TCAGACTTTCCTAAATAAAT	61	401
1320983	17135	17154	N/A	N/A	ACCATTTTTTTCACATACTTG	20	402
1320998	38790	38809	6062	6081	GGGATGATTTATTATTATT	53	403
1321043	27289	27308	N/A	N/A	TGGTGGGAATATTTATATCA	35	404

1321059	29175	29194	N/A	N/A	ACAGCCCCCTCCCAAGGAAC	87	405
1321125	24589	24608	N/A	N/A	ATATTAGAATCCATCTATTT	82	406
1321152	8429	8448	N/A	N/A	AGGTCTCCCCATCCTCAATT	75	407
1321156	35789	35808	3061	3080	AAGCCAGCGACCTTTTTCT	60	408
1321241	35642	35661	2914	2933	TACAACAATTATTTCTCTAA	80	409
1321296	32006	32025	N/A	N/A	CTTTCTATATATTTTTTGCA	67	410
1321325	30063	30082	N/A	N/A	TTGATATATTATCCAGTATA	46	411
1321382	38326	38345	5598	5617	TGTTGCATACAAATTCATA	82	412
1321435	5113	5132	N/A	N/A	GTATGACTATTTTTATGACT	43	413
1321442	21108	21127	N/A	N/A	TCCTTTACATTCTTAAAGGA	84	414
1321475	25628	25647	N/A	N/A	CTGACTCTTTCCATTTCCTC	38	415
1321497	30510	30529	N/A	N/A	TATAGATAACAAAACCTGCCT	80	416
1321501	11906	11925	N/A	N/A	TATGCCTCTTACCTTTTCTC	56	417
1321505	34330	34349	1602	1621	GCAGAAGATTCTTCAATGGC	35	418
1321600	18158	18177	N/A	N/A	CAACCCAACCTCACTGTTTA	82	419
1321636	9569	9588	N/A	N/A	ATCTTGCTAACATCACTCTC	95	420
1321694	22526	22545	N/A	N/A	TCAATCCTTTCTCTATAACAC	61	421
1321703	29703	29722	N/A	N/A	GCTTAGATTTCCAATAGAAA	7	422
1321715	32957	32976	N/A	N/A	TACTATCTCATGCTATGTTA	68	423
1321731	10691	10710	N/A	N/A	AATCTTGGAATAGCTAGGGA	73	424
1321745	25174	25193	N/A	N/A	TTCCTCTTCTCTTTTCTCTA	61	425
1321758	30204	30223	N/A	N/A	AAGTATTTGCCAAACAGCAA	63	426
1321791	19863	19882	N/A	N/A	AGTTATTTCTATTTTTGGTT	74	427
1321853	22808	22827	N/A	N/A	TCCCAAGTAACATTTATTTT	81	428
1321922	6204	6223	N/A	N/A	GCTTTTTTCACATCAAACCA	60	429
1321961	27046	27065	N/A	N/A	GACTGGTTTCCTTATCTCTC	63	430
1321980	13645	13664	N/A	N/A	TGGGCTCTCCCCAGAAGCCA	97	431
1322003	29467	29486	N/A	N/A	ATTTTTTCCTAATCCTTCCC	89	432
1322019	7665	7684	N/A	N/A	GATAGTTTTCTTAATCTAGA	80	433
1322084	6941	6960	N/A	N/A	AGGACATCCCAGACATTCTC	89	434
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	6	132
1322260	37033	37052	4305	4324	CCGTATTTTCCCTTCTCCAC	24	435
1322322	9254	9273	N/A	N/A	GTGTAACAACAACAACCGCC	93	436
1322323	36069	36088	3341	3360	TAGCAAGTAATTTAAACTA	94	437
1322381	38042	38061	5314	5333	TCCCTGTTTTCTTGGAGCCT	60	438
1322402	25224	25243	N/A	N/A	TTCTTTCCATCTCTTTTCTC	73	439
1322424	22310	22329	566	585	GATGTGTATCACTATTGCCT	6	440
1322552	26868	26887	N/A	N/A	GCTTTCTTCCCATTGCCACC	89	441
1322558	14018	14037	N/A	N/A	CATCATCACAAATAATTGAC	100	442
1322574	31735	31754	N/A	N/A	GAAAATATAATTAATCACT	87	443
1322634	37370	37389	4642	4661	TCTAAGAACTATCAATATGC	73	444
1322636	29957	29976	N/A	N/A	AACCTTATAAACATCCTTTT	55	445
1322645	24839	24858	N/A	N/A	TTTCCAACCTTTCTTTCCAC	50	446

1322648	33865	33884	N/A	N/A	TATGAATATTACAGTACACA	62	447
1322715	28590	28609	N/A	N/A	AGCTTTATTTACCCAAATCA	51	448
1322724	28452	28471	1199	1218	TCCAGACTGTTTTGGAGCAC	31	449
1322795	25808	25827	N/A	N/A	GCCTTGTTTCATACCTTATCT	38	450
1322796	31071	31090	N/A	N/A	CATTATTTAATTTCTCTCTA	80	451
1322847	15611	15630	N/A	N/A	TTCAAGATATACCCTAGCTC	70	452
1322863	13413	13432	N/A	N/A	CACCTTGAATACACTGGTCT	83	453
1322881	8748	8767	N/A	N/A	GTATCCAGCATAATGGTGCA	78	454
1322893	25499	25518	N/A	N/A	GAGGTATACACAAAAGACTA	66	455
1322913	16361	16380	N/A	N/A	TGTTCCCTTCTATATTCCTC	47	456
1322937	24241	24260	N/A	N/A	GTAGTTCATTTTCAACTAGA	52	457
1323004	25335	25354	N/A	N/A	CCCTTCTCCCTCATTTTTTC	77	458
1323040	5902	5921	N/A	N/A	CACTCTCTATCAACCTTGTA	89	459
1323055	11495	11514	N/A	N/A	AGAGAGTTCTTACTTTCCTT	102	460
1323057	26957	26976	N/A	N/A	CAGGTAACTATCACCCCAA	64	461
1323075	31286	31305	N/A	N/A	ACCACTATAACCAAATCAGA	44	462
1323112	20165	20184	N/A	N/A	TTTTTCTTACCTTTGCGAAA	94	463
1323124	19310	19329	N/A	N/A	GATGATTCCCTTCTGACCTC	48	464
1323126	34648	34667	1920	1939	TTTCTTTCCCTAAACAGGGA	108	465
1323141	25117	25136	N/A	N/A	TGCAGTTCTCTTTTATCAGC	16	466
1323191	27547	27566	N/A	N/A	GCCTCCTAAAATACAAACTG	79†	467
1323219	25743	25762	N/A	N/A	ACATTTTCAATTTCTGCAAC	50	468
1323240	26563	26582	N/A	N/A	CTTAAAAGAGGATCTAGGCC	79	469
1323263	20500	20519	N/A	N/A	ACCATATCACACATCACAC	61	470
1323299	12427	12446	N/A	N/A	TTAATTCTTTTCTCTTTCTC	81	471
1323318	28942	28961	N/A	N/A	ATTTTGTTAATATCTGAGTT	34	472
1323321	8261	8280	N/A	N/A	ACAGAGTTTAAACAAAAGATC	83	473
1323330	28116	28135	961	980	TTCCATTTATACAAATGGTT	101†	474
1323336	33549	33568	N/A	N/A	GTGTCATAAAAAAAGTCTCA	50	475

Table 7

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320920	8733	8752	N/A	N/A	GTGCATTACAGGAACTCCT	54	476
1320933	33807	33826	N/A	N/A	TTGTTAATATTTACGGAGCA	59	477
1320968	31946	31965	N/A	N/A	GAATTACTTTTATTATGTCT	50	478
1320991	32947	32966	N/A	N/A	TGCTATGTTATTACATGAAA	43	479
1321008	31731	31750	N/A	N/A	ATATAATTAAATCACTGATA	99	480
1321105	29466	29485	N/A	N/A	TTTTTTCCTAATCCTTCCCC	92	481
1321124	28588	28607	N/A	N/A	CTTTATTTACCCAAATCATA	72	482

1321127	30059	30078	N/A	N/A	TATATTATCCAGTATAGGTT	65	483
1321180	4797	4816	N/A	N/A	CTCTTTTTCTCTTCAAGACA	94	484
1321221	36068	36087	3340	3359	AGCAAGTAATTTAAACTAA	86	485
1321243	35788	35807	3060	3079	AGCCAGCGACCTTTTTCCTA	32	486
1321247	22525	22544	N/A	N/A	CAATCCTTTCCTATAACACA	86	487
1321293	11904	11923	N/A	N/A	TGCCTCTTACCTTTTCTCCT	73	488
1321313	22806	22825	N/A	N/A	CCAAGTAACATTTATTTTGC	57	489
1321318	12426	12445	N/A	N/A	TAATTCCTTTCTCTTTCTCC	109	490
1321429	27045	27064	N/A	N/A	ACTGGTTTCCTTATCTCTCT	46	491
1321434	8232	8251	N/A	N/A	TTGTAGTATTTACAATATCT	48	492
1321489	18367	18386	N/A	N/A	CCAAAAATATACACTAGCAT	72	493
1321515	38322	38341	5594	5613	GCATACAAATTCATAAGTA	31	494
1321583	34647	34666	1919	1938	TTCTTTCCCTAAACAGGGAA	97	495
1321606	10635	10654	N/A	N/A	GCAGCAGCAAGTACTACAAA	62	496
1321645	5901	5920	N/A	N/A	ACTCTCTATCAACCTTGTA	73	497
1321665	29169	29188	N/A	N/A	CCCTCCCAAGGAAGTATCCA	91	498
1321685	13367	13386	N/A	N/A	GATCATGTTATCAAAGATCC	113	499
1321710	6936	6955	N/A	N/A	ATCCCAGACATTCCTTTCCA	76	500
1321721	6203	6222	N/A	N/A	CTTTTTTCACATCAAACCAA	69	501
1321787	24240	24259	N/A	N/A	TAGTTCATTTTCAACTAGAA	71	502
1321804	27287	27306	N/A	N/A	GTGGGAATATTTATATCATA	36	503
1321851	37924	37943	5196	5215	TCTGCACACCTAAACCCCTT	69	504
1321865	33511	33530	N/A	N/A	TTTGTATGATTTTCATCCATA	35	505
1321873	24838	24857	N/A	N/A	TTCCAACCTTTCTTTCCCACC	27	506
1321893	19841	19860	N/A	N/A	AGAGTTATTTCTTCTACTTG	45	507
1321931	18151	18170	N/A	N/A	ACCTCACTGTTTACATCTGT	76	508
1321934	26852	26871	N/A	N/A	CACCTGGTGTCCAAATGTTC	83	509
1321953	9253	9272	N/A	N/A	TGTAACAACAACAACCGCCC	98	510
1321966	27545	27564	N/A	N/A	CTCCTAAAATACAAACTGGT	95	511
1321975	21107	21126	N/A	N/A	CCTTTACATTCTTAAAGGAA	101	512
1322100	29702	29721	N/A	N/A	CTTAGATTTCCAATAGAAAA	54	513
1322114	34329	34348	1601	1620	CAGAAGATTCTTCAATGGCT	44	514
1322150	20138	20157	487	506	AATGAGTCAACCTCATACCA	92	515
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	6	132
1322178	8428	8447	N/A	N/A	GGTCTCCCCATCCTCAATTT	96	516
1322228	31070	31089	N/A	N/A	ATTATTTAATTTCTCTCTAC	91	517
1322240	25171	25190	N/A	N/A	CTCTTCTCTTTTCTCTATTC	68	518
1322251	37369	37388	4641	4660	CTAAGAACTATCAATATGCT	90	519
1322294	15610	15629	N/A	N/A	TCAAGATATACCCTAGCTCA	81	520
1322315	7663	7682	N/A	N/A	TAGTTTTCTTAATCTAGAGT	68	521
1322321	28441	28460	1188	1207	TTGGAGCACCGATATAGATA	15	522
1322338	30509	30528	N/A	N/A	ATAGATAACAAACTGCCTT	65	523
1322423	31285	31304	N/A	N/A	CCACTATAACCAAATCAGAA	47	524

1322428	22309	22328	565	584	ATGTGTATCACTATTGCCTT	6	525
1322483	26956	26975	N/A	N/A	AGGTTAACTATCACCCCAAC	83	526
1322489	35640	35659	2912	2931	CAACAATTATTTCTCTAATT	96	527
1322618	5096	5115	N/A	N/A	ACTTCTGAAAGACTGAGCAA	55	528
	7602	7621					
1322622	9568	9587	N/A	N/A	TCTTGCTAACATCACTCTCC	77	529
1322688	29954	29973	N/A	N/A	CTTATAAACATCCTTTTGAA	66	530
1322713	25477	25496	N/A	N/A	GAACAGTTTCCTGATTGGTT	17	531
1322718	25807	25826	N/A	N/A	CCTTGTCATACCTTATCTC	37	532
1322735	37032	37051	4304	4323	CGTATTTTCCCTTCTCCACA	39	533
1322739	24588	24607	N/A	N/A	TATTAGAATCCATCTATTTT	98	534
1322831	20499	20518	N/A	N/A	CCATATCACCACATCACACA	74	535
1322907	28103	28122	948	967	AATGGTTTCCAGGATTCCTT	30†	536
1322974	38789	38808	6061	6080	GGATGATTTATTTATTATTT	90	537
1323071	25116	25135	N/A	N/A	GCAGTTCTCTTTTATCAGCT	6	538
1323072	26105	26124	N/A	N/A	GAGGTCAGACTCTCCCTTCC	87	539
1323098	25730	25749	N/A	N/A	CTGCAACCCTTATAATTTGT	21	540
1323119	25223	25242	N/A	N/A	TCTTTCCATCTCTTTTCTCC	69	541
1323147	14017	14036	N/A	N/A	ATCATCACAAATAATTGACC	88	542
1323150	30199	30218	N/A	N/A	TTTGCCAAACAGCAATGTAA	82	543
1323157	13644	13663	N/A	N/A	GGGTCTTCCCCAGAAGCCAT	87	544
1323168	17134	17153	N/A	N/A	CCATTTTTTCACATACTTGT	49	545
1323171	16360	16379	N/A	N/A	GTTCCCTTCTATATTCCTCC	41	546
1323172	25625	25644	N/A	N/A	ACTCTTTCCATTTCTTCAGT	44	547
1323179	35345	35364	2617	2636	ACTTTCCTAAATAAATTTCC	76	548
1323184	11429	11448	N/A	N/A	GTTGATAGGATAATTACCTC	81	549
1323244	28941	28960	N/A	N/A	TTTTGTAAATATCTGAGTTA	65	550
1323248	19285	19304	N/A	N/A	ATGAATAGACTTACCTTCCC	96	551
1323349	25334	25353	N/A	N/A	CCTTCTCCCTCATTTTCT	73	552

Table 8

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320946	27286	27305	N/A	N/A	TGGGAATATTTATATCATAA	12	553
1320957	4788	4807	N/A	N/A	TCTTCAAGACACTCATGGTA	87	554
1320987	32889	32908	N/A	N/A	AGATACCCAAATCAGTCTCT	65	555
1321086	8731	8750	N/A	N/A	GCATTCACAGGAACCTCTTA	51	556
1321099	10628	10647	N/A	N/A	CAAGTACTACAAAATGGTGA	86	557
1321142	9252	9271	N/A	N/A	GTAACAACAACAACCGCCCA	93	558
1321191	25806	25825	N/A	N/A	CTTGTCATACCTTATCTCT	52	559

1321208	34582	34601	1854	1873	CCCAGTGTAACCTCCTGCTGA	82	560
1321238	28098	28117	943	962	TTTCCAGGATTCTTTTAA	33†	561
1321257	28582	28601	N/A	N/A	TTACCCAAATCATAATTATA	95	562
1321276	20498	20517	N/A	N/A	CATATCACCACATCACACAT	77	563
1321316	16357	16376	N/A	N/A	CCCTTCTATATTCTCTCCTC	60	564
1321412	22524	22543	N/A	N/A	AATCCTTTCCTATAACACAA	69	565
1321469	37368	37387	4640	4659	TAAGAACTATCAATATGCTA	91	566
1321506	31730	31749	N/A	N/A	TATAATTAAATCACTGATAA	98	567
1321533	35639	35658	2911	2930	AACAATTATTTCTCTAATTA	100	568
1321579	25222	25241	N/A	N/A	CTTTCATCTCTTTTCTCCC	55	569
1321595	8425	8444	N/A	N/A	CTCCCCATCCTCAATTTTCT	96	570
1321625	25115	25134	N/A	N/A	CAGTTCTCTTTTATCAGCTT	1	571
1321676	22805	22824	N/A	N/A	CAAGTAACATTTATTTTGCT	86	572
1321719	5878	5897	N/A	N/A	TTGCCATTCCCCCATGCATC	95	573
1321738	31941	31960	N/A	N/A	ACTTTTATTATGTCTAGCTA	67	574
1321866	13339	13358	N/A	N/A	TGACAAGTCACTTCTCTGTC	99	575
1321892	29673	29692	N/A	N/A	GTAAAGAATTTACCAGCCT	44	576
1321948	25430	25449	N/A	N/A	ACATATGCACATAAATGCAT	98	577
1321958	19283	19302	N/A	N/A	GAATAGACTTACCTTCCCTA	81	578
1321989	14848	14867	N/A	N/A	GCTGTCTACCACCCTCATCC	77	579
1321993	12387	12406	N/A	N/A	AGAGAGTTTTATACTTTTCC	62	580
1322116	25729	25748	N/A	N/A	TGCAACCCTTATAATTTGTA	46	581
1322134	33508	33527	N/A	N/A	GTATGATTTTCATCCATAGAA	19	582
1322163	37031	37050	4303	4322	GTATTTTCCCTTCTCCACAT	44	583
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	6	132
1322222	11903	11922	N/A	N/A	GCCTCTTACCTTTTCTCCTC	69	584
1322229	27543	27562	N/A	N/A	CCTAAAATACAAACTGGTTT	93	585
1322336	19838	19857	N/A	N/A	GTTATTTCTTCTACTTGAGC	45	586
1322364	25623	25642	N/A	N/A	TCTTCCATTTCTTCAGTGC	18	587
1322426	35344	35363	2616	2635	CTTTCCTAAATAAATTTCTC	91	588
1322447	37923	37942	5195	5214	CTGCACACCTAAACCCCTTA	55	589
1322473	24587	24606	N/A	N/A	ATTAGAATCCATCTATTTTA	75	590
1322476	6195	6214	N/A	N/A	ACATCAAACCAACATGAGT	82	591
1322481	38788	38807	6060	6079	GATGATTTATTTATTATTTG	97	592
1322485	26954	26973	N/A	N/A	GTAACTATCACCCCAACAC	97	593
1322505	8231	8250	N/A	N/A	TGTAGTATTTACAATATCTT	48	594
1322507	6935	6954	N/A	N/A	TCCCAGACATTCTTTCCAT	75	595
1322510	13608	13627	N/A	N/A	TGCACTGTCCCCTCTGTCTA	93	596
1322524	29166	29185	N/A	N/A	TCCCAAGGAACATCCAGCC	94	597
1322547	20137	20156	486	505	ATGAGTCAACCTCATACCAT	88	598
1322561	24237	24256	N/A	N/A	TTCATTTTCAACTAGAAGCC	87	599
1322571	34327	34346	1599	1618	GAAGATTCTTCAATGGCTGT	57	600
1322585	30192	30211	N/A	N/A	AACAGCAATGTAACCAATCA	71	601

1322673	17109	17128	N/A	N/A	ACTGTATGTTTTCTTTTGAA	34	602
1322675	14016	14035	N/A	N/A	TCATCACAATAATTGACCA	92	603
1322685	11426	11445	N/A	N/A	GATAGGATAATTACCTCTTC	78	604
1322708	38321	38340	5593	5612	CATACAAATTCACCTAAGTAC	89	605
1322719	18149	18168	N/A	N/A	CTCACTGTTTACATCTGTCT	69	606
1322725	22308	22327	564	583	TGTGTATCACTATTGCCTTA	5	607
1322770	31067	31086	N/A	N/A	ATTTAATTTCTCTCTACCTG	79	608
1322771	28930	28949	N/A	N/A	TCTGAGTTAATCACATTTTT	32	609
1322781	31284	31303	N/A	N/A	CACTATAACCAAATCAGAAA	85	610
1322785	25332	25351	N/A	N/A	TTCTCCCTCATTTTTTCTGT	78	611
1322789	35784	35803	3056	3075	AGCGACCTTTTTCTAGGGA	23	612
1322791	30042	30061	N/A	N/A	GTTAAGATGGCAACTACAAT	46	613
1322794	5089	5108	N/A	N/A	AAAGACTGAGCAACATTACA	62	614
	7595	7614					
1322860	27044	27063	N/A	N/A	CTGGTTTCCTTATCTCTCTT	48	615
1322886	26835	26854	N/A	N/A	TTCTGCTACTCTAGAAGGAC	81	616
1322933	28436	28455	1183	1202	GCACCGATATAGATATGGAA	35	617
1323060	29951	29970	N/A	N/A	ATAAACATCCTTTTGAAAAA	102	618
1323079	33793	33812	N/A	N/A	GGAGCATTTTTAGAGTGGTA	27	619
1323132	29465	29484	N/A	N/A	TTTTTCCTAATCCTTCCCCC	90	620
1323146	25170	25189	N/A	N/A	TCTTCTCTTTTCTCTATTCA	66	621
1323151	21106	21125	N/A	N/A	CTTTACATTCTTAAAGGAAT	100	622
1323158	18352	18371	N/A	N/A	AGCATATGAAATACTTCATT	52	623
1323218	9567	9586	N/A	N/A	CTTGCTAACATCACTCTCCC	87	624
1323230	36065	36084	3337	3356	AAGTAATTTAAACTAAGTT	107	625
1323245	30508	30527	N/A	N/A	TAGATAACAAAACCTGCCTTA	80	626
1323266	26102	26121	N/A	N/A	GTCAGACTCTCCCTTCCTGA	62	627
1323268	24835	24854	N/A	N/A	CAACTTTCTTTCCACCGAA	54	628
1323302	7662	7681	N/A	N/A	AGTTTTCTTAATCTAGAGTC	62	629

Table 9

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320911	26096	26115	N/A	N/A	CTCTCCCTTCCTGATGGCCT	85	630
1320959	19820	19839	N/A	N/A	GCTAATGTCCTATTAACATT	48	631
1320963	27276	27295	N/A	N/A	TATATCATAAAAATCAGCAA	67	632
1320988	33507	33526	N/A	N/A	TATGATTTTCATCCATAGAAT	56	633
1321010	6926	6945	N/A	N/A	TTCCTTTCCATTGATTTCAA	68	634
1321047	30189	30208	N/A	N/A	AGCAATGTAACCAATCACAT	52	635
1321048	19239	19258	N/A	N/A	TTTCAAGGTTTCTCTGCCC	61	636

1321051	18139	18158	N/A	N/A	ACATCTGTCTTTCCTACTTC	79	637
1321071	25096	25115	N/A	N/A	TTTTAAAAATTTTAATGCTT	89	638
1321075	6171	6190	N/A	N/A	TGCAAGTTTTTTCATAAACAA	57	639
1321090	29574	29593	N/A	N/A	CTGACGGTATATATTATCTT	12	640
1321113	26953	26972	N/A	N/A	TTAACTATCACCCCAACACA	84	641
1321122	30039	30058	N/A	N/A	AAGATGGCAACTACAATTTA	52	642
1321145	25805	25824	N/A	N/A	TTGTTCATACCTTATCTCTT	41	643
1321169	35631	35650	2903	2922	TTTCTCTAATTAGATAGTTA	70	644
1321197	9566	9585	N/A	N/A	TTGCTAACATCACTCTCCCA	77	645
1321211	21085	21104	N/A	N/A	ATCGAGAATCCCAAACAGCC	67	646
1321236	10421	10440	N/A	N/A	ATAGGATACTACATCAGCTC	59	647
1321260	13338	13357	N/A	N/A	GACAAGTCACTTCTCTGTCT	94	648
1321268	31282	31301	N/A	N/A	CTATAACCAAATCAGAAAGT	76	649
1321275	8724	8743	N/A	N/A	CAGGAACTCCTTAAATATCA	79	650
1321306	9205	9224	N/A	N/A	AGCAATGACCAATCAAGAGC	57	651
1321317	18351	18370	N/A	N/A	GCATATGAAATACTTCATTC	27	652
1321323	16356	16375	N/A	N/A	CCTTCTATATTCTCCTTCT	60	653
1321401	8227	8246	N/A	N/A	GTATTTACAATATCTTGTGC	35	654
1321461	20497	20516	N/A	N/A	ATATCACCACATCACACATC	84	655
1321586	31886	31905	1419	1438	GTTTTGTTTTCTCACATACA	43	656
1321614	38319	38338	5591	5610	TACAAATTCACATAAGTACAA	97	657
1321628	22804	22823	N/A	N/A	AAGTAACATTTATTTTGCTT	63	658
1321648	24236	24255	N/A	N/A	TCATTTTCAACTAGAAGCCA	75	659
1321713	28421	28440	1168	1187	TGGAATGAATCACTAAGGGA	2	660
1321718	37029	37048	4301	4320	ATTTTCCCTTCTCCACATCC	70	661
1321744	5850	5869	N/A	N/A	GTATGAAGAATTTTCAGCAA	62	662
1321752	11901	11920	N/A	N/A	CTCTTACCTTTTCTCCTCTT	67	663
1321810	13974	13993	N/A	N/A	CAAGCAGTGCCTCTGAGCCC	99	664
1321842	25429	25448	N/A	N/A	CATATGCACATAAATGCATT	88	665
1321903	25318	25337	N/A	N/A	TTCTGTTTCTTTCCAGTTTC	50	666
1321924	32875	32894	N/A	N/A	GTCTCTATTATTTTCTGGAT	31	667
1321949	31066	31085	N/A	N/A	TTTAATTTCTCTCTACCTGA	71	668
1321976	26825	26844	N/A	N/A	CTAGAAGGACATCCTCCCA	90	669
1321999	25169	25188	N/A	N/A	CTTCTCTTTTCTCTATTCAT	63	670
1322099	28581	28600	N/A	N/A	TACCCAAATCATAATTATAA	91	671
1322105	24832	24851	N/A	N/A	CTTTCTTTCCACCGAAGTA	60	672
1322118	25220	25239	N/A	N/A	TTCCATCTCTTTTCTCCCCA	44	673
1322125	29464	29483	N/A	N/A	TTTTCTTAATCCTTCCCCCA	82	674
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	23	132
1322186	14845	14864	N/A	N/A	GTCTACCACCCTCATCCCCA	88	675
1322202	25621	25640	N/A	N/A	TTCCATTTCTTCAGTGCTT	9	676
1322270	22300	22319	556	575	ACTATTGCCTTATCTTCAGC	35	677
1322309	7661	7680	N/A	N/A	GTTTTCTTAATCTAGAGTCC	53	678

1322317	37890	37909	5162	5181	GCTGCTGCAAATATCACGGC	88	679
1322392	17084	17103	N/A	N/A	TCTATTCCTATCTTTTGCCT	82	680
1322421	28097	28116	942	961	TTCCAGGATTCTTTTAAA	41†	681
1322449	35783	35802	3055	3074	GCGACCTTTTTCCTAGGGAA	30	682
1322477	13591	13610	N/A	N/A	CTAGTGCCCTTTCATTTAC	86	683
1322564	8421	8440	N/A	N/A	CCATCCTCAATTTTCTGTTT	72	684
1322569	37367	37386	4639	4658	AAGAACTATCAATATGCTAA	77	685
1322695	29165	29184	N/A	N/A	CCCAAGGAACTATCCAGCCC	98	686
1322723	34309	34328	N/A	N/A	GTTTCAGAGAAATACTAATTT	74	687
1322736	35343	35362	2615	2634	TTTCCTAAATAAATTTCTTA	96	688
1322765	34581	34600	1853	1872	CCAGTGTAACCTCTGCTGAA	86	689
1322931	20135	20154	484	503	GAGTCAACCTCATACCATGA	46	690
1322997	25728	25747	N/A	N/A	GCAACCCTTATAATTTGTAT	44	691
1323015	11424	11443	N/A	N/A	TAGGATAATTACCTCTTCCA	89	692
1323073	29930	29949	N/A	N/A	TTAGTTGTTATGATTACCAC	31	693
1323080	36023	36042	3295	3314	ATGTAATTTCTTAAATTGGG	30	694
1323105	31720	31739	N/A	N/A	TCACTGATAAAATTTAGTCA	71	695
1323155	27529	27548	N/A	N/A	TGGTTTTTAAAGAAAAACCA	69	696
1323159	30483	30502	N/A	N/A	CAGTGGCTCACAAAACGATT	52	697
1323202	4786	4805	N/A	N/A	TTCAAGACACTCATGGTATC	86	698
1323235	12386	12405	N/A	N/A	GAGAGTTTTATACTTTTCCA	83	699
1323241	28929	28948	N/A	N/A	CTGAGTTAATCACATTTTTT	29	700
1323254	38785	38804	6057	6076	GATTTATTTATTATTTGTGT	58	701
1323291	27043	27062	N/A	N/A	TGGTTTCCTTATCTCTCTTT	56	702
1323307	33769	33788	N/A	N/A	TCTTATGGTTTAACTCCTTT	48	703
1323320	22522	22541	N/A	N/A	TCCTTTCCTATAACACAAAT	98	704
1323343	5087	5106	N/A	N/A	AGACTGAGCAACATTACAAT	62	705
	7593	7612					
1323345	24586	24605	N/A	N/A	TTAGAATCCATCTATTTTAC	75	706

Table 10

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320892	11423	11442	N/A	N/A	AGGATAATTACCTCTTCCAA	84	707
1321013	27038	27057	N/A	N/A	TCCTTATCTCTCTTTAGTGT	38	708
1321049	20114	20133	463	482	GAAGTGTTTTCTTTTCTGC	21	709
1321094	26824	26843	N/A	N/A	TAGAAGGACATCCTCCCCAC	92	710
1321115	31719	31738	N/A	N/A	CACTGATAAAATTTAGTCAC	84	711
1321282	27512	27531	N/A	N/A	CCATTACTAAAAATTAAGTT	101	712
1321288	19815	19834	N/A	N/A	TGTCCTATTAACATTTTAGC	56	713

1321299	30460	30479	N/A	N/A	TAGTTTCTCACTCACAAGTC	60	714
1321326	13590	13609	N/A	N/A	TAGTGCCCTTTTCATTTCACC	N.D.	715
1321331	11900	11919	N/A	N/A	TCTTACCTTTTCTCCTCTTT	80	716
1321452	12385	12404	N/A	N/A	AGAGTTTTATACTTTTCCAT	N.D.	717
1321480	38783	38802	6055	6074	TTTATTTATTATTTGTGTCC	60	718
1321547	30037	30056	N/A	N/A	GATGGCAACTACAATTTATT	25	719
1321570	9564	9583	N/A	N/A	GCTAACATCACTCTCCCAGA	54	720
1321574	14834	14853	N/A	N/A	TCATCCCCAATTTTTTGCTT	87	721
1321596	29462	29481	N/A	N/A	TTCTAATCCTTCCCCCATC	76	722
1321618	29569	29588	N/A	N/A	GGTATATATTATCTTTGTCA	1	723
1321635	33498	33517	N/A	N/A	ATCCATAGAATATACTTTCT	51	724
1321647	25299	25318	N/A	N/A	CTTCTGACTTTTCCTTTCT	51	725
1321670	31280	31299	N/A	N/A	ATAACCAAATCAGAAAGTTA	87	726
1321767	37889	37908	5161	5180	CTGCTGCAAATATCACGGCC	109	727
1321771	8722	8741	N/A	N/A	GGAACCTCCTTAAATATCATA	71	728
1321841	8226	8245	N/A	N/A	TATTTACAATATCTTGTGCA	47	729
1321859	25219	25238	N/A	N/A	TCCATCTCTTTTCTCCCCAT	37	730
1321860	28928	28947	N/A	N/A	TGAGTTAATCACATTTTTTT	N.D.	731
1321904	22803	22822	N/A	N/A	AGTAACATTTATTTTGCTTA	40	732
1321952	6170	6189	N/A	N/A	GCAAGTTTTTCATAAACAAA	43	733
1322048	25424	25443	N/A	N/A	GCACATAAATGCATTTGCAT	53	734
1322086	20496	20515	N/A	N/A	TATCACCACATCACACATCA	75	735
1322104	7640	7659	N/A	N/A	AGAATTGCATTTACTAGGCT	79	736
1322106	36022	36041	3294	3313	TGTAATTTCTTAAATTGGGT	24	737
1322139	28092	28111	937	956	GGATTCCTTTTTAAAAAGGC	78†	738
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	7	132
1322227	19238	19257	N/A	N/A	TTCAAGGTTTCCTCTGCCCT	67	739
1322261	13337	13356	N/A	N/A	ACAAGTCACTTCTCTGTCTT	93	740
1322291	16354	16373	N/A	N/A	TTCTATATTCCTCCTTCTGC	82	741
1322310	6921	6940	N/A	N/A	TTCCATTGATTTCAACCAAT	51	742
1322328	18345	18364	N/A	N/A	GAAATACTTCATTCTTGGCC	50	743
1322407	9204	9223	N/A	N/A	GCAATGACCAATCAAGAGCA	71	744
1322488	25168	25187	N/A	N/A	TTCTCTTTTCTCTATTTCATC	55	745
1322519	8409	8428	N/A	N/A	TTCTGTTTCATACTTGGAGT	72	746
1322521	29164	29183	N/A	N/A	CCAAGGAAGTATCCAGCCCA	85	747
1322578	35337	35356	2609	2628	AAATAAATTTCTTAAGGGCC	81	748
1322599	10420	10439	N/A	N/A	TAGGATACTACATCAGCTCA	65	749
1322608	16983	17002	N/A	N/A	ATAGTTTCTTTATACAAGTA	65	750
1322652	38318	38337	5590	5609	ACAAATTCACCTAAGTACAAA	88	751
1322664	35769	35788	3041	3060	AGGGAAGCATTCTTCTTCTA	83	752
1322666	34298	34317	N/A	N/A	TACTAATTTAAAAAAGGGA	102	753
1322670	25606	25625	N/A	N/A	TGCTTTGTACAATATGGTAA	27	754
1322679	32874	32893	N/A	N/A	TCTCTATTATTTTCTGGATA	54	755

1322693	34568	34587	1840	1859	TGCTGAAAAACCTTATACTT	91	756
1322711	24201	24220	N/A	N/A	AAAGCACACATTTTACTCA	89	757
1322732	13954	13973	N/A	N/A	TGGGTAGTAACAACAGCAGC	72	758
1322800	29927	29946	N/A	N/A	GTTGTTATGATTACCACCAC	19	759
1322801	5086	5105	N/A	N/A	GACTGAGCAACATTACAATC	55	760
	7592	7611					
1322817	35621	35640	2893	2912	TAGATAGTTACCTATTTTCT	67	761
1322825	4773	4792	N/A	N/A	TGGTATCTTAAAATACAGAT	77	762
1322897	37020	37039	4292	4311	TCTCCACATCCTACAAGGGC	70	763
1322904	24831	24850	N/A	N/A	TTTCTTTCCCACCGAAGTAT	47	764
1322938	31064	31083	N/A	N/A	TAATTTCTCTCTACCTGATT	141	765
1322967	28358	28377	N/A	N/A	TTGTAAAGAAATAATGTTCA	88	766
1322969	18138	18157	N/A	N/A	CATCTGTCTTTCCTACTTCA	69	767
1322975	26952	26971	N/A	N/A	TAATATCACCCCAACACAA	86	768
1322977	30188	30207	N/A	N/A	GCAATGTAAACCAATCACATA	52	769
1322990	21083	21102	N/A	N/A	CGAGAATCCCAAACAGCCAT	73	770
1323018	25095	25114	N/A	N/A	TTTAAAAATTTTAATGCTTA	100	771
1323037	25802	25821	N/A	N/A	TTCATACCTTATCTCTTTCC	49	772
1323043	25715	25734	N/A	N/A	TTTGTATACCACTCTTTAGT	49	773
1323111	22521	22540	N/A	N/A	CCTTTCCTATAACACAAATA	83	774
1323144	27275	27294	N/A	N/A	ATATCATAAAAATCAGCAAA	89	775
1323186	24585	24604	N/A	N/A	TAGAATCCATCTATTTTACA	70	776
1323269	28580	28599	N/A	N/A	ACCCAAATCATAATTATAAC	79	777
1323278	37356	37375	4628	4647	ATATGCTAATTTTCAGGCGG	40	778
1323279	26087	26106	N/A	N/A	CCTGATGGCCTCTAAGAAGT	95	779
1323300	5761	5780	N/A	N/A	GGACCTCTCCCAACTTTCTT	94	780
1323305	33765	33784	N/A	N/A	ATGGTTTAACTCCTTTGCTC	51	781
1323319	31883	31902	1416	1435	TTGTTTTCTCACATACAGCG	54	782
1323347	22299	22318	555	574	CTATTGCCTTATCTTCAGCT	26	783

Table 11

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320906	25591	25610	N/A	N/A	GGTAAGTACCCAAAAGAAGC	48	784
1320951	11899	11918	N/A	N/A	CTTACCTTTTCTCCTCTTTC	40	785
1320953	10274	10293	N/A	N/A	CCGTATACCACTTCAGCTTA	57	786
1321011	28090	28109	N/A	N/A	ATTCCTTTTAAAAAGGCGC	78†	787
1321032	8211	8230	N/A	N/A	GTGCAGAATATTATAATTCT	26	788
1321040	24580	24599	N/A	N/A	TCCATCTATTTTACAAGTGA	18	789
1321062	25714	25733	N/A	N/A	TTGTATACCACTCTTTAGTC	47	790

1321104	31865	31884	1398	1417	CGTCACTAAAAACACTGCTT	37	791
1321118	16353	16372	N/A	N/A	TCTATATTCCTCCTTCTGCC	N.D.	792
1321171	34567	34586	1839	1858	GCTGAAAAACCTTATACTTG	30	793
1321205	25165	25184	N/A	N/A	TCTTTTCTCTATTCATCTCC	75	794
1321312	22496	22515	N/A	N/A	TGGTTCTTTAAAAAAGTATA	71	795
1321357	25413	25432	N/A	N/A	CATTTCATTCTACCAGTCA	47	796
1321358	12381	12400	N/A	N/A	TTTATACTTTTCCATGTTT	80	797
1321397	27037	27056	N/A	N/A	CCTTATCTCTCTTTAGTGTC	49	798
1321440	29926	29945	N/A	N/A	TTGTTATGATTACCACCACT	28	799
1321490	33764	33783	N/A	N/A	TGGTTTAACTCCTTTGCTCC	59	800
1321503	9164	9183	N/A	N/A	GGTGTGTTTCTTTTGGCCA	63	801
1321521	33497	33516	N/A	N/A	TCCATAGAATATACTTTCTA	67	802
1321542	8721	8740	N/A	N/A	GAAGTCCTTAAATATCATAA	87	803
1321605	25218	25237	N/A	N/A	CCATCTCTTTTCTCCCCATA	46	804
1321643	18093	18112	N/A	N/A	AACTGTTTTACATCTAATC	75	805
1321644	13220	13239	N/A	N/A	AGTCCCCAACTACTATCATA	88	806
1321646	27274	27293	N/A	N/A	TATCATAAAAATCAGCAAAC	83	807
1321723	28329	28348	N/A	N/A	ACAATTTTAAAAACTTGCAC	139	808
1321769	16980	16999	N/A	N/A	GTTTCTTTTATACAAGTAACA	70	809
1321797	30458	30477	N/A	N/A	GTTTCTCACTCACAAGTCTA	42	810
1321817	20112	20131	461	480	AGTGTTCCTTTTCTGCTC	21	811
1321827	4772	4791	N/A	N/A	GGTATCTTAAAATACAGATT	71	812
1321855	31710	31729	N/A	N/A	AATTTAGTCACCTCAAGAAA	79	813
1321936	24200	24219	N/A	N/A	AAGCACACATTTTACTCAA	78	814
1321937	8398	8417	N/A	N/A	ACTTGGAGTCTCTAAAACCTT	65	815
1321981	32825	32844	N/A	N/A	ATCAAACACATTTTCTGTTC	63	816
1321990	11422	11441	N/A	N/A	GGATAATTACCTCTTCCAAA	82	817
1322164	30035	30054	N/A	N/A	TGGCAACTACAATTTATTGA	10	818
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	16	312
1322206	6145	6164	N/A	N/A	TCAAAGAAATTACTATGGGA	75	819
1322258	27511	27530	N/A	N/A	CATTACTAAAAATTAAGTTA	100	820
1322276	25026	25045	N/A	N/A	GCAGGTGTGATCATAACA	33	821
1322280	22773	22792	N/A	N/A	ACAATGTTTTTAAACATATAT	99	822
1322281	26071	26090	N/A	N/A	AAGTGAGCCACCATGAGCTC	100	823
1322296	37353	37372	4625	4644	TGCTAATTTTCAGGCGGTTA	30	824
1322362	36021	36040	3293	3312	GTAATTTCTTAAATTGGGTT	20	825
1322372	20495	20514	N/A	N/A	ATCACCACATCACACATCAA	60	826
1322398	19237	19256	N/A	N/A	TCAAGGTTTCCTCTGCCCTC	63	827
1322444	19814	19833	N/A	N/A	GTCTATTAAACATTTTAGCA	52	828
1322456	29519	29538	N/A	N/A	TGTTTGTCAACCCTTTTTTC	38	829
1322469	5085	5104	N/A	N/A	ACTGAGCAACATTACAATCT	46	830
	7591	7610					
1322509	38747	38766	6019	6038	AGGGAAGCTTAAAAACACAA	86	831

