DOUBLE STRANDED OLIGONUCLEOTIDE COMPOSITIONS AND METHODS RELATING THERETO

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/560,561, filed March 1, 2024, U.S. Provisional Application No. 63/636,435, filed April 19, 2024, U.S. Provisional Application No. 63/691,219, filed September 5, 2024, and U.S. Provisional Application No. 63/714,071, filed October 30, 2024.

This application is related to and incorporates herein by reference in their entireties U.S. Provisional Application No. 63/560,561, filed March 1, 2024, U.S. Provisional Application No. 63/636,435, filed April 19, 2024, U.S. Provisional Application No. 63/691,219, filed September 5, 2024, U.S. Provisional Application No. 63/714,071, filed October 30, 2024, WO 2021/234459, WO 2023/049218, WO 2024/182749, and PCT/US2025/013253, filed January 27, 2025.

BACKGROUND

Gene-targeting oligonucleotides are useful in various applications, *e.g.*, therapeutic, diagnostic, research and nanomaterials applications. The use of naturally-occurring nucleic acids (*e.g.*, unmodified DNA or RNA) in such applications can be limited by, for example, their susceptibility to endo- and exo-nucleases. As such, various synthetic counterparts have been developed to circumvent these shortcomings. These include synthetic oligonucleotides that contain chemical modifications, e.g., base modifications, sugar modifications, backbone modifications. There remains, however, a need in the art for double-stranded (ds) oligonucleotides with improved properties for use in connection with the above-described applications.

SUMMARY

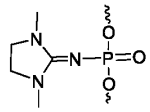
The present disclosure is directed, in part, to the recognition that controlling structural elements of the oligonucleotides of a double-stranded (ds) oligonucleotide can have a significant impact on the ds oligonucleotide's properties and/or activity. In certain embodiments, such structural elements include one or more of: (1) chemical modifications (*e.g.*, modifications of a sugar, base and/or internucleotidic linkage) and patterns thereof; and (2) alterations in stereochemistry (*e.g.*, stereochemistry of a backbone chiral internucleotidic linkage) and patterns thereof. One or more of such structural elements can, in certain

embodiments, be independently present in one or both oligonucleotides of a ds oligonucleotide. In certain embodiments, the properties and/or activities impacted by such structural elements include, but are not limited to, participation in, direction of a decrease in expression, activity or level of a gene or a gene product thereof, mediated, for example, by RNA interference (RNAi interference), RNase H-mediated knockdown, steric hindrance of translation, etc. Moreover, in certain embodiments, the properties and/or activities impacted by such structural elements include, but are not limited to, participation in, Ago2 loading, thermal stability, *in vivo* stability, delivery to tissues and into cells, among others.

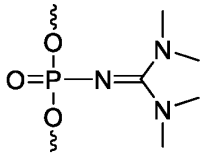
In certain embodiments, the present disclosure demonstrates that compositions comprising ds oligonucleotides (e.g., dsRNAi oligonucleotides, also referred to as dsRNAi agents) with controlled structural elements provide unexpected properties and/or activities.

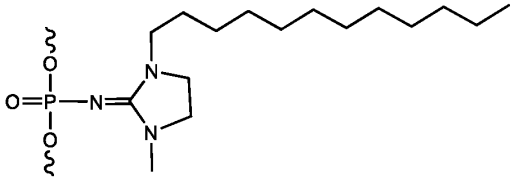
In certain embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of backbone chiral centers, can unexpectedly maintain or improve properties of ds oligonucleotides. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising a guide strand comprising backbone phosphoryl guanidine chiral centers in the Sp configuration.

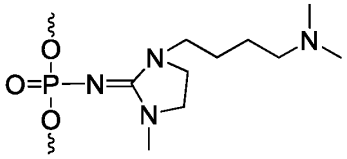
In certain embodiments, one or both of the guide strand and the passenger strand comprise a lipid ligand. In certain embodiments, one or both of the guide strand and the passenger strand comprise a non-lipid ligand.

In a first aspect, the invention relates to a double-stranded RNAi (dsRNAi) agent capable of directing target-specific RNA interference, the dsRNAi agent comprising a guide strand and a passenger strand, wherein: the guide strand is complementary or substantially complementary to a target RNA sequence; the guide strand comprises a seed region at its 5'-end region that is capable of mediating the initial recognition of the target RNA sequence, e.g., nucleotides at positions 2-6, at positions 2-7, or at positions 2-8, relative to the 5'-end of the guide strand; the guide strand comprises a backbone phosphoryl guanidine (PN) chiral center comprising the structure of, e.g.,  (n001), e.g., in the *S*p configuration, in the seed region, e.g., between the third (+3) nucleotide and the immediately downstream (+4) nucleotide, relative to its 5' terminal nucleotide; and one or both of the guide strand and the passenger strand comprise a lipid ligand and/or a non-lipid ligand. In an exemplary embodiment, only the passenger strand comprises one or more lipid ligands conjugated to the

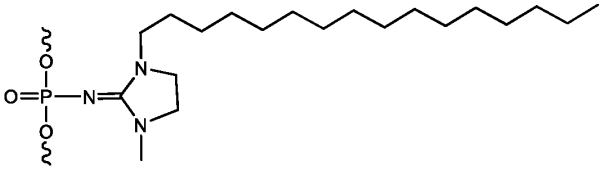
5'-end and/or the 3'-end thereof, and/or one or more internucleotidic linkages thereof. In an exemplary embodiment, only the passenger strand comprises one lipid ligand conjugated to one internucleotidic linkage thereof. In an exemplary embodiment, the passenger strand comprises one or more backbone PN chiral centers, e.g., independently between the +7 nucleotide and the +8 nucleotide, and/or between the +15 nucleotide and the +16 nucleotide thereof. In an exemplary embodiment, the passenger strand comprises one backbone PN chiral center between the +7 nucleotide and the +8 nucleotide thereof, e.g., in the *R*p configuration. In an exemplary embodiment, one or more backbone PN chiral centers, e.g., of the passenger strand, is/are modified with one or two of the lipid ligand, e.g., a saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain, thereby constituting a "backbone PN-lipid ligand". In an exemplary embodiment, the backbone PN-lipid ligand is selected from the group consisting of: a mono PN-lipid, a bis PN-lipid, a mono PN-PEG lipid, a bis PN-PEG lipid,

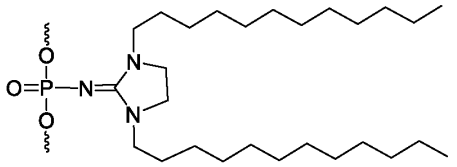
n003 having or comprising the structure of ,

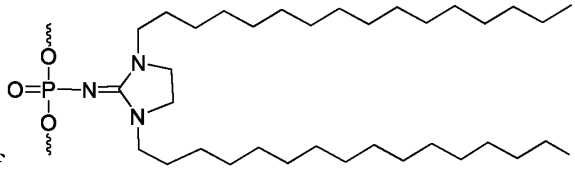
n009 having or comprising the structure of ,

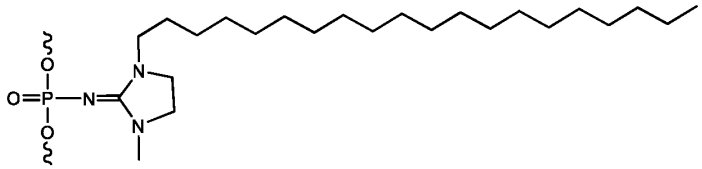
n029 having or comprising the structure of ,

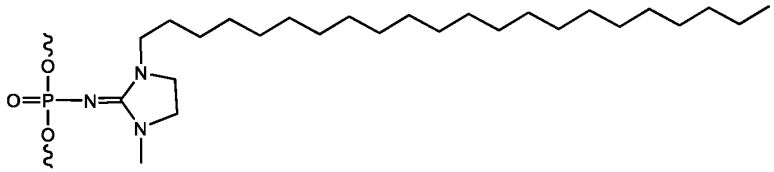
n033 having or comprising the structure of

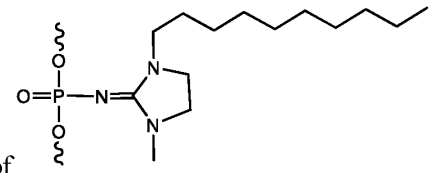
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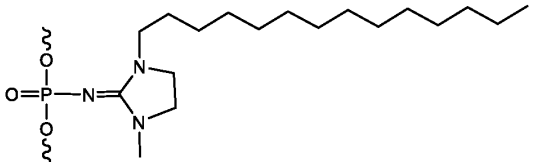
n039 having or comprising the structure of ,