1322514	35620	35639	2892	2911	AGATAGTTACCTATTTTCTA	56	832
1322548	26950	26969	N/A	N/A	ACTATCACCCCAACACAAAA	74	833
1322575	18344	18363	N/A	N/A	AAATACTTCATTCTTGGCCA	77	834
1322580	29461	29480	N/A	N/A	TCCTAATCCTTCCCCCATCA	74	835
1322586	25298	25317	N/A	N/A	TTCTGACTTTTCTTTCTG	47	836
1322592	37888	37907	5160	5179	TGCTGCAAATATCACGGCCT	87	837
1322610	13924	13943	N/A	N/A	GATGTGGTACCCCTGCCCC	N.D.	838
1322614	37019	37038	4291	4310	CTCCACATCCTACAAGGGCA	67	839
1322621	26820	26839	N/A	N/A	AGGACATCCTCCCCACTGGA	N.D.	840
1322730	28927	28946	N/A	N/A	GAGTTAATCACATTTTTTTT	33	841
1322758	25801	25820	N/A	N/A	TCATACCTTATCTCTTTCCT	45	842
1322779	9563	9582	N/A	N/A	CTAACATCACTCTCCAGAC	56	843
1322805	21070	21089	N/A	N/A	CAGCCATTATTTATGTGGGC	96	844
1322816	6919	6938	N/A	N/A	CCATTGATTTCAACCAATTA	35	845
1322824	14721	14740	N/A	N/A	CCAAACACTTTCCAAATCTA	61	846
1322866	35765	35784	3037	3056	AAGCATTCTTCTTCTATGTC	48	847
1322879	7639	7658	N/A	N/A	GAATTGCATTTACTAGGCTA	77	848
1322903	29134	29153	N/A	N/A	GTGCTGAGAATCCCAGGTTT	35	849
1322905	22294	22313	550	569	GCCTTATCTTCAGCTTCTAA	20	850
1322964	28579	28598	N/A	N/A	CCCAAATCATAATTATAACT	81	851
1322985	34278	34297	N/A	N/A	AAGAGTAGAAATCAATTATT	131	852
1322991	31060	31079	N/A	N/A	TTCTCTCTACCTGATTCCCT	48	853
1323020	30187	30206	N/A	N/A	CAATGTAACCAATCACATAA	74	854
1323048	5757	5776	N/A	N/A	CTCTCCCAACTTTCTTACGC	96	855
1323102	13589	13608	N/A	N/A	AGTGCCCTTTCATTTACCT	90	856
1323211	24824	24843	N/A	N/A	CCCACCGAAGTATCTACTAC	81	857
1323272	38295	38314	5567	5586	ACTCCTAGACTTTTGGGCCC	94	858
1323290	35336	35355	2608	2627	AATAAATTTCTAAGGGCCT	77	859
1323296	31270	31289	N/A	N/A	CAGAAAGTTAAAAATGCTGC	55	860

Table 12

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320935	25022	25041	N/A	N/A	GTGTGATCATACAACACTGC	65	861
1320997	16968	16987	N/A	N/A	AAGTAACATTAAATAAGGGT	22	862
1321034	29117	29136	N/A	N/A	TTTAGATGAATACATGGGAA	25	863
1321057	22495	22514	N/A	N/A	GGTTCTTTAAAAAAGTATAA	91	864
1321096	13217	13236	N/A	N/A	CCCCAACTACTATCATATTG	79	865
1321131	34223	34242	N/A	N/A	CTTTAGTTTCTTACATCCAT	45	866
1321139	36007	36026	3279	3298	TGGGTTTTTCTTCCTAGTTA	23	867

1321140	22288	22307	544	563	TCTTCAGCTTCTAAATGTAC	64	868
1321141	19216	19235	N/A	N/A	CCAAAAGCAAACCATCCCTT	102	869
1321146	31864	31883	1397	1416	GTCATAAAAACTGCTTT	43	870
1321155	7619	7638	N/A	N/A	AAAGGTACATTTATACAAC	43	871
1321162	6916	6935	N/A	N/A	TTGATTCAACCAATTACCA	70	872
1321175	35619	35638	2891	2910	GATAGTTACCTATTTTCTAT	37	873
1321210	26947	26966	N/A	N/A	ATCACCCCAACACAAAATCC	98	874
1321249	29924	29943	N/A	N/A	GTTATGATTACCACCACTTC	12	875
1321284	4771	4790	N/A	N/A	GTATCTTAAATACAGATTT	74	876
1321292	11897	11916	N/A	N/A	TACCTTTTCTCCTCTTTCTG	71	877
1321419	21053	21072	N/A	N/A	GGCTGTATATTTTATATTA	123	878
1321481	9156	9175	N/A	N/A	TCTTTTGTCCACCTGATTC	70	879
1321622	29518	29537	N/A	N/A	GTTTGTCAACCCTTTTTCAT	26	880
1321838	38279	38298	5551	5570	GCCCATGCTTATTACATAA	61	881
1321857	13921	13940	N/A	N/A	GTGGTACCCCTGCCCATC	94	882
1321864	33496	33515	N/A	N/A	CCATAGAATATACTTTCTAC	46	883
1321917	28815	28834	N/A	N/A	GTGACCCTCCCACCCAAGT	76	884
1321994	11421	11440	N/A	N/A	GATAATTACCTCTTCCAAAC	87	885
1322007	5755	5774	N/A	N/A	CTCCCAACTTTCTTACGCAA	60	886
1322009	27500	27519	N/A	N/A	ATTAAGTTATATAAATTTGC	93	887
1322033	29458	29477	N/A	N/A	TAATCCTTCCCCCATCATAA	76	888
1322044	25590	25609	N/A	N/A	GTAAGTACCCAAAAGAAGCT	54	889
1322046	28577	28596	N/A	N/A	CAATCATAATTATAACTCT	85	890
1322047	25164	25183	N/A	N/A	CTTTTCTCTATTCTCTCCT	50	891
1322066	31256	31275	N/A	N/A	TGCTGCTGCCAAAAAAGCAT	95	892
1322068	24198	24217	N/A	N/A	GCACACATTTTACTCAAGT	42	893
1322074	8394	8413	N/A	N/A	GGAGTCTCTAAACTTCATC	101	894
1322080	25799	25818	N/A	N/A	ATACCTTATCTCTTTCCTTA	61	895
1322087	16352	16371	N/A	N/A	CTATATTCCTCCTTCTGCCT	65	896
1322095	28312	28331	N/A	N/A	CACCAGAGAATTACAATCTC	80	897
1322135	31054	31073	N/A	N/A	CTACCTGATTCCCTGATCTA	70	898
1322136	30185	30204	N/A	N/A	ATGTAACCAATCACATAATC	57	899
1322170	25713	25732	N/A	N/A	TGTATACCACTCTTAGTCC	11	900
1322175	33762	33781	N/A	N/A	GTTTAACTCCTTTGCTCCTA	39	901
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	7	132
1322207	26056	26075	N/A	N/A	AGCTCTAGAAATAAATTCTG	81	902
1322216	24579	24598	N/A	N/A	CCATCTATTTTACAAGTGAA	11	903
1322314	35289	35308	2561	2580	ATGTTTGAAATATCTCCCGA	50	904
1322352	18330	18349	N/A	N/A	TGGCCAGTTTCACTCCAC	64	905
1322375	22768	22787	N/A	N/A	GTTTTTAACATATATTGACC	45	906
1322401	20493	20512	N/A	N/A	CACCACATCACACATCAAAC	101	907
1322403	37018	37037	4290	4309	TCCACATCCTACAAGGGCAT	40	908
1322406	18092	18111	N/A	N/A	AACTGTTTTACATCTAATCA	63	909

1322418	25297	25316	N/A	N/A	TCTGACTTTTCCTTTCCTGT	24	910
1322467	25217	25236	N/A	N/A	CATCTCTTTTCTCCCCATAA	31	911
1322482	9561	9580	N/A	N/A	AACATCACTCTCCCAGACTA	71	912
1322513	24821	24840	N/A	N/A	ACCGAAGTATCTACTACAAA	28	913
1322515	27027	27046	N/A	N/A	CTTTAGTGTCTCCTTAGTCC	25	914
1322520	14644	14663	N/A	N/A	AAGTAGAGTCACATACTTTT	88	915
1322531	31708	31727	N/A	N/A	TTTAGTCACCTCAAGAAATC	105	916
1322550	12377	12396	N/A	N/A	ATACTTTTCCATGTTTTCAA	65	917
1322551	26818	26837	N/A	N/A	GACATCCTCCCCACTGGAGA	87	918
1322587	27260	27279	N/A	N/A	GCAAACACTACAAAATAGGA	29	919
1322727	19813	19832	N/A	N/A	TCCTATTAACATTTTAGCAT	35	920
1322868	30033	30052	N/A	N/A	GCAACTACAATTTATTGAAT	32	921
1322922	35764	35783	3036	3055	AGCATTCTTCTTCTATGTCA	26	922
1322952	25409	25428	N/A	N/A	TGCATTCTACCAGTCACCCT	30	923
1322959	10270	10289	N/A	N/A	ATACCACTTCAGCTTAGGCA	38	924
1322980	34566	34585	1838	1857	CTGAAAAACCTTATACTTGA	36	925
1322994	30448	30467	N/A	N/A	CACAAGTCTACAGACTGGCT	63	926
1323027	37680	37699	4952	4971	AAGTAACTTTTTTATAAGTT	105	927
1323038	38745	38764	6017	6036	GGAAGCTTAAAAACACAAGT	69	928
1323045	8210	8229	N/A	N/A	TGCAGAATATTATAATTCTA	53	929
1323088	13587	13606	N/A	N/A	TGCCCTTTCATTTACCTTT	84	930
1323096	28045	28064	N/A	N/A	CATTAGATATTTATTAAGTA	104	931
1323128	32814	32833	N/A	N/A	TTTCTGTTCATTACCTAGCT	42	932
1323169	20111	20130	460	479	GTGTTTTCTTTTTCTGCTCT	9	933
1323207	6113	6132	N/A	N/A	CTAGTACCCACATCCTAGGA	86	934
1323239	5084	5103	N/A	N/A	CTGAGCAACATTACAATCTC	35	935
	7590	7609					
1323326	37318	37337	4590	4609	TGCATGGTATTTCTAAGTAA	26	936
1323342	8717	8736	N/A	N/A	TCCTTAAATATCATAAAGGA	86	937

Table 13

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320907	29116	29135	N/A	N/A	TTAGATGAATACATGGGAAT	71	938
1320931	26817	26836	N/A	N/A	ACATCCTCCCCACTGGAGAA	86	939
1320992	25408	25427	N/A	N/A	GCATTCTACCAGTCACCCTT	41	940
1321012	31255	31274	N/A	N/A	GCTGCTGCCAAAAAAGCATA	98	941
1321033	38743	38762	6015	6034	AAGCTTAAAAACACAAGTGT	90	942
1321039	8716	8735	N/A	N/A	CCTTAAATATCATAAAGGAC	106	943
1321053	11417	11436	N/A	N/A	ATTACCTCTTCCAAACTTTA	90	944

1321137	11896	11915	N/A	N/A	ACCTTTTCTCCTCTTTCTGT	96	945
1321176	26944	26963	N/A	N/A	ACCCCAACACAAAATCCCCA	84	946
1321267	25021	25040	N/A	N/A	TGTGATCATACAACACTGCA	108	947
1321286	21051	21070	N/A	N/A	CTGTATATTTTTATATTAGC	81	948
1321333	35615	35634	2887	2906	GTTACCTATTTTCTATGACT	57	949
1321337	28042	28061	N/A	N/A	TAGATATTTATTAAGTATTT	113	950
1321345	35267	35286	2539	2558	AAGAATGAAACAGAATGTTA	111	951
1321346	27026	27045	N/A	N/A	TTTAGTGTCTCCTTAGTCCA	62	952
1321399	16951	16970	N/A	N/A	GGTATCTGAAATAATTCCTT	84	953
1321425	30184	30203	N/A	N/A	TGTAACCAATCACATAATCC	98	954
1321437	34214	34233	N/A	N/A	CTTACATCCATTACTGAGAA	71	955
1321454	5083	5102	N/A	N/A	TGAGCAACATTACAATCTCA	74	956
	7589	7608					
1321460	5709	5728	N/A	N/A	CAAGTGACTGCAACACCCTC	108	957
1321491	12355	12374	N/A	N/A	TACTGACTGCTCTCTTTTCA	99	958
1321529	37002	37021	4274	4293	GCATTGCTCCTTTTTAGGCT	38	959
1321538	18091	18110	N/A	N/A	ACTGTTTTACATCTAATCAA	64	960
1321540	24818	24837	N/A	N/A	GAAGTATCTACTACAAAATT	79	961
1321573	25296	25315	N/A	N/A	CTGACTTTTCCTTTCCTGTC	52	962
1321629	6112	6131	N/A	N/A	TAGTACCCACATCCTAGGAA	91	963
1321652	30428	30447	N/A	N/A	GGGCAGCTCCCACGGAGGCT	96	964
1321690	29456	29475	N/A	N/A	ATCCTTCCCCCATCATAAAA	116	965
1321774	31707	31726	N/A	N/A	TTAGTCACCTCAAGAAATCA	105	966
1321815	31855	31874	1388	1407	AACACTGCTTTTATTCAGCT	55	967
1321824	19806	19825	N/A	N/A	AACATTTTAGCATACACCCT	99	968
1321835	20492	20511	N/A	N/A	ACCACATCACACATCAAACA	115	969
1321849	35998	36017	3270	3289	CTTCCTAGTTACATTTTCC	79	970
1321868	9560	9579	N/A	N/A	ACATCACTCTCCCAGACTAC	107	971
1321992	29923	29942	N/A	N/A	TTATGATTACCACCACTTCA	65	972
1322031	13913	13932	N/A	N/A	CCCTGCCCCATCTCCCACTG	88	973
1322070	22748	22767	N/A	N/A	TATCATGTAAACTTCAGCAA	87	974
1322127	13586	13605	N/A	N/A	GCCCTTTCATTTACCTTTC	106	975
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	17	132
1322192	34564	34583	1836	1855	GAAAAACCTTATACTTGACA	70	976
1322226	25568	25587	N/A	N/A	GAGATCAGCTATCAGAAATA	68	977
1322356	6838	6857	N/A	N/A	TTTCCAGATCGAACCAATCA	89	978
1322368	27499	27518	N/A	N/A	TTAAGTTATATAAATTTGCA	111	979
1322377	24197	24216	N/A	N/A	CACACATTTTTACTCAAGTG	97	980
1322379	4744	4763	N/A	N/A	ACTAACTAAATTCTCACAGA	100	981
1322399	33493	33512	N/A	N/A	TAGAATATACTTTCTACGCT	90	982
1322422	22479	22498	N/A	N/A	ATAAAGTCAAATTTTAGGAT	101	983
1322438	16350	16369	N/A	N/A	ATATTCCTCCTTCTGCCTGC	77	984
1322465	30032	30051	N/A	N/A	CAACTACAATTTATTGAATC	81	985

1322499	33756	33775	N/A	N/A	CTCCTTTGCTCCTAACACCT	92	986
1322518	24529	24548	N/A	N/A	AGCTCAATGTCATCCAGTTA	42	987
1322563	19212	19231	N/A	N/A	AAGCAAACCATCCCTTCTGC	111	988
1322624	25163	25182	N/A	N/A	TTTTCTCTATTCATCTCCTA	86	989
1322637	22249	22268	N/A	N/A	GCTGCAAAAAAATCAAAACA	113	990
1322642	25215	25234	N/A	N/A	TCTCTTTTCTCCCCATAACC	105	991
1322691	9038	9057	N/A	N/A	ATAGACCAAAATTAAGTGA	55	992
1322731	8393	8412	N/A	N/A	GAGTCTCTAAAACTTCATCC	115	993
1322757	37676	37695	4948	4967	AACTTTTTTATAAGTTGCAA	96	994
1322769	31052	31071	N/A	N/A	ACCTGATTCCCTGATCTATA	70	995
1322809	28814	28833	N/A	N/A	TGACCCTCCCAACCAAGTA	111	996
1322818	14642	14661	N/A	N/A	GTAGAGTCACATACTTTTGA	94	997
1322833	37308	37327	4580	4599	TTCTAAGTAAACTTCTGTTC	80	998
1322849	28576	28595	N/A	N/A	AAATCATAATTATAACTCTA	80	999
1322929	10150	10169	N/A	N/A	GAGTAGTTCCACCTCTGCTT	129	1000
1322966	26055	26074	N/A	N/A	GCTCTAGAAATAAATTCTGC	90	1001
1323028	28311	28330	N/A	N/A	ACCAGAGAATTACAATCTCC	100	1002
1323031	27259	27278	N/A	N/A	CAAACACTACAAAATAGGAC	96	1003
1323059	20109	20128	458	477	GTTTTCTTTTTCTGCTCTTA	5	1004
1323118	29517	29536	N/A	N/A	TTTGTCACCCCTTTTTTCAT	93	1005
1323130	38277	38296	5549	5568	CCATTGCTTATTACATAAAA	103	1006
1323152	7618	7637	N/A	N/A	AAGGTACATTTATACAACTT	38	1007
1323165	25795	25814	N/A	N/A	CTTATCTCTTTCCTTATGGC	56	1008
1323178	35753	35772	3025	3044	TCTATGTCAGTCTCCTATCA	53	1009
1323198	18329	18348	N/A	N/A	GGCCAGTTTTCACTTCCACT	50	1010
1323205	13215	13234	N/A	N/A	CCAACACTATCATATTGGA	134	1011
1323309	N/A	N/A	1581	1600	GTTTCAGAGAAATACTCATCT	51	1012
1323315	25712	25731	N/A	N/A	GTATACCACTCTTTAGTCCT	44	1013
1323329	8196	8215	N/A	N/A	ATTCTAGTAATTTTGGGCCT	132	1014

Table 14

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320885	18088	18107	N/A	N/A	GTTTTACATCTAATCAAGAT	72	1015
1320895	21050	21069	N/A	N/A	TGTATATTTTTATATTAGCA	100	1016
1320945	8698	8717	N/A	N/A	ACTGATCTCTCACTTTGATA	91	1017
1320956	19210	19229	N/A	N/A	GCAAACCATCCCTTCTGCTT	116	1018
1320974	38273	38292	5545	5564	TGCTTATTACATAAAATTGT	122	1019
1320989	30183	30202	N/A	N/A	GTAACCAATCACATAATCCG	94	1020
1321024	35613	35632	2885	2904	TACCTATTTTCTATGACTTC	82	1021

1321080	12350	12369	N/A	N/A	ACTGCTCTCTTTTCACTTCC	104	1022
1321087	37292	37311	4564	4583	GTTTCAGAAAAAATACTTGTC	54	1023
1321192	25710	25729	N/A	N/A	ATACCACTCTTTAGTCCTAA	23	1024
1321199	20491	20510	N/A	N/A	CCACATCACACATCAAACAG	111	1025
1321253	19801	19820	N/A	N/A	TTTAGCATACACCCTTCCAC	111	1026
1321278	16334	16353	N/A	N/A	CTGCCTCTCCTCTTGAATAA	106	1027
1321285	25403	25422	N/A	N/A	CTACCAGTCACCCCTTGGTTC	98	1028
1321322	13911	13930	N/A	N/A	CTGCCCCATCTCCCACTGCA	119	1029
1321344	8392	8411	N/A	N/A	AGTCTCTAAAACTTCATCCC	94	1030
1321368	13213	13232	N/A	N/A	AACTACTATCATATTGGAGT	87	1031
1321402	30031	30050	N/A	N/A	AACTACAATTTATTGAATCT	84	1032
1321405	28648	28667	N/A	N/A	CAGGCCACTGCATCCAGCCC	127	1033
1321414	22470	22489	N/A	N/A	AATTTTAGGATTAATTCGCC	135	1034
1321416	27498	27517	N/A	N/A	TAAGTTATATAAAATTTGCAA	118	1035
1321439	29100	29119	N/A	N/A	GAATCATGTTAAAAATGCAA	110	1036
1321455	30396	30415	N/A	N/A	TAGGTCAGCTCCAGCAGCCT	99	1037
1321465	26796	26815	N/A	N/A	GCAAAAATTCTGAGATGGCCC	79	1038
1321466	38720	38739	5992	6011	TTCAGGTTCCCAGCCTGAAT	101	1039
1321500	29455	29474	N/A	N/A	TCCTTCCCCCATCATAAAAT	65	1040
1321601	22747	22766	N/A	N/A	ATCATGTAAACTTCAGCAAT	65	1041
1321637	16947	16966	N/A	N/A	TCTGAAATAATTCCTTCTCT	86	1042
1321664	9026	9045	N/A	N/A	TAAGTCAATTTACCATCTA	90	1043
1321696	24525	24544	N/A	N/A	CAATGTCATCCAGTTAGTTA	68	1044
1321697	14640	14659	N/A	N/A	AGAGTCACATACTTTTGATA	105	1045
1321702	18327	18346	N/A	N/A	CCAGTTTTCACTTCCACTTT	51	1046
1321733	22238	22257	N/A	N/A	ATCAAAACAATTACTATGGA	93	1047
1321750	7617	7636	N/A	N/A	AGGTACATTTATACAACCTC	28	1048
1321780	6835	6854	N/A	N/A	CCAGATCGAACCAATCAAAT	54	1049
1321802	24816	24835	N/A	N/A	AGTATCTACTACAAAATTTT	73	1050
1321811	5082	5101	N/A	N/A	GAGCAACATTACAATCTCAT	58	1051
1321879	25565	25584	N/A	N/A	ATCAGCTATCAGAAATACCT	75	1052
1321930	31254	31273	N/A	N/A	CTGCTGCCAAAAAAGCATAT	101	1053
1321956	37665	37684	4937	4956	AAGTTGCAAATTTCTAGTCA	55	1054
1321960	31043	31062	N/A	N/A	CCTGATCTATAAAATCGGGA	95	1055
1321978	29922	29941	N/A	N/A	TATGATTACCACCACTTCAG	55	1056
1322017	N/A	N/A	1580	1599	TTCAGAGAAATACTCATCTA	88	1057
1322026	33754	33773	N/A	N/A	CCTTTGCTCCTAACACCTCT	87	1058
1322143	33476	33495	N/A	N/A	GCTGATAGAATATTTTAGTC	86	1059
1322148	31854	31873	1387	1406	ACACTGCTTTTATTCAGCTT	55	1060
1322149	11415	11434	N/A	N/A	TACCTCTTCCAAACTTTACA	115	1061
1322160	27245	27264	N/A	N/A	TAGGACTTTTTCTTTCTGGA	11	1062
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	15	132
1322190	27023	27042	N/A	N/A	AGTGTCTCCTTAGTCCACTC	88	1063

1322225	25214	25233	N/A	N/A	CTCTTTTCTCCCCATAACCC	85	1064
1322271	25794	25813	N/A	N/A	TTATCTCTTTCCTTATGGCT	63	1065
1322303	8144	8163	N/A	N/A	GCTAGTGATTTCTCAGGGA	58	1066
1322360	34548	34567	1820	1839	GACACAGTTCATTTCTGGTC	120	1067
1322459	28310	28329	N/A	N/A	CCAGAGAATTACAATCTCCA	107	1068
1322534	35748	35767	3020	3039	GTCAGTCTCCTATCATTGCC	47	1069
1322633	10137	10156	N/A	N/A	TCTGCTTGACTCCACAGGGA	66	1070
1322654	29516	29535	N/A	N/A	TTGTCAACCCTTTTTTCATT	81	1071
1322669	28033	28052	N/A	N/A	ATTAAGTATTTACAATTGCC	113	1072
1322686	28575	28594	N/A	N/A	AATCATAATTATAACTCTAA	98	1073
1322733	35996	36015	3268	3287	TCCTAGTTACATTTTTCCCC	56	1074
1322766	24154	24173	N/A	N/A	GCTCGCATTTTATCATTATA	45	1075
1322787	35104	35123	2376	2395	TTGGTCTGACTCATCTCATC	59	1076
1322793	20102	20121	451	470	TTTTCTGCTCTTATACGCAA	48	1077
1322804	34198	34217	N/A	N/A	AGAAAACCTATCTTCTGGCA	80	1078
1322846	4740	4759	N/A	N/A	ACTAAATTCTCACAGAACTA	118	1079
1322854	6111	6130	N/A	N/A	AGTACCCACATCCTAGGAAA	123	1080
1322864	26052	26071	N/A	N/A	CTAGAAATAAATTCTGCCAA	76	1081
1322895	25162	25181	N/A	N/A	TTTCTCTATTCATCTCCTAC	75	1082
1322972	25295	25314	N/A	N/A	TGACTTTTCCTTCTCTGTCT	52	1083
1322989	25019	25038	N/A	N/A	TGATCATACAACACTGCAGC	150	1084
1323042	5703	5722	N/A	N/A	ACTGCAACACCTCTTCCAA	100	1085
1323089	11895	11914	N/A	N/A	CCTTTTCTCCTCTTTCTGTA	98	1086
1323164	9557	9576	N/A	N/A	TCACTCTCCCAGACTACATT	98	1087
1323183	36959	36978	4231	4250	CAGTGGTGAACACAGGGCCA	83	1088
1323313	26943	26962	N/A	N/A	CCCCAACACAAAATCCCCAA	105	1089
1323325	13582	13601	N/A	N/A	TTTCATTTACCTTTTCAGGA	107	1090
1323335	31683	31702	N/A	N/A	ATATGTGCTTTCTCAATTTT	78	1091

Table 15

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320889	37291	37310	4563	4582	TTCAGAAAAAATACTTGTC	83	1092
1320899	21049	21068	N/A	N/A	GTATATTTTTATATTAGCAT	109	1093
1320918	34178	34197	N/A	N/A	TGCATATTA AAAAGTCGCCT	80	1094
1320939	12347	12366	N/A	N/A	GCTCTCTTTTCACTTCCAGA	63	1095
1320961	33714	33733	N/A	N/A	GGGTA CTTGCTTACCTGCCC	92	1096
1320985	13878	13897	N/A	N/A	ATAGTGTATCTCAGCAGCTT	55	1097
1320990	38698	38717	5970	5989	AAATTGTATTCAATTTCCGA	77	1098
1321020	28561	28580	N/A	N/A	CTCTAAGTTACAAAATTATA	104	1099

1321045	14613	14632	313	332	GAAAAAGTCACATTCCCGAC	65	1100
1321065	25018	25037	N/A	N/A	GATCATACAACACTGCAGCC	72	1101
1321101	35995	36014	3267	3286	CCTAGTTACATTTTCCCCC	56	1102
1321109	19800	19819	N/A	N/A	TTAGCATACACCCTTCCACT	76	1103
1321130	29454	29473	N/A	N/A	CCTTCCCCCATCATAAAATT	88	1104
1321228	26942	26961	N/A	N/A	CCCAACACAAAATCCCCAAA	100	1105
1321230	20091	20110	440	459	TATACGCAATTTAATTTCTT	72	1106
1321239	37660	37679	4932	4951	GCAAATTTCTAGTCAGACTC	30	1107
1321259	25213	25232	N/A	N/A	TCTTTTCTCCCCATAACCCA	77	1108
1321294	35102	35121	2374	2393	GGTCTGACTCATCTCATCCA	60	1109
1321347	22237	22256	N/A	N/A	TCAAAACAATTACTATGGAA	93	1110
1321349	25793	25812	N/A	N/A	TATCTCTTTCCTTATGGCTT	40	1111
1321386	18061	18080	N/A	N/A	CAGAAGCTACTTTTATATTT	70	1112
1321388	4733	4752	N/A	N/A	TCTCACAGAACTATTTGCCT	77	1113
1321426	31682	31701	N/A	N/A	TATGTGCTTTCTCAATTTTT	55	1114
1321427	5061	5080	N/A	N/A	GAGATAACATTTTCATTGAGT	52	1115
1321519	35570	35589	2842	2861	GCTACTGTTCTAATAAGTTT	76	1116
1321559	31041	31060	N/A	N/A	TGATCTATAAAATCGGGACA	54	1117
1321620	6831	6850	N/A	N/A	ATCGAACCAATCAAATGTAC	82	1118
1321659	25706	25725	N/A	N/A	CACTCTTTAGTCCTAAACCA	97	1119
1321705	25293	25312	N/A	N/A	ACTTTTCCTTTCCTGTCTTA	104	1120
1321747	24454	24473	N/A	N/A	ACCCACCTCCCAGTCGGTCA	99	1121
1321809	9025	9044	N/A	N/A	AACTGCAATTTACCATCTAA	80	1122
1321899	10107	10126	N/A	N/A	AGCTGCTTAAAGTTTAGCTT	95	1123
1321926	13581	13600	N/A	N/A	TTCATTTACCTTTCAGGAC	75	1124
1322059	27018	27037	N/A	N/A	CTCCTTAGTCCACTCTCCCA	97	1125
1322102	31853	31872	1386	1405	CACTGCTTTTATTCAGCTTT	76	1126
1322110	33475	33494	N/A	N/A	CTGATAGAATATTTTAGTCT	67	1127
1322131	24153	24172	N/A	N/A	CTCGCATTTTATCATTATAA	20	1128
1322152	34547	34566	1819	1838	ACACAGTTCATTTCTGGTCA	50	1129
1322154	36833	36852	4105	4124	ACAAGGCTTTTCCAAAGGTC	52	1130
1322157	19182	19201	N/A	N/A	CCGTAATTTCTTCTATTACA	99	1131
1322172	13178	13197	N/A	N/A	CGTATAGTAATATTTACTTT	99	1132
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	12	1132
1322182	6090	6109	N/A	N/A	GTATACTACATATTTGTGGA	66	1133
1322199	29098	29117	N/A	N/A	ATCATGTTAAAAATGCAAAT	91	1134
1322224	18324	18343	N/A	N/A	GTTTTCACCTTCCACTTTTAC	78	1135
1322242	38272	38291	5544	5563	GCTTATTACATAAAAATTGTT	85	1136
1322267	30182	30201	N/A	N/A	TAACCAATCACATAATCCGG	100	1137
1322308	22746	22765	N/A	N/A	TCATGTAAACTTCAGCAATA	59	1138
1322332	29921	29940	N/A	N/A	ATGATTACCACCACTTCAGA	56	1139
1322380	28032	28051	N/A	N/A	TTAAGTATTTACAATTGCCA	75	1140
1322390	30387	30406	N/A	N/A	TCCAGCAGCCTCTAATCCTC	94	1141

1322410	25161	25180	N/A	N/A	TTCTCTATTCATCTCCTACA	72	1142
1322427	11413	11432	N/A	N/A	CCTCTTCCAAACTTTACAGA	100	1143
1322458	24814	24833	N/A	N/A	TATCTACTACAAAATTTTGT	99	1144
1322471	16327	16346	N/A	N/A	TCCTCTTGAATAATTAAGTA	83	1145
1322474	11883	11902	N/A	N/A	TTTCTGTAACCTTACATAGTA	110	1146
1322529	25564	25583	N/A	N/A	TCAGCTATCAGAAATACCTC	72	1147
1322584	8682	8701	N/A	N/A	GATAAGTTATATATTTTTTA	98	1148
1322623	26786	26805	N/A	N/A	GAGATGGCCCCCAAGATTCC	98	1149
1322640	8391	8410	N/A	N/A	GTCTCTAAAACTTCATCCCT	100	1150
1322665	9499	9518	N/A	N/A	TTGTTGTTAATCCTGTGCCA	59	1151
1322671	7980	7999	N/A	N/A	TTGCTCTATTATTATTGGCA	55	1152
1322786	26042	26061	N/A	N/A	ATTCTGCCAACAACATGTGA	82	1153
1322869	32768	32787	N/A	N/A	ATACCTCATCTATACTGGAA	73	1154
1322873	28308	28327	N/A	N/A	AGAGAATTACAATCTCCAGT	111	1155
1322875	29515	29534	N/A	N/A	TGTCAACCCCTTTTTTCATTA	32	1156
1322941	30024	30043	N/A	N/A	ATTTATTGAATCTCTACTAC	75	1157
1322988	27244	27263	N/A	N/A	AGGACTTTTTCTTTCTGGAA	26	1158
1322996	27484	27503	N/A	N/A	TTGCAAATAAAAAATTGTTT	119	1159
1323041	5702	5721	N/A	N/A	CTGCAACACCCTCTTCCAAA	73	1160
1323091	31242	31261	N/A	N/A	AAGCATATGATCTATTCCTA	34	1161
1323100	35747	35766	3019	3038	TCAGTCTCCTATCATTGCCA	24	1162
1323139	20489	20508	N/A	N/A	ACATCACACATCAAACAGCC	69	1163
1323160	28639	28658	N/A	N/A	GCATCCAGCCCACATAAAGT	90	1164
1323162	16946	16965	N/A	N/A	CTGAAATAATTCTTCTCTA	107	1165
1323213	25402	25421	N/A	N/A	TACCAGTCACCCTTGTTTCA	83	1166
1323249	7614	7633	N/A	N/A	TACATTTATACAACCTTCTGA	109	1167
1323264	22469	22488	N/A	N/A	ATTTTAGGATTAATTCGCCT	58	1168

Table 16

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320891	13865	13884	N/A	N/A	GCAGCTTTCCCCTCTGTGTT	98	1169
1320900	25704	25723	N/A	N/A	CTCTTTAGTCCTAAACCACA	69	1170
1320936	14607	14626	307	326	GTCACATTCCCGACAGACTC	100	1171
1320954	4732	4751	N/A	N/A	CTCACAGAACTATTTGCCTT	82	1172
1320966	18059	18078	N/A	N/A	GAAGCTACTTTTATATTTTC	64	1173
1320984	38659	38678	5931	5950	CAGGAGAGATCTACTTATCT	75	1174
1321063	29918	29937	N/A	N/A	ATTACCACCACTTCAGAGAA	71	1175
1321078	35746	35765	3018	3037	CAGTCTCCTATCATTGCCAT	45	1176
1321148	6052	6071	N/A	N/A	TATCATGTACCACACAGGTA	64	1177

1321167	38205	38224	5477	5496	AGTTTGTTCATAGAAACAC	120	1178
1321189	29449	29468	N/A	N/A	CCCCATCATAAAATTAATA	100	1179
1321263	25160	25179	N/A	N/A	TCTCTATTCATCTCCTACAA	77	1180
1321335	34166	34185	N/A	N/A	AGTCGCCTAAGAACATACTA	54	1181
1321336	25289	25308	N/A	N/A	TTCTTTTCCTGTCTTAGCTA	63	1182
1321383	25212	25231	N/A	N/A	CTTTTCTCCCCATAACCCAT	75	1183
1321438	8388	8407	N/A	N/A	TCTAAAACCTTCATCCCTGAA	131	1184
1321446	31681	31700	N/A	N/A	ATGTGCTTTCTCAATTTTTT	36	1185
1321459	7979	7998	N/A	N/A	TGCTCTATTATTATTGGCAA	105	1186
1321495	7588	7607	N/A	N/A	GAGCAACATTACAATCTCAC	68	1187
1321498	16915	16934	N/A	N/A	TGTTTCATAAGGAAATTCCAA	71	1188
1321543	33456	33475	N/A	N/A	TTCTGGATATATACAGATGC	113	1189
1321569	30181	30200	N/A	N/A	AACCAATCACATAATCCGGC	76	1190
1321619	29088	29107	N/A	N/A	AAATGCAAATTCCTGAGTTC	91	1191
1321640	22223	22242	N/A	N/A	ATGGAACTTTATTAATACAA	78	1192
1321653	18318	18337	N/A	N/A	ACTTCCACTTTTACATATCT	69	1193
1321793	11847	11866	N/A	N/A	TAATGATGTCCATAAGTCT	100	1194
1321850	9469	9488	N/A	N/A	TGAGCTATAAACTTAAGGTC	71	1195
1321852	29512	29531	N/A	N/A	CAACCCTTTTTTCATTACCT	91	1196
1321910	24150	24169	N/A	N/A	GCATTTTATCATTATAAGGT	9	1197
1321911	31842	31861	1375	1394	TTCAGCTTTTCATCCATGGT	57	1198
1321969	21034	21053	N/A	N/A	AGCATATTAAACATTAATAAC	108	1199
1322005	25792	25811	N/A	N/A	ATCTCTTTCCTTATGGCTTC	44	1200
1322036	25561	25580	N/A	N/A	GCTATCAGAAATACCTCTCA	52	1201
1322042	5036	5055	N/A	N/A	ACATGATTATTTCTTTGGGA	28	1202
1322054	35547	35566	2819	2838	ATCAGAGGTCTTAATGCATA	29	1203
1322076	27017	27036	N/A	N/A	TCCTTAGTCCACTCTCCCAC	95	1204
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	10	132
1322236	25394	25413	N/A	N/A	ACCCTTGTTCAAAATTAAC	95	1205
1322248	19799	19818	N/A	N/A	TAGCATACACCCTTCCACTC	79	1206
1322289	32728	32747	1532	1551	GAAGACATAATTGATGCATC	38	1207
1322290	28560	28579	N/A	N/A	TCTAAGTTACAAAATTATAC	136	1208
1322293	12315	12334	N/A	N/A	TGGAGCATTTCATCATAAGGC	83	1209
1322319	22457	22476	N/A	N/A	ATTCGCCTAATTTTCTCTC	55	1210
1322384	31241	31260	N/A	N/A	AGCATATGATCTATTCCTAA	19	1211
1322419	33713	33732	N/A	N/A	GGTACTTGCTTACCTGCCCT	95	1212
1322442	26941	26960	N/A	N/A	CCAACACAAAATCCCCAAA	121	1213
1322503	36426	36445	3698	3717	TCAATGACCCACCATGCTCT	100	1214
1322511	35101	35120	2373	2392	GTCTGACTCATCTCATCCAA	64	1215
1322512	27223	27242	N/A	N/A	GCCAGCTGCTAAACATGCGC	110	1216
1322516	9022	9041	N/A	N/A	TGCAATTTACCATCTAAGTC	64	1217
1322530	26761	26780	N/A	N/A	CCTGGTGTACACATCCTGTA	116	1218
1322553	20487	20506	N/A	N/A	ATCACACATCAAACAGCCTC	84	1219

1322556	13177	13196	N/A	N/A	GTATAGTAATATTTACTTTA	95	1220
1322663	19176	19195	N/A	N/A	TTTCTTCTATTACATCATCA	71	1221
1322689	13580	13599	N/A	N/A	TCATTTACCTTTTCAGGACT	117	1222
1322700	28307	28326	N/A	N/A	GAGAATTACAATCTCCAGTA	86	1223
1322707	20090	20109	439	458	ATACGCAATTTAATTTCTTC	51	1224
1322712	16324	16343	N/A	N/A	TCTTGAATAATTAAGTAGAA	133	1225
1322714	5701	5720	N/A	N/A	TGCAACACCCTCTTCCAAAC	78	1226
1322747	27456	27475	N/A	N/A	GAGGTAATAAATAAATTCAT	66	1227
1322837	9896	9915	N/A	N/A	GCAGCTTCCTCAGCTTGGCT	126	1228
1322843	30022	30041	N/A	N/A	TTATTGAATCTCTACTACTT	83	1229
1322889	31019	31038	N/A	N/A	TATTGCTGCTATCTGTATCA	39	1230
1322901	28638	28657	N/A	N/A	CATCCAGCCCACATAAAGTT	95	1231
1322950	24813	24832	N/A	N/A	ATCTACTACAAAATTTTGTC	88	1232
1322956	24395	24414	N/A	N/A	AGAAGCATAATCAAAACAAA	102	1233
1322983	22723	22742	N/A	N/A	GGAAGATGCCAAAATTGACA	75	1234
1323014	37637	37656	4909	4928	AAAGTTCACAATTCTAGGGA	103	1235
1323022	37281	37300	4553	4572	ATACTTGTCACCTTACAGCTA	85	1236
1323034	34537	34556	1809	1828	TTTCTGGTCATACAAAGTCC	78	1237
1323085	11412	11431	N/A	N/A	CTCTTCCAAACTTTACAGAC	119	1238
1323095	6760	6779	N/A	N/A	GGACCTTGACCACCTTGGGC	126	1239
1323136	26040	26059	N/A	N/A	TCTGCCAACAACATGTGAGC	92	1240
1323194	35994	36013	3266	3285	CTAGTTACATTTTCCCCCT	63	1241
1323231	25004	25023	N/A	N/A	GCAGCCTCAATTCCTGGCCT	140	1242
1323285	8661	8680	N/A	N/A	AAGATCAGCTTTTAAATTCA	86	1243
1323294	28028	28047	N/A	N/A	GTATTTACAATTGCCAGACA	93	1244
1323317	30386	30405	N/A	N/A	CCAGCAGCCTCTAATCCTCC	112	1245

Table 17

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320909	24115	24134	N/A	N/A	TTTGTATTACACTATGTAA	73	1246
1320923	25784	25803	N/A	N/A	CCTTATGGCTTCTTTGGTCT	31	1247
1320925	7585	7604	N/A	N/A	CAACATTACAATCTCACTGA	68	1248
1320950	8660	8679	N/A	N/A	AGATCAGCTTTTAAATTCAT	94	1249
1320982	20087	20106	436	455	CGCAATTTAATTTCTTCATA	51	1250
1321006	13864	13883	N/A	N/A	CAGCTTTCCCCTCTGTGTTA	124	1251
1321036	35543	35562	2815	2834	GAGGTCTTAATGCATAGTAA	27	1252
1321054	6759	6778	N/A	N/A	GACCTTGACCACCTTGGGCA	99	1253
1321064	26760	26779	N/A	N/A	CTGGTGTACACATCCTGTAT	105	1254
1321095	29893	29912	N/A	N/A	AGCAAAGTCTCCAAGAGGTA	44	1255

1321097	25211	25230	N/A	N/A	TTTTCTCCCCATAACCCATT	95	1256
1321100	12314	12333	N/A	N/A	GGAGCATTTTCTCATAAGGCT	90	1257
1321119	35745	35764	3017	3036	AGTCTCCTATCATTGCCATT	45	1258
1321165	24812	24831	N/A	N/A	TCTACTACAAAATTTTGTC	89	1259
1321174	37280	37299	4552	4571	TACTTGTCACCTACAGCTAA	84	1260
1321181	5673	5692	N/A	N/A	GTTACTAGCATTATGCTTCA	103	1261
1321217	30384	30403	N/A	N/A	AGCAGCCTCTAATCCTCCTT	89	1262
1321265	25159	25178	N/A	N/A	CTCTATTTCATCTCCTACAAT	71	1263
1321280	11818	11837	N/A	N/A	TCACTTGTTTTTTCTACAAT	82	1264
1321300	25560	25579	N/A	N/A	CTATCAGAAATACCTCTCAT	71	1265
1321365	27455	27474	N/A	N/A	AGGTAATAAATAAATTCATC	115	1266
1321366	19797	19816	N/A	N/A	GCATACACCCTTCCACTCTT	53	1267
1321371	21014	21033	N/A	N/A	TGGTAAAGTTTTCAATCCAT	64	1268
1321512	25703	25722	N/A	N/A	TCTTTAGTCCTAAACCACAC	97	1269
1321516	26038	26057	N/A	N/A	TGCCAACAACATGTGAGCTT	100	1270
1321517	28295	28314	N/A	N/A	CTCCAGTAAAACTACTGCC	118	1271
1321523	36313	36332	3585	3604	ATCACAGCCCTCCCGAGGGC	148	1272
1321528	29448	29467	N/A	N/A	CCCATCATAAAATTAAATAC	124	1273
1321532	25280	25299	N/A	N/A	TGTCCTTAGCTATACTTGCCT	95	1274
1321554	25393	25412	N/A	N/A	CCCTTGTTTCAAAATTAACA	98	1275
1321561	27016	27035	N/A	N/A	CCTTAGTCCACTCTCCCACA	92	1276
1321608	31015	31034	N/A	N/A	GCTGCTATCTGTATCAGTCA	36	1277
1321609	28559	28578	N/A	N/A	CTAAGTTACAAAATTATACT	122	1278
1321612	37617	37636	4889	4908	GCTGTTCTAATTTTTAGTTA	95	1279
1321641	38204	38223	5476	5495	GTTTGTTCATAGAAACACT	98	1280
1321654	14599	14618	299	318	CCCGACAGACTCATCGCTCC	95	1281
1321675	19173	19192	N/A	N/A	CTTCTATTACATCATCAGAA	67	1282
1321678	11411	11430	N/A	N/A	TCTTCCAACTTTACAGACA	124	1283
1321709	20485	20504	N/A	N/A	CACACATCAAACAGCCTCCT	93	1284
1321734	33446	33465	N/A	N/A	ATACAGATGCTCCTAACTTA	54	1285
1321764	24394	24413	N/A	N/A	GAAGCATAATCAAAACAAAC	111	1286
1321819	7957	7976	N/A	N/A	TCCTTTTAATAATTTTTTCA	93	1287
1321848	31680	31699	N/A	N/A	TGTGCTTTCTCAATTTTTTA	56	1288
1321858	34165	34184	N/A	N/A	GTCGCCTAAGAACATACTAA	96	1289
1321869	16907	16926	N/A	N/A	AGGAAATTCCAACTAAGGG	60	1290
1321915	22222	22241	N/A	N/A	TGGAACTTTATTAATACAAT	93	1291
1322056	13570	13589	N/A	N/A	TTTCAGGACTTCCTTAAGCA	89	1292
1322091	4731	4750	N/A	N/A	TCACAGAACTATTTGCCTTA	73	1293
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	12	132
1322180	38633	38652	5905	5924	CTGAAGAGCCTCCTTGGAAC	81	1294
1322184	27992	28011	N/A	N/A	GGTTACAGAAATAAATAGTA	64	1295
1322237	18058	18077	N/A	N/A	AAGCTACTTTTATATTTTCT	67	1296
1322257	35992	36011	3264	3283	AGTTACATTTTTCCCCCTCA	52	1297

1322264	33706	33725	N/A	N/A	GCTTACCTGCCCTTAGTGAC	69	1298
1322355	9817	9836	N/A	N/A	AGCTGGGATCTTCTTGTTTA	93	1299
1322414	31840	31859	1373	1392	CAGCTTTTCATCCATGGTGT	38	1300
1322415	9467	9486	N/A	N/A	AGCTATAAACTTAAGGTCTC	75	1301
1322430	27222	27241	N/A	N/A	CCAGCTGCTAAACATGCGCC	106	1302
1322431	30180	30199	N/A	N/A	ACCAATCACATAATCCGGCA	76	1303
1322470	32677	32696	1481	1500	CGGGAGAGCAAATAATGCAA	21	1304
1322478	5035	5054	N/A	N/A	CATGATTATTTCTTTGGGAA	43	1305
1322504	18316	18335	N/A	N/A	TTCCACTTTTACATATCTGA	50	1306
1322508	29076	29095	N/A	N/A	CTGAGTTCCATCCCCAGAGA	88	1307
1322582	6051	6070	N/A	N/A	ATCATGTACCACACAGGTAT	96	1308
1322602	8387	8406	N/A	N/A	CTAAAACTTCATCCCTGAAT	131	1309
1322604	34536	34555	1808	1827	TTCTGGTCATACAAAGTCCT	91	1310
1322629	35100	35119	2372	2391	TCTGACTCATCTCATCCAAT	56	1311
1322643	22701	22720	N/A	N/A	CTGTTTATATATTTATTGAA	102	1312
1322752	9021	9040	N/A	N/A	GCAATTTACCATCTAAGTCT	65	1313
1322841	29511	29530	N/A	N/A	AACCCTTTTTTCATTACCTC	103	1314
1322850	16323	16342	N/A	N/A	CTTGAATAATTAAGTAGAAA	124	1315
1323001	30021	30040	N/A	N/A	TATTGAATCTCTACTACTTG	74	1316
1323084	22456	22475	N/A	N/A	TTCGCCTAATTTTTCTCTCA	58	1317
1323099	31237	31256	N/A	N/A	TATGATCTATTCCCTAAGAGA	71	1318
1323117	26938	26957	N/A	N/A	ACACAAAATCCCCAAAAGCC	117	1319
1323197	24921	24940	N/A	N/A	GGCCAGTTCTCTTTCATTTA	111	1320
1323250	28637	28656	N/A	N/A	ATCCAGCCCACATAAAGTTT	106	1321
1323304	13034	13053	N/A	N/A	TGTCTGTTTAATCTGACATA	116	1322

Table 18

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320903	22219	22238	N/A	N/A	AACTTTATTAATACAATGCC	91	1323
1320912	35736	35755	3008	3027	TCATTGCCATTTTCTGGTCC	48	1324
1320932	9806	9825	N/A	N/A	TCTTGTTTATCTCCTTGCCA	85	1325
1320995	37562	37581	4834	4853	AAGGAATAAGACCTACATCA	67	1326
1321016	6035	6054	N/A	N/A	GTATATGGTTTCCTAAGCCA	73	1327
1321019	31011	31030	N/A	N/A	CTATCTGTATCAGTCAGCTA	37	1328
1321108	9446	9465	N/A	N/A	CCTGAGCCTTTCCCTAGGTA	89	1329
1321153	22699	22718	N/A	N/A	GTTTATATATTTATTGAATC	98	1330
1321196	37267	37286	4539	4558	CAGCTAAGCATATACTGATA	82	1331
1321202	35533	35552	2805	2824	TGCATAGTAAAAGATTGCCT	91	1332
1321204	20479	20498	N/A	N/A	TCAAACAGCCTCCTCTGGAA	101	1333

1321206	13845	13864	N/A	N/A	AACTGCATCATAACTGGTGA	104	1334
1321214	28558	28577	N/A	N/A	TAAGTTACAAAATTATACTA	111	1335
1321266	27015	27034	N/A	N/A	CTTAGTCCACTCTCCCACAT	84	1336
1321320	26758	26777	N/A	N/A	GGTGTACACATCCTGTATAA	89	1337
1321334	24918	24937	N/A	N/A	CAGTTCTCTTTTCATTTATGC	46	1338
1321381	23677	23696	N/A	N/A	ATAGAATATCCCCAACACAC	98	1339
1321385	36292	36311	3564	3583	GCTGCCTTCAACCTTTTCTT	90	1340
1321472	34162	34181	N/A	N/A	GCCTAAGAACATACTAATTG	94	1341
1321487	38623	38642	5895	5914	TCCTTGGAACGAACTAATCC	102	1342
1321563	25558	25577	N/A	N/A	ATCAGAAATACCTCTCATT	70	1343
1321658	28294	28313	N/A	N/A	TCCAGTAAAAACTACTGCCT	85	1344
1321682	31818	31837	1351	1370	GCTCTGGCTTTTCACACAATA	43	1345
1321698	25158	25177	N/A	N/A	TCTATTCATCTCCTACAATT	91	1346
1321699	26937	26956	N/A	N/A	CACAAAATCCCCAAAAGCCT	111	1347
1321704	25279	25298	N/A	N/A	GTCTTAGCTATACTTGCCTT	67	1348
1321746	29073	29092	N/A	N/A	AGTTCATCCCCAGAGATAA	80	1349
1321749	25392	25411	N/A	N/A	CCTTGGTTCAAAATTAACAC	107	1350
1321768	27447	27466	N/A	N/A	AATAAATTCATCTTGTCTTA	75	1351
1321790	7931	7950	N/A	N/A	GTTATGTAAACATTAACATAC	77	1352
1321799	25990	26009	N/A	N/A	GACTGACTCCTTGACTGCTT	66	1353
1321826	13011	13030	N/A	N/A	ATAGCAATTCTGACAGCTT	89	1354
1321871	33443	33462	N/A	N/A	CAGATGCTCCTAACTTACAA	74	1355
1321894	4958	4977	N/A	N/A	TGGACCTCTCCTCTCAACAA	79	1356
1321907	32676	32695	1480	1499	GGGAGAGCAAATAATGCAAT	22	1357
1321938	35097	35116	2369	2388	GACTCATCTCATCCAATGCA	50	1358
1321979	18057	18076	N/A	N/A	AGCTACTTTTATATTTTCTT	53	1359
1321983	18313	18332	N/A	N/A	CACCTTTTACATATCTGAGGC	43	1360
1322015	5669	5688	N/A	N/A	CTAGCATTATGCTTCAGCCA	97	1361
1322035	19165	19184	N/A	N/A	ACATCATCAGAAACCACAAA	87	1362
1322037	11817	11836	N/A	N/A	CACCTGTTTTTTTCTACAATT	88	1363
1322055	31677	31696	N/A	N/A	GCTTTCTCAATTTTTTATGT	37	1364
1322130	27221	27240	N/A	N/A	CAGCTGCTAAACATGCGCCA	98	1365
1322169	22454	22473	N/A	N/A	CGCCTAATTTTTCTCTCACA	40	1366
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	3	132
1322191	13569	13588	N/A	N/A	TTCAGGACTTCCTTAAGCAT	90	1367
1322238	8659	8678	N/A	N/A	GATCAGCTTTTAAATTCATT	66	1368
1322263	21012	21031	N/A	N/A	GTAAAGTTTTTCAATCCATTT	13	1369
1322273	11394	11413	N/A	N/A	ACAGTGGCTTTCAAAGATAA	97	1370
1322282	12313	12332	N/A	N/A	GAGCATTTCTCATAAGGCTG	85	1371
1322329	35988	36007	3260	3279	ACATTTTTCCCCCTCAGTTC	78	1372
1322342	25702	25721	N/A	N/A	CTTTAGTCCTAAACCACACA	85	1373
1322404	34515	34534	1787	1806	CTGTAGTTCTTCACTTGTTT	33	1374
1322408	8980	8999	N/A	N/A	TGCAATAGACTCCAGAGTTC	83	1375

1322420	30018	30037	N/A	N/A	TGAATCTCTACTACTTGTC	33	1376
1322466	25775	25794	N/A	N/A	TTCTTTGGTCTCTTTAGCCC	23	1377
1322479	7570	7589	N/A	N/A	ACTGAGATAACTTTTCAGGAT	70	1378
1322490	27988	28007	N/A	N/A	ACAGAAATAAATAGTATCCA	90	1379
1322498	38177	38196	5449	5468	CGGTTATGTCCTTCTACAAT	51	1380
1322542	25207	25226	N/A	N/A	CTCCCCATAACCCATTTTTC	95	1381
1322706	16297	16316	N/A	N/A	AGGAAGAGACATCAACACTC	69	1382
1322710	33688	33707	N/A	N/A	ACTTGCTCAAATTCACAAAA	64	1383
1322909	29892	29911	N/A	N/A	GCAAAGTCTCCAAGAGGTAA	46	1384
1322957	30142	30161	N/A	N/A	ACTGAGACAATTCATGTACA	84	1385
1322958	29510	29529	N/A	N/A	ACCCTTTTTTCATTACCTCC	83	1386
1322963	6749	6768	N/A	N/A	ACCTTGGGCACATGTGGCCA	92	1387
1322968	30380	30399	N/A	N/A	GCCTCTAATCCTCCTTGGAC	109	1388
1323047	14598	14617	298	317	CCGACAGACTCATCGCTCCT	51	1389
1323058	29447	29466	N/A	N/A	CCATCATAAAATTAAATACT	104	1390
1323121	8383	8402	N/A	N/A	AACTTCATCCCTGAATAGAA	92	1391
1323145	16875	16894	N/A	N/A	TGGTAACCAAACCTCAAAGTT	65	1392
1323188	24801	24820	N/A	N/A	ATTTTGTCAAACCACTAAA	80	1393
1323192	24389	24408	N/A	N/A	ATAATCAAAACAACTGGGC	84	1394
1323255	4725	4744	N/A	N/A	AACTATTTGCCTTACTGCCT	84	1395
1323287	28636	28655	N/A	N/A	TCCAGCCCACATAAAGTTTA	105	1396
1323303	19793	19812	N/A	N/A	ACACCCTTCCACTCTTTTTC	76	1397
1323314	20086	20105	435	454	GCAATTTAATTTCTTCATAA	68	1398
1323331	31236	31255	N/A	N/A	ATGATCTATTCCTAAGAGAA	53	1399

Table 19

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1321114	25701	25720	N/A	N/A	TTTAGTCCTAAACCACACAA	91	1400
1321132	30006	30025	N/A	N/A	ACTTGTCAGCAATGTGCTA	87	1401
1321160	31676	31695	N/A	N/A	CTTTCTCAATTTTTTATGTT	39	1402
1321179	35096	35115	2368	2387	ACTCATCTCATCCAATGCAA	56	1403
1321255	25157	25176	N/A	N/A	CTATTCATCTCCTACAATTT	89	1404
1321279	26936	26955	N/A	N/A	ACAAAATCCCCAAAAGCCTA	98	1405
1321330	20076	20095	425	444	TTCTTCATAAACATTCAGCT	56	1406
1321338	5657	5676	N/A	N/A	TTCAGCCAAATCCCCAAGGA	101	1407
1321340	11816	11835	N/A	N/A	ACTTGTTTTTCTACAATTA	98	1408
1321354	18714	18733	N/A	N/A	GCTAGACTGATCTTAAACTC	94	1409
1321378	38176	38195	5448	5467	GGTTATGTCCTTCTACAATT	45	1410
1321398	12969	12988	N/A	N/A	AACTTTTTCCATCCCTTCAA	93	1411

1321410	25989	26008	N/A	N/A	ACTGACTCCTTGACTGCTTA	81	1412
1321421	12250	12269	N/A	N/A	AAACTGTATTTCTCCCTCAT	89	1413
1321464	38620	38639	5892	5911	TTGGAACGAACATAATCCTGA	106	1414
1321525	24917	24936	N/A	N/A	AGTTCTCTTTCATTTATGCA	58	1415
1321527	34506	34525	1778	1797	TTCACCTGTTTTACTTTTCGC	21	1416
1321535	8657	8676	N/A	N/A	TCAGCTTTTAAATTCATTTA	103	1417
1321546	9425	9444	N/A	N/A	GTACAGTGACTTTCTAATTT	59	1418
1321567	33686	33705	N/A	N/A	TTGCTCAAATTCACAAAACC	92	1419
1321656	11379	11398	N/A	N/A	GATAAAGTCTTTTATTAGCA	89	1420
1321688	27212	27231	N/A	N/A	AACATGCGCCAGCATACCAA	129	1421
1321693	13832	13851	N/A	N/A	CTGGTGATATCACCTGGAT	103	1422
1321726	29446	29465	N/A	N/A	CATCATAAAATTAATACTA	111	1423
1321739	27440	27459	N/A	N/A	TCATCTTGTCCTAATTATTT	56	1424
1321807	21010	21029	N/A	N/A	AAAGTTTTCAATCCATTTTA	67	1425
1321818	36289	36308	3561	3580	GCCTTCAACCTTTTCTTCCA	77	1426
1321822	37266	37285	4538	4557	AGCTAAGCATATACTGATAA	76	1427
1321829	30994	31013	N/A	N/A	CTATCGCCAGAATAATGTCT	67	1428
1321831	16296	16315	N/A	N/A	GGAAGAGACATCAACACTCC	69	1429
1321844	35720	35739	2992	3011	GTCCCAAGACTTCTTGCCATA	75	1430
1321883	30379	30398	N/A	N/A	CCTCTAATCCTCCTTGACC	104	1431
1321900	31226	31245	N/A	N/A	CCTAAGAGAATTCTAATTGA	85	1432
1321919	25206	25225	N/A	N/A	TCCCCATAACCCATTTTTC	112	1433
1321933	24799	24818	N/A	N/A	TTTGTCAAACCACTAAAGT	78	1434
1321944	25766	25785	N/A	N/A	CTCTTTAGCCCCTATTCACC	73	1435
1321974	29052	29071	N/A	N/A	GATTCAGTAACAATAGGCTC	38	1436
1322124	22218	22237	N/A	N/A	ACTTTATTAATACAATGCCA	105	1437
1322142	6033	6052	N/A	N/A	ATATGGTTTCCTAAGCCAAC	95	1438
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	1	132
1322188	18056	18075	N/A	N/A	GCTACTTTTATATTTCTTA	62	1439
1322193	34160	34179	N/A	N/A	CTAAGAACATACTAATTGCC	89	1440
1322283	28627	28646	N/A	N/A	CATAAAGTTTAAAAATTTCC	112	1441
1322288	33439	33458	N/A	N/A	TGCTCCTAACTTACAATGGA	80	1442
1322316	37531	37550	4803	4822	GTGCAGGTACATATATGAAT	33	1443
1322337	14583	14602	283	302	CTCCTGTTCCACCTCAGGAT	93	1444
1322353	29822	29841	N/A	N/A	AGGTTTGTCTGATCTACAGA	53	1445
1322354	29509	29528	N/A	N/A	CCCTTTTTTCATTACCTCCC	75	1446
1322388	35987	36006	3259	3278	CATTTTCCCCCTCAGTTCA	91	1447
1322486	28557	28576	N/A	N/A	AAGTTACAAAATTATACTAT	103	1448
1322497	22453	22472	N/A	N/A	GCCTAATTTTCTCTCACAT	25	1449
1322517	8939	8958	N/A	N/A	TGCCAGTACAATTCTTGCTCT	82	1450
1322555	25556	25575	N/A	N/A	CAGAAATACCTCTCATTATC	82	1451
1322596	31816	31835	1349	1368	TCTGGCTTTCACACAATATA	45	1452
1322607	32662	32681	1466	1485	TGCAATACAAATTCCAATA	42	1453

1322649	16873	16892	N/A	N/A	GTAACCAAACCTCAAAGTTCA	77	1454
1322696	19786	19805	N/A	N/A	TCCACTCTTTTTCAATGCAT	63	1455
1322726	25265	25284	N/A	N/A	TGCCTTTGCTCTCTCTACTC	79	1456
1322835	28285	28304	N/A	N/A	AACTACTGCCTTACCTTGTA	103	1457
1322874	24388	24407	N/A	N/A	TAATCAAAACAAACTGGGCA	77	1458
1322888	25391	25410	N/A	N/A	CTTGTTTCAAATTAACACT	39	1459
1322898	23462	23481	N/A	N/A	ACTTCACCTTTAAACCCTTCC	88	1460
1322961	7569	7588	N/A	N/A	CTGAGATAACTTTCAGGATC	93	1461
1322992	7831	7850	N/A	N/A	TGGACATTTAATCTAATATA	88	1462
1323000	9805	9824	N/A	N/A	CTTGTTTATCTCCTTGCCAT	96	1463
1323061	4957	4976	N/A	N/A	GGACCTCTCCTCTCAACAAA	87	1464
1323101	20416	20435	N/A	N/A	ACTAAGTCTTAGATTTGTCA	44	1465
1323106	27978	27997	N/A	N/A	ATAGTATCCACACTCAGGAA	58	1466
1323109	35516	35535	2788	2807	CCTGGCTTTAATCCTAAACC	89	1467
1323200	8369	8388	N/A	N/A	ATAGAATACATCACATCCCC	84	1468
1323209	26752	26771	N/A	N/A	CACATCCTGTATAATCCCCT	57	1469
1323223	18312	18331	N/A	N/A	ACTTTTACATATCTGAGGCC	80	1470
1323229	4724	4743	N/A	N/A	ACTATTTGCCTTACTGCCTT	90	1471
1323243	27014	27033	N/A	N/A	TTAGTCCACTCTCCCACATA	94	1472
1323271	6734	6753	N/A	N/A	GGCCAGGACCTCTTGAGGCT	106	1473
1323297	13568	13587	N/A	N/A	TCAGGACTTCCTTAAGCATT	78	1474
1323306	30132	30151	N/A	N/A	TTCATGTACAATACTTAGCA	44	1475
1323334	22675	22694	N/A	N/A	ACAAAACATCTTCCTTACCT	96	1476

Table 20

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320893	31815	31834	1348	1367	CTGGCTTTCACACAATATAC	59	1477
1320996	36288	36307	3560	3579	CCTTCAACCTTTTCTTCCAC	81	1478
1321026	30131	30150	N/A	N/A	TCATGTACAATACTTAGCAT	60	1479
1321061	9748	9767	N/A	N/A	AATCCTGGCATTTCCTCCCA	93	1480
1321107	25554	25573	N/A	N/A	GAAATACCTCTCATTATCTA	110	1481
1321190	30378	30397	N/A	N/A	CTCTAATCCTCCTTGGACCA	106	1482
1321209	24371	24390	N/A	N/A	GCAAAAAGGAAATTTATGGAA	103	1483
1321232	29819	29838	N/A	N/A	TTTGTCTGATCTACAGACAT	127	1484
1321261	23374	23393	N/A	N/A	CTTGACCTTAATTATTGGAA	61	1485
1321262	12248	12267	N/A	N/A	ACTGTATTTCTCCCTCATTC	98	1486
1321329	28274	28293	N/A	N/A	TACCTTGTATTTTCAAGTATCA	91	1487
1321355	4952	4971	N/A	N/A	TCTCCTCTCAACAAATGGCA	103	1488
1321369	35914	35933	3186	3205	GCTAGACGAGAAGCCAGCCT	115	1489

1321372	33685	33704	N/A	N/A	TGCTCAAATTCACAAAACCC	109	1490
1321406	25765	25784	N/A	N/A	TCTTTAGCCCCTATTACCT	106	1491
1321493	13830	13849	N/A	N/A	GGTGATATCACCTGGATCA	141	1492
1321499	29051	29070	N/A	N/A	ATTGAGTAACAATAGGCTCA	56	1493
1321510	8368	8387	N/A	N/A	TAGAATACATCACATCCCCT	100	1494
1321526	16705	16724	N/A	N/A	ATGTATGTATACACAATGTG	81	1495
	16730	16749					
1321578	18282	18301	N/A	N/A	GCTGGCATTAAAAATACCTT	91	1496
1321611	27208	27227	N/A	N/A	TGCGCCAGCATACCAATGGA	88	1497
1321660	25700	25719	N/A	N/A	TTAGTCCTAAACCACACAAC	118	1498
1321662	29508	29527	N/A	N/A	CCTTTTTTCATTACCTCCCC	83	1499
1321700	30002	30021	N/A	N/A	GTCCAGCAATGTGCTAGGTA	53	1500
1321763	5653	5672	N/A	N/A	GCCAAATCCCCAAGGAAGGA	100	1501
1321781	13567	13586	N/A	N/A	CAGGACTTCCTTAAGCATTT	102	1502
1321812	34505	34524	1777	1796	TCACTTGTTTTACTTTTCGCT	36	1503
1321951	7806	7825	N/A	N/A	AATGCATTTATAATTTTGGT	99	1504
1321964	35719	35738	2991	3010	TCCCAAGACTTCTTGCATAC	60	1505
1321987	26748	26767	N/A	N/A	TCCTGTATAATCCCCCTCCTC	94	1506
1321988	9423	9442	N/A	N/A	ACAGTGACTTTCTAATTTTC	78	1507
1322020	6028	6047	N/A	N/A	GTTTCCTAAGCCAACAGGTA	75	1508
1322032	31674	31693	N/A	N/A	TTCTCAATTTTTTATGTTCA	34	1509
1322060	25968	25987	N/A	N/A	CAGAAGAGCCAGCTAAGCCA	136	1510
1322062	16295	16314	N/A	N/A	GAAGAGACATCAACACTCCA	107	1511
1322126	37530	37549	4802	4821	TGCAGGTACATATATGAATA	52	1512
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	19	132
1322196	27977	27996	N/A	N/A	TAGTATCCCACTCAGGAAA	120	1513
1322204	22673	22692	N/A	N/A	AAAACATCTTCCTTACCTGT	112	1514
1322218	6710	6729	N/A	N/A	CATGAATGCATCCTTAACCT	89	1515
1322230	35069	35088	2341	2360	GACAGGCTTTTTTCATGATTT	52	1516
1322243	34159	34178	N/A	N/A	TAAGAACATACTAATTGCCT	95	1517
1322249	22217	22236	N/A	N/A	CTTTATTAATACAATGCCAA	115	1518
1322286	4717	4736	N/A	N/A	GCCTTACTGCCTTCTGCCC	92	1519
1322304	29391	29410	N/A	N/A	GAAGAATGCTTTCCAATGGT	48	1520
1322313	25264	25283	N/A	N/A	GCCTTTGCTCTCTCTACTCC	108	1521
1322351	28556	28575	N/A	N/A	AGTTACAAAATTATACTATA	105	1522
1322365	20075	20094	424	443	TCTTCATAAACATTCAGCTT	94	1523
1322369	20390	20409	N/A	N/A	TAGCTTTGTCTTTACAGCCC	110	1524
1322370	27013	27032	N/A	N/A	TAGTCCACTCTCCACATAC	98	1525
1322382	24915	24934	N/A	N/A	TTCTCTTTCATTTATGCAGC	33	1526
1322450	17708	17727	N/A	N/A	TCATATGCAATAATTAGCTC	61	1527
1322480	38175	38194	5447	5466	GTTATGTCCTTCTACAATTC	63	1528
1322496	20999	21018	N/A	N/A	TCCATTTTAACTAATTAATC	135	1529
1322506	8938	8957	N/A	N/A	GCCAGTACAATTCCTGTCTA	66	1530

1322576	25155	25174	N/A	N/A	ATTCATCTCCTACAATTTTC	108	1531
1322615	38583	38602	5855	5874	AAGGGCAAACAGTTTAGTTC	87	1532
1322620	26930	26949	N/A	N/A	TCCCCAAAAGCCTACAGGAC	121	1533
1322682	35515	35534	2787	2806	CTGGCTTTAATCCTAAACCA	122	1534
1322762	12968	12987	N/A	N/A	ACTTTTCCATCCCTTCAAT	89	1535
1322767	32661	32680	1465	1484	GCAATACAAATTCCAACAT	46	1536
1322788	25205	25224	N/A	N/A	CCCCATAACCCATTTTTCCT	126	1537
1322820	11812	11831	N/A	N/A	GTTTTTCTACAATTAAGTA	80	1538
1322834	37241	37260	4513	4532	CATGTAGAACATAATGCAGA	86	1539
1322853	11378	11397	N/A	N/A	ATAAAGTCTTTTATTAGCAG	112	1540
1322892	8656	8675	N/A	N/A	CAGCTTTTAAATTCATTTAT	131	1541
1322894	18628	18647	N/A	N/A	GCCCGGCCAATTTAGCAGAT	116	1542
1322917	14582	14601	282	301	TCCTGTTCCACCTCAGGATA	144	1543
1322921	33438	33457	N/A	N/A	GCTCCTAACTTACAATGGAA	72	1544
1322936	24798	24817	N/A	N/A	TTGTCAAAACCACTAAAGTA	91	1545
1323054	27439	27458	N/A	N/A	CATCTTGTCTTAATTATTTT	88	1546
1323065	25390	25409	N/A	N/A	TTGGTTCAAAATTAACACTA	72	1547
1323067	22452	22471	N/A	N/A	CCTAATTTTTCTCTCACATC	81	1548
1323175	31224	31243	N/A	N/A	TAAGAGAATTCTAATTGATT	124	1549
1323215	30992	31011	N/A	N/A	ATCGCCAGAATAATGTCTAA	59	1550
1323252	28626	28645	N/A	N/A	ATAAAGTTTAAAAATTTCCC	132	1551
1323261	7545	7564	N/A	N/A	TGAGCTGTAACTTAAGGTC	85	1552
1323295	19785	19804	N/A	N/A	CCACTCTTTTCAATGCATA	52	1553

Table 21

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320887	13557	13576	N/A	N/A	TTAAGCATTTCTCGCAGGGC	85	1554
1320947	31660	31679	N/A	N/A	TGTTCAAGTCTAACATTGGCC	38	1555
1320999	17660	17679	N/A	N/A	ACTAATGTAATATTTACTTC	93	1556
1321025	18611	18630	N/A	N/A	GATTTGAGAACTTTTACCTA	76	1557
1321031	5637	5656	N/A	N/A	AGGATAAAAAGACTCAGCCA	87	1558
1321041	13820	13839	N/A	N/A	CCCTGGATCACCACCTGGGT	106	1559
1321055	24370	24389	N/A	N/A	CAAAAGGAAATTTATGGAAT	107	1560
1321128	N/A	N/A	1119	1138	AAGCTTGTATTTTCAATATCA	39	1561
1321138	30351	30370	N/A	N/A	TGTGGAATACATTTTATTCC	86	1562
1321150	22669	22688	N/A	N/A	CATCTTCCTTACCTGTGGTC	82	1563
1321154	8366	8385	N/A	N/A	GAATACATCACATCCCCTTA	85	1564
1321219	22447	22466	N/A	N/A	TTTTTCTCTCACATCGATTA	99	1565
1321225	33684	33703	N/A	N/A	GCTCAAATTCACAAAACCCA	65	1566

1321289	16703	16722	N/A	N/A	GTATGTATACACAATGTGTG	94	1567
	16728	16747					
1321339	34494	34513	1766	1785	ACTTTCGCTTTCATCTTCAT	54	1568
1321341	6672	6691	N/A	N/A	AAGTTGATTTTCAGACCGGTC	91	1569
1321361	4942	4961	N/A	N/A	ACAAATGGCATTCCAAAGTT	72	1570
1321375	25699	25718	N/A	N/A	TAGTCCTAAACCACACAACA	76	1571
1321396	12577	12596	N/A	N/A	AAGTATGGAATTTAATCCAT	95	1572
1321407	19778	19797	N/A	N/A	TTTTCAATGCATATAAGCCA	47	1573
1321411	12247	12266	N/A	N/A	CTGTATTTCTCCCTCATTC	78	1574
1321470	29507	29526	N/A	N/A	CTTTTTTCATTACCTCCCCA	79	1575
1321474	8857	8876	N/A	N/A	GTATTTGTAAAACTGCTTC	72	1576
1321566	27011	27030	N/A	N/A	GTCCACTCTCCACATACCA	69	1577
1321568	11288	11307	N/A	N/A	CAGCTGCTTTACCTGTGTTC	92	1578
1321597	29370	29389	N/A	N/A	TTGGAGGAAAACAAACAAC	68	1579
1321602	25389	25408	N/A	N/A	TGGTTCAAAATTAACACTAA	95	1580
1321613	20996	21015	N/A	N/A	ATTTTAACATAATTAATCCAT	103	1581
1321661	25263	25282	N/A	N/A	CCTTTGCTCTCTCTACTCCT	62	1582
1321755	25154	25173	N/A	N/A	TTCATCTCCTACAATTTTCC	63	1583
1321759	26742	26761	N/A	N/A	ATAATCCCCTCCTCTTGAGC	66	1584
1321785	35712	35731	2984	3003	ACTTCTTGCATACACTATCT	47	1585
1321794	8653	8672	N/A	N/A	CTTTTAAATTCATTTATGGT	77	1586
1321798	18281	18300	N/A	N/A	CTGGCATTAAAAATACCTTA	78	1587
1321837	34158	34177	N/A	N/A	AAGAACATACTAATTGCCTT	69	1588
1321840	7543	7562	N/A	N/A	AGCTGTAAACTTAAGGTCTT	70	1589
1321909	30130	30149	N/A	N/A	CATGTACAATACTTAGCATA	74	1590
1321947	20389	20408	N/A	N/A	AGCTTTGTCTTTACAGCCCC	75	1591
1321971	37224	37243	4496	4515	AGAGTGGAATGCAACTGCCT	64	1592
1322010	24913	24932	N/A	N/A	CTCTTTCATTTATGCAGCGC	35	1593
1322065	14549	14568	249	268	TGATGTGCGACCTCTACTTTT	55	1594
1322121	29811	29830	N/A	N/A	ATCTACAGACATCTGAAAAC	102	1595
1322147	28555	28574	N/A	N/A	GTTACAAAATTATACTATAC	91	1596
1322156	11799	11818	N/A	N/A	TTAAGTAATATCAAATGGTA	88	1597
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	2	132
1322179	22207	22226	N/A	N/A	ACAATGCCAAAACCTTCATT	85	1598
1322223	9422	9441	N/A	N/A	CAGTGACTTTCTAATTTTCC	66	1599
1322235	25551	25570	N/A	N/A	ATACCTCTCATTATCTATTT	54	1600
1322268	35514	35533	2786	2805	TGGCTTTAATCCTAAACCAT	86	1601
1322275	38172	38191	5444	5463	ATGTCCTTCTACAATTCAGT	49	1602
1322448	4716	4735	N/A	N/A	CCTTACTGCCTTCCTGCCCC	98	1603
1322460	20038	20057	387	406	ATTTGGTACTAGTAATATTC	38	1604
1322463	35059	35078	2331	2350	TTCATGATTTTACACATGGA	66	1605
1322523	27438	27457	N/A	N/A	ATCTTGTCCTAATTATTTTA	51	1606
1322536	5985	6004	N/A	N/A	GCTCACAGACCACCTGGACT	88	1607

1322579	27966	27985	N/A	N/A	CTCAGGAAACTCACAAACAA	89	1608
1322589	9744	9763	N/A	N/A	CTGGCATTTCCTCCCATTCT	85	1609
1322600	33437	33456	N/A	N/A	CTCCTAACTTACAATGGAAT	92	1610
1322609	35882	35901	3154	3173	GACAGAGACCACCCATAACA	64	1611
1322613	37529	37548	4801	4820	GCAGGTACATATATGAATAT	36	1612
1322680	24797	24816	N/A	N/A	TGTCAAAACCACTAAAGTAA	55	1613
1322759	7805	7824	N/A	N/A	ATGCATTTATAATTTTGGTT	81	1614
1322773	28625	28644	N/A	N/A	TAAAGTTTAAAAATTTCCCC	113	1615
1322790	31222	31241	N/A	N/A	AGAGAATTCTAATTGATTTA	95	1616
1322798	25949	25968	N/A	N/A	ACGCTTGGA CTCTGACTCA	52	1617
1322803	30985	31004	N/A	N/A	GAATAATGTCTAACAAGCCG	32	1618
1322855	25204	25223	N/A	N/A	CCCATAACCCATTTTTCCTT	74	1619
1322858	16293	16312	N/A	N/A	AGAGACATCAACACTCCAGA	44	1620
1322877	29029	29048	N/A	N/A	AATCTGTATTTTAAAAGCAA	103	1621
1322946	38557	38576	5829	5848	GCAAGGCTATGCAATACCAC	61	1622
1322954	27207	27226	N/A	N/A	GCGCCAGCATACCAATGGAC	95	1623
1323008	23336	23355	N/A	N/A	CAGGATACTTTCATATTTTA	18	1624
1323127	29989	30008	N/A	N/A	CTAGGTATTTTCATATTTGT	21	1625
1323217	31814	31833	1347	1366	TGGCTTTCACACAATATACA	41	1626
1323232	25764	25783	N/A	N/A	CTTTAGCCCCTATTCACCTT	69	1627
1323234	26925	26944	N/A	N/A	AAAAGCCTACAGGACAGCCT	58	1628
1323237	36287	36306	3559	3578	CTTCAACCTTTTCTTCCACC	43	1629
1323308	32554	32573	N/A	N/A	GCTGTGTGAAAGACTAGCCA	97	1630

Table 22

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320897	25923	25942	N/A	N/A	CTTTGAGACAATAAACAGCT	53	1631
1320958	7528	7547	N/A	N/A	GTCTTGAGTTTTCAACATGA	39	1632
1320969	27965	27984	N/A	N/A	TCAGGAAACTCACAAACAAT	91	1633
1321007	24796	24815	N/A	N/A	GTCAAAACCACTAAAGTAAT	58	1634
1321091	16702	16721	N/A	N/A	TATGTATACACAATGTGTGT	86	1635
	16727	16746					
1321116	20658	20677	N/A	N/A	ACAATGATAAACCTATTTTA	87	1636
1321126	38553	38572	5825	5844	GGCTATGCAATACCACAGCA	82	1637
1321158	16292	16311	N/A	N/A	GAGACATCAACACTCCAGAA	42	1638
1321168	11752	11771	N/A	N/A	CTGCTTTACCAAGTCTGTTA	96	1639
1321173	24355	24374	N/A	N/A	GGAATGGA ACTTACTGGAGC	55†	1640
1321194	26740	26759	N/A	N/A	AATCCCCTCCTCTTGAGCAT	59	1641
1321237	25763	25782	N/A	N/A	TTTAGCCCCTATTCACCTTT	74	1642

1321301	22657	22676	801	820	CTGTGGTCTTTATACAATGT	33	1643
1321308	35711	35730	2983	3002	CTTCTTGACATACACTATCTT	74	1644
1321373	35058	35077	2330	2349	TCATGATTTTACACATGGAA	38	1645
1321418	18608	18627	N/A	N/A	TTGAGAACTTTTACCTATGT	47	1646
1321536	13532	13551	N/A	N/A	TAGCGGTAATGAACTCCCTT	76	1647
1321544	5984	6003	N/A	N/A	CTCACAGACCACCTGGACTC	91	1648
1321549	30866	30885	N/A	N/A	GTCTGTACAAGAAATTTCAA	67	1649
1321550	12245	12264	N/A	N/A	GTATTTCTCCCTCATTCTG	90	1650
1321590	31659	31678	N/A	N/A	GTTCACTCTAACATTGGCCT	57	1651
1321615	6482	6501	N/A	N/A	GGACTGGCCTATACAGCCTC	102	1652
1321630	35881	35900	3153	3172	ACAGAGACCACCCATAACAA	77	1653
1321711	36286	36305	3558	3577	TTCAACCTTTTCTTCCACCA	43	1654
1321766	37213	37232	4485	4504	CAACTGCCTTTTCATGTCTA	45	1655
1321776	33683	33702	N/A	N/A	CTCAAATTCACAAAACCCAC	84	1656
1321779	20033	20052	382	401	GTA TAGTAATATTCTGACA	38	1657
1321800	25262	25281	N/A	N/A	CTTTGCTCTCTCTACTCCTC	56	1658
1321845	38171	38190	5443	5462	TGTCCTTCTACAATTCAGTA	54	1659
1321861	24894	24913	N/A	N/A	CCTGGACTTCATCCATGTTT	86	1660
1321888	32480	32499	N/A	N/A	GCACTGAGTCCACAGCAACC	69	1661
1321889	8836	8855	N/A	N/A	TTGTGTTAAACATAAATCTC	90	1662
1321897	26905	26924	N/A	N/A	GAGGTTGACCCTAATCTTGT	82	1663
1321908	27437	27456	N/A	N/A	TCTTGTCTTAATTATTTTAC	58	1664
1321925	28263	28282	1108	1127	TCAGTATCAAACCTTATCTC	66	1665
1321932	7790	7809	N/A	N/A	TGGTTGCTTTCAACCTTTCA	97	1666
1321963	12576	12595	N/A	N/A	AGTATGGAATTTAATCCATT	93	1667
1321984	8652	8671	N/A	N/A	TTTTAAATTCATTTATGGTT	98	1668
1321985	22206	22225	N/A	N/A	CAATGCCAAAACCTTCATTC	85	1669
1321996	25698	25717	N/A	N/A	AGTCCTAAACCACACAACAC	83	1670
1322021	11175	11194	N/A	N/A	TTTTAGGATCCTCCTATTCT	97	1671
1322052	9743	9762	N/A	N/A	TGGCATTTCTCCCATCTC	148	1672
1322053	22446	22465	N/A	N/A	TTTTCTCTCACATCGATTAA	85	1673
1322090	33435	33454	N/A	N/A	CCTAACTTACAATGGAATTA	78	1674
1322122	25388	25407	N/A	N/A	GGTTCAAAATTAACACTAAA	44	1675
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	1	132
1322213	14521	14540	N/A	N/A	TTTTAGATTTTTTCCACCTA	62	1676
1322252	29988	30007	N/A	N/A	TAGGTATTTTCATATTTGTT	17	1677
1322327	29028	29047	N/A	N/A	ATCTGTATTTTAAAAGCAAA	104	1678
1322341	34157	34176	N/A	N/A	AGAACATACTAATTGCCTTA	50	1679
1322376	29368	29387	N/A	N/A	GGAGGAAAACAAACAACCTGT	58	1680
1322435	9421	9440	N/A	N/A	AGTGACTTTCTAATTTTCCC	63	1681
1322532	25550	25569	N/A	N/A	TACCTCTCATTATCTATTTG	52	1682
1322540	30115	30134	N/A	N/A	GCATAGTACCTTACATATAA	8	1683
1322554	28554	28573	N/A	N/A	TTACAAAATTATACTATACA	107	1684

1322590	31813	31832	1346	1365	GGCTTTCACACAATATACAG	39	1685
1322632	29506	29525	N/A	N/A	TTTTTTCATTACCTCCCCAA	69	1686
1322647	20388	20407	N/A	N/A	GCTTTGTCTTTACAGCCCCC	57	1687
1322659	17659	17678	N/A	N/A	CTAATGTAATATTTACTTCA	79	1688
1322776	29807	29826	N/A	N/A	ACAGACATCTGAAAACCGAC	68	1689
1322813	31215	31234	N/A	N/A	TCTAATTGATTTACAAGTAC	50	1690
1322836	19763	19782	N/A	N/A	AGCCAAGTTATTACTTATGA	32	1691
1322912	30350	30369	N/A	N/A	GTGGAATACATTTTATTCCT	98	1692
1322928	34493	34512	1765	1784	CTTTCGCTTTCATCTTCATT	59	1693
1322998	18279	18298	N/A	N/A	GGCATTA AAAATACCTTAAA	59	1694
1323030	37483	37502	4755	4774	ACACAGGTACATATTATATA	51	1695
1323066	35512	35531	2784	2803	GCTTTAATCCTAAACCATGT	60	1696
1323081	23330	23349	N/A	N/A	ACTTTCATATTTTAACATTC	39	1697
1323120	25153	25172	N/A	N/A	TCATCTCCTACAATTTTCCA	66	1698
1323176	27206	27225	N/A	N/A	CGCCAGCATACCAATGGACA	92	1699
1323190	28624	28643	N/A	N/A	AAAGTTTAAAAATTTCCCCC	97	1700
1323201	25203	25222	N/A	N/A	CCATAACCCATTTTTCCTTC	64	1701
1323212	27010	27029	N/A	N/A	TCCACTCTCCCACATACCAT	70	1702
1323214	13819	13838	N/A	N/A	CCTGGATCACCACCTGGGTC	105	1703
1323267	4906	4925	N/A	N/A	TCAGGCCTTCCACACTGACC	98	1704
1323286	8364	8383	N/A	N/A	ATACATCACATCCCCTTATC	88	1705
1323312	5600	5619	N/A	N/A	TGACAGATCATTCATAAGTC	88	1706
1323328	4681	4700	N/A	N/A	CTGGA AAAACCGTCACAGAC	109	1707