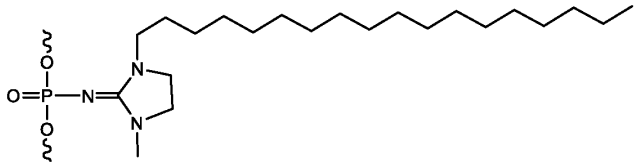
n040 having or comprising the structure of ,

n076 having or comprising the structure of ,

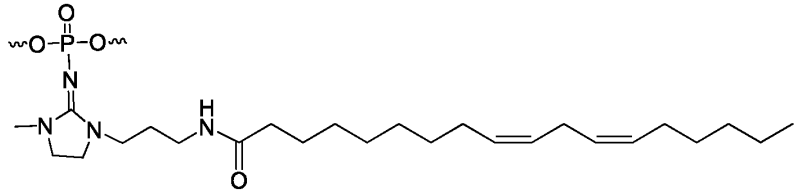
n077 having or comprising the structure of ,

n082 having or comprising the structure of ,

n083 having or comprising the structure of ,

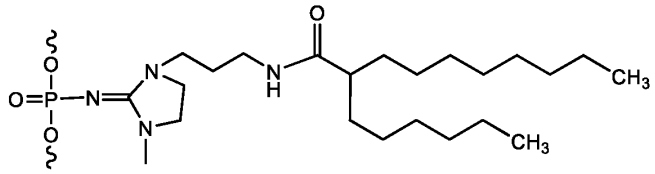
n084 having or comprising the structure of ,

n086 having or comprising the structure of



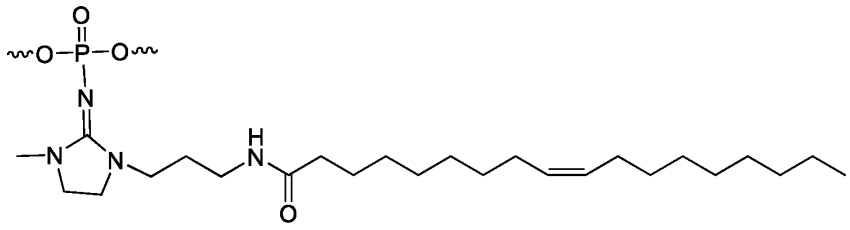
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n087 having or comprising the structure of



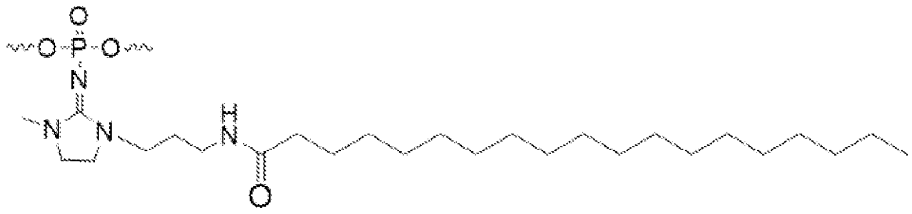
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n088 having or comprising the structure of



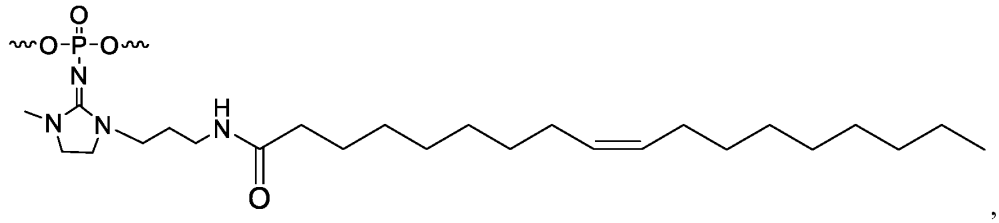
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n089 having or comprising the structure of



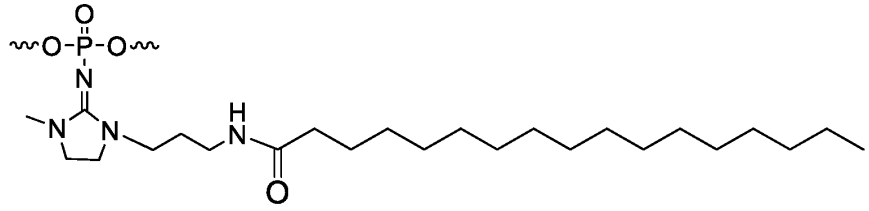
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n090 having or comprising the structure of