Table 23

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320908	35057	35076	2329	2348	CATGATTTTACACATGGAAA	52	1708
1320914	38168	38187	5440	5459	CCTTCTACAATTCAGTAAAA	61	1709
1320928	27436	27455	N/A	N/A	CTTGTCCTAATTATTTTACT	51	1710
1320940	27009	27028	N/A	N/A	CCACTCTCCCACATACCATG	71	1711
1320975	36281	36300	3553	3572	CCTTTTCTTCCACCAGGATC	39	1712
1320976	24893	24912	N/A	N/A	CTGGACTTCATCCATGTTTA	57	1713
1320977	13511	13530	N/A	N/A	GCTTTTGTCTATCTAAGAAC	85	1714
1321066	22656	22675	800	819	TGTGGTCTTTATACAATGTA	24	1715
1321084	9419	9438	N/A	N/A	TGACTTTCTAATTTTCCCCA	79	1716
1321123	33680	33699	N/A	N/A	AAATTCACAAAACCCACCCT	93	1717
1321151	19762	19781	N/A	N/A	GCCAAGTTATTACTTATGAA	15	1718
1321198	23329	23348	N/A	N/A	CTTTCATATTTTAACATTCC	48	1719
1321220	24353	24372	N/A	N/A	AATGGA ACTTACTGGAGCCA	87†	1720

1321303	14343	14362	N/A	N/A	ATGCTGATAATTACATTTCT	102	1721
1321319	38552	38571	5824	5843	GCTATGCAATACCACAGCAA	101	1722
1321350	13818	13837	N/A	N/A	CTGGATCACCACCTGGGTCA	102	1723
1321390	8835	8854	N/A	N/A	TGTGTTAAACATAAAATCTCC	68	1724
1321409	18248	18267	N/A	N/A	AGGTTCCACATCAGAATCTA	101	1725
1321423	30345	30364	N/A	N/A	ATACATTTTATTCTGGCAA	89	1726
1321457	5955	5974	N/A	N/A	GATGCTAGCCCTGATTCTCT	82	1727
1321483	27941	27960	N/A	N/A	GAGATATGCATCTAACATAA	53	1728
1321514	11706	11725	N/A	N/A	ATGTAATTCATTGAATTCTT	90	1729
1321576	25152	25171	N/A	N/A	CATCTCCTACAATTTTCCAA	77	1730
1321584	26718	26737	N/A	N/A	GCAGGACCTGTAAATACGAT	96	1731
1321585	26903	26922	N/A	N/A	GGTTGACCCTAATCTTGTCC	59	1732
1321599	29987	30006	N/A	N/A	AGGTATTTTCATATTTGTTA	11	1733
1321617	29797	29816	N/A	N/A	GAAAACCGACCATAATTCTC	87	1734
1321655	34492	34511	1764	1783	TTTCGCTTTCATCTTCATTA	51	1735
1321716	33361	33380	N/A	N/A	CTGAGAAGAATCACATTACA	82	1736
1321762	25922	25941	N/A	N/A	TTTGAGACAATAAACAGCTG	86	1737
1321770	29505	29524	N/A	N/A	TTTTTCATTACCTCCCCAAC	91	1738
1321786	30113	30132	N/A	N/A	ATAGTACCTTACATATAAGT	69	1739
1321792	12575	12594	N/A	N/A	GTATGGAATTTAATCCATTT	108	1740
1321806	37482	37501	4754	4773	CACAGGTACATATTATATAT	71	1741
1321823	29366	29385	N/A	N/A	AGGAAAACAAACAACGTAC	80	1742
1321896	22437	22456	N/A	N/A	ACATCGATTAAACAGAGGTA	76	1743
1321921	29027	29046	N/A	N/A	TCTGTATTTTAAAAGCAAAC	84	1744
1322024	25548	25567	N/A	N/A	CCTCTCATTATCTATTTGGT	53	1745
1322040	28552	28571	N/A	N/A	ACAAAATTATACTATACAGT	100	1746
1322050	18607	18626	N/A	N/A	TGAGAACTTTTACCTATGTT	46	1747
1322075	5599	5618	N/A	N/A	GACAGATCATTCATAAGTCA	96	1748
1322083	25200	25219	N/A	N/A	TAACCCATTTTTCCTTCTAC	75	1749
1322085	35879	35898	3151	3170	AGAGACCACCCATAACAAGA	83	1750
1322089	9742	9761	N/A	N/A	GGCATTTCTCCCATCTCC	69	1751
1322112	8637	8656	N/A	N/A	TGGTTCCTACAATATTTCTT	49	1752
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	5	132
1322200	8362	8381	N/A	N/A	ACATCACATCCCCTTATCCC	89	1753
1322217	31173	31192	N/A	N/A	CATTGTATTACCTCTGATTA	31	1754
1322221	32473	32492	N/A	N/A	GTCCACAGCAACCATAGGCA	57	1755
1322253	22203	22222	N/A	N/A	TGCCAAAACCTTCATTCAAC	71	1756
1322312	4905	4924	N/A	N/A	CAGGCCTTCCACACTGACCA	99	1757
1322363	6481	6500	N/A	N/A	GACTGGCCTATACAGCCTCA	101	1758
1322386	7788	7807	N/A	N/A	GTTGCTTTCAACCTTTCACA	67	1759
1322389	25261	25280	N/A	N/A	TTTGCTCTCTACTCCTCT	81	1760
1322393	17649	17668	N/A	N/A	ATTTACTTCATGAAATCCGT	27	1761
1322397	30794	30813	N/A	N/A	GCTGAGGAAATCCCTATTTC	73	1762

1322405	4620	4639	N/A	N/A	GGCTTAGTAAACCTCGAGAA	58	1763
1322432	16650	16669	N/A	N/A	TGTAATGTATATATACAGTA	95	1764
1322436	20653	20672	N/A	N/A	GATAAACCTATTTTATGGTA	83	1765
1322545	27192	27211	N/A	N/A	TGGACACTGATTAAGTGCTA	102	1766
1322559	35706	35725	2978	2997	TGCATACACTATCTTCTGGC	16	1767
1322577	28259	28278	1104	1123	TATCAAACCTTTATCTCTTCA	76	1768
1322625	12191	12210	N/A	N/A	GTTTGAGTATATCATCCCAT	69	1769
1322644	7526	7545	N/A	N/A	CTTGAGTTTTCAACATGATT	59	1770
1322661	35511	35530	2783	2802	CTTTAATCCTAAACCATGTA	93	1771
1322729	25385	25404	N/A	N/A	TCAAAATTAACACTAAAAGA	89	1772
1322806	25697	25716	N/A	N/A	GTCCTAAACCACACAACACT	72	1773
1322890	31658	31677	N/A	N/A	TTCAGTCTAACATTGGCCTC	84	1774
1322914	31812	31831	1345	1364	GCTTTCACACAATATACAGT	34	1775
1322925	37135	37154	4407	4426	CGCTTGTTCACTGAAAACCA	73	1776
1322932	20342	20361	N/A	N/A	GAGAACCCTACTACAGGGA	13	1777
1322934	25762	25781	N/A	N/A	TTAGCCCCTATTACCTTTA	53	1778
1322962	20032	20051	381	400	TACTAGTAATATTCTGACAC	67	1779
1322999	28623	28642	N/A	N/A	AAGTTTAAAAATTTCCCCCA	93	1780
1323131	34117	34136	N/A	N/A	AGTGAGGTCACTCATATCTT	77	1781
1323196	16269	16288	N/A	N/A	CTGAGTCTTTAGAAATGCAA	53	1782
1323242	24795	24814	N/A	N/A	TCAAAACCACTAAAGTAATA	96	1783
1323276	11174	11193	N/A	N/A	TTTAGGATCCTCCTATTCTT	107	1784

Table 24

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320924	12573	12592	N/A	N/A	ATGGAATTTAATCCATTTAC	101	1785
1320930	28549	28568	N/A	N/A	AAATTATACTATACAGTCTT	71	1786
1320979	7787	7806	N/A	N/A	TTGCTTTCAACCTTTCACAT	63	1787
1321004	35877	35896	3149	3168	AGACCACCCATAACAAGAGT	108	1788
1321052	38159	38178	5431	5450	ATTCAGTAAAACAAACACTG	104	1789
1321074	29986	30005	N/A	N/A	GGTATTTTCATATTTGTTAC	13	1790
1321076	4619	4638	N/A	N/A	GCTTAGTAAACCTCGAGAAC	97	1791
1321117	4889	4908	N/A	N/A	ACCATGTCAATTACAAGCTT	63	1792
1321212	28997	29016	N/A	N/A	ATGCAGCTCACCATAACTC	41	1793
1321248	26902	26921	N/A	N/A	GTTGACCCTAATCTTGTCCT	59	1794
1321272	22638	22657	782	801	TACTGGACTATAGACACCAA	53	1795
1321290	22436	22455	N/A	N/A	CATCGATTAAACAGAGGTAA	85	1796
1321380	9416	9435	N/A	N/A	CTTTCTAATTTTCCCCATAA	87	1797
1321400	25696	25715	N/A	N/A	TCCTAAACCACACAACACTT	77	1798

1321449	25258	25277	N/A	N/A	GCTCTCTCTACTCCTCTGCC	73	1799
1321453	24885	24904	N/A	N/A	CATCCATGTTTAGCTAGCCT	13	1800
1321502	24790	24809	N/A	N/A	ACCACTAAAGTAATAAAGAA	103	1801
1321509	30793	30812	N/A	N/A	CTGAGGAAATCCCTATTTCC	88	1802
1321539	5598	5617	N/A	N/A	ACAGATCATTCTATAAGTCAA	74	1803
1321580	34113	34132	N/A	N/A	AGGTCACTCATATCTTAGTA	30	1804
1321581	25353	25372	N/A	N/A	ATAGCGGTACTTACACTTCC	28	1805
1321591	31130	31149	N/A	N/A	GGTTTTGGCCTCAAACCTGCC	84	1806
1321598	20639	20658	N/A	N/A	ATGGTAACAAACATTTGCCA	91	1807
1321701	31458	31477	N/A	N/A	ATGCAGATGCCACCACGCCT	91	1808
1321717	20024	20043	373	392	ATATTCTGACACCCAGACAA	28	1809
1321724	29365	29384	N/A	N/A	GGAAAACAAACAACTGTACT	85	1810
1321772	28622	28641	N/A	N/A	AGTTTAAAAATTTCCCCCAA	83	1811
1321828	7458	7477	N/A	N/A	AAGTCCCCCAACCATCAGAA	85	1812
1321863	8834	8853	N/A	N/A	GTGTTAAACATAAATCTCCA	49	1813
1321882	35023	35042	2295	2314	GTTTGTCTCAACTCTTTTAA	20	1814
1321906	8361	8380	N/A	N/A	CATCACATCCCCTTATCCCA	81	1815
1321972	37481	37500	4753	4772	ACAGGTACATATTATATATA	58	1816
1321982	13776	13795	N/A	N/A	ACTGATGGCACCAGTGCCCT	105	1817
1322002	27181	27200	N/A	N/A	TAAGTGCTAAAATAGAGACA	84	1818
1322012	29796	29815	N/A	N/A	AAAACCGACCATAATTCTCA	65	1819
1322071	35446	35465	2718	2737	AACAGAAGTCCCTCAACATT	90	1820
1322107	27936	27955	N/A	N/A	ATGCATCTAACATAAAAAGAA	71	1821
1322113	28255	28274	1100	1119	AAACTTTATCTCTTCAGACC	72	1822
1322119	18244	18263	N/A	N/A	TCCACATCAGAATCTATTTTC	72	1823
1322120	11173	11192	N/A	N/A	TTAGGATCCTCCTATTCTTG	106	1824
1322140	14341	14360	N/A	N/A	GCTGATAATTACATTTCTGC	83	1825
1322158	34489	34508	1761	1780	CGCTTTCATCTTCATTAGAA	47	1826
1322161	20300	20319	N/A	N/A	GCAGGAAGAAGATATAGGTT	64	1827
1322173	12187	12206	N/A	N/A	GAGTATATCATCCCATCCTC	88	1828
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	1	132
1322201	25198	25217	N/A	N/A	ACCCATTTTTCTTCTACTT	58	1829
1322211	13510	13529	N/A	N/A	CTTTTGTCTATCTAAGAACA	91	1830
1322219	22202	22221	N/A	N/A	GCCAAAACCTTCATTCAACA	67	1831
1322234	19741	19760	N/A	N/A	CTGAATTTTAAATACAGTT	106	1832
1322262	38542	38561	5814	5833	ACCACAGCAAACCTTCATTCA	91	1833
1322344	25150	25169	N/A	N/A	TCTCCTACAATTTTCCAATC	92	1834
1322452	23328	23347	N/A	N/A	TTTCATATTTTAAACATTCCA	59	1835
1322468	25546	25565	N/A	N/A	TCTCATTATCTATTTGGTGA	42	1836
1322500	33359	33378	N/A	N/A	GAGAAGAATCACATTACAGA	62	1837
1322525	31811	31830	1344	1363	CTTTCACACAATATACAGTC	39	1838
1322527	11698	11717	N/A	N/A	CATTGAATTCTTCAACTGTA	102	1839
1322588	36280	36299	3552	3571	CTTTTCTTCCACCAGGATCA	64	1840

1322601	25761	25780	N/A	N/A	TAGCCCCTATTCACCTTTAC	59	1841
1322638	9741	9760	N/A	N/A	GCATTTCTCCCATTTCTCCA	79	1842
1322753	37125	37144	4397	4416	CTGAAAACACAGATGGTCT	69	1843
1322826	17634	17653	N/A	N/A	TCCGTTTCATAATATAACTT	60	1844
1322848	25921	25940	N/A	N/A	TTGAGACAATAAACAGCTGT	68	1845
1322924	5935	5954	N/A	N/A	TTGGGTACCCCTCCTCACTA	89	1846
1322927	24341	24360	916	935	TGGAGCCACTGAACTTGAAA	1†	1847
1322930	30112	30131	N/A	N/A	TAGTACCTTACATATAAGTA	55	1848
1322965	8636	8655	N/A	N/A	GGTTCCTACAATATTTCTTT	46	1849
1323032	35705	35724	2977	2996	GCATACACTATCTTCTGGCA	31	1850
1323050	26715	26734	N/A	N/A	GGACCTGTAAATACGATGGA	88	1851
1323078	27435	27454	N/A	N/A	TTGTCCTAATTATTTTACTA	83	1852
1323082	33679	33698	N/A	N/A	AATTCACAAAACCCACCCTA	107	1853
1323086	29504	29523	N/A	N/A	TTTTCACTACCTCCCCAACT	89	1854
1323093	18606	18625	N/A	N/A	GAGAACTTTTACCTATGTTA	24	1855
1323115	27008	27027	N/A	N/A	CACTCTCCCACATACCATGT	78	1856
1323189	30309	30328	N/A	N/A	AGCCAAGCCAAACCCTGCAA	82	1857
1323204	6425	6444	N/A	N/A	TGTCTGTTAACATAAGCATAA	86	1858
1323227	32457	32476	N/A	N/A	GGCAATGACATTTACATTTA	9	1859
1323289	16254	16273	N/A	N/A	TGCAAGGTCCAATATATCGA	28	1860
1323332	16591	16610	N/A	N/A	ATTTGTTTATATATGCATAC	86	1861

Table 25

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320894	25149	25168	N/A	N/A	CTCCTACAATTTTCCAATCA	97	1862
1320904	25875	25894	N/A	N/A	GTTACAGACACAGAAAACCTA	98	1863
1320922	31129	31148	N/A	N/A	GTTTTGGCCTCAAACCTGCCT	79	1864
1320937	12504	12523	N/A	N/A	AAGTTTTCTAATAATATCCT	105	1865
1320952	31810	31829	1343	1362	TTTCACACAATATACAGTCA	49	1866
1321089	7443	7462	N/A	N/A	CAGAATGGACCCCTTCTCCT	95	1867
1321102	20015	20034	364	383	CACCCAGACAATTTTATCCA	72	1868
1321144	38157	38176	5429	5448	TCAGTAAAACAAACACTGCC	100	1869
1321183	22426	22445	N/A	N/A	ACAGAGGTAAAAATAATGCT	71	1870
1321224	36262	36281	3534	3553	CATCTGTTTTTTCAGCAGAA	79	1871
1321245	5546	5565	N/A	N/A	CCAAGTGAACCTCAGGTCT	57	1872
1321273	6420	6439	N/A	N/A	GTAACTAAGCATAACAGTA	77	1873
1321302	27112	27131	N/A	N/A	GTAAGTTGCCAGAAACCAA	92	1874
1321377	34109	34128	N/A	N/A	CACTCATATCTTAGTACCTT	19	1875
1321387	28621	28640	N/A	N/A	GTTTAAAAATTTCCCCCAA	102	1876

1321447	23327	23346	N/A	N/A	TTCATATTTTAAACATTCCAC	41	1877
1321463	9740	9759	N/A	N/A	CATTCCTCCCATTCTCCAT	105	1878
1321471	25257	25276	N/A	N/A	CTCTCTCTACTCCTCTGCCA	77	1879
1321473	33358	33377	N/A	N/A	AGAAGAATCACATTACAGAC	80	1880
1321488	35830	35849	3102	3121	GCTCAGGCTTCCAGTGAAC	68	1881
1321607	32456	32475	N/A	N/A	GCAATGACATTTACATTTAA	37	1882
1321616	38540	38559	5812	5831	CACAGCAAACCTTCATTCAAT	83	1883
1321634	33650	33669	N/A	N/A	ATGGTTTCCCAGGAACAGAT	44	1884
1321672	4888	4907	N/A	N/A	CCATGTCAATTACAAGCTTA	74	1885
1321695	26700	26719	N/A	N/A	ATGGAGGCCCTCCTCTCATA	100	1886
1321737	25536	25555	N/A	N/A	TATTTGGTGACCTATTATT	67	1887
1321741	35445	35464	2717	2736	ACAGAAGTCCCTCAACATTT	60	1888
1321777	8631	8650	N/A	N/A	CTACAATATTTCTTTTACTT	102	1889
1321854	22633	22652	777	796	GACTATAGACACCAATTTTC	25	1890
1321874	37093	37112	4365	4384	CCTTGTGCTCCAACCTCCTA	63	1891
1321884	27935	27954	N/A	N/A	TGCATCTAACATAAAAAGAAA	87	1892
1321895	37480	37499	4752	4771	CAGGTACATATTATATATAA	45	1893
1321905	20250	20269	N/A	N/A	TTAGATTTTGCATCATGCAA	92	1894
1321942	24783	24802	N/A	N/A	AAGTAATAAAGAAAATAGGA	94	1895
1321967	29976	29995	N/A	N/A	TATTTGTTACTTCCTTTTAA	63	1896
1321973	7785	7804	N/A	N/A	GCTTTC AACCTTTTACATTC	53	1897
1321986	16580	16599	N/A	N/A	TATGCATACACAATTACTGA	80	1898
1322008	24878	24897	N/A	N/A	GTTTAGCTAGCCTCTGCTCA	81	1899
1322023	34488	34507	1760	1779	GCTTTCATCTTCATTAGAAT	32	1900
1322077	11669	11688	N/A	N/A	TGGTTGTTTTTCATCATGTT	50	1901
1322081	12185	12204	N/A	N/A	GTATATCATCCCATCCTCTT	99	1902
1322141	11170	11189	N/A	N/A	GGATCCTCCTATTCTTGCTCT	104	1903
1322155	35685	35704	2957	2976	TGGCATGTATACTAAACTT	29	1904
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	2	132
1322231	5934	5953	N/A	N/A	TGGGTACCCCTCCTCACTAC	123	1905
1322239	8831	8850	N/A	N/A	TTAAACATAAATCTCCAACCT	81	1906
1322255	25197	25216	N/A	N/A	CCCATTTTTCTTCTACTTA	72	1907
1322301	9414	9433	N/A	N/A	TTCTAATTTTCCCATAAAT	116	1908
1322325	29795	29814	N/A	N/A	AAACCGACCATAATTCTCAA	58	1909
1322346	26893	26912	N/A	N/A	AATCTTGTCCCATTCTACTT	102	1910
1322378	28254	28273	1099	1118	AACTTTATCTCTTCAGACCA	64	1911
1322434	31457	31476	N/A	N/A	TGCAGATGCCACCACGCCTA	75	1912
1322454	30111	30130	N/A	N/A	AGTACCTTACATATAAGTAT	48	1913
1322493	30792	30811	N/A	N/A	TGAGGAAATCCCTATTTCCA	101	1914
1322528	25695	25714	N/A	N/A	CCTAAACCACACAACACTTT	99	1915
1322535	18590	18609	N/A	N/A	GTTAAGCCCATTGACCATAA	14	1916
1322541	20638	20657	N/A	N/A	TGGTAACAAACATTTGCCAA	95	1917
1322641	4606	4625	N/A	N/A	CGAGAACTGACAATTATGCT	52	1918

1322668	28996	29015	N/A	N/A	TGCAGCTCACCCATAACTCT	52	1919
1322698	19725	19744	N/A	N/A	AGTTCTTTATATAATTTTGT	80	1920
1322709	29503	29522	N/A	N/A	TTTCATTACCTCCCCAACTA	89	1921
1322738	16253	16272	N/A	N/A	GCAAGGTCCAATATATCGAT	23	1922
1322810	27434	27453	N/A	N/A	TGTCCTAATTATTTTACTAC	66	1923
1322821	13755	13774	N/A	N/A	AGTCTGGACATCCAGCTGCC	87	1924
1322828	22201	22220	N/A	N/A	CCAAAACCTTCATTCAACAA	76	1925
1322857	27007	27026	N/A	N/A	ACTCTCCACATACCATGTC	63	1926
1322906	30296	30315	N/A	N/A	CCTGCAAGCACACTTAAGGC	112	1927
1322939	28541	28560	N/A	N/A	CTATACAGTCTTTTACCTC	87	1928
1322943	25352	25371	N/A	N/A	TAGCGGTACTTACACTTCCC	9	1929
1322945	8360	8379	N/A	N/A	ATCACATCCCCTTATCCCAC	80	1930
1322960	13505	13524	N/A	N/A	GTCTATCTAAGAACATCTTA	98	1931
1322986	24315	24334	890	909	GTTTGCATATGTATAATCCC	N.D.	1932
1323017	35021	35040	2293	2312	TTGTCTCAACTCTTTTAATT	28	1933
1323062	14338	14357	N/A	N/A	GATAATTACATTTCTGCATC	86	1934
1323135	18242	18261	N/A	N/A	CACATCAGAATCTATTTCTA	65	1935
1323163	29360	29379	N/A	N/A	ACAAACAACGTACTACATA	81	1936
1323298	17632	17651	N/A	N/A	CGTTTCATAATATAACTTCA	76	1937
1323340	25760	25779	N/A	N/A	AGCCCCTATTACCTTTACA	75	1938

Table 26

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320905	26987	27006	N/A	N/A	GCCGCATGCACCTTCCTCAA	63	1939
1320941	29790	29809	N/A	N/A	GACCATAATTCTCAATGGGC	57	1940
1320942	29354	29373	N/A	N/A	AACTGTACTACATAAATTCT	81	1941
1320970	33357	33376	N/A	N/A	GAAGAATCACATTACAGACT	62	1942
1321017	13754	13773	N/A	N/A	GTCTGGACATCCAGCTGCCC	94	1943
1321022	30295	30314	N/A	N/A	CTGCAAGCACACTTAAGGCC	97	1944
1321037	5931	5950	N/A	N/A	GTACCCCTCCTCACTACAAA	112	1945
1321134	12503	12522	N/A	N/A	AGTTTTCTAATAATATCCTT	99	1946
1321254	6412	6431	N/A	N/A	AGCATAACAGTATCTACACT	74	1947
1321264	37089	37108	4361	4380	GTGCTCCAACCTTCCTAGAGA	54	1948
1321291	14296	14315	N/A	N/A	GATTTTTTTTCCTCTTGAA	68	1949
1321309	22191	22210	N/A	N/A	CATTCAACAAATAATTCTGA	92	1950
1321342	19688	19707	N/A	N/A	AGCAGAGAAATAAATGACCC	71	1951
1321408	20592	20611	N/A	N/A	GCTGTTTTACATTTTTTTTC	37	1952
1321443	17631	17650	N/A	N/A	GTTTCATAATATAACTTCAT	91	1953
1321444	13500	13519	N/A	N/A	TCTAAGAACATCTTAATTTC	111	1954

1321458	20014	20033	363	382	ACCCAGACAATTTTATCCAA	32	1955
1321553	27107	27126	N/A	N/A	TTGCCCAGAAACCAACAGCT	99	1956
1321556	34487	34506	1759	1778	CTTTCATCTTCATTAGAATA	101	1957
1321627	30791	30810	N/A	N/A	GAGGAAATCCCTATTTCCAA	101	1958
1321631	5537	5556	N/A	N/A	ACTTCAGGTCTACAACCTAA	71	1959
1321667	28995	29014	N/A	N/A	GCAGCTCACCCATAACTCTA	38	1960
1321680	11127	11146	N/A	N/A	CAAGGCAACACCTCTTGGTG	99	1961
1321729	35019	35038	2291	2310	GTCTCAACTCTTTTAATTTTC	11	1962
1321732	37436	37455	4708	4727	ATAAAATTATTTCTGGCTCT	59	1963
1321742	11666	11685	N/A	N/A	TTGTTTTTCATCATGTTTAA	95	1964
1321756	25872	25891	N/A	N/A	ACAGACACAGAAAACCTAACA	86	1965
1321820	16252	16271	N/A	N/A	CAAGGTCCAATATATCGATT	24	1966
1321867	27421	27440	N/A	N/A	TTACTACATTTTATTTTCTA	107	1967
1321872	25351	25370	N/A	N/A	AGCGGTACTTACACTTCCCT	8	1968
1321875	25694	25713	N/A	N/A	CTAAACCACACAACACTTTG	81	1969
1321898	26699	26718	N/A	N/A	TGGAGGCCCTCCTCTCATAA	101	1970
1321918	12181	12200	N/A	N/A	ATCATCCCATCCTCTTCTGC	92	1971
1321927	33959	33978	N/A	N/A	ATGTTTGTATCCAACACATA	90	1972
1321939	26892	26911	N/A	N/A	ATCTTGTCCTTCTACTTA	99	1973
1321950	25196	25215	N/A	N/A	CCATTTTTCTTCTACTTAA	83	1974
1321959	24873	24892	N/A	N/A	GCTAGCCTCTGCTCAACCAC	89	1975
1321997	18241	18260	N/A	N/A	ACATCAGAATCTATTTCTAA	87	1976
1322011	28253	28272	1098	1117	ACTTTATCTCTTCAGACCAA	57	1977
1322043	38156	38175	5428	5447	CAGTAAAACAAACACTGCCA	89	1978
1322082	35820	35839	3092	3111	CCAGTGGAACATTCTTCTTC	39	1979
1322093	25535	25554	N/A	N/A	ATTTGGTGACCTATTATTT	42	1980
1322094	29974	29993	N/A	N/A	TTTGTTACTTCCTTTTAAAC	76	1981
1322132	35683	35702	2955	2974	GCATGTATACTAAAACCTGT	82	1982
1322153	8822	8841	N/A	N/A	AATCTCCAAGTAGATTGCAA	83	1983
1322166	27934	27953	N/A	N/A	GCATCTAACATAAAAGAAAA	92	1984
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	2	132
1322197	22603	22622	747	766	GTAGTGCTGCTTTAACTTTT	4	1985
1322232	25256	25275	N/A	N/A	TCTCTCTACTCCTCTGCCAC	68	1986
1322245	29502	29521	N/A	N/A	TTCATTACCTCCCCAACTAA	94	1987
1322324	4603	4622	N/A	N/A	GAACTGACAATTATGCTTCA	110	1988
1322349	N/A	N/A	1288	1307	TTCTCGATAATTTTCTCTC	44	1989
1322361	7438	7457	N/A	N/A	TGGACCCCTTCTCCTGACCA	108	1990
1322412	7784	7803	N/A	N/A	CTTTCAACCTTTCACATTCA	81	1991
1322433	22425	22444	N/A	N/A	CAGAGGTAAAAATAATGCTT	53	1992
1322440	23326	23345	N/A	N/A	TCATATTTTAAACATTCCACT	30	1993
1322445	25148	25167	N/A	N/A	TCCTACAATTTTCCAATCAA	86	1994
1322484	31456	31475	N/A	N/A	GCAGATGCCACCACGCCTAA	64	1995
1322487	24782	24801	N/A	N/A	AGTAATAAAGAAAATAGGAA	100	1996

1322491	28612	28631	N/A	N/A	TTTCCCCCAAATTTTACATT	100	1997
1322492	35442	35461	2714	2733	GAAGTCCCTCAACATTTTAA	58	1998
1322595	32451	32470	N/A	N/A	GACATTTACATTTAAAGATT	70	1999
1322699	16577	16596	N/A	N/A	GCATACACAATTACTGAAGC	45	2000
1322701	8359	8378	N/A	N/A	TCACATCCCCTTATCCCCT	85	2001
1322728	4875	4894	N/A	N/A	AAGCTTATCTTCTCAGGTGC	49	2002
1322783	20240	20259	N/A	N/A	CATCATGCAAATGAATGGCT	84	2003
1322808	9394	9413	N/A	N/A	GCAGTTGTTTTTAAATGTCC	65	2004
1322880	9715	9734	N/A	N/A	CATCCCCTTTTCTCTGCTC	87	2005
1322883	25759	25778	N/A	N/A	GCCCCCTATTCACCTTTACAT	85	2006
1322900	38537	38556	5809	5828	AGCAAACCTTCATTCAATGAA	88	2007
1322982	18584	18603	N/A	N/A	CCCATTGACCATAAGTAGCA	50	2008
1323013	33636	33655	N/A	N/A	ACAGATTCTATGTTTAGGCC	53	2009
1323029	24311	24330	886	905	GCATATGTATAATCCCATT	N.D.	2010
1323046	36251	36270	3523	3542	TCAGCAGAAATGACTACTTA	56	2011
1323258	31128	31147	N/A	N/A	TTTTGGCCTCAAACCTGCCTT	85	2012
1323259	30110	30129	N/A	N/A	GTACCTTACATATAAGTATT	61	2013
1323262	31793	31812	1326	1345	TCAGTGGTTTCAAATTAGGA	7	2014
1323324	8630	8649	N/A	N/A	TACAATATTTCTTTTACTTC	97	2015

Table 27

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320926	27931	27950	N/A	N/A	TCTAACATAAAAGAAAACCA	74	2016
1321050	31317	31336	N/A	N/A	TGTGTGAGAAATATAAATTT	62	2017
1321060	14177	14196	N/A	N/A	GTTCAACTGTTTTATGGCCT	94	2018
1321083	N/A	N/A	1287	1306	TCTCGATAATTTTCTCTCA	25	2019
1321085	6409	6428	N/A	N/A	ATAACAGTATCTACACTGCT	105	2020
1321088	4574	4593	N/A	N/A	ACTGTCATTTTTTATTGGCC	46	2021
1321092	37425	37444	4697	4716	TCTGGCTCTAATGATACAAA	26	2022
1321103	9714	9733	N/A	N/A	ATCCCCTTTTCTCTGCTCA	79	2023
1321135	33626	33645	N/A	N/A	TGTTTAGGCCTTCACCATTC	40	2024
1321227	5924	5943	N/A	N/A	TCCTCACTACAAAATTACCT	103	2025
1321246	27420	27439	N/A	N/A	TACTACATTTTATTTTCTAA	92	2026
1321256	31118	31137	N/A	N/A	AAACTGCCTTATTAAGAGTA	84	2027
1321310	24309	24328	884	903	ATATGTATAATCCCATTAA	50	2028
1321321	25534	25553	N/A	N/A	TTTGGTGACCCTATTATTTA	23	2029
1321353	26985	27004	N/A	N/A	CGCATGCACCTTCCTCAAAT	89	2030
1321376	29789	29808	N/A	N/A	ACCATAATTCTCAATGGGCT	43	2031
1321394	7437	7456	N/A	N/A	GGACCCCTTCTCTGACCAA	71	2032

1321417	8357	8376	N/A	N/A	ACATCCCCTTATCCCCTCT	80	2033
1321430	8629	8648	N/A	N/A	ACAATATTTCTTTTACTTCT	68	2034
1321450	18565	18584	N/A	N/A	AGAGAACTATCTTCTGGGA	52	2035
1321462	29973	29992	N/A	N/A	TTGTTACTTCCTTTTAAACC	27	2036
1321482	37088	37107	4360	4379	TGCTCCAACCTCCTAGAGAC	75	2037
1321485	24867	24886	N/A	N/A	CTCTGCTCAACCACATAGAA	82	2038
1321504	24766	24785	N/A	N/A	GGAAGGCTAATTTTTTGAAT	23	2039
1321541	20591	20610	N/A	N/A	CTGTTTTACATTTTTTTTCC	14	2040
1321623	11067	11086	N/A	N/A	TCTTGATTCCAGATGAAGGT	68	2041
1321657	35438	35457	2710	2729	TCCCTCAACATTTTTTAGGGA	104	2042
1321677	32401	32420	N/A	N/A	GGAGAAATACAATATTGACA	32	2043
1321686	16559	16578	N/A	N/A	GCTGTGAGATTCATATGCCA	94	2044
1321708	28611	28630	N/A	N/A	TTCCCCCAAATTTTACATTC	96	2045
1321714	25869	25888	N/A	N/A	GACACAGAAAATAACATCT	60	2046
1321720	30294	30313	N/A	N/A	TGCAAGCACACTTAAGGCCT	101	2047
1321753	16064	16083	N/A	N/A	GCCCAGTTAACAATATATTT	84	2048
1321757	12502	12521	N/A	N/A	GTTTTCTAATAATATCCTTT	51	2049
1321795	17627	17646	N/A	N/A	CATAATATAACTTCATGCCA	72	2050
1321891	12180	12199	N/A	N/A	TCATCCCATCCTCTTCTGCA	99	2051
1321998	19687	19706	N/A	N/A	GCAGAGAAATAAATGACCCA	59	2052
1322072	36248	36267	3520	3539	GCAGAAATGACTACTTAAAC	27	2053
1322088	22187	22206	N/A	N/A	CAACAAATAATTCTGAGCAC	52	2054
1322117	38155	38174	5427	5446	AGTAAAACAAACACTGCCAC	76	2055
1322128	35018	35037	2290	2309	TCTCAACTCTTTTAATTCT	11	2056
1322133	34485	34504	1757	1776	TTCATCTTCATTAGAATAAT	71	2057
1322138	35819	35838	3091	3110	CAGTGGAACATTCTTCTTCC	24	2058
1322165	22599	22618	743	762	TGCTGCTTTAACTTTTAGAC	27	2059
1322171	28230	28249	1075	1094	GATGTGTTATTTCCATCAGA	38	2060
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	7	132
1322189	13743	13762	N/A	N/A	CAGCTGCCCCTCACACACCT	79	2061
1322266	26697	26716	N/A	N/A	GAGGCCCTCCTCTCATAATT	84	2062
1322306	29353	29372	N/A	N/A	ACTGTACTACATAAATTCTT	61	2063
1322371	38516	38535	5788	5807	ACTGAGCTCCAGCCATGTCT	71	2064
1322453	25191	25210	N/A	N/A	TTTCCTTCTACTTAATTTTC	75	2065
1322533	28994	29013	N/A	N/A	CAGCTCACCCATAACTCTAC	51	2066
1322591	25255	25274	N/A	N/A	CTCTCTACTCCTCTGCCACC	50	2067
1322721	5533	5552	N/A	N/A	CAGGTCTACAACCTAAGTCT	105	2068
1322799	29496	29515	N/A	N/A	ACCTCCCCAACTAAACAACCT	75	2069
1322814	30790	30809	N/A	N/A	AGGAAATCCCTATTTCCAAA	99	2070
1322844	20207	20226	N/A	N/A	GCTCTGGTAATATTTACTAA	20	2071
1322870	27105	27124	N/A	N/A	GCCCAGAAACCAACAGCTAA	70	2072
1322871	25146	25165	N/A	N/A	CTACAATTTTCCAATCAATA	84	2073
1322876	23269	23288	N/A	N/A	TAGCAACTACTTCCCCACCT	69	2074

1322926	33958	33977	N/A	N/A	TGTTTGTATCCAACACATAT	52	2075
1322935	25758	25777	N/A	N/A	CCCCTATTACCTTTACATT	67	2076
1323007	25692	25711	N/A	N/A	AAACCACACAACACTTTGCA	53	2077
1323044	8809	8828	N/A	N/A	ATTGCAAGTTCCTTAAGGGC	51	2078
1323056	20013	20032	362	381	CCCAGACAATTTTATCCAAT	17	2079
1323077	26891	26910	N/A	N/A	TCTTGTCCTTCTACTTAT	58	2080
1323133	30109	30128	N/A	N/A	TACCTTACATATAAGTATTC	53	2081
1323138	13499	13518	N/A	N/A	CTAAGAACATCTTAATTTCC	86	2082
1323167	31792	31811	1325	1344	CAGTGGTTTCAAATTAGGAA	4	2083
1323177	11614	11633	N/A	N/A	GTTTTCCTGATTTCATTGAAC	59	2084
1323185	22424	22443	N/A	N/A	AGAGGTAAAAATAATGCTTA	57	2085
1323193	25350	25369	N/A	N/A	GCGGTACTTACACTTCCCTT	26	2086
1323208	18232	18251	N/A	N/A	TCTATTTCTAAAAATCCAGA	76	2087
1323228	35681	35700	2953	2972	ATGTATACTAAACTTGTAC	75	2088
1323238	9393	9412	N/A	N/A	CAGTTGTTTTTAAATGTCCT	27	2089
1323260	4862	4881	N/A	N/A	CAGGTGCAAAACAAAGTCAA	82	2090
1323284	33356	33375	N/A	N/A	AAGAATCACATTACAGACTT	55	2091
1323338	7782	7801	N/A	N/A	TTCAACCTTTCACATTCATT	77	2092

Table 28

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320896	8627	8646	N/A	N/A	AATATTTCTTTTACTTCTGC	58	2093
1320910	4573	4592	N/A	N/A	CTGTCATTTTTTATTGGCCT	54	2094
1320965	33953	33972	N/A	N/A	GTATCCAACACATATATATC	43	2095
1321001	5923	5942	N/A	N/A	CCTCACTACAAAATTACCTC	96	2096
1321003	35668	35687	2940	2959	CTTGTAACACTCTCAGATC	43	2097
1321009	31107	31126	N/A	N/A	TTAAGAGTATCACTTACAGC	29	2098
1321070	25145	25164	N/A	N/A	TACAATTTTCCAATCAATAT	77	2099
1321111	35425	35444	2697	2716	TTAGGGATCATCTTTCTGGC	18	2100
1321163	31315	31334	N/A	N/A	TGTGAGAAATATAAATTTGT	63	2101
1321244	23267	23286	N/A	N/A	GCAACTACTTCCCCACCTTT	75	2102
1321283	22057	22076	N/A	N/A	AGCAGCAGTCTAACACTGAA	61	2103
1321324	8808	8827	N/A	N/A	TTGCAAGTTCCTTAAGGGCA	63	2104
1321327	11016	11035	N/A	N/A	GCTCAGGATCTCAGAAACCT	51	2105
1321328	29972	29991	N/A	N/A	TGTTACTTCTTTTAAACCT	17	2106
1321351	38154	38173	5426	5445	GTAAACAAACACTGCCACA	57	2107
1321360	27930	27949	N/A	N/A	CTAACATAAAAGAAAACCAA	68	2108
1321363	26692	26711	N/A	N/A	CCTCCTCTCATAATTAGGTT	69	2109
1321391	33625	33644	N/A	N/A	GTTTAGGCCTTCACCATTC	73	2110

1321477	18564	18583	N/A	N/A	GAGAAACTATCTTCTGGGAA	43	2111
1321479	25347	25366	N/A	N/A	GTACTTACACTTCCCTTCTC	69	2112
1321557	12148	12167	N/A	N/A	TGTGAAGAAATCTGCTGTTA	59	2113
1321649	7781	7800	N/A	N/A	TCAACCTTTTACATTCAATTT	56	2114
1321687	25533	25552	N/A	N/A	TTGGTGACCCTATTATTTAT	15	2115
1321740	12500	12519	N/A	N/A	TTTCTAATAATATCCTTTGC	67	2116
1321784	35818	35837	3090	3109	AGTGGAACATTCTTCTTCCT	64	2117
1321814	29352	29371	N/A	N/A	CTGTACTACATAAAATTCCTTT	40	2118
1321821	27097	27116	N/A	N/A	ACCAACAGCTAAAAGCATCT	65	2119
1321881	25691	25710	N/A	N/A	AACCACACAACACTTTGCAA	56	2120
1321886	17618	17637	N/A	N/A	ACTTCATGCCATCTTTGCCT	61	2121
1321977	5532	5551	N/A	N/A	AGGTCTACAACCTAAGTCTA	56	2122
1322061	14141	14160	N/A	N/A	TGTATGTTTCATAGATAGATA	39	2123
1322063	9388	9407	N/A	N/A	GTTTTTAAATGTCCTAGTCT	54	2124
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	3	132
1322194	38470	38489	5742	5761	CAGGCTCTATCTCCACAGGC	54	2125
1322195	13740	13759	N/A	N/A	CTGCCCCTCACACACCTGGA	70	2126
1322233	8356	8375	N/A	N/A	CATCCCCCTTATCCCACTCTA	75	2127
1322292	4847	4866	N/A	N/A	GTCAAGACTCCATCTACCCA	74	2128
1322295	28610	28629	N/A	N/A	TCCCCCAAATTTTACATTCA	73	2129
1322345	35017	35036	2289	2308	CTCAACTCTTTTAATTTCTT	9	2130
1322359	30293	30312	N/A	N/A	GCAAGCACACTTAAGGCCTC	60	2131
1322400	36186	36205	3458	3477	TTTGTCTCTTTTCTTTCACT	25	2132
1322439	30100	30119	N/A	N/A	TATAAGTATTCAATAAGAGT	46	2133
1322446	16539	16558	N/A	N/A	GTTTTAGTTACAACCTCGAGA	33	2134
1322464	25253	25272	N/A	N/A	CTCTACTCCTCTGCCACCAA	48	2135
1322544	18231	18250	N/A	N/A	CTATTTCTAAAAATCCAGAA	61	2136
1322570	28227	28246	1072	1091	GTGTTATTTCCATCAGATGC	0	2137
1322573	25757	25776	N/A	N/A	CCCTATTACCTTTACATTT	75	2138
1322597	25190	25209	N/A	N/A	TTCCTTCTACTTAATTTTCC	61	2139
1322606	19685	19704	N/A	N/A	AGAGAAATAAATGACCCATA	37	2140
1322619	24866	24885	N/A	N/A	TCTGCTCAACCACATAGAAC	66	2141
1322635	26984	27003	N/A	N/A	GCATGCACCTTCTCAAATC	81	2142
1322674	31766	31785	1299	1318	CATCAGTTTTTTTCTCGATA	11	2143
1322676	28538	28557	N/A	N/A	TACAGTCTTTTTACCTCAGC	48	2144
1322742	11610	11629	N/A	N/A	TCCTGATTCAATTGAACTATC	58	2145
1322761	16063	16082	N/A	N/A	CCCAGTTAACAATATATTTA	68	2146
1322768	20203	20222	N/A	N/A	TGGTAATATTTACTAAAGAA	59	2147
1322775	13498	13517	N/A	N/A	TAAGAACATCTTAATTTCTT	81	2148
1322792	28993	29012	N/A	N/A	AGCTCACCATAACTCTACA	31	2149
1322823	24731	24750	N/A	N/A	ACTGAGATCATTTTAAGGAC	24	2150
1322832	32367	32386	N/A	N/A	GCAAGTATCCTTCAGCACTT	30	2151
1322899	29788	29807	N/A	N/A	CCATAATTCTCAATGGGCTA	30	2152

1322942	34481	34500	1753	1772	TCTTCATTAGAATAATTTCC	56	2153
1322947	29491	29510	N/A	N/A	CCCAACTAAACAACCTTTTGTG	67	2154
1322981	25868	25887	N/A	N/A	ACACAGAAAACCTAACATCTA	60	2155
1323090	20012	20031	361	380	CCAGACAATTTTATCCAATT	11	2156
1323110	22598	22617	742	761	GCTGCTTTAACTTTTAGACA	34	2157
1323129	37087	37106	4359	4378	GCTCCAACCTCCTAGAGACC	58	2158
1323140	33347	33366	N/A	N/A	ATTACAGACTTTATTACTT	59	2159
1323170	37420	37439	4692	4711	CTCTAATGATACAAATCTTT	51	2160
1323174	9713	9732	N/A	N/A	TCCCACCTTTCTCTGCTCAC	57	2161
1323181	22420	22439	N/A	N/A	GTAAAAATAATGCTTACTTC	67	2162
1323216	30785	30804	N/A	N/A	ATCCCTATTTCCAAAACAAC	64	2163
1323224	20589	20608	N/A	N/A	GTTTTACATTTTTTTTCCAA	34	2164
1323253	24307	24326	882	901	ATGTATAATCCCATTTAAGA	34	2165
1323275	7331	7350	N/A	N/A	CTGGAATTCAGAAAAAGCTA	67	2166
1323280	27416	27435	N/A	N/A	ACATTTTATTTTCTAAGCTC	51	2167
1323288	6408	6427	N/A	N/A	TAACAGTATCTACACTGCTC	72	2168
1323339	26889	26908	N/A	N/A	TTGTCCCATTCTACTTATTC	58	2169

Table 29

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320898	37086	37105	4358	4377	CTCCAACCTCCTAGAGACCT	59	2170
1320986	24306	24325	881	900	TGTATAATCCCATTTAAGAA	50	2171
1321073	16062	16081	N/A	N/A	CCAGTTAACAATATATTTAC	58	2172
1321185	5519	5538	N/A	N/A	AAGTCTAGTTCCTAAACTA	66	2173
1321223	8351	8370	N/A	N/A	CCTTATCCCACTCTAGAATT	72	2174
1321226	30098	30117	N/A	N/A	TAAGTATTCAATAAGAGTTT	58	2175
1321231	20192	20211	N/A	N/A	ACTAAAGAATATAATTCAGC	72	2176
1321311	38469	38488	5741	5760	AGGCTCTATCTCCACAGGCT	57	2177
1321348	16479	16498	N/A	N/A	CCGGAGGGCCTAATGCCTTA	69	2178
1321395	33346	33365	N/A	N/A	TTACAGACTTTATTACTTA	59	2179
1321478	31765	31784	1298	1317	ATCAGTTTTTTTCTCGATAA	47	2180
1321496	26691	26710	N/A	N/A	CTCCTCTCATAATTAGGTTA	64	2181
1321551	29488	29507	N/A	N/A	AACTAAACAACTTTTGGGC	34	2182
1321632	37416	37435	4688	4707	AATGATACAAATCTTTCATA	68	2183
1321722	25247	25266	N/A	N/A	TCCTCTGCCACCAATGTATA	53	2184
1321736	25346	25365	N/A	N/A	TACTTACACTTCCCTTCTCC	66	2185
1321748	25755	25774	N/A	N/A	CTATTACCTTTACATTTTC	69	2186
1321761	28537	28556	N/A	N/A	ACAGTCTTTTACCTCAGCA	17	2187
1321839	9379	9398	N/A	N/A	TGTCCTAGTCTTTAATATCC	55	2188

1321876	27414	27433	N/A	N/A	ATTTTATTTTCTAAGCTCTT	58	2189
1321885	25690	25709	N/A	N/A	ACCACACAACACTTTGCAAT	55	2190
1321901	8807	8826	N/A	N/A	TGCAAGTTCCTTAAGGGCAG	60	2191
1321912	4846	4865	N/A	N/A	TCAAGACTCCATCTACCCAG	76	2192
1322014	35424	35443	2696	2715	TAGGGATCATCTTTCTGGCA	24	2193
1322039	6407	6426	N/A	N/A	AACAGTATCTACACTGCTCT	71	2194
1322058	36182	36201	3454	3473	TCTCTTTTCTTCACTGGTC	17	2195
1322067	14114	14133	N/A	N/A	TTCTTGACTTACAATGGTGT	66	2196
1322137	33622	33641	N/A	N/A	TAGGCCTTCACCATTCAGTG	64	2197
1322159	30285	30304	N/A	N/A	ACTTAAGGCCTCTGTTCTCA	42	2198
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	8	132
1322183	22597	22616	741	760	CTGCTTTAACTTTTAGACAA	6	2199
1322209	13738	13757	N/A	N/A	GCCCCTCACACACCTGGATC	75	2200
1322210	25144	25163	N/A	N/A	ACAATTTTCCAATCAATATA	74	2201
1322244	11574	11593	N/A	N/A	TTGTTGAGTTTCCTTAAGAT	85	2202
1322311	9707	9726	N/A	N/A	TTTTCTCTGCTCACTAGGAT	56	2203
1322331	19640	19659	N/A	N/A	GCTCTGTTAAAAATAGCTGT	61	2204
1322358	11009	11028	N/A	N/A	ATCTCACAAACCTACTGAGA	70	2205
1322417	12499	12518	N/A	N/A	TTCTAATAATATCCTTTGCC	59	2206
1322437	5922	5941	N/A	N/A	CTCACTACAAAATTACCTCT	67	2207
1322472	30784	30803	N/A	N/A	TCCCTATTCCAAAACAACC	57	2208
1322538	38145	38164	5417	5436	AACTGCGCACAAACACCCTC	48	2209
1322543	32359	32378	N/A	N/A	CCTTCAGCACTTTTACACCA	43	2210
1322557	8626	8645	N/A	N/A	ATATTTCTTTTACTTCTGCC	49	2211
1322567	26888	26907	N/A	N/A	TGTCCCATTCTACTTATTCA	59	2212
1322605	N/A	N/A	670	689	TCAATCCTTTCTTCTACACC	45	2213
1322672	27871	27890	N/A	N/A	GGTGGCTCATATCAATATGC	28	2214
1322677	28226	28245	1071	1090	TGTTATTTCCATCAGATGCT	24	2215
1322681	24729	24748	N/A	N/A	TGAGATCATTTTAAGGACTC	42	2216
1322697	29968	29987	N/A	N/A	ACTTCCTTTTAAACCTTATA	23	2217
1322722	28989	29008	N/A	N/A	CACCCATAACTCTACAGTGC	56	2218
1322741	18212	18231	N/A	N/A	AACTCTCATTATAAACAGAA	58	2219
1322745	26983	27002	N/A	N/A	CATGCACCTTCCTCAAATCC	59	2220
1322815	17617	17636	N/A	N/A	CTTCATGCCATCTTTGCCTC	67	2221
1322838	23231	23250	N/A	N/A	ACTCATAGTTCAGCTACCTC	49	2222
1322845	34479	34498	1751	1770	TTCATTAGAATAATTTCTTG	53	2223
1322852	N/A	N/A	218	237	TAGATTTTTTCCACCTGCGG	35	2224
1322861	18534	18553	N/A	N/A	TCAAGCCTAATTCATTAGCT	54	2225
1322882	35667	35686	2939	2958	TTGTACACACTCTCAGATCT	63	2226
1322902	25867	25886	N/A	N/A	CACAGAAAATAACATCTAA	80	2227
1322908	7315	7334	N/A	N/A	GCTAACCACCATTAAACAACA	55	2228
1322987	28609	28628	N/A	N/A	CCCCCAAATTTTACATTCAA	93	2229
1323006	21952	21971	N/A	N/A	TGATGACCACATCTATGCTA	52	2230

1323010	20008	20027	357	376	ACAATTTTATCCAATTATCC	48	2231
1323012	31313	31332	N/A	N/A	TGAGAAATATAAATTTGTTT	79	2232
1323023	33952	33971	N/A	N/A	TATCCAACACATATATATCC	64	2233
1323039	27090	27109	N/A	N/A	GCTAAAAGCATCTCAGTTCA	43	2234
1323052	29336	29355	N/A	N/A	CTTTTGTCCCATAAGAACCA	40	2235
1323087	13497	13516	N/A	N/A	AAGAACATCTTAATTTCTT	67	2236
1323097	35016	35035	2288	2307	TCAACTCTTTTAATTTCTTT	24	2237
1323104	25189	25208	N/A	N/A	TCCTTCTACTTAATTTTCCT	40	2238
1323154	24865	24884	N/A	N/A	CTGCTCAACCACATAGAACA	72	2239
1323173	20539	20558	N/A	N/A	GCAGATGAATTTACATTGA	11	2240
1323182	31104	31123	N/A	N/A	AGAGTATCACTTACAGCTGT	51	2241
1323187	25532	25551	N/A	N/A	TGGTGACCCTATTATTTATT	12	2242
1323225	35817	35836	3089	3108	GTGGAACATTCTTCTCCTC	65	2243
1323316	12100	12119	N/A	N/A	TTGATGCCTTTCTCTTGCTA	62	2244
1323327	29779	29798	N/A	N/A	TCAATGGGCTACATTAAGCT	42	2245
1323341	7778	7797	N/A	N/A	ACCTTTCACATTCATTTTCA	62	2246

Table 30

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320886	35664	35683	2936	2955	TACACACTCTCAGATCTTAA	39	2247
1320890	37076	37095	4348	4367	CTAGAGACCTAACAATTTCA	79	2248
1320915	30783	30802	N/A	N/A	CCCTATTTCCAAAACAACCA	99	2249
1320944	35816	35835	3088	3107	TGGAACATTCTTCTCCTCT	91	2250
1320960	19594	19613	N/A	N/A	TTCTGGATCTTATCTTCCTT	97	2251
1320962	6361	6380	N/A	N/A	AAACACTTAGATTACTGCCT	71	2252
1321177	25531	25550	N/A	N/A	GGTGACCCTATTATTTATTC	28	2253
1321218	25865	25884	N/A	N/A	CAGAAAATAACATCTAATA	98	2254
1321252	12046	12065	N/A	N/A	CAACAGATAATAATGTGCTT	73	2255
1321297	N/A	N/A	216	235	GATTTTTTCCACCTGCGGCT	55	2256
1321315	34719	34738	1991	2010	GGCCTGTAATTTTCATTTTAA	106	2257
1321362	36181	36200	3453	3472	CTCTTTTCTTTCACTGGTCC	36	2258
1321370	22413	22432	N/A	N/A	TAATGCTTACTTCTACACCT	84	2259
1321384	5921	5940	N/A	N/A	TCACTACAAAATTACCTCTC	100	2260
1321413	9677	9696	N/A	N/A	TCTTTGATGCACTCTAGCAC	89	2261
1321467	18174	18193	N/A	N/A	AAACTTAATATAATTTCAAC	94	2262
1321592	24305	24324	880	899	GTATAATCCCATTTAAGAAC	26	2263
1321593	N/A	N/A	1284	1303	CGATAATTTTTCTCTCAGCA	39	2264
1321621	28195	28214	1040	1059	AAGGTAAATTCCTTTTGGGA	58	2265
1321727	9377	9396	N/A	N/A	TCCTAGTCTTTAATATCCGG	73	2266

1321751	20538	20557	N/A	N/A	CAGATGAATTTTCACATTGAA	40	2267
1321760	33951	33970	N/A	N/A	ATCCAACACATATATATCCA	49	2268
1321765	27076	27095	N/A	N/A	AGTTCAAGCCCAGAACTCTA	92	2269
1321913	7312	7331	N/A	N/A	AACCACCATTAACAACAACA	86	2270
1321940	34475	34494	1747	1766	TTAGAATAATTTCTGAATC	81	2271
1321946	29967	29986	N/A	N/A	CTTCCTTTTAAACCTTATAA	67	2272
1321955	8347	8366	N/A	N/A	ATCCCACTCTAGAATTCTTA	88	2273
1321965	30272	30291	N/A	N/A	GTTCTCAGCACATCTACTTG	64	2274
1322006	31758	31777	1291	1310	TTTTTCTCGATAATTTTCT	53	2275
1322078	30089	30108	N/A	N/A	AATAAGAGTTTCTATAGTAA	93	2276
1322079	16061	16080	N/A	N/A	CAGTTAACAATATATTTACA	94	2277
1322097	8624	8643	N/A	N/A	ATTTCTTTTACTTCTGCCTT	74	2278
1322101	37407	37426	4679	4698	AATCTTTCATATAAATTCTT	89	2279
1322167	18533	18552	N/A	N/A	CAAGCCTAATTCATTAGCTG	80	2280
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	9	132
1322278	21405	21424	N/A	N/A	CCCCACTTTTTTTTGAGATA	102	2281
1322298	13737	13756	N/A	N/A	CCCCTCACACACCTGGATCA	97	2282
1322299	26982	27001	N/A	N/A	ATGCACCTTCTCAAATCCA	65	2283
1322339	29335	29354	N/A	N/A	TTTTGTCCATAAGAACCBA	77	2284
1322343	33619	33638	N/A	N/A	GCCTTCACCATTCAAGTGCTT	83	2285
1322357	25666	25685	N/A	N/A	GCTAACTGCTTTCAATTTTT	52	2286
1322396	24728	24747	N/A	N/A	GAGATCATTTTAAGGACTCA	63	2287
1322455	25345	25364	N/A	N/A	ACTTACACTTCCCTTCTCCC	72	2288
1322495	38468	38487	5740	5759	GGCTCTATCTCCACAGGCTC	109	2289
1322539	20176	20195	N/A	N/A	CAGCTAGCAACTTTTTCTTA	86	2290
1322565	23224	23243	N/A	N/A	GTTCAAGCTACCTCCTGCTTC	93	2291
1322581	26886	26905	N/A	N/A	TCCCATTTCTACTTATTCAGC	65	2292
1322598	13496	13515	N/A	N/A	AGAACATCTTAATTTCTTAA	68	2293
1322631	17558	17577	N/A	N/A	TTGGCATGAAATATATTCAA	93	2294
1322651	22565	22584	709	728	GGTGAGAGTTTATAAATTTT	2	2295
1322658	31082	31101	N/A	N/A	GGTCTTGCAAGCATTATTTA	21	2296
1322687	8795	8814	N/A	N/A	AAGGGCAGAATTTATATCGC	46	2297
1322743	16472	16491	N/A	N/A	GCCTAATGCCTTATTTCTTC	74	2298
1322744	25143	25162	N/A	N/A	CAATTTTCCAATCAATATAA	100	2299
1322754	25238	25257	N/A	N/A	ACCAATGTATATCTTTCTTT	57	2300
1322764	11572	11591	N/A	N/A	GTTGAGTTTCCTTAAGATCA	84	2301
1322778	4841	4860	N/A	N/A	ACTCCATCTACCCAGAGGCA	79	2302
1322884	29487	29506	N/A	N/A	ACTAAACAACCTTTTTGGGCA	33	2303
1322887	20004	20023	353	372	TTTTATCCAATTATCCATCC	57	2304
1322923	35423	35442	2695	2714	AGGGATCATCTTTCTGGCAT	29	2305
1322944	25754	25773	N/A	N/A	TATTCACCTTTACATTTTCA	88	2306
1322953	38140	38159	5412	5431	GCCACAAACACCCCTCAGGTT	80	2307
1322978	28988	29007	N/A	N/A	ACCCATAACTCTACAGTGCA	43	2308

1322984	14052	14071	N/A	N/A	GCTGGCTTCCTCCCTGCAGT	102	2309
1323009	28607	28626	N/A	N/A	CCCAAATTTTACATTCAAGC	79	2310
1323036	25188	25207	N/A	N/A	CCTTCTACTTAATTTTCCTC	69	2311
1323069	11008	11027	N/A	N/A	TCTCACAAACCTACTGAGAC	89	2312
1323114	31296	31315	N/A	N/A	TTTTAGATACACCACTATAA	76	2313
1323123	29777	29796	N/A	N/A	AATGGGCTACATTAAGCTAT	69	2314
1323161	27870	27889	N/A	N/A	GTGGCTCATATCAATATGCA	64	2315
1323166	12498	12517	N/A	N/A	TCTAATAATATCCTTTGCCC	87	2316
1323206	5183	5202	N/A	N/A	AAATGTCTTCCCATATTTTG	77	2317
	7685	7704					
1323210	24864	24883	N/A	N/A	TGCTCAACCACATAGAACAT	97	2318
1323220	33046	33065	N/A	N/A	TGGCCAAGAATCACAGGCTT	99	2319
1323273	32357	32376	N/A	N/A	TTCAGCACTTTTACACCATA	53	2320
1323301	7777	7796	N/A	N/A	CCTTTCACATTCATTTTCAC	90	2321
1323323	27393	27412	N/A	N/A	GGGCTATCTTTATCTATTGT	52	2322
1323348	26680	26699	N/A	N/A	ATTAGGTTACATTAAGTGGC	24	2323

Table 31

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320973	24304	24323	879	898	TATAATCCCATTTAAGAACA	75	2324
1320978	27075	27094	N/A	N/A	GTTCAAGCCCAGAACTCTAA	73	2325
1320980	21126	21145	N/A	N/A	TGGGCCACTACACTCAGCTC	98	2326
1321014	34440	34459	1712	1731	ACTGTATTTTTTATGATCTT	49	2327
1321170	25664	25683	N/A	N/A	TAAGTCTTTCAATTTTGA	83	2328
1321222	16466	16485	N/A	N/A	TGCCTTATTTCTTCATTGCC	84	2329
1321234	24698	24717	N/A	N/A	GAGTTCTTAGAAAAAGATCA	61	2330
1321251	28194	28213	1039	1058	AGGTAAATTCCTTTTGGAA	40	2331
1321270	25344	25363	N/A	N/A	CTTACACTTCCCTTCTCCCT	73	2332
1321364	28987	29006	N/A	N/A	CCCATAACTCTACAGTGCAA	54	2333
1321374	20002	20021	351	370	TTATCCAATTATCCATCCCA	43	2334
1321379	4827	4846	N/A	N/A	GAGGCATCTGCATAACTGAC	60	2335
1321415	31295	31314	N/A	N/A	TTTAGATACACCACTATAAC	73	2336
1321420	38417	38436	5689	5708	AGGATGCTCAACCCTGGGCT	85	2337
1321424	33606	33625	N/A	N/A	AGTGCTTTCATTTAATATGC	54	2338
1321432	18171	18190	N/A	N/A	CTTAATATAATTTCAACCCA	97	2339
1321522	18530	18549	N/A	N/A	GCCTAATTCATTAGCTGATT	50	2340
1321534	29746	29765	N/A	N/A	TGTCAGACAATTAAGGG	40	2341
1321577	34718	34737	1990	2009	GCCTGTAATTTTCATTTTAA	84	2342
1321626	13493	13512	N/A	N/A	ACATCTTAATTTCTTATGC	77	2343

1321633	16060	16079	N/A	N/A	AGTTAACAATATATTTACAA	103	2344
1321673	7311	7330	N/A	N/A	ACCACCATTAACAACAACAC	91	2345
1321683	37075	37094	4347	4366	TAGAGACCTAACAATTTTAC	85	2346
1321691	4050	4069	142	161	AGGACGACCATCATCTGGGA	63	2347
1321735	14026	14045	N/A	N/A	TGTGGTGACATCATCACAAA	106	2348
1321788	33037	33056	N/A	N/A	ATCACAGGCTTTAAACGGTA	37	2349
1321825	26679	26698	N/A	N/A	TTAGGTTACATTAAGTGGCA	51	2350
1321832	26981	27000	N/A	N/A	TGCACCTTCCTCAAATCCAG	58	2351
1321833	25141	25160	N/A	N/A	ATTTTCCAATCAATATAAAC	105	2352
1321846	32356	32375	N/A	N/A	TCAGCACTTTTACACCATAC	30	2353
1321878	20528	20547	N/A	N/A	TCACATTGAATTCTATGTTA	39	2354
1321902	9676	9695	N/A	N/A	CTTTGATGCACTCTAGCACT	70	2355
1321916	5182	5201	N/A	N/A	AATGTCTTCCCATATTTTGG	49	2356
	7684	7703					
1321920	19593	19612	N/A	N/A	TCTGGATCTTATCTTCCTTA	76	2357
1321929	31079	31098	N/A	N/A	CTTGCAAGCATTATTTAATT	64	2358
1321962	25862	25881	N/A	N/A	AAAACATAACATCTAATAGTT	95	2359
1322027	30269	30288	N/A	N/A	CTCAGCACATCTACTTGGGC	82	2360
1322038	8551	8570	N/A	N/A	TAGAACCTTCTTAACTGAGA	82	2361
1322049	29476	29495	N/A	N/A	TTTTGGGCAATTTTTTCCTA	51	2362
1322115	25187	25206	N/A	N/A	CTTCTACTTAATTTTCTCT	68	2363
1322145	37406	37425	4678	4697	ATCTTTCATATAAATTCCTTA	85	2364
1322168	36125	36144	3397	3416	GCCACCAGAATTTCCAGACT	68	2365
1322174	5920	5939	N/A	N/A	CACTACAAAATTACCTCTCA	91	2366
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	3	132
1322205	27392	27411	N/A	N/A	GGCTATCTTTATCTATTGTA	42	2367
1322277	12487	12506	N/A	N/A	CCTTTGCCCTTTCTTCCTC	85	2368
1322285	24863	24882	N/A	N/A	GCTCAACCACATAGAACATA	60	2369
1322287	29966	29985	N/A	N/A	TTCCTTTTAAACCTTATAAA	101	2370
1322300	22560	22579	704	723	GAGTTTATAAATTTTATGTC	58	2371
1322305	23175	23194	N/A	N/A	GTCATTACAAAATATTTGAA	60	2372
1322307	26885	26904	N/A	N/A	CCCATTCTACTTATTCAGCT	50	2373
1322367	7774	7793	N/A	N/A	TTCACATTCAATTTTACGAC	27	2374
1322451	35402	35421	2674	2693	TGCAGCTGTTTTCTAGGGTA	30	2375
1322457	27869	27888	N/A	N/A	TGGCTCATATCAATATGCAA	62	2376
1322462	12025	12044	N/A	N/A	GGAGAGAACCCTTTTTGGGTT	81	2377
1322475	31755	31774	N/A	N/A	TTCTCGATAATTTTCTCTA	46	2378
1322627	6357	6376	N/A	N/A	ACTTAGATTACTGCCTGGCA	100	2379
1322662	22411	22430	N/A	N/A	ATGCTTACTTCTACACCTGA	73	2380
1322667	11007	11026	N/A	N/A	CTCACAAACCTACTGAGACA	100	2381
1322684	24245	24264	820	839	GGAGGTAGTTCATTTTCAAC	17	2382
1322702	25753	25772	N/A	N/A	ATTCACCTTTACATTTTCAA	73	2383
1322705	25235	25254	N/A	N/A	AATGTATATCTTTCTTTCCA	56	2384

1322756	28536	28555	N/A	N/A	CAGTCTTTTTACCTCAGCAT	41	2385
1322774	17557	17576	N/A	N/A	TGGCATGAAATATATTCAAT	73	2386
1322822	30088	30107	N/A	N/A	ATAAGAGTTTCTATAGTAAC	61	2387
1322859	30782	30801	N/A	N/A	CCTATTTCCAAAACAACCAC	91	2388
1322872	8343	8362	N/A	N/A	CACTCTAGAATTCTTAACCTT	93	2389
1322878	33948	33967	N/A	N/A	CAACACATATATATCCAGAA	44	2390
1322910	29328	29347	N/A	N/A	CCATAAGAACCAATTTTTGT	95	2391
1322911	8794	8813	N/A	N/A	AGGGCAGAATTTATATCGCT	78	2392
1322919	13736	13755	N/A	N/A	CCCTCACACACCTGGATCAC	91	2393
1322976	25530	25549	N/A	N/A	GTGACCCTATTATTTATTCA	42	2394
1323033	35815	35834	3087	3106	GGAACATTCTTCTTCCTCTT	44	2395
1323107	9376	9395	N/A	N/A	CCTAGTCTTTAATATCCGGC	91	2396
1323113	28606	28625	N/A	N/A	CCAAATTTTACATTCAAGCT	82	2397
1323203	11552	11571	N/A	N/A	TTAGTTTGAATTCCTTTTCC	87	2398
1323221	35657	35676	2929	2948	TCTCAGATCTTAAATAACAA	68	2399
1323265	38139	38158	5411	5430	CCACAAACACCCTCAGGTTC	82	2400

Table 32

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320938	29327	29346	N/A	N/A	CATAAGAACCAATTTTTGTC	109	2401
1320949	27070	27089	N/A	N/A	AGCCCAGAACTCTAATAGCC	81	2402
1320972	8550	8569	N/A	N/A	AGAAGTTTCTTAACTGAGAC	95	2403
1321018	22391	22410	647	666	AGAGTTTTTCCAGATAACTA	108	2404
1321021	34712	34731	1984	2003	AATTCATTTTTAAATAGTT	108	2405
1321027	9375	9394	N/A	N/A	CTAGTCTTTAATATCCGGCT	80	2406
1321046	25752	25771	N/A	N/A	TTCACCTTTACATTTTCAAT	67	2407
1321149	32355	32374	N/A	N/A	CAGCACTTTTACACCATACA	32	2408
1321178	3964	3983	56	75	TCCTAAGTCACACCGCCCCT	89	2409
1321195	23174	23193	N/A	N/A	TCATTACAAAATATTTGAAC	28	2410
1321213	29965	29984	N/A	N/A	TCCTTTTAAACCTTATAAAC	92	2411
1321215	25139	25158	N/A	N/A	TTTCCAATCAATATAAACTA	159	2412
1321240	11999	12018	N/A	N/A	ATTTGGAATCATTGAGCTT	87	2413
1321295	N/A	N/A	1283	1302	GATAATTTTTCTCTCAGCAT	62	2414
1321367	37402	37421	4674	4693	TTCATATAAATTCTTAGATT	113	2415
1321422	24651	24670	N/A	N/A	GGGAAATAACACATGCAACT	37	2416
1321428	31752	31771	N/A	N/A	TCGATAATTTTTCTCTAGAA	60	2417
1321431	21125	21144	N/A	N/A	GGGCCACTACACTCAGCTCC	53	2418
1321436	35812	35831	3084	3103	ACATTCTTCTTCTCTTGCA	45	2419
1321448	38116	38135	5388	5407	GTTTAGATTTTCATTATTCA	192	2420

1321494	30086	30105	N/A	N/A	AAGAGTTTCTATAGTAACAA	70	2421
1321518	7310	7329	N/A	N/A	CCACCATTAACAACAACACA	95	2422
1321545	26980	26999	N/A	N/A	GCACCTTCCTCAAATCCAGA	41	2423
1321548	10780	10799	N/A	N/A	GGTATGGTTTTAATTTGGGA	37	2424
1321552	28986	29005	N/A	N/A	CCATAACTCTACAGTGCAAA	33	2425
1321565	31294	31313	N/A	N/A	TTAGATACACCACTATAACC	91	2426
1321582	20517	20536	N/A	N/A	TCTATGTTAAATCAGTGACC	55	2427
1321679	7772	7791	N/A	N/A	CACATTCATTTTCACGACCA	46	2428
1321684	33605	33624	N/A	N/A	GTGCTTTCATTTAATATGCT	75	2429
1321730	17556	17575	N/A	N/A	GGCATGAAATATATTCAATA	79	2430
1321836	31078	31097	N/A	N/A	TTGCAAGCATTATTTAATTT	77	2431
1321862	25861	25880	N/A	N/A	AAACTAACATCTAATAGTTG	103	2432
1321914	24303	24322	878	897	ATAATCCCATTTAAGAACAT	72	2433
1321943	20000	20019	349	368	ATCCAATTATCCATCCCAGT	7	2434
1321954	20172	20191	N/A	N/A	TAGCAACTTTTTCTTACCTT	77	2435
1322025	35655	35674	2927	2946	TCAGATCTTAAATACAACA	72	2436
1322029	32970	32989	N/A	N/A	TAAGGACAATCATTACTATC	79	2437
1322034	25343	25362	N/A	N/A	TTACACTTCCCTTCTCCCTC	96	2438
1322041	13729	13748	N/A	N/A	ACACCTGGATCACCTGCGC	113	2439
1322096	22559	22578	703	722	AGTTTATAAATTTTATGTCT	46	2440
1322098	28193	28212	1038	1057	GGTAAATTCCTTTTTGGAAA	21	2441
1322162	14025	14044	N/A	N/A	GTGGTGACATCATCACAAAT	119	2442
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	6	132
1322187	16465	16484	N/A	N/A	GCCTTATTTCTTCATTGCCT	9	2443
1322198	29745	29764	N/A	N/A	GTCAGACAATTAAAAAGGGA	37	2444
1322269	33946	33965	N/A	N/A	ACACATATATATCCAGAAGA	61	2445
1322272	18167	18186	N/A	N/A	ATATAATTTCAACCCAACCT	0	2446
1322279	16059	16078	N/A	N/A	GTTAACAATATATTTACAAA	116	2447
1322366	6306	6325	N/A	N/A	CTATAAATTATATCTTGCCA	57	2448
1322373	26654	26673	N/A	N/A	GAAGGTATTTACAGATGTA	27	2449
1322394	8793	8812	N/A	N/A	GGGCAGAATTTATATCGCTT	81	2450
1322429	34411	34430	1683	1702	GATTAGTTTCTTCTACTGTA	45	2451
1322443	5917	5936	N/A	N/A	TACAAAATTACCTCTCACTC	104	2452
1322526	29475	29494	N/A	N/A	TTTGGGCAATTTTTCTCTAA	83	2453
1322546	8339	8358	N/A	N/A	CTAGAATTCTTAACCTGGTT	67	2454
1322562	4825	4844	N/A	N/A	GGCATCTGCATAACTGACTC	57	2455
1322568	25186	25205	N/A	N/A	TTCTACTTAATTTTCCTCTT	75	2456
1322612	28605	28624	N/A	N/A	CAAATTTTACATTCAAGCTT	98	2457
1322617	37074	37093	4346	4365	AGAGACCTAACAATTTCACT	79	2458
1322653	5181	5200	N/A	N/A	ATGTCTTCCCATATTTTGGA	26	2459
	7683	7702					
1322656	38375	38394	5647	5666	CAGCTCTTCCATGATGAATA	87	2460
1322797	18488	18507	N/A	N/A	AGATGCCATTTTAAAGACGA	69	2461

1322811	27388	27407	N/A	N/A	ATCTTTATCTATTGTAGCTA	101	2462
1322830	11549	11568	N/A	N/A	GTTTGAATTCCTTTTCCAGC	72	2463
1322856	9668	9687	N/A	N/A	CACTCTAGCACTCTTAGTTA	96	2464
1322891	35401	35420	2673	2692	GCAGCTGTTTTCTAGGGTAA	33	2465
1322951	30268	30287	N/A	N/A	TCAGCACATCTACTTGGGCT	86	2466
1322971	19589	19608	N/A	N/A	GATCTTATCTTCCTTATTGA	79	2467
1323005	26884	26903	N/A	N/A	CCATTCTACTTATTCAGCTT	52	2468
1323011	12482	12501	N/A	N/A	GCCCCCTTCTTCTCTCTTA	103	2469
1323024	25529	25548	N/A	N/A	TGACCCTATTATTTATTCAC	63	2470
1323026	36124	36143	3396	3415	CCACCAGAATTCCCAGACTT	69	2471
1323064	27840	27859	N/A	N/A	TTAGTTAGAATTTCCAGGAA	60	2472
1323074	25233	25252	N/A	N/A	TGTATATCTTTCTTTCCATC	45	2473
1323116	25662	25681	N/A	N/A	ACTGCTTTCAATTTTGAAC	62	2474
1323122	13492	13511	N/A	N/A	CATCTTAATTTCTTATGCT	99	2475
1323292	30781	30800	N/A	N/A	CTATTTCCAAAACAACCACC	96	2476
1323322	24848	24867	N/A	N/A	ACATAGTTCTTCCAACCTT	66	2477

Table 33

Reduction of IFNAR1 RNA by 5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages in A431 cells

Compound Number	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	Sequence (5' to 3')	IFNAR1 (% UTC)	SEQ ID NO
1320921	13728	13747	N/A	N/A	CACCTGGATCACCTGCGCA	76	2478
1320993	29326	29345	N/A	N/A	ATAAGAACCAATTTTGTCC	105	2479
1321000	34657	34676	1929	1948	AAGATGTTTTTCTTTCCCT	79	2480
1321028	14024	14043	N/A	N/A	TGGTGACATCATCACAATA	84	2481
1321038	22363	22382	619	638	GTAAAGCTTAAACCATCCAA	26	2482
1321068	32354	32373	N/A	N/A	AGCACTTTTACACCATACAA	37	2483
1321069	8325	8344	N/A	N/A	TTGGTTCTCATCCATTTGTT	59	2484
1321072	24846	24865	N/A	N/A	ATAGTTCTTTCCAACCTTCT	65	2485
1321098	25750	25769	N/A	N/A	CACCTTTACATTTTCAATTT	83	2486
1321110	25232	25251	N/A	N/A	GTATATCTTTCTTTCCATCT	26	2487
1321136	25138	25157	N/A	N/A	TTCCAATCAATATAAACTAC	69	2488
1321147	26882	26901	N/A	N/A	ATTCTACTTATTCAGCTTTC	67	2489
1321200	13491	13510	N/A	N/A	ATCTTAATTTCTTATGCTT	82	2490
1321207	9374	9393	N/A	N/A	TAGTCTTTAATATCCGGCTC	88	2491
1321269	16463	16482	N/A	N/A	CTTATTTCTTCATTGCCTGC	65	2492
1321298	31751	31770	N/A	N/A	CGATAATTTTCTCTAGAAA	76	2493
1321307	7307	7326	N/A	N/A	CCATTAACAACAACACAGAC	96	2494
1321314	30267	30286	N/A	N/A	CAGCACATCTACTTGGGCTC	83	2495
1321433	38367	38386	5639	5658	CCATGATGAATACCTTTTAA	79	2496
1321445	26978	26997	N/A	N/A	ACCTTCCTCAAATCCAGAGC	70	2497

1321492	29744	29763	N/A	N/A	TCAGACAATTAAAAAGGGAA	72	2498
1321508	11965	11984	N/A	N/A	TCTGTATCTCTCTCCAGACT	82	2499
1321560	18487	18506	N/A	N/A	GATGCCATTTTAAAGACGAT	17	2500
1321562	28534	28553	N/A	N/A	GTCTTTTTTACCTCAGCATTT	61	2501
1321587	25342	25361	N/A	N/A	TACACTTCCCTTCTCCCTCA	72	2502
1321588	26631	26650	N/A	N/A	AAGGTCCCAAATCAGTTGAA	33	2503
1321603	35654	35673	2926	2945	CAGATCTTAAAATACAACAA	84	2504
1321674	28166	28185	1011	1030	GAGGAAAGACACACTGGGTA	N.D.	2505
1321692	N/A	N/A	220	239	TTTAGATTTTTTCCACCTGC	37	2506
1321706	5179	5198	N/A	N/A	GTCTTCCCATATTTTGGACA	95	2507
1321743	12479	12498	N/A	N/A	CCTTCTCTCCTCTCTTATTA	105	2508
1321789	31077	31096	N/A	N/A	TGCAAGCATTATTTAATTTTC	26	2509
1321808	36121	36140	3393	3412	CCAGAATTCCCAGACTTCCT	56	2510
1321813	30780	30799	N/A	N/A	TATTTCCAAAACAACCACCA	91	2511
1321816	31293	31312	N/A	N/A	TAGATACACCACTATAACCA	60	2512
1321880	N/A	N/A	521	540	TGGAGGACCAATCTGAGCTT	33	2513
1321890	38115	38134	5387	5406	TTTAGATTTTCATTCAATCAA	69	2514
1321923	24646	24665	N/A	N/A	ATAACACATGCAACTAGTTA	82	2515
1321935	25528	25547	N/A	N/A	GACCCTATTATTTATTCACT	45	2516
1321991	32969	32988	N/A	N/A	AAGGACAATCATTACTATCT	42	2517
1322016	22857	22876	N/A	N/A	GCCTGAACTTTTAAGTAGAA	57	2518
1322051	17392	17411	N/A	N/A	CAGCACGCACCACCACATCC	156	2519
1322092	37401	37420	4673	4692	TCATATAAATTCTTAGATTA	109	2520
1322176	24313	24332	888	907	TTGCATATGTATAATCCCAT	5	132
1322208	33922	33941	N/A	N/A	CAATTGAGAAATTATTGGCT	109	2521
1322247	30082	30101	N/A	N/A	GTTTCTATAGTAACAATTAT	66	2522
1322297	10779	10798	N/A	N/A	GTATGGTTTTAATTTGGGAA	35	2523
1322330	29472	29491	N/A	N/A	GGGCAATTTTTTCCTAATCC	27	2524
1322383	25842	25861	N/A	N/A	GTCTACTTAAAAAAAATCTG	72	2525
1322501	27839	27858	N/A	N/A	TAGTTAGAATTTCCAGGAAT	43	2526
1322522	18166	18185	N/A	N/A	TATAATTTCAACCCAACCTC	91	2527
1322549	5916	5935	N/A	N/A	ACAAAATTACCTCTCACTCT	88	2528
1322594	24299	24318	874	893	TCCCATTTAAGAACATAGTT	48	2529
1322603	37071	37090	4343	4362	GACCTAACAATTTCACTGGT	92	2530
1322611	19999	20018	348	367	TCCAATTATCCATCCAGTT	24	2531
1322630	9667	9686	N/A	N/A	ACTCTAGCACTCTTAGTTAA	89	2532
1322655	25661	25680	N/A	N/A	CTGCTTTCATTTTTGAACC	61	2533
1322660	28596	28615	N/A	N/A	CATTCAAGCTTTATTTACCC	50	2534
1322737	25183	25202	N/A	N/A	TACTTAATTTTCTCTTCTC	88	2535
1322755	16056	16075	N/A	N/A	AACAATATATTTACAAAGTG	95	2536
1322782	34409	34428	1681	1700	TTAGTTTCTTCTACTGTAGC	61	2537
1322784	6279	6298	N/A	N/A	GCTAACCTAATTTTAAATTA	103	2538
1322851	21124	21143	N/A	N/A	GGCCACTACACTCAGCTCCT	96	2539

1322916	27345	27364	N/A	N/A	CATATGTTCCCAACTCCATA	49	2540
1322979	22542	22561	686	705	TCTGGAATAAATATTTTCAA	52	2541
1322993	4815	4834	N/A	N/A	TAAGTACTCCCTTTACTCT	91	2542
1322995	29964	29983	N/A	N/A	CCTTTTAAACCTTATAAACA	97	2543
1323002	35385	35404	2657	2676	GTAAGCTACTTTCCAGAAAA	64	2544
1323016	8549	8568	N/A	N/A	GAACTTTCTTAAGTGAACA	87	2545
1323051	33604	33623	N/A	N/A	TGCTTTCATTTAATATGCTA	90	2546
1323063	11548	11567	N/A	N/A	TTTGAATTCCTTTTCCAGCA	74	2547
1323076	27069	27088	N/A	N/A	GCCCAGAACTCTAATAGCCT	46	2548
1323094	20508	20527	N/A	N/A	AATCAGTGACCATATCACCA	53	2549
1323143	35811	35830	3083	3102	CATTCTTCTTCCTTGCAC	57	2550
1323156	28976	28995	N/A	N/A	ACAGTGCAAAACATGAAAAA	93	2551
1323199	8792	8811	N/A	N/A	GGCAGAATTTATATCGCTTC	84	2552
1323251	7771	7790	N/A	N/A	ACATTCATTTTCACGACCAA	50	2553
1323256	19588	19607	N/A	N/A	ATCTTATCTTCCTTATTGAA	85	2554

Example 3: Effect of modified oligonucleotides on human IFNAR1 *in vitro*, multiple doses

Modified oligonucleotides selected from the examples above were tested at various doses in A431 cells.

- 5 Cultured A431 cells at a density of 10,000 cells per well were treated by free uptake with various concentrations of modified oligonucleotide as specified in the tables below. After a treatment period of approximately 48 hours, total RNA was isolated from the cells and IFNAR1 RNA levels were measured by quantitative real-time RTPCR. Human IFNAR1 primer-probe set RTS44352 (described herein above) was used to measure RNA levels as described above. IFNAR1 RNA levels were normalized to total RNA content, as measured by RIBOGREEN®. Reduction of IFNAR1 RNA is presented in the tables below as percent IFNAR1 RNA, relative to untreated control cells (% UTC).

The half maximal inhibitory concentration (IC₅₀) of each modified oligonucleotide was calculated using a linear regression on a log/linear plot of the data in Excel and is also presented in the tables below. N.D. in the tables below refers to instances where the value was Not Defined.

Table 34

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	16 nM	80 nM	400 nM	2000 nM	
1273126	63	15	7	4	0.02
1273127	37	9	5	4	< 0.02
1273131	64	14	5	2	0.02
1273135	31	3	1	1	< 0.02
1273136	18	3	1	1	< 0.02
1273141	9	3	1	1	< 0.02
1273142	58	20	6	3	< 0.02
1273144	21	3	2	1	< 0.02
1273147	33	8	3	3	< 0.02

1273150	52	13	4	3	< 0.02
1273157	57	18	5	2	< 0.02
1273158	63	17	4	2	0.02
1273166	86	24	6	4	0.05
1273176	44	9	6	6	< 0.02
1273177	66	20	7	6	0.02
1273181	37	8	2	1	< 0.02
1273191	51	13	5	5	< 0.02
1273192	40	6	3	2	< 0.02
1273196	12	3	3	3	< 0.02

Table 35

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321056	60	31	19	11	0.12
1321058	77	48	28	15	0.37
1321187	61	32	16	8	0.12
1321277	60	39	23	11	0.15
1321555	65	48	36	26	0.32
1321707	81	51	36	17	0.48
1321856	80	54	34	25	0.55
1321877	29	11	5	3	< 0.08
1321995	34	18	10	7	< 0.08
1322064	58	37	25	20	0.12
1322108	58	44	32	25	0.18
1322176	57	34	19	9	0.11
1322246	53	32	21	13	< 0.08
1322250	63	38	17	9	0.16
1322326	71	43	24	15	0.26
1322416	60	40	27	15	0.16
1322537	64	49	31	16	0.27
1323149	66	44	24	17	0.23
1323257	80	47	31	18	0.41

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Table 36

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1320946	61	30	14	7	0.11
1320983	59	35	21	15	0.12
1321332	62	41	24	13	0.17

1321484	41	29	23	20	< 0.08
1321625	22	10	6	4	< 0.08
1321703	31	18	0	8	< 0.08
1322176	65	34	18	10	0.16
1322260	59	40	28	23	0.15
1322321	82	47	28	12	0.39
1322424	53	23	12	7	< 0.08
1322428	57	27	12	7	0.08
1322502	56	31	19	14	0.09
1322713	56	N.D.	N.D.	86	< 0.08
1322724	74	37	30	23	0.28
1322725	56	31	15	7	0.09
1323053	46	26	17	13	< 0.08
1323071	35	15	7	5	< 0.08
1323098	73	43	22	12	0.27
1323141	58	30	19	10	0.10

Table 37

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321049	53	35	20	17	< 0.08
1321090	41	19	10	6	< 0.08
1321317	77	45	28	21	0.37
1321326	115	117	110	106	> 5
1321452	114	102	95	85	> 5
1321547	68	43	26	13	0.24
1321618	16	6	3	2	< 0.08
1321713	55	21	9	4	< 0.08
1321860	100	70	52	35	1.57
1322106	63	41	28	20	0.20
1322134	45	28	16	11	< 0.08
1322176	58	34	19	11	0.11
1322202	35	17	10	6	< 0.08
1322364	60	35	24	16	0.13
1322670	81	61	40	27	0.74
1322789	46	27	22	20	< 0.08
1322800	58	31	20	12	0.10
1323241	87	56	37	24	0.68
1323347	70	49	32	21	0.35

Table 38

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1320997	74	63	40	26	0.68
1321032	57	37	25	21	0.11
1321040	50	26	17	10	< 0.08
1321118	97	77	72	65	> 5
1321139	73	61	42	34	0.80
1321249	69	40	21	9	0.22
1321529	55	43	37	30	0.14
1321817	49	29	19	13	< 0.08
1322164	45	24	13	8	< 0.08
1322170	53	30	17	11	0.07
1322176	58	30	17	10	0.09
1322216	56	29	14	8	0.08
1322362	52	36	24	17	< 0.08
1322610	132	126	130	115	> 5
1322621	83	69	66	50	> 5
1322905	56	31	18	11	0.09
1323059	33	13	6	4	< 0.08
1323152	84	53	36	22	0.57
1323169	33	17	11	8	< 0.08

Table 39

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1320923	70	48	28	21	0.32
1320992	84	62	42	27	0.81
1321036	71	40	20	15	0.23
1321192	73	43	22	13	0.27
1321239	62	39	30	25	0.17
1321750	81	47	28	19	0.41
1321910	48	19	11	7	< 0.08
1322042	68	45	29	22	0.27
1322054	72	51	33	24	0.41
1322131	57	33	21	18	0.10
1322160	38	20	8	6	< 0.08
1322176	55	32	17	11	0.08
1322384	67	41	23	13	0.21
1322470	83	46	24	14	0.38

1322518	75	51	39	31	0.56
1322875	72	49	31	19	0.35
1322988	64	41	27	23	0.20
1323100	76	41	29	21	0.34
1323315	73	59	44	36	0.88

Table 40

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321527	55	32	19	13	0.09
1321599	43	27	11	6	< 0.08
1321608	67	39	27	22	0.22
1321812	49	32	17	12	< 0.08
1321907	61	35	18	12	0.13
1321974	85	57	41	36	0.95
1322032	54	31	19	13	< 0.08
1322176	43	20	10	6	< 0.08
1322252	72	46	27	15	0.31
1322263	50	26	14	9	< 0.08
1322316	41	6	18	25	< 0.08
1322382	63	46	26	17	0.22
1322466	52	36	19	15	< 0.08
1322497	53	32	20	13	< 0.08
1322540	48	26	14	8	< 0.08
1322803	59	45	29	24	0.18
1322836	71	38	24	18	0.24
1323008	85	56	32	19	0.55
1323127	56	38	23	15	0.12

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Table 41

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321066	85	60	44	28	0.85
1321074	51	26	15	12	< 0.08
1321151	36	18	11	7	< 0.08
1321377	68	36	22	14	0.20
1321453	38	23	15	9	< 0.08
1321581	76	43	27	17	0.32
1321854	65	47	26	15	0.24
1321882	48	33	24	17	< 0.08

1322176	50	26	12	6	< 0.08
1322217	66	45	26	22	0.25
1322393	58	31	21	14	0.10
1322535	55	28	17	8	< 0.08
1322559	54	31	14	9	< 0.08
1322738	74	52	35	26	0.48
1322932	75	55	47	37	0.93
1322943	51	23	13	6	< 0.08
1322986	27	13	4	2	< 0.08
1323093	71	45	26	17	0.28
1323227	66	35	17	7	0.16

Table 42

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321321	30	14	6	3	< 0.08
1321504	32	12	5	2	< 0.08
1321541	51	30	18	12	< 0.08
1321687	56	30	17	10	0.08
1321729	49	24	15	11	< 0.08
1321820	55	35	21	16	0.09
1321872	54	30	14	7	< 0.08
1322128	66	49	N.D.	14	< 0.08
1322176	51	25	11	5	< 0.08
1322197	33	14	6	4	< 0.08
1322345	74	33	N.D.	N.D.	N.D.
1322570	40	24	12	8	< 0.08
1322844	75	54	33	19	0.44
1323029	N.D.	10	4	3	< 0.08
1323056	41	29	20	15	< 0.08
1323090	64	36	15	7	0.15
1323167	N.D.	1	10	5	< 0.08
1323262	36	23	14	8	< 0.08

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Table 43

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321111	50	32	23	18	< 0.08
1321177	60	44	33	26	0.19
1321328	59	41	27	22	0.15

1321592	87	65	42	26	0.87
1321761	64	40	28	15	0.20
1322014	50	37	25	22	< 0.08
1322058	45	32	23	18	< 0.08
1322176	50	26	12	7	< 0.08
1322183	39	21	13	7	< 0.08
1322651	52	23	12	8	< 0.08
1322658	41	26	18	14	< 0.08
1322672	95	80	55	41	2.34
1322677	56	37	25	19	0.11
1322697	91	65	41	35	1.12
1322923	63	36	26	23	0.16
1323097	66	59	39	31	0.54
1323173	61	35	23	13	0.14
1323187	61	35	20	12	0.13
1323348	69	42	25	16	0.24

Table 44

Dose-dependent reduction of human IFNAR1 RNA in A431 cells by modified oligonucleotides

Compound No.	IFNAR1 RNA (% UTC)				IC ₅₀ (μM)
	78.125 nM	312.5 nM	1250 nM	5000 nM	
1321038	85	56	30	15	0.51
1321110	82	51	32	21	0.49
1321195	37	N.D.	N.D.	56	4.69
1321560	92	65	42	24	0.89
1321789	48	34	19	13	< 0.08
1321846	81	21	8	15	0.20
1321880	64	45	29	22	0.23
1321943	46	25	14	6	< 0.08
1322098	87	64	40	28	0.87
1322176	44	23	10	7	< 0.08
1322187	70	52	40	36	0.59
1322272	114	112	98	94	> 5
1322330	65	46	26	19	0.24
1322367	74	61	42	29	0.73
1322373	62	46	26	16	0.21
1322451	48	45	32	32	< 0.08
1322611	80	50	31	17	0.43
1322653	63	44	26	16	0.21
1322684	51	31	17	9	< 0.08

Example 4: Design of modified oligonucleotides complementary to human IFNAR1 nucleic acid

Modified oligonucleotides complementary to a human IFNAR1 nucleic acid were designed, as described in the tables below. “Start site” indicates the 5’-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. “Stop site” indicates the 3’-most nucleoside to which the modified oligonucleotide is complementary in the target nucleic acid sequence. Each modified oligonucleotide listed in the tables below is 100% complementary to SEQ ID NO 1 (described herein above), to SEQ ID NO 2 (described herein above), or to both. ‘N/A’ indicates that the modified oligonucleotide is not 100% complementary to that particular target nucleic acid sequence.

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5’ to 3’): eeeeeeeeeeeeeeeeee; wherein each “d” represents a 2’-β-D-deoxyribose sugar moiety, and each “e” represents a 2’-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5’ to 3’): sooooooooooooo; wherein each “s” represents a phosphorothioate internucleoside linkage, and each “o” represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 45

5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human IFNAR1

Compound Number	Sequence (5’ to 3’)	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	SEQ ID NO
1413519	GCTGTTTACATTTTTTTC	20592	20611	N/A	N/A	1952
1413521	GCATTTATAATTTTGGTTGC	7803	7822	N/A	N/A	2555
1413522	CTGGTTTATTTTTTTTGGCT	27811	27830	N/A	N/A	128
1413523	TTTTCTTTTCTGCTCTTAT	20108	20127	457	476	2556
1413525	CTGCTTTCAATTTTGAACC	25661	25680	N/A	N/A	2533
1413529	ACGCAATTTAATTTCTTCAT	20088	20107	437	456	2557
1413530	TGGTTTTGTCTTCACATA	31888	31907	1421	1440	2558
1413531	ACTGCTTTCAATTTTGAAC	25662	25681	N/A	N/A	2474
1413534	TGCTTTTATTCAGCTTTTCA	31850	31869	1383	1402	2559
1413535	TCTCAACTCTTTAATTTCT	35018	35037	2290	2309	2056
1413541	CCTTATTTCTTCATTGCCTG	16464	16483	N/A	N/A	2560
1413547	GTTTGAATTCCTTTTCCAGC	11549	11568	N/A	N/A	2463
1413548	GTTGTTTTTCATCATGTTTT	11667	11686	N/A	N/A	2561
1413550	CTGCTTTTATTCAGCTTTTC	31851	31870	1384	1403	2562
1413551	TTCAACCTTTTCTCCACCA	36286	36305	3558	3577	1654
1413553	TTGCATATGTATAATCCCA	24314	24333	889	908	2563
1413554	GCTTTCAATTTTGAACCAC	25659	25678	N/A	N/A	2564
1413555	ATTTCTTTTACTTCTGCCTT	8624	8643	N/A	N/A	2278
1413559	TCACTCATATCTTAGTACCT	34110	34129	N/A	N/A	2565
1413560	TTACATTTTCAATTTCTGCA	25745	25764	N/A	N/A	2566
1413561	GTTCAACTGTTTTATGGCCT	14177	14196	N/A	N/A	2018
1413562	CCTCTCTTATTATTTATCAT	12471	12490	N/A	N/A	222

1413563	CTTGTTTTACTTTCGCTTTC	34502	34521	1774	1793	2567
1413564	CTGACAATTATGCTTCAGTC	4600	4619	N/A	N/A	2568
1413567	GTTCTAATTTTATGTTACAA	37614	37633	4886	4905	2569
1413568	TCCTAGTTACATTTTCCCC	35996	36015	3268	3287	1074
1413570	TCTTGCATACACTATCTTCT	35709	35728	2981	3000	2570
1413574	AGGCATTTTTGTCAAGCCTA	18545	18564	N/A	N/A	2571
1413576	TCACCTTTACATTTTCAATT	25751	25770	N/A	N/A	2572
1413578	TTTCACATTCATTTTCACGA	7775	7794	N/A	N/A	2573
1413579	AGCAACTTTTTCTTACCTTT	20171	20190	N/A	N/A	154
1413580	GCTTTAACTTTTAGACAATA	22595	22614	739	758	2574
1413583	CCACTCTTTTCAATGCATA	19785	19804	N/A	N/A	1553
1413585	CCTACAATATTTCTTTTACT	8632	8651	N/A	N/A	2575
1413586	CCTTACCTTGATTTTCAGTA	28277	28296	N/A	N/A	2576
1413587	CCTCATTTTTCTGTTTCTT	25327	25346	N/A	N/A	2577
1413588	TTGTAGACTTGTTCTACCAC	8584	8603	N/A	N/A	2578
1413589	CTGTTACTTCTTTGATGCAC	9685	9704	N/A	N/A	2579
1413591	TGCTATTTTAGAATTCTTT	12085	12104	N/A	N/A	2580
1413593	ATCTTCTTTTCATTGGGCCA	11520	11539	N/A	N/A	247
1413596	TTGAGTATATCATCCCATCC	12189	12208	N/A	N/A	2581
1413597	ATCCTCCTATTCTTGTCTTC	11168	11187	N/A	N/A	2582
1413598	GCATTATTTAATTTCTCTCT	31072	31091	N/A	N/A	335
1413600	GCTCTATTATTATTGGCAAT	7978	7997	N/A	N/A	2583
1413601	TTCATATTTTAACATTCCAC	23327	23346	N/A	N/A	1877
1413602	GTTTTGTTTTTTTTAGCACT	13429	13448	N/A	N/A	2584
1413603	TCTTCATTAGAATAATTTCC	34481	34500	1753	1772	2153
1413604	TCTACTTATTCAGCTTTCTT	26880	26899	N/A	N/A	2585
1413605	GCTGTGAGATTCATATGCCA	16559	16578	N/A	N/A	2044
1413608	AGTGCTTTCATTTAATATGC	33606	33625	N/A	N/A	2338
1413609	TCTGTTTCATACTTGAGATC	8408	8427	N/A	N/A	2586
1413614	GTTGCCAAGCATCCTGCACT	29202	29221	N/A	N/A	2587
1413615	GTGATATTAGATTCTTCCTT	19081	19100	N/A	N/A	2588
1413616	ACGCCTAATTTTTTTTCTT	31444	31463	N/A	N/A	2589
1413619	ACCCTATTATTATTCACCTT	25527	25546	N/A	N/A	142
1413621	CTCAACATTTTATGGGATCA	35435	35454	2707	2726	2590
1413623	TGGTTTTGTTTTTTTTAGCA	13431	13450	N/A	N/A	2591
1413624	TTGCTATTTTAGAATTCTT	12086	12105	N/A	N/A	2592
1413625	TGGTTGTTTTTCATCATGTT	11669	11688	N/A	N/A	1901
1413627	TCTTTTTTTTCTTAAGCCAG	24621	24640	N/A	N/A	2593
1413630	TCACAGTTTAGATTTTCATTC	38121	38140	5393	5412	2594
1413631	TCAGTTTGATTAGTTTCTTC	34418	34437	1690	1709	2595
1413636	CCCTATTATTATTCACCTTC	25526	25545	N/A	N/A	218
1413637	CTACAATTTATTGAATCTCT	30029	30048	N/A	N/A	2596
1413638	TGTGCATATGTTCCCAACTC	27349	27368	N/A	N/A	2597

1413639	CCCCAATTTTTTGCTTCAAC	14830	14849	N/A	N/A	2598
1413640	CTGCAAATATCACGGCCTCT	37886	37905	5158	5177	2599
1413643	CCCTCATTTTTTCTGTTTCT	25328	25347	N/A	N/A	2600
1413644	TTCTTTTTTTTCTTAAGCCA	24622	24641	N/A	N/A	2601
1413646	CTTCATACTTGATTTGCATT	8776	8795	N/A	N/A	2602
1413647	GCTACTTTTATATTTTCTTA	18056	18075	N/A	N/A	1439
1413650	AGCTACTTTTATATTTTCTT	18057	18076	N/A	N/A	1359
1413651	TCACATTCATTTTCACGACC	7773	7792	N/A	N/A	2603
1413652	GCTGGTTTATTTTTTTTGGC	27812	27831	N/A	N/A	2604
1413653	AGAGTTTATACTTTTCCAT	12385	12404	N/A	N/A	717
1413654	TTTGTTTTTTTAGCACTTT	13427	13446	N/A	N/A	2605
1413655	TTGTGCTTATATTTTCAATT	34387	34406	1659	1678	2606
1413656	CCTATTATTTATTCATTCT	25525	25544	N/A	N/A	2607
1413658	GCTATACTTGCCTTTGCTCT	25273	25292	N/A	N/A	2608
1413660	TCCAACACATATATATCCAG	33950	33969	N/A	N/A	2609
1413661	TTTCCAGTTTCTTCTGACTT	25309	25328	N/A	N/A	2610
1413662	ACTTGATTTGCATTTTTTCA	8770	8789	N/A	N/A	2611
1413663	TCGCTTTCATCTTCATTAGA	34490	34509	1762	1781	2612
1413664	CCCTTTTTTTCATTACCTCCC	29509	29528	N/A	N/A	1446
1413665	TGGCCTCAATTTGATTTTAC	14163	14182	N/A	N/A	2613
1413666	AGCATTATTTAATTTCTCTC	31073	31092	N/A	N/A	2614
1413667	TAGCAACTTTTTCTTACCTT	20172	20191	N/A	N/A	2435
1413668	GTTACCTATTTTCTATGACT	35615	35634	2887	2906	949
1413669	ATTCCTATCTTTTGCCTACC	17081	17100	N/A	N/A	2615
1413670	CACCAATGTATATCTTTCTT	25239	25258	N/A	N/A	2616
1413671	ACTGCTTTTATTCAGCTTTT	31852	31871	1385	1404	2617
1413674	TTTGCATTTTTTCAGAGTAT	8764	8783	N/A	N/A	2618
1413675	AACTGCTTTTATTCAGCTT	31854	31873	1387	1406	1060
1413676	GCATTTTTTTCAGAGTATCCA	8761	8780	N/A	N/A	2619
1413677	GTTACACTTTCCTTTTTTTTC	24630	24649	N/A	N/A	206
1413679	TTTGAATTCCTTTTCCAGCA	11548	11567	N/A	N/A	2547
1413682	GTGACCCTATTATTTATTCA	25530	25549	N/A	N/A	2394
1413685	GTATTTTCATATTTGTTACT	29985	30004	N/A	N/A	2620
1413690	GTTTAGATTTTCATTTCATCA	38116	38135	5388	5407	2420
1413691	TGTATATTTTATATTAGCA	21050	21069	N/A	N/A	1016
1413692	TTGTTTATACCTTATCTCTT	25805	25824	N/A	N/A	643
1413695	GCTGATAATTACATTTCTGC	14341	14360	N/A	N/A	1825
1413696	ACTGTCATTTTTTATTGGCC	4574	4593	N/A	N/A	2021
1413697	TTTTGTTTTTTTAGCACTT	13428	13447	N/A	N/A	2621
1413698	CACTTGTTTTACTTTCGCTT	34504	34523	1776	1795	2622
1413701	TTTCCAACCTTCTTTCCAC	24839	24858	N/A	N/A	446
1413702	CCTAGTTACATTTTCCCCC	35995	36014	3267	3286	1102
1413704	TCTCTTTTATCAGCTTTTTA	25111	25130	N/A	N/A	2623

1413706	GCTTCATACTTGATTTGCAT	8777	8796	N/A	N/A	2624
1413708	CCTTTCACATTCATTTTCAC	7777	7796	N/A	N/A	2321
1413711	TTTCATATTTGTTACTTCCT	29981	30000	N/A	N/A	2625
1413714	CCTCAATTTGATTTTCACATT	14160	14179	N/A	N/A	2626
1413715	CGCTTCATACTTGATTTGCA	8778	8797	N/A	N/A	2627
1413716	CACTTGTTTTTTCTACAATT	11817	11836	N/A	N/A	1363
1413717	TGTCCACTCTTTTTGCTTCC	7211	7230	N/A	N/A	2628
1413720	CTGTCATTTTTTTATTGGCCT	4573	4592	N/A	N/A	2094
1413721	TGGTTATTTTTTTTGGCTT	27810	27829	N/A	N/A	2629
1413722	TTTCATTTAATATGCTAGCT	33601	33620	N/A	N/A	2630
1413724	ACTGACAATTATGCTTCAGT	4601	4620	N/A	N/A	2631
1413731	TTGGCTTTTTTTTGAGACC	27797	27816	N/A	N/A	2632
1413733	GCCTCAATTTGATTTTCACAT	14161	14180	N/A	N/A	2633
1413734	TTGCATTTTTTCAGAGTATC	8763	8782	N/A	N/A	2634
1413735	AGTTGATTTTTTTTCCTCTT	14300	14319	N/A	N/A	2635
1413736	TTCATATTTGTTACTTCCTT	29980	29999	N/A	N/A	2636
1413737	GCTGTTCTAATTTTTAGTTA	37617	37636	4889	4908	1279
1413738	GTTCATACCTTATCTCTTTC	25803	25822	N/A	N/A	2637
1413740	CCTTCAACCTTTTCTTCCAC	36288	36307	3560	3579	1478
1413741	GCTGCTTTAACTTTTAGACA	22598	22617	742	761	2157
1413742	TTTCCATTTCTTCAGTGCTT	25621	25640	N/A	N/A	676
1413743	TGTATTTTTTATGATCTTCA	34438	34457	1710	1729	2638
1413745	TTCCTTTAATGATGTCCCAT	11853	11872	N/A	N/A	2639
1413746	GAGCCTTACTCTTTGTCCCC	23134	23153	N/A	N/A	2640
1413748	ACTTGTTTTTTCTACAATTA	11816	11835	N/A	N/A	1408
1489468	TTTACATTTTTTTTCCAAAT	20587	20606	N/A	N/A	2641
1489469	TGGTGCTGTTTTACATTTTTT	20596	20615	N/A	N/A	2642
1489471	GTGCTGTTTTACATTTTTTTT	20594	20613	N/A	N/A	2643
1489472	CTGTTTTACATTTTTTTTCC	20591	20610	N/A	N/A	2040
1489473	TGTTTTACATTTTTTTTCCA	20590	20609	N/A	N/A	2644
1489474	GTTTTACATTTTTTTTCCAA	20589	20608	N/A	N/A	2164
1489475	TTTTACATTTTTTTTCCAAA	20588	20607	N/A	N/A	2645
1489476	GTGGTGCTGTTTTACATTTT	20597	20616	N/A	N/A	2646
1492042	TATTTTTTTTGGCTTTTTTT	27805	27824	N/A	N/A	2647
1492043	CAAGCTGGTTTATTTTTTTT	27815	27834	N/A	N/A	2648
1492044	AAGCTGGTTTATTTTTTTTG	27814	27833	N/A	N/A	2649
1492045	TTATTTTTTTTGGCTTTTTT	27806	27825	N/A	N/A	2650
1492046	TTTATTTTTTTTGGCTTTTTT	27807	27826	N/A	N/A	2651
1492047	GTTTATTTTTTTTGGCTTTT	27808	27827	N/A	N/A	2652
1492048	GGTTTATTTTTTTTGGCTTT	27809	27828	N/A	N/A	2653
1492051	TATTTGTTACTTCCTTTTAA	29976	29995	N/A	N/A	1896
1492052	TATTTTCATATTTGTTACTT	29984	30003	N/A	N/A	2654
1492053	ATATTTGTTACTTCCTTTTA	29977	29996	N/A	N/A	2655

1492054	CATATTTGTTACTTCCTTTT	29978	29997	N/A	N/A	2656
1492055	TTTTCATATTTGTTACTTCC	29982	30001	N/A	N/A	2657
1492056	ATTTTCATATTTGTTACTTC	29983	30002	N/A	N/A	2658
1492087	CCATTTCTTCAGTGCTTTGT	25618	25637	N/A	N/A	2659
1492088	TTCCATTTCTTCAGTGCTTT	25620	25639	N/A	N/A	2660
1492089	CTTTCCATTTCTTCAGTGCT	25622	25641	N/A	N/A	2661
1492090	TCTTTCCATTTCTTCAGTGC	25623	25642	N/A	N/A	587
1492091	CTCTTTCCATTTCTTCAGTG	25624	25643	N/A	N/A	2662
1492092	TCCATTTCTTCAGTGCTTTG	25619	25638	N/A	N/A	2663

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeeeeeeeeeeeeee; wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): sooooooooooooo; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 46

5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human IFNAR1

Compound Number	Sequence (5' to 3')	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	SEQ ID NO
1410683	AAGTGTTTTCTTTTCTGCT	20113	20132	462	481	2664
1489455	TTTTCTTTTCTGCTCTTAT	20108	20127	457	476	2556
1489456	TTTCTTTTCTGCTCTTATA	20107	20126	456	475	2665
1489457	TTCTTTTCTGCTCTTATAC	20106	20125	455	474	2666
1489458	TCTTTTCTGCTCTTATACG	20105	20124	454	473	2667
1489459	CTTTTCTGCTCTTATACGC	20104	20123	453	472	2668
1489461	CTCTTTCCATTTCTTCAGTG	25624	25643	N/A	N/A	2662
1489462	CTTTCCATTTCTTCAGTGCT	25622	25641	N/A	N/A	2661
1489463	TTCCATTTCTTCAGTGCTTT	25620	25639	N/A	N/A	2660
1489464	TCCATTTCTTCAGTGCTTTG	25619	25638	N/A	N/A	2663
1489467	CCATTTCTTCAGTGCTTTGT	25618	25637	N/A	N/A	2659
1489524	TATCCAATTATCCATCCAG	20001	20020	350	369	2669
1489525	TTTATCCAATTATCCATCCC	20003	20022	352	371	2670
1492035	CATATGTATAATCCCATTTA	24310	24329	885	904	2671
1492036	TGCATATGTATAATCCCATT	24312	24331	887	906	2672
1492037	TTTGCATATGTATAATCCCA	24314	24333	889	908	2563
1492038	TGTTTGCATATGTATAATCC	24316	24335	891	910	2673
1492039	CATGTTTGCATATGTATAAT	24318	24337	893	912	2674
1492040	TCATGTTTGCATATGTATAA	24319	24338	894	913	2675
1492041	GTCATGTTTGCATATGTATA	24320	24339	895	914	2676
1492067	AATTTTCTCTCACATCGAT	22449	22468	N/A	N/A	2677
1492068	CTAATTTTCTCTCACATCG	22451	22470	N/A	N/A	2678

1492069	TCGCCTAATTTTCTCTCAC	22455	22474	N/A	N/A	2679
1492070	AATTCGCCTAATTTTCTCT	22458	22477	N/A	N/A	2680
1492071	TAATTTTCTCTCACATCGA	22450	22469	N/A	N/A	2681

The modified oligonucleotides in the table below are 5-10-5 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeeeeeeeeeee; wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The internucleoside linkages are described in the table below, wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 47

5-10-5 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human IFNAR1

Compound Number	Sequence (5' to 3')	Internucleoside Linkage (5' to 3')	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	SEQ ID NO
1521445	TATCCAATTATCCATCCCAG	soosossssssssooss	20001	20020	350	369	2669
1521493	GTTTGCATATGTATAATCCC	soosossssssssooss	24315	24334	890	909	1932
1521448	TATCCAATTATCCATCCCAG	soossssssssssooss	20001	20020	350	369	2669
1521496	GTTTGCATATGTATAATCCC	soossssssssssooss	24315	24334	890	909	1932
1521446	TATCCAATTATCCATCCCAG	sossoossssssssooss	20001	20020	350	369	2669
1521494	GTTTGCATATGTATAATCCC	sossoossssssssooss	24315	24334	890	909	1932
1521449	TATCCAATTATCCATCCCAG	sossssssssssooss	20001	20020	350	369	2669
1521497	GTTTGCATATGTATAATCCC	sossssssssssooss	24315	24334	890	909	1932
1521499	GTTTGCATATGTATAATCCC	sossssssssssooss	24315	24334	890	909	1932
1521447	TATCCAATTATCCATCCCAG	ssossoossssssooss	20001	20020	350	369	2669
1521495	GTTTGCATATGTATAATCCC	ssossoossssssooss	24315	24334	890	909	1932
1521498	GTTTGCATATGTATAATCCC	sssoossssssssooss	24315	24334	890	909	1932
1521500	GTTTGCATATGTATAATCCC	ssssossssssssooss	24315	24334	890	909	1932

The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeeeeeeeeeee; wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The gapmers have an internucleoside linkage motif of (from 5' to 3'): soooooossssssooss; wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 48

6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human IFNAR1

Compound Number	Sequence (5' to 3')	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	SEQ ID NO
1489477	CTTTTCTGCTCTTATACGC	20104	20123	453	472	2668
1489478	AAGTGTTTCTTTTCTGCT	20113	20132	462	481	2664

1489479	GAAGTGTTTTCTTTTTCTGC	20114	20133	463	482	709
1489480	TTCTTTTTCTGCTCTTATAC	20106	20125	455	474	2666
1489481	TTTCTTTTTCTGCTCTTATA	20107	20126	456	475	2665
1489482	TTTTCTTTTTCTGCTCTTAT	20108	20127	457	476	2556
1489483	GTTTTCTTTTTCTGCTCTTA	20109	20128	458	477	1004
1489484	TCTTTTTCTGCTCTTATACG	20105	20124	454	473	2667
1489485	TGTTTTCTTTTTCTGCTCTT	20110	20129	459	478	2682
1489486	AGTGTTTTCTTTTTCTGCTC	20112	20131	461	480	811
1489487	GTGTTTTCTTTTTCTGCTCT	20111	20130	460	479	933
1489488	TTTACATTTTTTTTCCAAAT	20587	20606	N/A	N/A	2641
1489489	TGGTGCTGTTTTACATTTTT	20596	20615	N/A	N/A	2642
1489491	TTTTACATTTTTTTTCCAAA	20588	20607	N/A	N/A	2645
1489493	TGTTTTACATTTTTTTTCCA	20590	20609	N/A	N/A	2644
1489494	CTGTTTTACATTTTTTTTCC	20591	20610	N/A	N/A	2040
1489497	GCTGTTTTACATTTTTTTTTC	20592	20611	N/A	N/A	1952
1489498	TGCTGTTTTACATTTTTTTT	20593	20612	N/A	N/A	2683
1489500	GTGCTGTTTTACATTTTTTT	20594	20613	N/A	N/A	2643
1489503	GGTGCTGTTTTACATTTTTTT	20595	20614	N/A	N/A	2684
1489505	GTGGTGCTGTTTTACATTTT	20597	20616	N/A	N/A	2646
1489508	GTTTTACATTTTTTTTCCAA	20589	20608	N/A	N/A	2164
1489513	CCATTTCTTCAGTGCTTTGT	25618	25637	N/A	N/A	2659
1489514	TTTCCATTTCTTCAGTGCTT	25621	25640	N/A	N/A	676
1489515	CTCTTTCCATTTCTTCAGTG	25624	25643	N/A	N/A	2662
1489516	ACTCTTTCCATTTCTTCAGT	25625	25644	N/A	N/A	547
1489517	TCCATTTCTTCAGTGCTTTG	25619	25638	N/A	N/A	2663
1489518	TTCCATTTCTTCAGTGCTTT	25620	25639	N/A	N/A	2660
1489519	CTTTCCATTTCTTCAGTGCT	25622	25641	N/A	N/A	2661
1489520	TCTTTCCATTTCTTCAGTGC	25623	25642	N/A	N/A	587
1489527	TTTTATCCAATTATCCATCC	20004	20023	353	372	2304
1489531	CCAATTATCCATCCCAGTTC	19998	20017	N/A	N/A	116
1489532	TCCAATTATCCATCCCAGTT	19999	20018	348	367	2531
1489533	ATCCAATTATCCATCCCAGT	20000	20019	349	368	2434
1489534	TATCCAATTATCCATCCCAG	20001	20020	350	369	2669
1489535	TTATCCAATTATCCATCCCA	20002	20021	351	370	2334
1489536	TTTATCCAATTATCCATCCC	20003	20022	352	371	2670
1492074	ATATTTGTTACTTCCTTTTA	29977	29996	N/A	N/A	2655
1492075	TCATATTTGTTACTTCCTTT	29979	29998	N/A	N/A	2685
1492076	TTCATATTTGTTACTTCCTT	29980	29999	N/A	N/A	2636
1492077	TTTTCATATTTGTTACTTCC	29982	30001	N/A	N/A	2657
1492078	ATTTTCATATTTGTTACTTC	29983	30002	N/A	N/A	2658
1492080	TATTTGTTACTTCCTTTTAA	29976	29995	N/A	N/A	1896
1492081	CATATTTGTTACTTCCTTTT	29978	29997	N/A	N/A	2656
1492082	TTTCATATTTGTTACTTCCT	29981	30000	N/A	N/A	2625

1492122	ATTTTCTCTCACATCGATT	22448	22467	N/A	N/A	2686
1492123	AATTCGCCTAATTTTCTCT	22458	22477	N/A	N/A	2680
1492124	AATTTTCTCTCACATCGAT	22449	22468	N/A	N/A	2677
1492125	TAATTTTCTCTCACATCGA	22450	22469	N/A	N/A	2681
1492126	CTAATTTTCTCTCACATCG	22451	22470	N/A	N/A	2678
1492127	CCTAATTTTCTCTCACATC	22452	22471	N/A	N/A	1548
1492128	GCCTAATTTTCTCTCACAT	22453	22472	N/A	N/A	1449
1492129	CGCCTAATTTTCTCTCACA	22454	22473	N/A	N/A	1366
1492130	TCGCCTAATTTTCTCTCAC	22455	22474	N/A	N/A	2679
1492131	TTCGCCTAATTTTCTCTCA	22456	22475	N/A	N/A	1317
1492132	ATTCGCCTAATTTTCTCTC	22457	22476	N/A	N/A	1210

The modified oligonucleotides in the table below are 6-10-4 MOE gapmers. The gapmers are 20 nucleosides in length, wherein the sugar motif for the gapmers is (from 5' to 3'): eeeeeeddddddddeeee; wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, and each "e" represents a 2'-MOE sugar moiety. The internucleoside linkages are described in the table below, wherein each "s" represents a phosphorothioate internucleoside linkage, and each "o" represents a phosphodiester internucleoside linkage. Each cytosine residue is a 5-methyl cytosine.

Table 49

6-10-4 MOE gapmers with mixed PO/PS internucleoside linkages complementary to human IFNAR1

Compound Number	Sequence (5' to 3')	Internucleoside Linkage (5' to 3')	SEQ ID NO 1 Start Site	SEQ ID NO 1 Stop Site	SEQ ID NO 2 Start Site	SEQ ID NO 2 Stop Site	SEQ ID NO
1492136	CATTCTTCAGTGCTTTGTA	s0000ssssssssssoss	25617	25636	N/A	N/A	2687
1492137	CCATTCTTCAGTGCTTTGT	s0000ssssssssssoss	25618	25637	N/A	N/A	2659
1492138	TCCATTCTTCAGTGCTTTG	s0000ssssssssssoss	25619	25638	N/A	N/A	2663
1492139	TTCCATTCTTCAGTGCTTT	s0000ssssssssssoss	25620	25639	N/A	N/A	2660
1492140	TTCCATTCTTCAGTGCTT	s0000ssssssssssoss	25621	25640	N/A	N/A	676
1492141	CTTTCCATTCTTCAGTGCT	s0000ssssssssssoss	25622	25641	N/A	N/A	2661
1492142	TCTTTCCATTCTTCAGTGC	s0000ssssssssssoss	25623	25642	N/A	N/A	587
1492143	CTTTTCCATTCTTCAGTG	s0000ssssssssssoss	25624	25643	N/A	N/A	2662
1521478	TCGCCTAATTTTCTCTCAC	s0000ssssssssssoss	22455	22474	N/A	N/A	2679
1521593	ATCCAATTATCCATCCCAGT	s0000ssssssssssoss	20000	20019	349	368	2434
1521608	TTATCCAATTATCCATCCCA	s0000ssssssssssoss	20002	20021	351	370	2334
1521479	TCGCCTAATTTTCTCTCAC	s0000ssssssssssoss	22455	22474	N/A	N/A	2679
1521502	CTTTCCATTCTTCAGTGCT	s0000ssssssssssoss	25622	25641	N/A	N/A	2661
1521594	ATCCAATTATCCATCCCAGT	s0000ssssssssssoss	20000	20019	349	368	2434
1521609	TTATCCAATTATCCATCCCA	s0000ssssssssssoss	20002	20021	351	370	2334
1521468	CTGTTTTACATTTTTTTTCC	s0000ssssssssssoss	20591	20610	N/A	N/A	2040
1521483	TCGCCTAATTTTCTCTCAC	s0000ssssssssssoss	22455	22474	N/A	N/A	2679
1521506	CTTTCCATTCTTCAGTGCT	s0000ssssssssssoss	25622	25641	N/A	N/A	2661
1521598	ATCCAATTATCCATCCCAGT	s0000ssssssssssoss	20000	20019	349	368	2434

1521613	TTATCCAATTATCCATCCCA	sooooooooooooo	20002	20021	351	370	2334
1521480	TCGCCTAATTTTCTCTCAC	soosoooooooooooo	22455	22474	N/A	N/A	2679
1521503	CTTTCCATTTCTTCAGTGCT	soosoooooooooooo	25622	25641	N/A	N/A	2661
1521595	ATCCAATTATCCATCCCAGT	soosoooooooooooo	20000	20019	349	368	2434
1521610	TTATCCAATTATCCATCCCA	soosoooooooooooo	20002	20021	351	370	2334
1521469	CTGTTTTACATTTTTTTTCC	soosoooooooooooo	20591	20610	N/A	N/A	2040
1521484	TCGCCTAATTTTCTCTCAC	soosoooooooooooo	22455	22474	N/A	N/A	2679
1521507	CTTTCCATTTCTTCAGTGCT	soosoooooooooooo	25622	25641	N/A	N/A	2661
1521599	ATCCAATTATCCATCCCAGT	soosoooooooooooo	20000	20019	349	368	2434
1521614	TTATCCAATTATCCATCCCA	soosoooooooooooo	20002	20021	351	370	2334
1521472	CTGTTTTACATTTTTTTTCC	soosoooooooooooo	20591	20610	N/A	N/A	2040
1521487	TCGCCTAATTTTCTCTCAC	soosoooooooooooo	22455	22474	N/A	N/A	2679
1521510	CTTTCCATTTCTTCAGTGCT	soosoooooooooooo	25622	25641	N/A	N/A	2661
1521602	ATCCAATTATCCATCCCAGT	soosoooooooooooo	20000	20019	349	368	2434
1521617	TTATCCAATTATCCATCCCA	soosoooooooooooo	20002	20021	351	370	2334
1521481	TCGCCTAATTTTCTCTCAC	sosooooooooooooo	22455	22474	N/A	N/A	2679
1521504	CTTTCCATTTCTTCAGTGCT	sosooooooooooooo	25622	25641	N/A	N/A	2661
1521596	ATCCAATTATCCATCCCAGT	sosooooooooooooo	20000	20019	349	368	2434
1521611	TTATCCAATTATCCATCCCA	sosooooooooooooo	20002	20021	351	370	2334
1521470	CTGTTTTACATTTTTTTTCC	sosooooooooooooo	20591	20610	N/A	N/A	2040
1521485	TCGCCTAATTTTCTCTCAC	sosooooooooooooo	22455	22474	N/A	N/A	2679
1521508	CTTTCCATTTCTTCAGTGCT	sosooooooooooooo	25622	25641	N/A	N/A	2661
1521600	ATCCAATTATCCATCCCAGT	sosooooooooooooo	20000	20019	349	368	2434
1521615	TTATCCAATTATCCATCCCA	sosooooooooooooo	20002	20021	351	370	2334
1521473	CTGTTTTACATTTTTTTTCC	sosooooooooooooo	20591	20610	N/A	N/A	2040
1521488	TCGCCTAATTTTCTCTCAC	sosooooooooooooo	22455	22474	N/A	N/A	2679
1521511	CTTTCCATTTCTTCAGTGCT	sosooooooooooooo	25622	25641	N/A	N/A	2661
1521603	ATCCAATTATCCATCCCAGT	sosooooooooooooo	20000	20019	349	368	2434
1521618	TTATCCAATTATCCATCCCA	sosooooooooooooo	20002	20021	351	370	2334
1521467	CTGTTTTACATTTTTTTTCC	ssoooooooooooooooo	20591	20610	N/A	N/A	2040
1521482	TCGCCTAATTTTCTCTCAC	ssoooooooooooooooo	22455	22474	N/A	N/A	2679
1521505	CTTTCCATTTCTTCAGTGCT	ssoooooooooooooooo	25622	25641	N/A	N/A	2661
1521597	ATCCAATTATCCATCCCAGT	ssoooooooooooooooo	20000	20019	349	368	2434
1521612	TTATCCAATTATCCATCCCA	ssoooooooooooooooo	20002	20021	351	370	2334
1521471	CTGTTTTACATTTTTTTTCC	sssooooooooooooooooo	20591	20610	N/A	N/A	2040
1521486	TCGCCTAATTTTCTCTCAC	sssooooooooooooooooo	22455	22474	N/A	N/A	2679
1521509	CTTTCCATTTCTTCAGTGCT	sssooooooooooooooooo	25622	25641	N/A	N/A	2661
1521601	ATCCAATTATCCATCCCAGT	sssooooooooooooooooo	20000	20019	349	368	2434
1521616	TTATCCAATTATCCATCCCA	sssooooooooooooooooo	20002	20021	351	370	2334
1521474	CTGTTTTACATTTTTTTTCC	sssooooooooooooooooo	20591	20610	N/A	N/A	2040
1521489	TCGCCTAATTTTCTCTCAC	sssooooooooooooooooo	22455	22474	N/A	N/A	2679
1521512	CTTTCCATTTCTTCAGTGCT	sssooooooooooooooooo	25622	25641	N/A	N/A	2661
1521604	ATCCAATTATCCATCCCAGT	sssooooooooooooooooo	20000	20019	349	368	2434

Example 5: Activity of modified oligonucleotides complementary to human IFNAR1 in transgenic mice

Modified oligonucleotides described above were tested in a human IFNAR1 transgenic mouse model. Transgenic mice that express a human IFNAR1 transcript were generated.

Exons 1-6 and ~4.9kB of upstream sequence of the human IFNAR1 gene from fosmid ABCS-41091_400N2 was subcloned into a BAC, CTD-2289N21, containing exons 7-11 of the human IFNAR1 genes and 56 kB of downstream sequence, to generate a complete IFNAR1 transgene. The engineered BAC was digested with NotI to remove the BAC backbone. The purified BAC fragment, containing the complete human IFNAR1 gene, was introduced into fertilized eggs from C57BL/6 mice by pronuclear injection to produce three founder lines. Line 17505 was used in the experiments described herein.

Treatment

Transgenic mice were divided into groups of 2 mice each. Each mouse received a single ICV bolus of 200 or 300 µg of modified oligonucleotide. A group of 2-4 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from cortical brain tissue and spinal cord for RTPCR analysis to measure amount of IFNAR1 RNA using human primer probe set RTS44352 (described herein above). Results are presented as percent human IFNAR1 relative to PBS control, normalized to 18S ribosomal RNA. 18S ribosomal RNA was amplified using mouse 18S prime probe set PPS54360 (forward sequence GGAAGTGGAGCCATGATTAAGA, designated herein as SEQ ID NO: 9; reverse sequence ACCTCCGACTTTCGTTCTTG, designated herein as SEQ ID NO: 10; probe sequence AAGACGGACCAGAGCGAAAGCAT, designated herein as SEQ ID NO: 11). The values marked by the symbol “†” indicate that the modified oligonucleotide is complementary to the amplicon region of the primer probe set. Additional assays may be used to measure the potency and efficacy of the modified oligonucleotides complementary to the amplicon region.

Table 50

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1321090	46	68
1321151	28	45
1321321	67	87
1321504	66	100
1321599	59	107
1321618	23	50
1321625	32	78

1321713	51	94
1321872	26	68
1321877	36	63
1321910	42	61
1321943	17	23
1321995	43	50
1322160	43	76
1322176	33	41
1322183	29	65
1322197	44	85
1322202	20	17
1322424	39	54
1322428	34	50
1322943	40	78
1322986	22	25
1323059	19	11
1323071	36	57
1413519	22	16
1413522	40	39
1413525	58	92
1413529	51	80
1413534	47	70
1413547	67	87
1413548	72	90
1413550	34	53
1413553	31	42
1413554	37	42
1413563	47	52
1413585	72	78
1413587	56	67
1413593	73	78
1413601	48	76
1413604	77	98
1413614	61	104
1413619	68	92
1413621	58	84
1413623	67	97
1413624	82	113
1413630	36	53
1413636	89	78
1413639	59	65
1413643	54	76
1413647	64	62

1413650	74	74
1413651	56	60
1413671	54	64
1413676	31	41
1413695	74	88
1413696	74	80
1413697	88	92
1413698	40	37
1413706	66	80
1413711	50	49
1413714	69	86
1413720	67	62
1413721	39	23
1413731	55	46
1413733	77	76
1413735	46	53
1413736	48	26
1413737	85	76
1413738	39	39
1413741	31	51
1413742	27	30
1413748	83	99

Table 51

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1321040	59	78
1321074	58	81
1321277	75	92
1321527	36	41
1321541	39	37
1321703	30	36
1321729	31	47
1321789	67	75
1322032	58	63
1322134	52	71
1322170	46	60
1322246	71	81
1322263	39	53
1322497	26	30

1322535	37	42
1322540	52	61
1322559	38	70
1322570	38	66
1322651	51	66
1322658	48	64
1322684	52	80
1323056	48	39
1323262	58	71
1413523	63	55
1413530	59	81
1413531	78	93
1413541	44	46
1413555	83	91
1413559	65	57
1413560	71	91
1413561	69	97
1413564	96	108
1413568	55	66
1413574	100	107
1413576	85	76
1413578	65	67
1413580	49	62
1413583	51	46 [‡]
1413586	112	107
1413589	99	97
1413597	101	96
1413598	60	64
1413602	96	96
1413609	112	110
1413615	54	57
1413616	97	102
1413627	43	38
1413640	64	65
1413644	37	38
1413646	73	85
1413652	66	78
1413654	92	94
1413655	68	82
1413658	72	83
1413661	77	85
1413662	64	76
1413664	88	85

1413665	102	91
1413666	80	85
1413674	71	86
1413675	71	71
1413677	55	44
1413682	70	65
1413685	72	86
1413690	70	73
1413691	109	102
1413702	62	59
1413704	48	36
1413708	108	99
1413716	118	102
1413717	59	64

‡ Indicates fewer than 2 samples available

Table 52

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 200 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1320892	82	93
1320910	55	86
1320934	83	97
1320943	93	101
1321027	82	94
1321049	63	81
1321056	25	49
1321060	69	89
1321103	63	89
1321187	53	49
1321222	63	80
1321287	82	88
1321293	73	78
1321324	72	104
1321366	50	60
1321453	31	49
1321456	102	107
1321686	67	78
1321752	77	88
1321801	42	83
1321811	76	105

1321812	50	60
1321817	49	75
1321866	93	104
1321973	68	86
1321979	81	89
1322058	43	64
1322064	65	88
1322077	96	102
1322112	85	95
1322140	65	99
1322164	67	86
1322187	27	41
1322188	84	80
1322237	84	93
1322282	101	111
1322293	83	98
1322309	81	113
1322316	45	72
1322369	60	93
1322504	54	49
1322564	95	105
1322625	74	97
1322671	84	89
1322696	65	51
1322716	64	81
1322717	76	88
1322720	97	88
1322731	91	85
1322800	72	70
1322827	81	98
1322918	79	112
1323015	88	101
1323053	46	40
1323107	85	100
1323169	26	32
1323251	64	89
1323277	98	99
1413535	50	56
1413551	50	53
1413562	89	120
1413591	99	107
1413600	78	78
1413608	62	98

1413637	75	88
1413638	62	70
1413653	94	97
1413663	77	83
1413669	92	91
1413679	91	98
1413715	63	80
1413724	91	105
1413734	71	79
1413743	82	96
1413745	101	109
1413746	74	91

Table 53

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1413521	65	82
1413567	74	85
1413570	59	58
1413579	83	89
1413588	90	100
1413596	77	89
1413603	69	94
1413605	68	83
1413625	89	104
1413631	71	81
1413656	90	81
1413660	76	94
1413667	81	92
1413668	43	48
1413670	71	80
1413692	63	60
1413701	52	45
1413722	73	79
1413740	53	64

Table 54

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1321374	61	44
1321408	29	12
1321541	27	18
1322611	29	27
1323169	17	18
1323224	46	53
1410683	55	61
1489455	47	47
1489456	47	65
1489457	48	52
1489462	36	46
1489468	93	79
1489471	28	69
1489472	18	24
1489473	53	71
1489474	39	64
1489475	54	93
1489478	49	64
1489480	38	44
1489481	40	52
1489482	41	49
1489483	13	17
1489484	35	43
1489485	24	38
1489486	31	30
1489487	20	19
1489488	89	104
1489491	75	92
1489493	31	18
1489494	18	8
1489497	22	14
1489498	31	48
1489500	36	70
1489508	29	31
1489514	29	26
1489519	15	11
1489524	22	14
1489525	32	25

1489531	45	46
1489532	36	37
1489533	16	19
1489534	25	35
1489535	22	18
1489536	34	39
1492042	65	87
1492045	67	87
1492046	70	87
1492047	36	39
1492048	21	24
1492054	55	64
1492069	23	24
1492075	29	36
1492081	49	55
1492089	28	41
1492125	71	100
1492126	65‡	82
1492127	48	71
1492128	29	41
1492129	15	19
1492130	17	19
1492131	20	28
1492132	33	36
1492140	26	22
1492141	14	15‡

‡ Indicates fewer than 2 samples available

Table 55

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1322169	25	45
1322187	22	20
1322319	31	54
1322364	42	39
1322927	68†	73†
1323067	54	51
1323084	31	44
1323172	41	34
1489458	47	51

1489459	46	38
1489461	55	67
1489463	33	31
1489464	37	46
1489467	42	45
1489469	37	46
1489476	43	63
1489477	32	27
1489479	55	79
1489489	38	43
1489503	55	66
1489505	50	52
1489513	37	43
1489515	25	33
1489516	36	48
1489517	45	57
1489518	35	32
1489520	34	35
1489527	54	59
1492035	64	69
1492036	40	40
1492037	29	23
1492038	43	42
1492039	34	40
1492040	59	73
1492041	47	56
1492043	59	76
1492044	60	80
1492051	81	89
1492052	92	87
1492053	65	82
1492055	63	75
1492056	55	79
1492067	82	87
1492068	55	56
1492074	69	62
1492076	38	37
1492077	29	34
1492078	49	47
1492080	67	80
1492082	19	10
1492087	39	59
1492088	29	28

1492090	37	36
1492091	45	72
1492092	35	46
1492122	62	84
1492123	46	59
1492124	71	97
1492136	54	72
1492137	15	29
1492138	22	25
1492139	30	28
1492142	35	41
1492143	42	64
1492069	20	18
1492070	56	67
1492071	65	85
1492075	26	55

Table 56

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1521445	38	38
1521446	27	25
1521447	24	33
1521448	27	25
1521449	27	29
1521467	23	11
1521468	30	26
1521469	26	20
1521470	44	43
1521471	31	15
1521472	34	27
1521473	35	34
1521474	37	27
1521478	23	24
1521479	23	22
1521480	29	24
1521481	26	17
1521482	25	29
1521483	26	13
1521484	25	26

1521485	27	21
1521486	26	23
1521487	30	24
1521488	27	25
1521489	32	25
1521493	21	23
1521494	27	33
1521495	33	35
1521496	24	32
1521497	28	22
1521498	28	37
1521499	27	20
1521500	19	24
1521502	29	13
1521503	21	27
1521504	21	14
1521505	27	28
1521506	22	23
1521507	31	29
1521508	21	14
1521509	35	31
1521510	22	18
1521511	23	16
1521512	17	11
1521593	21	19
1521594	20	21
1521595	22	20
1521596	16	19
1521597	25	22
1521598	16	17
1521599	22	22
1521600	22	27
1521601	21	18
1521602	23	24
1521603	20	21
1521604	30	28
1521608	42	19
1521609	21	22
1521610	28	16
1521611	29	28
1521612	30	23
1521613	32	23
1521614	26	17

1521615	27	18
1521616	38	43

Table 57

Reduction of human IFNAR1 RNA in transgenic mice (n=2) treated with 300 µg of modified oligonucleotide

Compound ID	IFNAR1 RNA (% control)	
	Spinal Cord	Cortex
PBS	100	100
1521617	20	16
1521618	29	41

Example 6: Potency of modified oligonucleotides complementary to human IFNAR1 RNA in transgenic mice

Modified oligonucleotides described above were tested in human IFNAR1 transgenic mice (described herein above).

Treatment

Human IFNAR1 transgenic mice were divided into groups of 4 mice each. Each mouse received a single ICV bolus of modified oligonucleotide at the doses indicated in tables below. A group of 4 mice received PBS as a negative control.

RNA analysis

Two weeks post treatment, mice were sacrificed, and RNA was extracted from the spinal cord, cortex, and cerebellum for quantitative real-time RTPCR analysis of RNA expression of IFNAR1 using primer probe set RTS44352 (described herein above). Results are presented as percent human IFNAR1 RNA relative to PBS control, adjusted to 18S PCR (described herein above).

The half maximal effective dose (ED₅₀) of each modified oligonucleotide was calculated using GraphPad Prism 7 software (GraphPad Software, San Diego, CA). ED₅₀ values were calculated from dose and individual animal IFNAR1 RNA levels using custom equation: Agonist vs response – Variable slope (four parameters) $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + (10^{\log \text{ED}_{50} / X})^{\text{HillSlope}})$, with the following constraints: bottom > 0, top = 100.

As shown in the table below, treatment with modified oligonucleotides resulted in dose-responsive reduction of IFNAR1 RNA in comparison to the PBS control.

Table 58

Reduction of human IFNAR1 RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Cerebellum	
		IFNAR1 RNA (% control)	ED ₅₀ (µg)	IFNAR1 RNA (% control)	ED ₅₀ (µg)	IFNAR1 RNA (% control)	ED ₅₀ (µg)
PBS	N/A	100	N/A	100	N/A	100	N/A
1489493	10	96	154	89	243	87	350
	30	62		69		68	

	100	71		79		77	
	300	40		42		51	
	700	32		26		38	
1489494	10	100	79	85	92	81	105
	30	73		83		75	
	100	49		50		51	
	300	22		15		31	
	700	13		6		19	
1489525	10	77	319	79	31	78	215
	30	60		32		51	
	100	75		63		71	
	300	50		24		46	
	700	43		21		37	
1489535	10	99	114	83	88	72	133
	30	88		73		73	
	100	64		56		59	
	300	30		16		37	
	700	22		7		26	
1492037	10	118	83	85	17	81	155
	30	73		39		64	
	100	60		37		61	
	300	37		24		43	
	700	26		16		29	
1492069	10	96	104	84	47	74	129
	30	80		69		75	
	100	60		34		48	
	300	28		20		43	
	700	23 $\frac{1}{2}$		12		29	
1492082	10	98	177	75	50	76	142
	30	53		46		55	
	100	71		46		66	
	300	41		15		39	
	700	29		14		33	
1492131	10	114	83	77	32	77	105
	30	92		63		68	
	100	57		24		48	
	300	39		21		40	
	700	27		13		23	
1521512	10	113	29	79	18	70	12.5
	30	53		32		44	
	100	50		33		45	
	300	31		9		33	
	700	20		7		27	

‡ Indicates fewer than 4 samples available

Table 59

Reduction of human IFNAR1 RNA in transgenic mice

Compound ID	Dose (µg)	Spinal Cord		Cortex		Cerebellum	
		IFNAR1 RNA (% control)	ED ₅₀ (µg)	IFNAR1 RNA (% control)	ED ₅₀ (µg)	IFNAR1 RNA (% control)	ED ₅₀ (µg)
PBS	N/A	100	N/A	100	N/A	100	N/A
1489477	10	86	91.9	100‡	245	98	480
	30	77		96		88	
	100	54		72		74	
	300	29		51		62	
	700	24		28		41	

‡ Indicates fewer than 4 samples available

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CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion of an IFNAR1 nucleic acid, and wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
2. The oligomeric compound of claim 1, wherein the IFNAR1 nucleic acid has the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
3. The oligomeric compound of claim 1 or claim 2, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 5085-5133, 19997-20061, 20076-20133, 20528-20616, 22294-22329, 22453-22476, 22595-22626, 25530-25565, 25606-25652, 25710-25767, 25768-25827, 28421-28468, 29924-29949, 29968-30021, 31072-31096, 31792-31837, 32353-32386, or 35016-35042 of SEQ ID NO: 1.
4. The oligomeric compound of any of claims 1-3, wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 20003-20022, 20104-20123, 20591-20610, 22455-22474, 22456-22475, or 29981-30000 of SEQ ID NO: 1.
5. The oligomeric compound of any of claims 1-4, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of the IFNAR1 nucleic acid.
6. An oligomeric compound comprising a modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-2687, and wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.
7. The oligomeric compound of claim 6, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 12-2687.
8. The oligomeric compound of claim 7, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any of SEQ ID NOs: 12-2687.
9. The oligomeric compound of any of claims 6-8, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-89.
10. The oligomeric compound of any of claims 6-8, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 90-2687.
11. The oligomeric compound of any of claims 6-10, wherein the modified oligonucleotide has a nucleobase sequence comprising at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

12. The oligomeric compound of claim 11, wherein the modified oligonucleotide consists of 20 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises the nucleobase sequence of any of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

13. The oligomeric compound of claim 12, wherein the modified oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence of any one of SEQ ID NOs: 1317, 2040, 2625, 2668, 2670, or 2679.

14. The oligomeric compound of any of claims 6-12, wherein the nucleobase sequence of the modified oligonucleotide is at least 85%, at least 90%, at least 95%, or 100% complementary to an equal length portion of an IFNAR1 nucleic acid, wherein the IFNAR1 nucleic acid has the nucleobase sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

15. The oligomeric compound of any of claims 1-14, wherein the modified oligonucleotide consists of 10 to 25, 10 to 30, 10 to 50, 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 22, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

16. The oligomeric compound of any of claims 1-14, wherein the modified oligonucleotide consists of 20 linked nucleosides.

17. The oligomeric compound of any of claims 1-16, wherein at least one nucleoside of the modified oligonucleotide comprises a modified sugar moiety.

18. The oligomeric compound of claim 17, wherein the modified sugar moiety comprises a bicyclic sugar moiety.

19. The oligomeric compound of claim 18, wherein the bicyclic sugar moiety comprises a 2'-4' bridge selected from -O-CH₂- and -O-CH(CH₃)-.

20. The oligomeric compound of claim 17, wherein the modified sugar moiety comprises a non-bicyclic modified sugar moiety.

21. The oligomeric compound of claim 20, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or 2'-OMe sugar moiety.

22. The oligomeric compound of any of claims 1-21, wherein at least one nucleoside of the modified oligonucleotide compound comprises a sugar surrogate.

23. The oligomeric compound of any of claims 1-22, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

24. The oligomeric compound of claim 23, wherein at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.

25. The oligomeric compound of claim 22 or claim 23, wherein each internucleoside linkage is a modified internucleoside linkage.

26. The oligomeric compound of claim 25, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

27. The oligomeric compound of any of claims 22-25, wherein at least one internucleoside linkage of the modified oligonucleotide is a phosphodiester internucleoside linkage.

28. The oligomeric compound of any of claims 1-23, wherein each internucleoside linkage of the modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

29. The oligomeric compound of any of claims 1-26 or 28, wherein at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 18 internucleoside linkages of the modified oligonucleotide are phosphorothioate internucleoside linkages.

[illegible]

31. The oligomeric compound of any of claims 1-30, wherein the modified oligonucleotide comprises at least one modified nucleobase.

32. The oligomeric compound of claim 31, wherein the modified nucleobase is 5-methyl cytosine.

33. The oligomeric compound of claim 32, wherein each cytosine is a 5-methyl cytosine.

34. The oligomeric compound of any of claims 1-33, wherein the modified oligonucleotide comprises a deoxy region.

35. The oligomeric compound of claim 34, wherein each nucleoside of the deoxy region is a 2'-β-D-deoxynucleoside.

36. The oligomeric compound of claim 34 or claim 35, wherein the deoxy region consists of 6, 7, 8, 9, 10, or 6-10 linked nucleosides.

37. The oligomeric compound of any of claims 34-36, wherein each nucleoside immediately adjacent to the deoxy region comprises a modified sugar moiety.

38. The oligomeric compound of any of claims 34-37, wherein the deoxy region is flanked on the 5'-side by a 5'-external region consisting of 1-6 linked 5'-external region nucleosides and on the 3'-side by a 3'-external region consisting of 1-6 linked 3'-external region nucleosides; wherein

the 3'-most nucleoside of the 5' external region comprises a modified sugar moiety; and

the 5'-most nucleoside of the 3' external region comprises a modified sugar moiety.

39. The oligomeric compound of claim 38, wherein each nucleoside of the 3' external region comprises a modified sugar moiety.

40. The oligomeric compound of claim 38 or claim 39, wherein each nucleoside of the 5' external region comprises a modified sugar moiety.

41. The oligomeric compound of claim 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 5 linked nucleosides;

a deoxy region consisting of 10 linked nucleosides; and

a 3' external region consisting of 5 linked nucleosides;

wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a 2'-MOE nucleoside.

42. The oligomeric compound of claim 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 6 linked nucleosides;

a deoxy region consisting of 10 linked nucleosides; and

a 3' external region consisting of 4 linked nucleosides;

wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a 2'-MOE nucleoside.

43. The oligomeric compound of claim 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 3 linked nucleosides;

a deoxy region consisting of 10 linked nucleosides; and

a 3' external region consisting of 3 linked nucleosides;

wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a cEt nucleoside.

44. The oligomeric compound of claim 40, wherein the modified oligonucleotide has:

a 5' external region consisting of 1-6 linked nucleosides;

a deoxy region consisting of 6-10 linked nucleosides; and

a 3' external region consisting of 1-6 linked nucleosides;

wherein each of the 5' external region nucleosides and each of the 3' external region nucleosides is a cEt nucleoside or a 2'-MOE nucleoside, and wherein each of the deoxy region nucleosides is a 2'-β-D-deoxynucleoside.

45. The oligomeric compound of any of claims 38-39 or 41-44, wherein the modified oligonucleotide has a sugar motif comprising:

a 5' external region consisting of 3-6 linked nucleosides;

a deoxy region consisting of 7-8 linked nucleosides; and

a 3' external region consisting of 3-6 linked nucleosides;

wherein each of the 3' external region nucleosides is selected from a 2'-MOE nucleoside and a cEt nucleoside, and the 5' external region has the following formula:

$$(N_k)_n(N_d)(N_x)$$

wherein each N_k is a bicyclic nucleoside, N_x is a 2'-OMe nucleoside, and N_d is a 2'-β-D-deoxynucleoside; and n is from 1-4.

46. An oligomeric compound of any of claims 1-38, wherein the modified oligonucleotide has a sugar motif (5' to 3') selected from eeeeeeeeeeeeeeeeeee, eeeeeeeeeeeeeeeeeee, and kkkkkkkkkkkkkkk, wherein each "d" represents a 2'-β-D-deoxyribose sugar moiety, each "e" represents a 2'-MOE sugar moiety, and each "k" represents a cEt modified sugar moiety.

47. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: ${}^mC_{es}T_{eo}T_{eo}T_{eo}T_{eo}T_{eo}{}^mC_{ds}T_{ds}G_{ds}{}^mC_{ds}T_{ds}{}^mC_{ds}T_{ds}T_{ds}A_{ds}T_{ds}A_{eo}{}^mC_{es}G_{es}{}^mC_e$ (SEQ ID NO 2668), wherein:

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

48. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: ${}^m\text{C}_{\text{es}}\text{T}_{\text{eo}}\text{G}_{\text{eo}}\text{T}_{\text{eo}}\text{T}_{\text{eo}}\text{T}_{\text{eo}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{eo}}\text{T}_{\text{es}}{}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO 2040), wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

49. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $\text{T}_{\text{es}}\text{T}_{\text{eo}}\text{T}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{es}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO 2670), wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

50. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $\text{T}_{\text{es}}{}^m\text{C}_{\text{eo}}\text{G}_{\text{eo}}{}^m\text{C}_{\text{eo}}{}^m\text{C}_{\text{es}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}{}^m\text{C}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{es}}\text{A}_{\text{es}}{}^m\text{C}_{\text{e}}$ (SEQ ID NO 2679), wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

51. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $\text{T}_{\text{es}}\text{T}_{\text{eo}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{eo}}\text{A}_{\text{eo}}\text{T}_{\text{eo}}\text{A}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{G}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{ds}}\text{A}_{\text{ds}}{}^m\text{C}_{\text{ds}}\text{T}_{\text{ds}}\text{T}_{\text{eo}}{}^m\text{C}_{\text{es}}{}^m\text{C}_{\text{es}}\text{T}_{\text{e}}$ (SEQ ID NO 2625), wherein:

A = an adenine nucleobase,
 ${}^m\text{C}$ = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

52. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $T_{es}T_{eo}{}^mC_{eo}G_{eo}{}^mC_{eo}{}^mC_{eo}T_{ds}A_{ds}A_{ds}T_{ds}T_{ds}T_{ds}T_{ds}{}^mC_{ds}T_{ds}{}^mC_{eo}T_{es}{}^mC_{es}A_e$ (SEQ ID NO 1317), wherein:

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,
 d = a 2'-β-D-deoxyribosyl sugar moiety,
 s = a phosphorothioate internucleoside linkage, and
 o = a phosphodiester internucleoside linkage.

53. The oligomeric compound of any of claims 1-52, consisting of the modified oligonucleotide.

54. The oligomeric compound of any of claims 1-52, wherein the oligomeric compound comprises a conjugate group.

55. The oligomeric compound of claim 54, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

56. The oligomeric compound of claim 54 or claim 55, wherein the conjugate linker consists of a single bond.

57. The oligomeric compound of any of claims 55 or 56, wherein the conjugate linker is cleavable.

58. The oligomeric compound of any of claims 55-57, wherein the conjugate linker comprises 1-3 linker-nucleosides.

59. The oligomeric compound of any of claims 55-57, wherein the conjugate linker does not comprise any linker nucleosides.

60. The oligomeric compound of any of claims 54-59, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

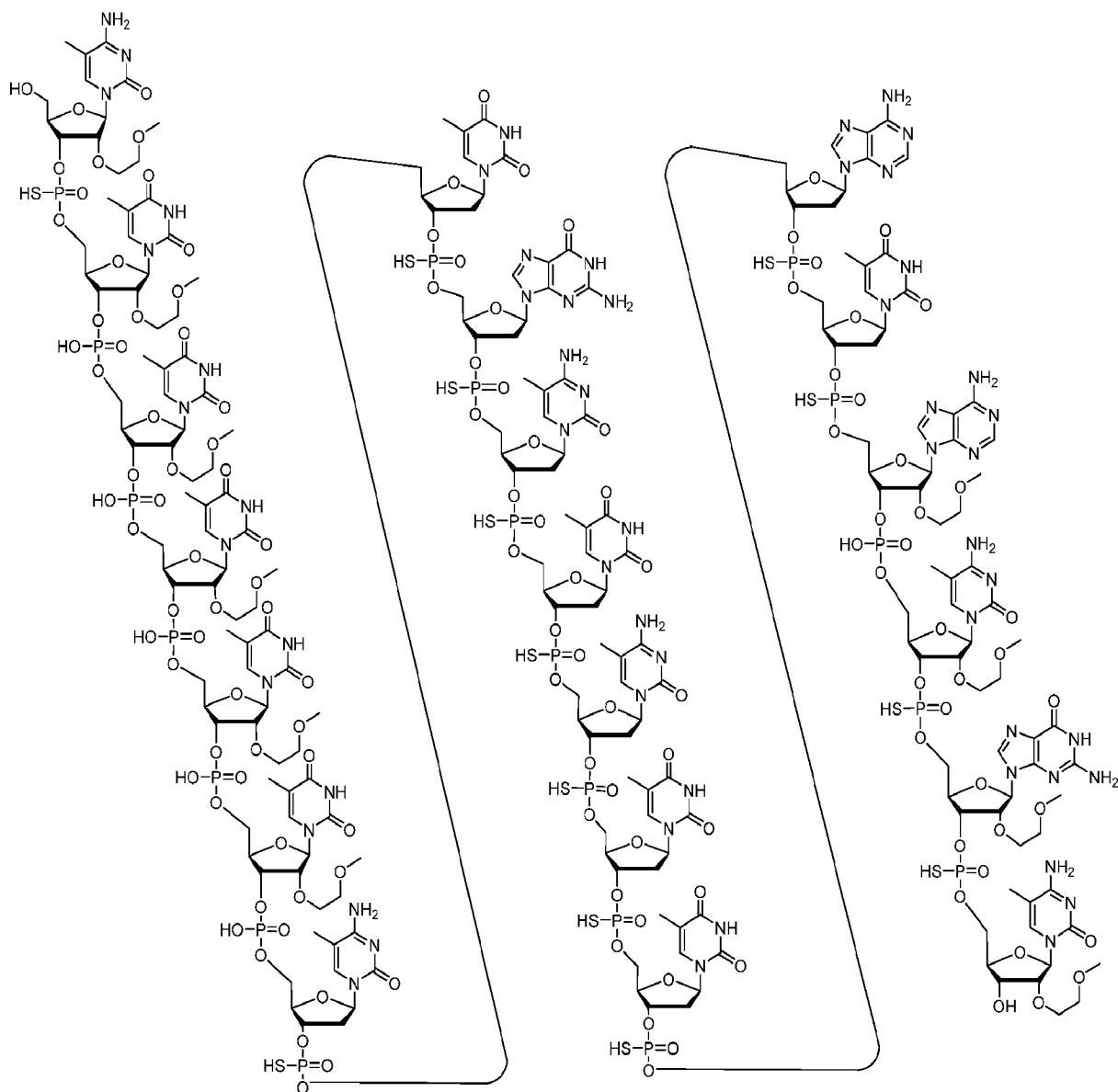
61. The oligomeric compound of any of claims 54-59, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

62. The oligomeric compound of any of claims 1 to 61, wherein the oligomeric compound comprises a terminal group.

63. The oligomeric compound of claim 62, wherein the terminal group is an abasic sugar moiety.

64. The oligomeric compound of any one of claims 1-62, wherein the oligomeric compound is a singled-stranded oligomeric compound.

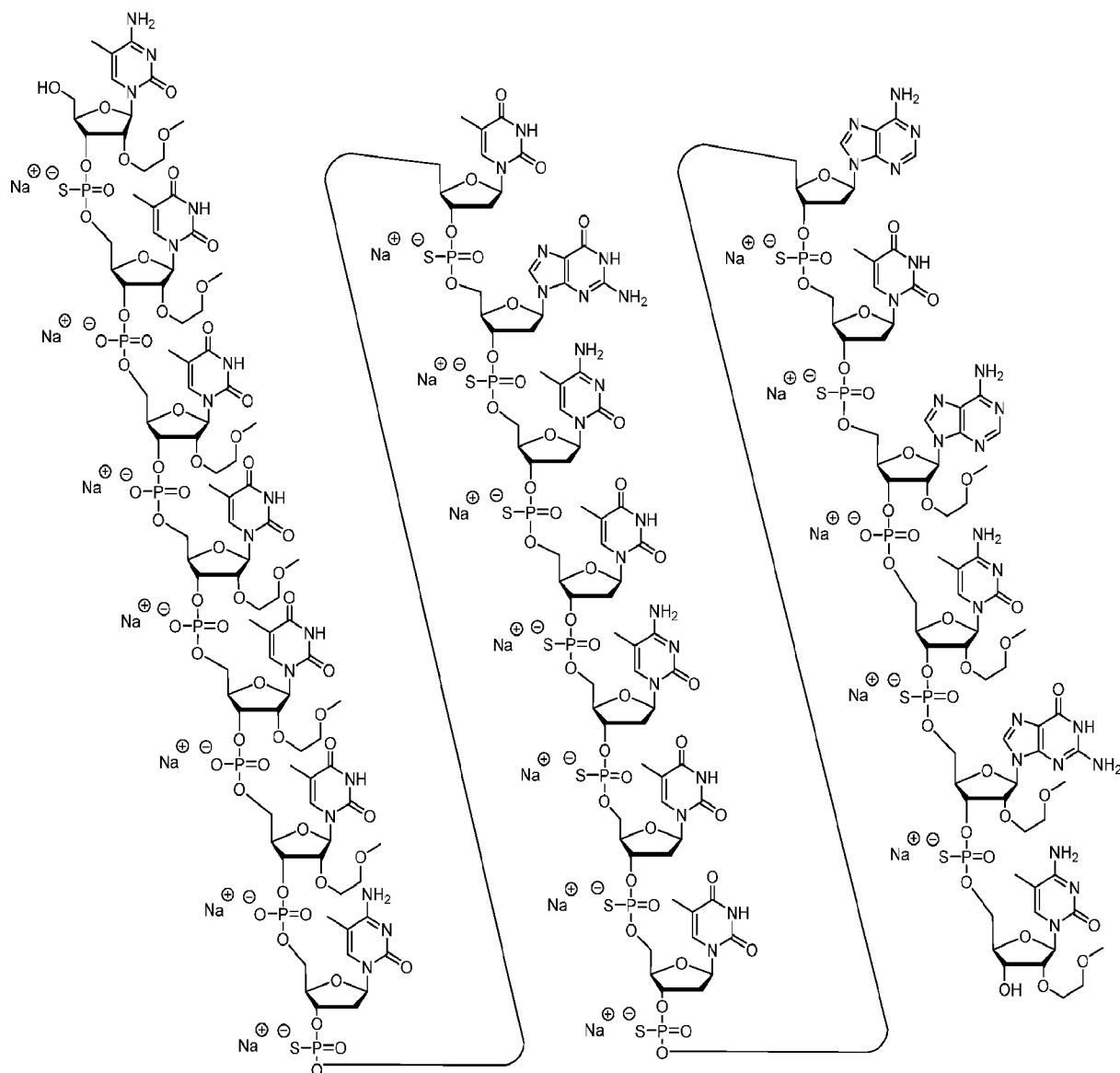
65. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2668), or a salt thereof.

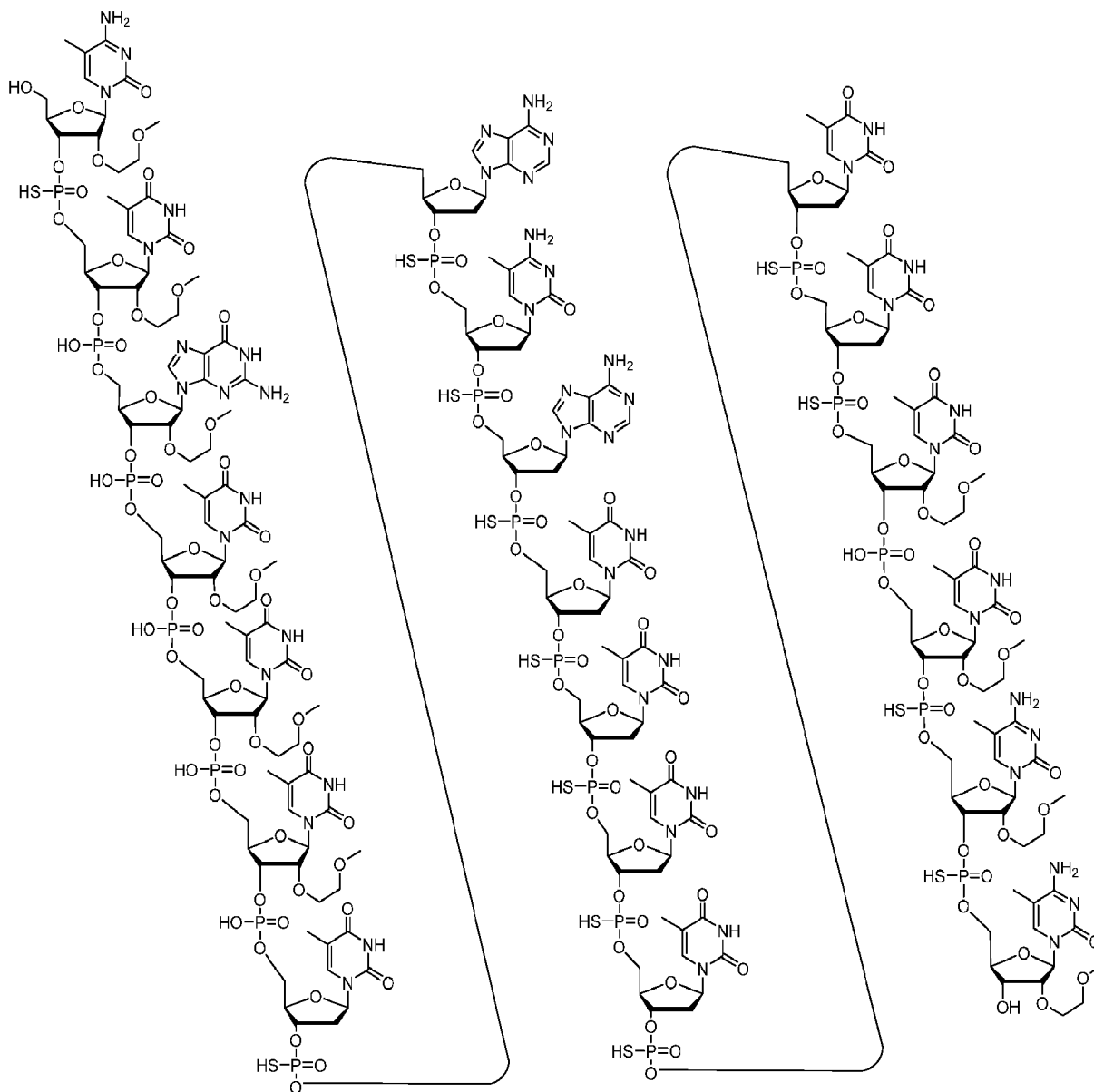
66. The modified oligonucleotide of claim 65, which is the sodium salt or the potassium salt.

67. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2668).

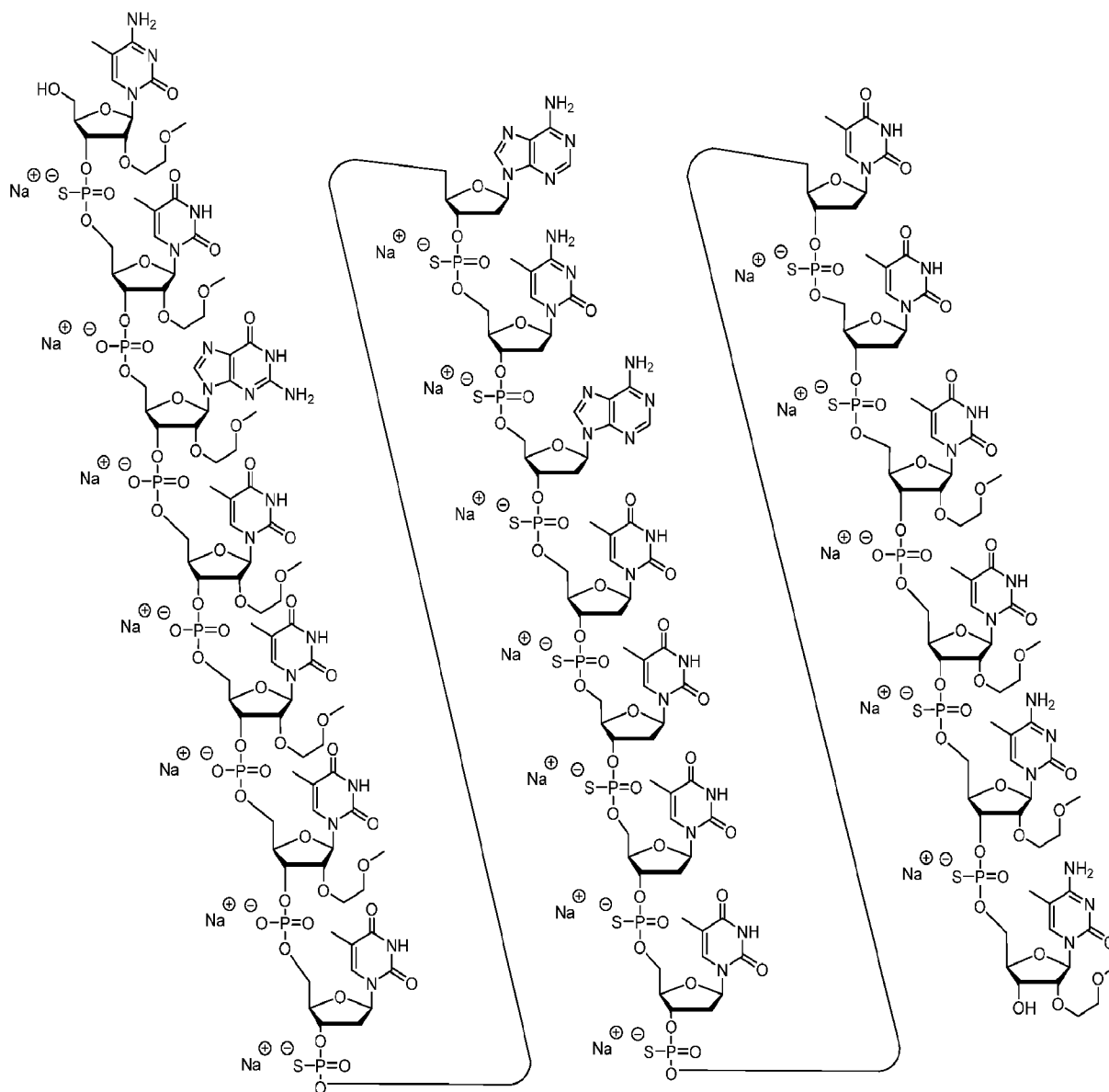
68. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2040), or a salt thereof.

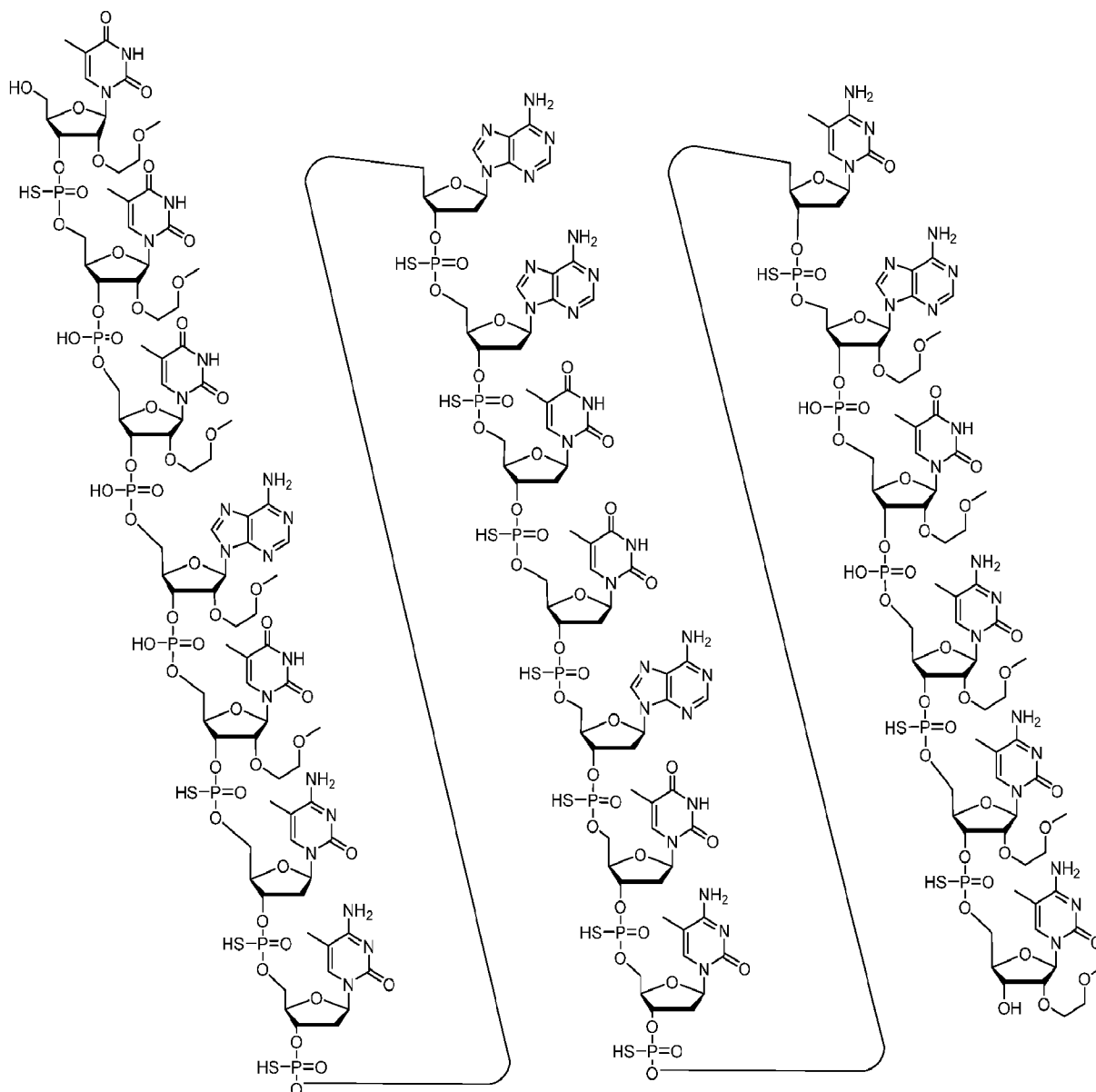
69. The modified oligonucleotide of claim 68, which is the sodium salt or the potassium salt.

70. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2040).

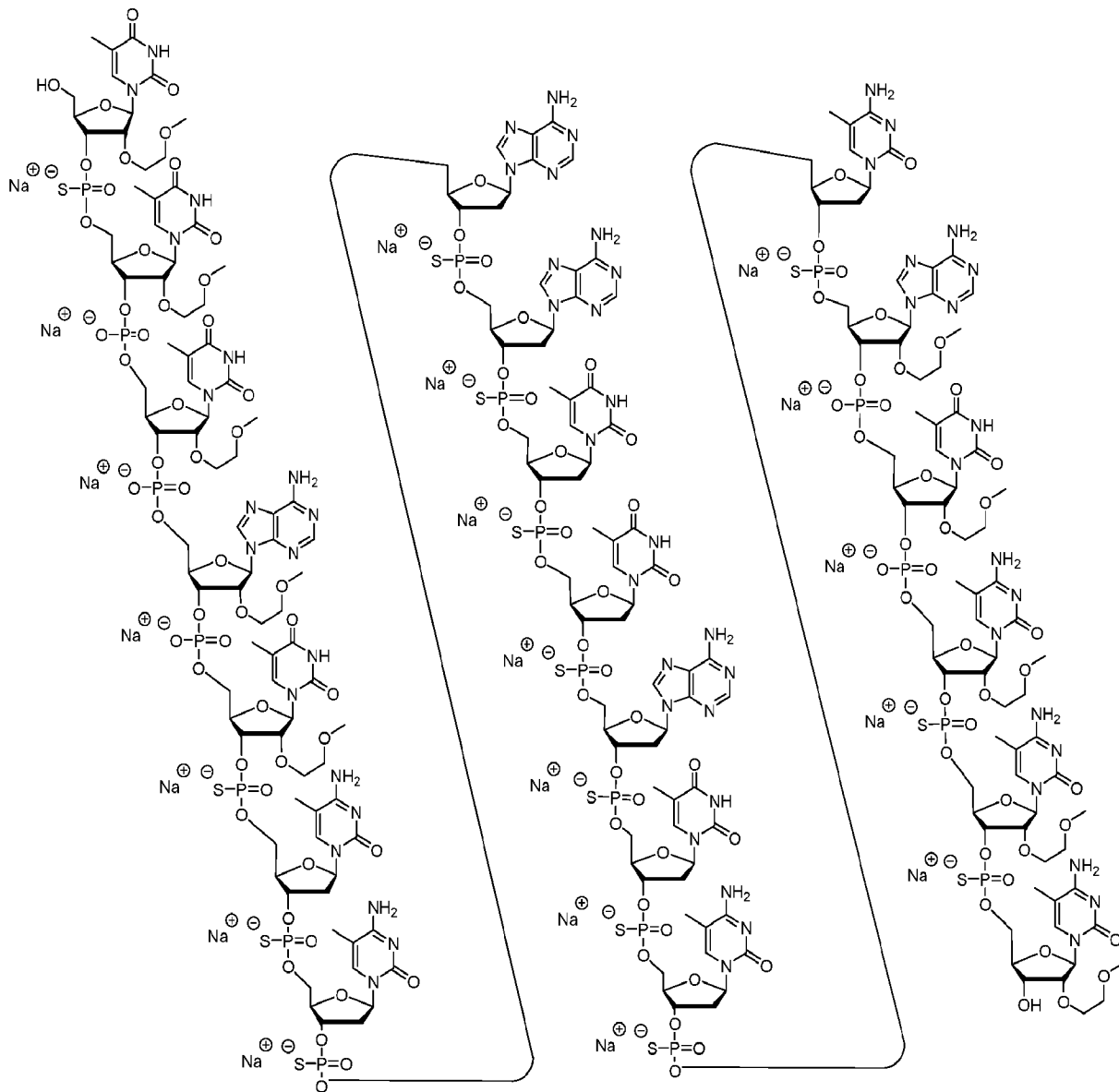
71. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2670), or a salt thereof.

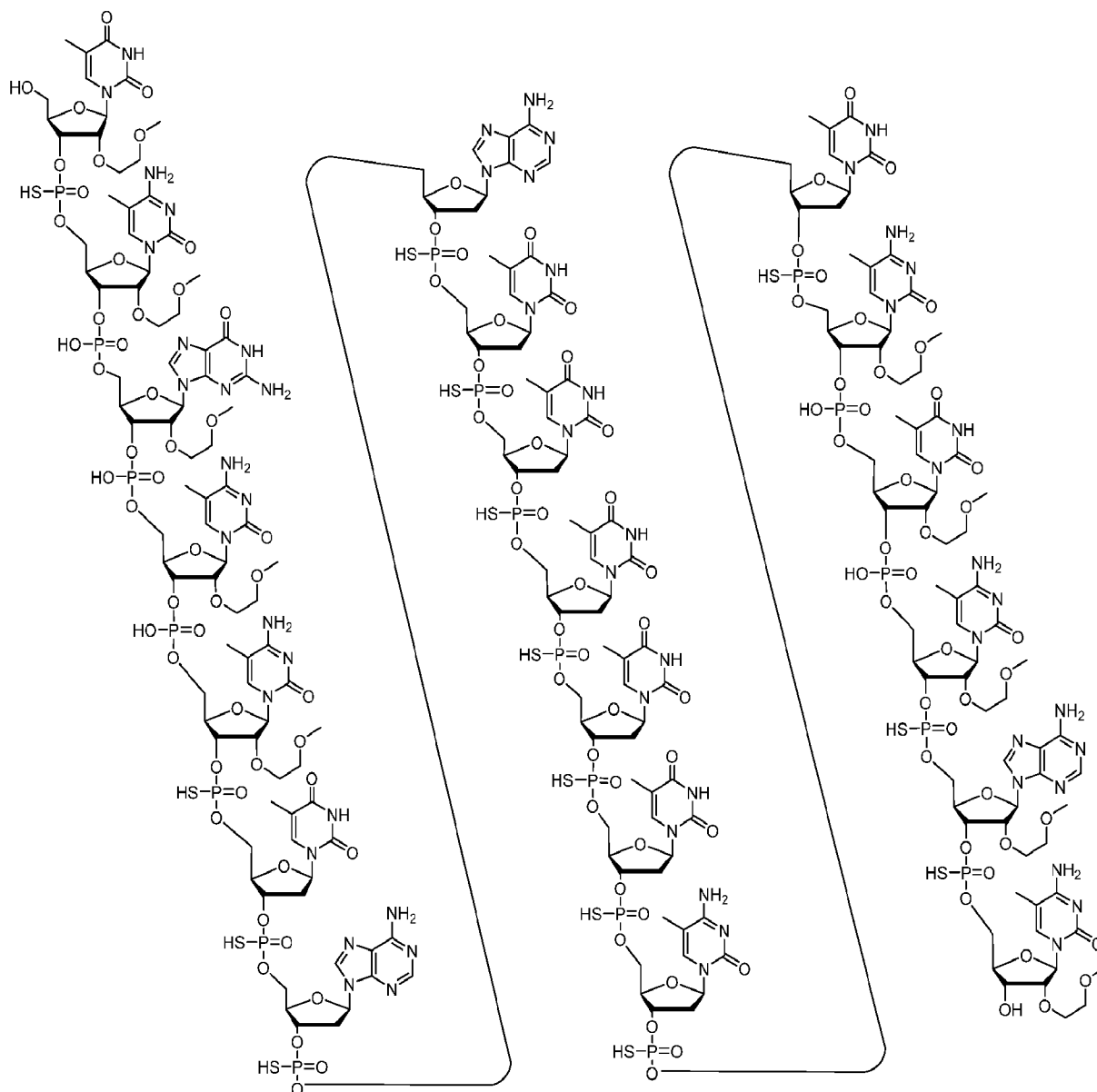
72. The modified oligonucleotide of claim 71, which is the sodium salt or the potassium salt.

73. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2670).

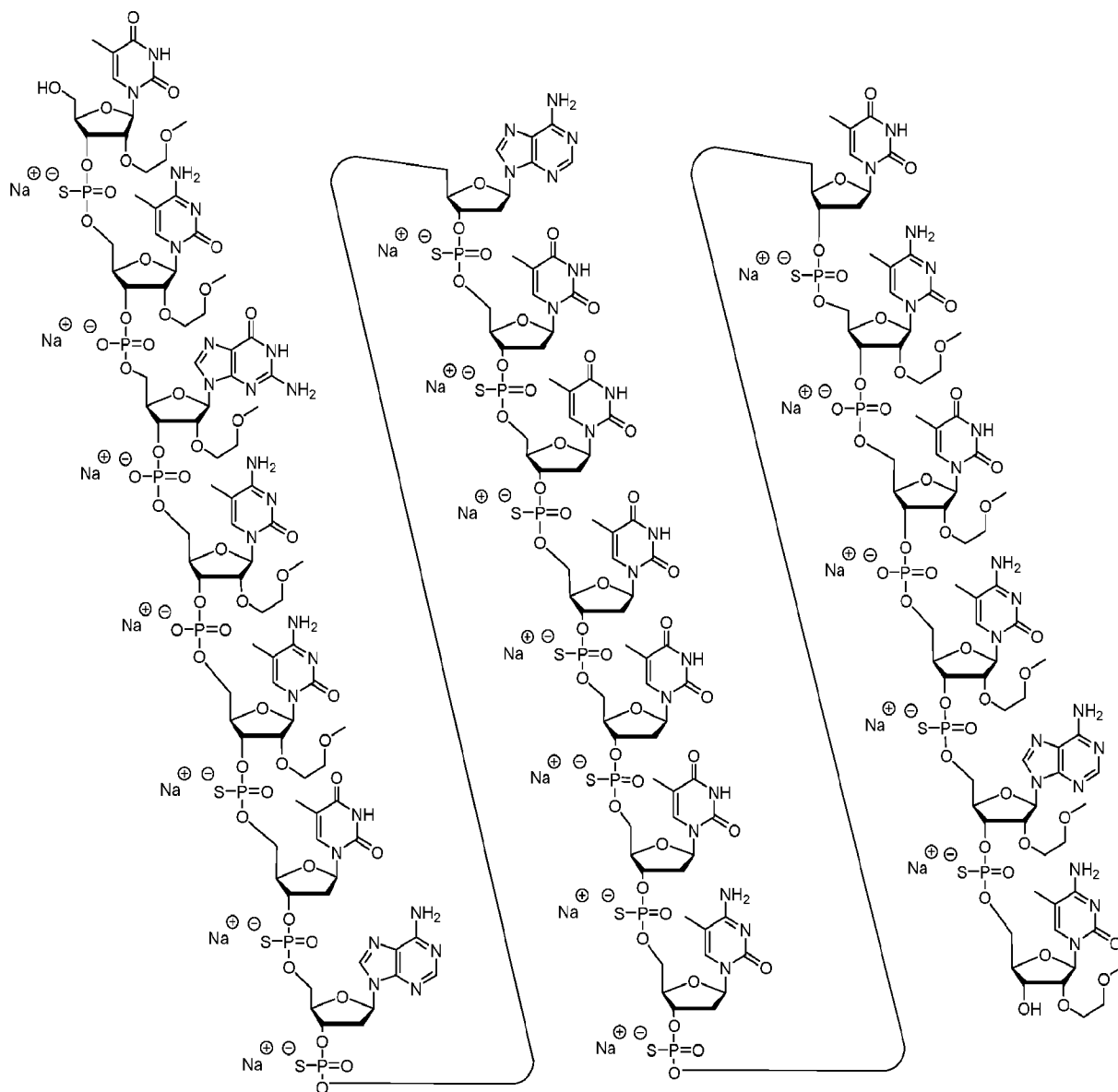
74. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2679), or a salt thereof.

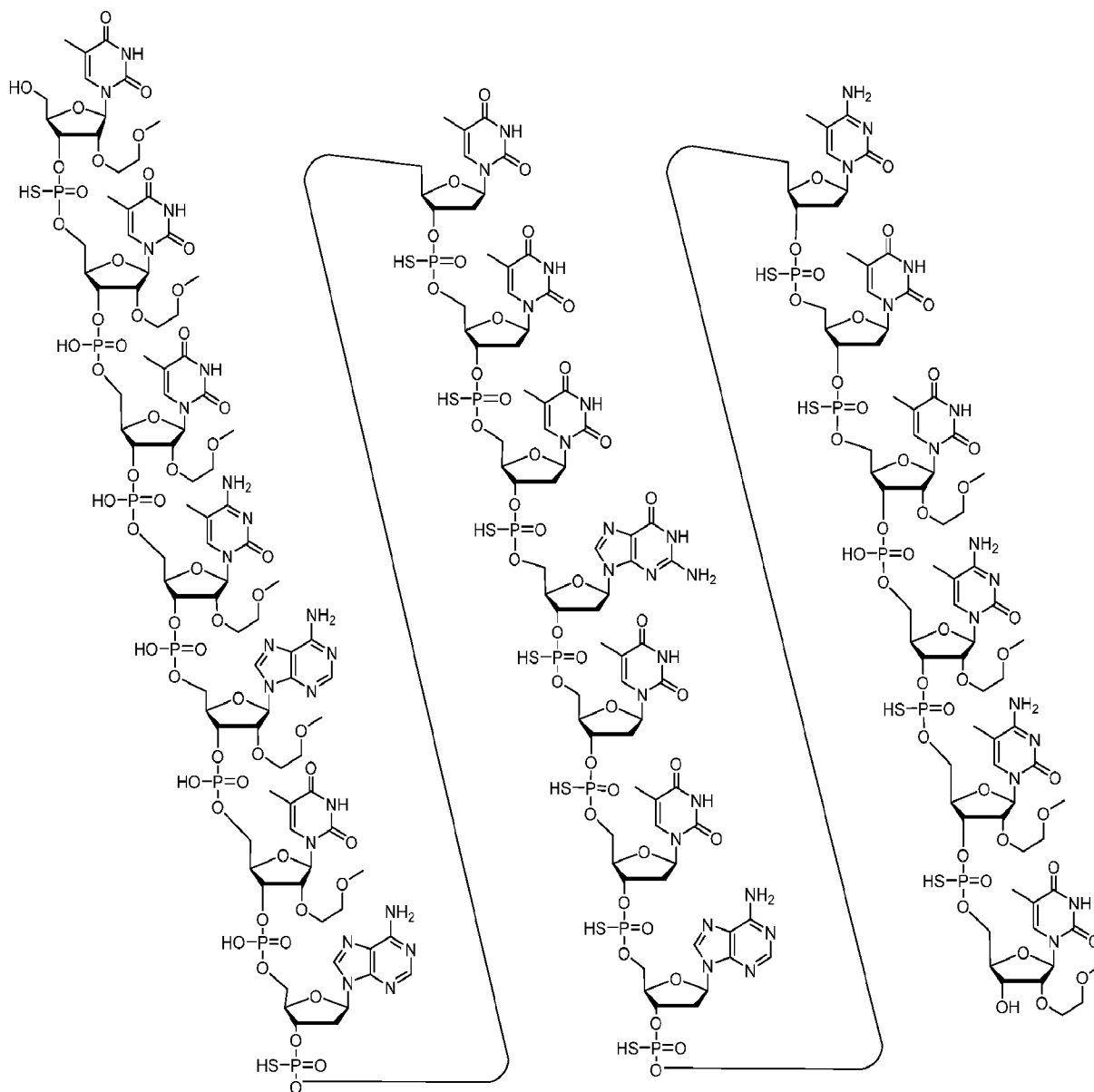
75. The modified oligonucleotide of claim 74, which is the sodium salt or the potassium salt.

76. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2679).

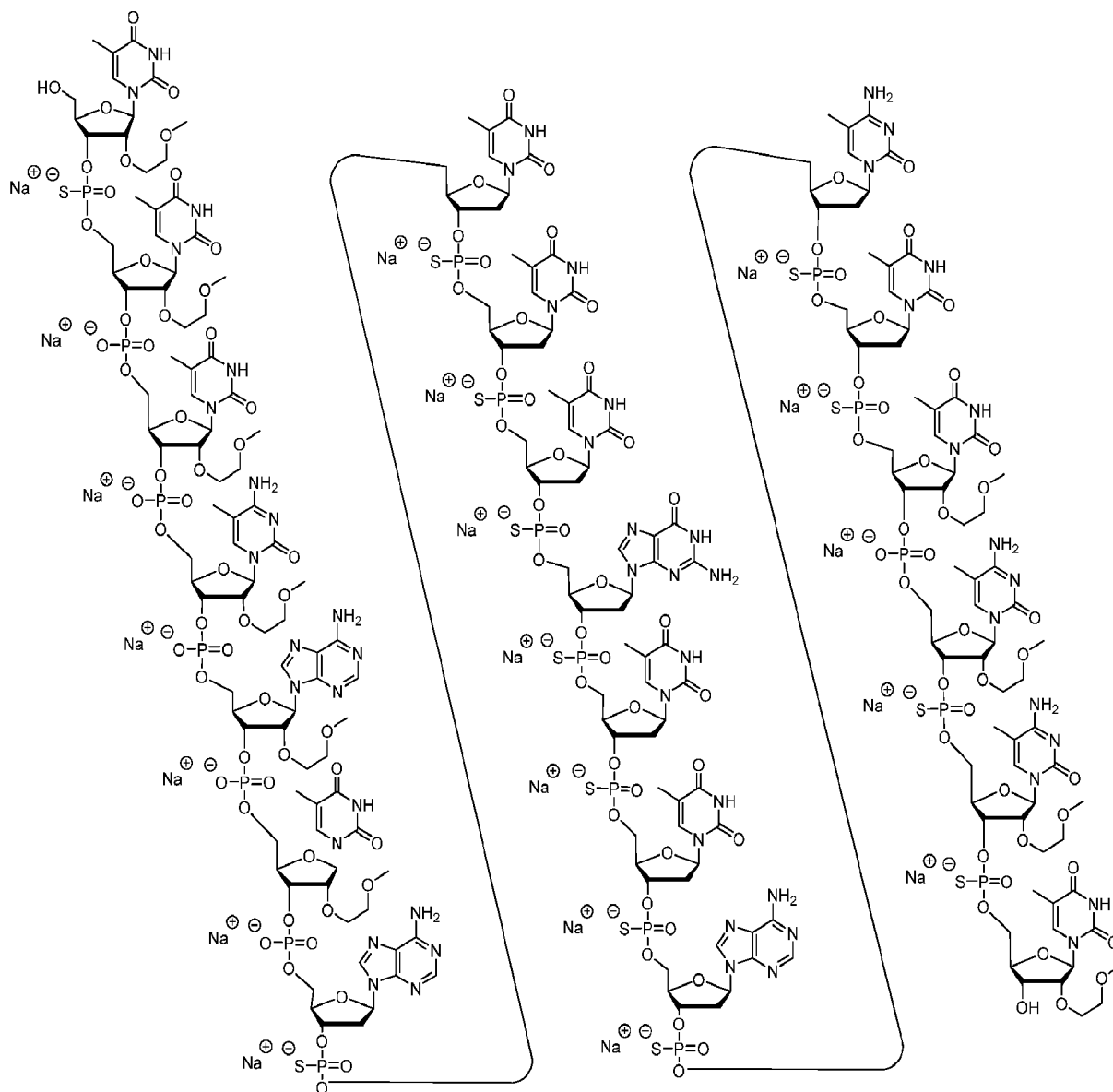
77. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2625), or a salt thereof.

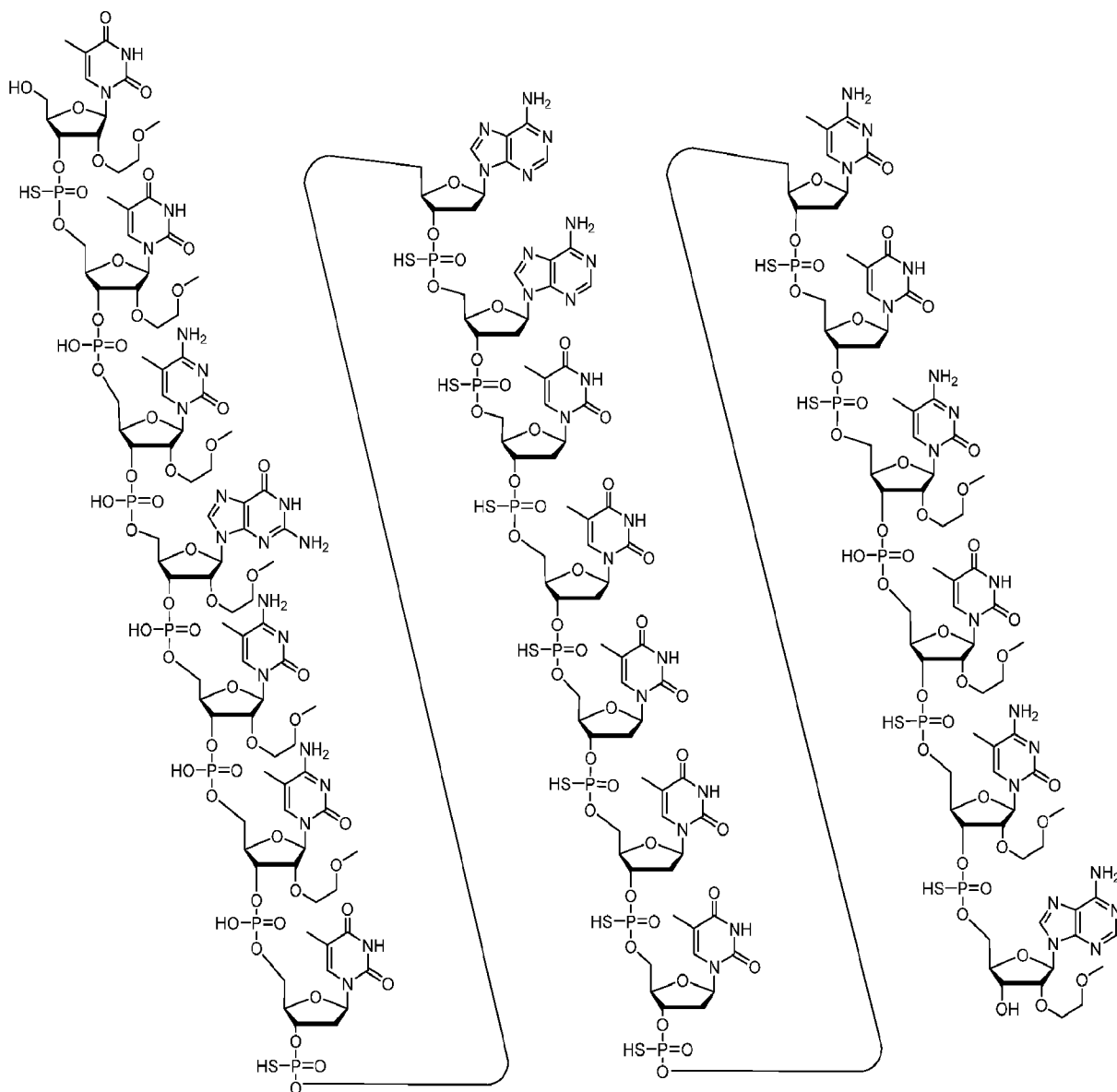
78. The modified oligonucleotide of claim 77, which is the sodium salt or the potassium salt.

79. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 2625).

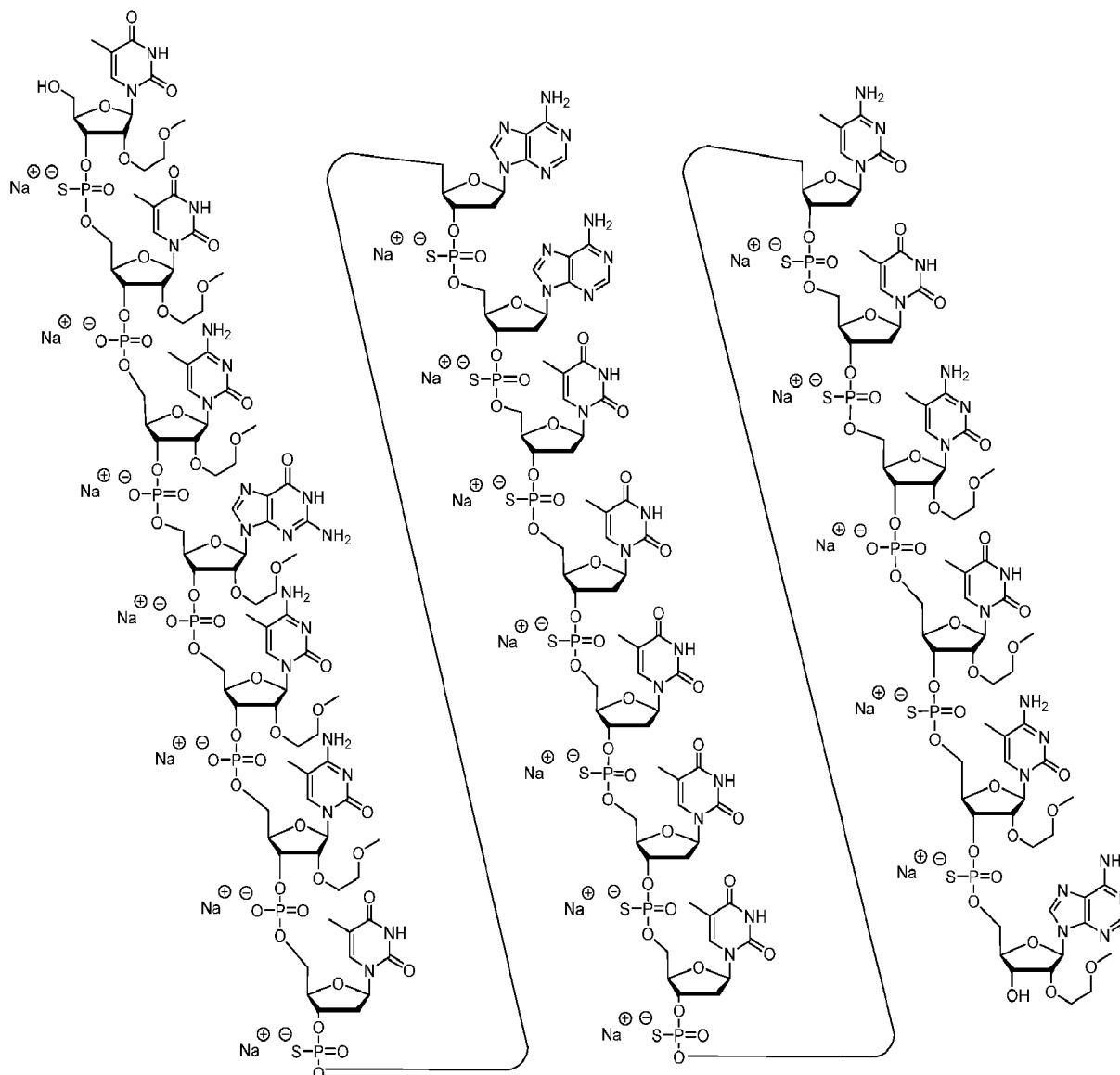
80. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 1317), or a salt thereof.

81. The modified oligonucleotide of claim 80, which is the sodium salt or the potassium salt.

82. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO 1317).

83. A chirally enriched population of oligomeric compounds of any of claims 1-64 or a chirally enriched population of modified oligonucleotides of any of claims 65-82, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

84. The chirally enriched population of claim 83, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*Sp*) or (*Rp*) configuration.

85. The chirally enriched population of claim 83, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

86. The chirally enriched population of claim 83, wherein the population is enriched for modified oligonucleotides having the (*Rp*) configuration at one particular phosphorothioate internucleoside linkage and the (*Sp*) configuration at each of the remaining phosphorothioate internucleoside linkages.

87. The chirally enriched population of claim 83, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *Sp*, *Sp*, and *Rp* configurations, in the 5' to 3' direction.

88. A population of oligomeric compounds of any of claims 1-64, or a population of modified oligonucleotides of any of claims 65-82, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

89. An oligomeric duplex comprising a first oligomeric compound comprising a first modified oligonucleotide and a second oligomeric compound comprising a second modified oligonucleotide, wherein the first oligomeric compound is an oligomeric compound of any of claims 1-64.

90. The oligomeric duplex of claim 89, wherein the second modified oligonucleotide consists of 8 to 80 linked nucleosides, and wherein the nucleobase sequence of the second modified oligonucleotide comprises a complementary region of at least 8 nucleobases that is at least 90% complementary to an equal length portion of the first modified oligonucleotide.

91. The oligomeric duplex of claim 89 or claim 90, wherein the first modified oligonucleotide comprises a 5'-stabilized phosphate group.

92. The oligomeric duplex of claim 91, wherein the 5'-stabilized phosphate group comprises a cyclopropyl phosphonate or a vinyl phosphonate.

93. The oligomeric duplex of any of claims 89-92, wherein the first modified oligonucleotide comprises a glycol nucleic acid (GNA) sugar surrogate.

94. The oligomeric duplex of any of claims 89-92, wherein the first modified oligonucleotide comprises a 2'-NMA sugar moiety.

95. The oligomeric duplex of any of claims 89-94, wherein at least one nucleoside of the second modified oligonucleotide comprises a modified sugar moiety.

96. The oligomeric duplex of claim 95, wherein the modified sugar moiety of the second modified oligonucleotide comprises a bicyclic sugar moiety.

97. The oligomeric duplex of claim 96, wherein the bicyclic sugar moiety of the second modified oligonucleotide comprises a 2'-4' bridge selected from -O-CH₂- and -O-CH(CH₃)-.

98. The oligomeric duplex of claim 95, wherein the modified sugar moiety of the second modified oligonucleotide comprises a non-bicyclic modified sugar moiety.

99. The oligomeric duplex of claim 98, wherein the non-bicyclic modified sugar moiety of the second modified oligonucleotide is a 2'-MOE sugar moiety, a 2'-F sugar moiety, or 2'-OMe sugar moiety.

100. The oligomeric duplex of any of claims 89-99, wherein at least one nucleoside of the second modified oligonucleotide comprises a sugar surrogate.

101. The oligomeric duplex of any of claims 89-100, wherein at least one internucleoside linkage of the second modified oligonucleotide is a modified internucleoside linkage.

102. The oligomeric duplex of claim 101, wherein at least one modified internucleoside linkage of the second modified oligonucleotide is a phosphorothioate internucleoside linkage.

103. The oligomeric duplex of any of claims 89-102, wherein at least one internucleoside linkage of the second modified oligonucleotide is a phosphodiester internucleoside linkage.

104. The oligomeric duplex of any of claims 89-101 or 103, wherein each internucleoside linkage of the second modified oligonucleotide is independently selected from a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

105. The oligomeric duplex of any of claims 89-104, wherein the second modified oligonucleotide comprises at least one modified nucleobase.

106. The oligomeric duplex of claim 105, wherein the modified nucleobase of the second modified oligonucleotide is 5-methylcytosine.

107. The oligomeric duplex of any of claims 89-106, wherein the second modified oligonucleotide comprises a conjugate group.

108. The oligomeric duplex of claim 107, wherein the conjugate group comprises a conjugate linker and a conjugate moiety.

109. The oligomeric duplex of claim 107 or claim 108, wherein the conjugate group is attached to the second modified oligonucleotide at the 5'-end of the second modified oligonucleotide.

110. The oligomeric duplex of claim 107 or claim 108, wherein the conjugate group is attached to the second modified oligonucleotide at the 3'-end of the second modified oligonucleotide.

111. The oligomeric duplex of any of claims 107-110, wherein the conjugate group comprises a lipid.

112. The oligomeric duplex of any of claims 107-111, wherein the second modified oligonucleotide comprises a terminal group.

113. The oligomeric duplex of claim 112, wherein the terminal group is an abasic sugar moiety.

114. The oligomeric duplex of any of claims 89-113, wherein the second modified oligonucleotide consists of 10 to 25, 10 to 30, 10 to 50, 12 to 20, 12 to 25, 12 to 30, 12 to 50, 13 to 20, 13 to 25, 13 to 30, 13 to 50, 14 to 20, 14 to 25, 14 to 30, 14 to 50, 15 to 20, 15 to 25, 15 to 30, 15 to 50, 16 to 18, 16 to 20, 16 to 25, 16 to 30, 16 to 50, 17 to 20, 17 to 25, 17 to 30, 17 to 50, 18 to 20, 18 to 22, 18 to 25, 18 to 30, 18 to 50, 19 to 20, 19 to 25, 19 to 30, 19 to 50, 20 to 25, 20 to 30, 20 to 50, 21 to 25, 21 to 30, 21 to 50, 22 to 25, 22 to 30, 22 to 50, 23 to 25, 23 to 30, or 23 to 50 linked nucleosides.

115. An antisense agent comprising an antisense compound, wherein the antisense compound is the oligomeric compound of any of claims 1-64 or the modified oligonucleotide of any of claims 65-82.

116. The antisense agent of claim 115, wherein the antisense agent is the oligomeric duplex of any of claims 89-114.

117. The antisense agent of claim 115 or claim 116, wherein the antisense agent is:

- i. an RNase H agent capable of reducing the amount of IFNAR1 nucleic acid through the activation of RNase H; or
- ii. an RNAi agent capable of reducing the amount of IFNAR1 nucleic acid through the activation of RISC/Ago2.

118. The antisense agent of any of claims 115-117, wherein the antisense agent comprises a conjugate group, wherein the conjugate group comprises a cell-targeting moiety.

119. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-64, a modified oligonucleotide of any of claims 65-82, a population of any of claims 83-88, an oligomeric duplex of any of claims 89-114, or an antisense agent of any of claims 115-118, and a pharmaceutically acceptable diluent or carrier.

120. The pharmaceutical composition of claim 119, wherein the pharmaceutically acceptable diluent is phosphate-buffered saline or artificial cerebrospinal fluid.

121. The pharmaceutical composition of claim 120, wherein the pharmaceutical composition consists essentially of the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, or the antisense agent, and the phosphate-buffered saline or the artificial cerebrospinal fluid.

122. A method comprising administering to a subject an oligomeric compound of any of claims 1-64, a modified oligonucleotide of any of claims 65-82, a population of any of claims 83-88, an oligomeric duplex of any of claims 89-114, an antisense agent of any of claims 115-118, or a pharmaceutical composition of any of claims 119-121.

123. A method of treating a disease associated with type I interferon signaling comprising administering to a subject having a disease associated with type I interferon signaling a therapeutically effective amount of an oligomeric compound of any of claims 1-64, a modified oligonucleotide of any of claims 65-82, a population of any of claims 83-88, an oligomeric duplex of any of claims 89-114, an antisense agent of any of claims 115-118, or a pharmaceutical composition of any of claims 119-121, thereby treating the disease associated with type I interferon signaling.

124. The method of claim 123, wherein the disease associated with type I interferon signaling is Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, or ataxia telangiectasia.

125. The method of claim 123 or claim 124, wherein the disease is associated with an elevated level of interferon-alpha in the subject.

126. The method of any of claims 122-125, wherein the subject has a mutation in a gene selected from TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, MDA5, USP18, LSM11, and RNU7-1.

127. The method of any of claims 123-126, wherein administering the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition reduces seizures, dystonia, spasticity, white matter abnormalities, T cell infiltration, B cell infiltration, striatal necrosis, brain atrophy, basal ganglia calcification, or microencephaly in the subject; or improves feeding, motor development, language development, or social skill development in the subject.

128. The method of any of claims 123-127, wherein administering the oligomeric compound, the modified oligonucleotide, the population, the oligomeric duplex, the antisense agent, or the pharmaceutical composition reduces interferon alpha and/or lymphocytosis in the cerebrospinal fluid of the subject.

129. The method of any of claims 122-128, wherein the subject is human.

130. A method of reducing expression of IFNAR1 in a cell comprising contacting the cell with an oligomeric compound of any of claims 1-64, a modified oligonucleotide of any of claims 65-82, a population of any of claims 83-88, an oligomeric duplex of any of claims 89-114, an antisense agent of any of claims 115-118, or a pharmaceutical composition of any of claims 119-121.

131. The method of claim 130, wherein the cell is a neuron or a glial cell, optionally wherein the cell is an astrocyte or microglial cell.

132. The method of claim 130 or claim 131, wherein the cell is a human cell.

133. Use of an oligomeric compound of any of claims 1-64, a modified oligonucleotide of any of claims 65-82, a population of any of claims 83-88, an oligomeric duplex of any of claims 89-114, an antisense agent of any of claims 115-118, or a pharmaceutical composition of any of claims 119-121 for treating a disease associated with type I interferon signaling.

134. Use of an oligomeric compound of any of claims 1-64, a modified oligonucleotide of any of claims 65-82, a population of any of claims 83-88, an oligomeric duplex of any of claims 89-114, an antisense agent of any of claims 115-118, or a pharmaceutical composition of any of claims 119-121 in the manufacture of a medicament for treating a disease associated with type I interferon signaling.

135. The use of claim 133 or claim 134, wherein the disease is associated with an elevated level of interferon alpha.

136. The use of any of claims 133-135, wherein the disease associated with type I interferon signaling is Aicardi-Goutières Syndrome, stroke, neuropsychiatric systemic lupus erythematosus, neuroinflammation following traumatic brain injury, neuro-autoimmune disorders, Alzheimer's disease, post-operative delirium and cognitive decline, cranial radiation-induced cognitive decline, viral infection-induced cognitive decline, neuromyelitis optica, or ataxia telangiectasia.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/033936

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C12N 15/11 (2022.01)

ADD. - A61P 25/14; C07H 21/02 (2022.01)

CPC - INV. - C12N 15/11 (2022.08)

ADD. - C07H 21/02; A61P 25/14 (2022.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/072991 A1 (IONIS PHARMACEUTICALS INC.) 09 April 2020 (09.04.2020) entire document	1-3, 6-9
A	WO 1996/023878 A1 (HYBRIDON INC. et al) 08 August 1996 (08.08.1996) entire document	1-3, 6-9
A	US 2020/0399381 A1 (I-MAB BIOPHARMA US LIMITED) 24 December 2020 (24.12.2020) entire document	1-3, 6-9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

07 October 2022

Date of mailing of the international search report

OCT 27 2022

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/033936

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. ☒ forming part of the international application as filed:

☒ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NO: 12 was searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/033936

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4, 5, 11-46, 53-64, 83-136
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6-9

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/033936

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3, 6-10, 47-52, and 65-82 are drawn to oligomeric compounds, and modified oligonucleotides thereof.

The first invention of Group I+ is restricted to an oligomeric compound comprising a modified oligonucleotide selected to be SEQ ID NO: 12. It is believed that claims 1-3 and 6-9 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO: 12.

Applicant is invited to elect additional modified oligonucleotides, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an oligomeric compound comprising a modified oligonucleotide selected to be SEQ ID NO: 13. Additional modified oligonucleotides, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element, requiring the selection of alternative modified oligonucleotides where "wherein the nucleobase sequence of the modified oligonucleotide is at least 80% complementary to an equal length portion within nucleobases 5085-5133, 19997-20061, 20076-20133, 20528-20616, 22294-22329, 22453-22476, 22595-22626, 25530-25565, 25606-25652, 25710-25767, 25768-25827, 28421-28468, 29924-29949, 29968-30021, 31072-31096, 31792-31837, 32353-32386, or 35016-35042 of SEQ ID NO: 1" and "modified oligonucleotide consisting of 8 to 80 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-2687."

Additionally, even if Groups I+ were considered to share the technical features of an oligomeric compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2020/072991 A1 to Ionis Pharmaceuticals Inc. (hereinafter, "Ionis") teaches an oligomeric compound comprising a modified oligonucleotide (Pg. 1, Lns. 25-26, the present disclosure provides oligomeric compounds comprising modified oligonucleotides having one or more stereo-non-standard nucleosides), wherein the modified oligonucleotide has at least one modification selected from a modified sugar moiety and a modified internucleoside linkage (Pg. 19, Lns. 4-5, [i])n certain embodiments, modified sugar moieties are stereo-non-standard sugar moieties. In certain embodiments, sugar moieties are substituted furanosyl stereo-standard sugar moieties).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.