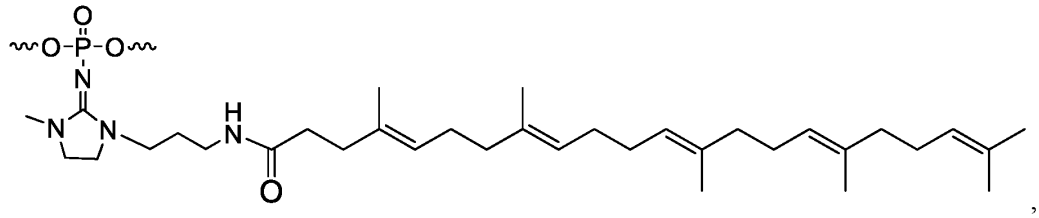
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n091 having or comprising the structure of



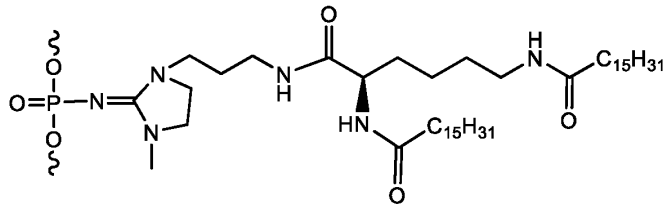
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n092 having or comprising the structure of



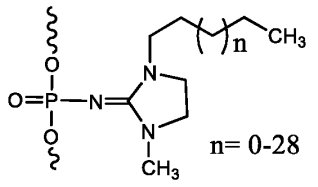
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and a PN-lipid having or comprising the structure of



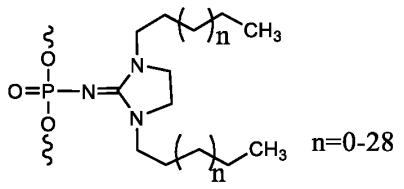
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In an exemplary embodiment, the mono PN-lipid is or comprises the structure of, e.g.,



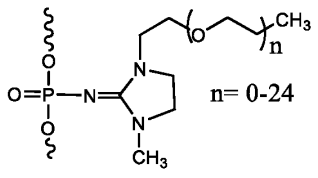
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In an exemplary embodiment, the bis PN-lipid is or comprises the structure of, e.g.,



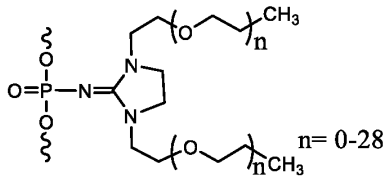
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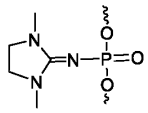
In an exemplary embodiment, the mono PN-PEG lipid is or comprises the structure of, e.g.,



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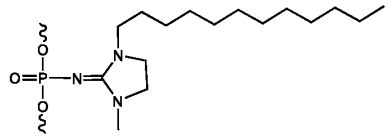
In an exemplary embodiment, the bis PN-PEG lipid is or comprises the structure of, e.g.,

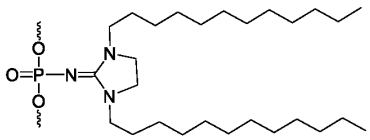


. In an exemplary embodiment, the passenger strand further comprises a backbone phosphorothioate (PS) chiral center independently between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide, and/or a backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide. In an exemplary embodiment, the passenger strand comprises backbone PS chiral centers, e.g., independently between the +1 nucleotide and the +2 nucleotide, and between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, thereof, e.g., in the *S*p configuration. In an exemplary embodiment, the guide strand further comprises a backbone PN chiral center, e.g., independently between the +7 nucleotide and the +8 nucleotide, and/or a backbone PN chiral center between the +18 nucleotide and the +19 nucleotide, thereof. In an exemplary embodiment, the guide strand comprises backbone PN chiral centers comprising the structure of, e.g., 

(n001), e.g., independently between the +7 nucleotide and the +8 nucleotide, and between the +18 nucleotide and the +19 nucleotide thereof, e.g., in the *S*p configuration. In an exemplary embodiment, the guide strand comprises a backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, between the +21 nucleotide and the +22 nucleotide, between the +20 nucleotide and the +21 nucleotide, and/or between the +19 nucleotide and the +20 nucleotide. In an exemplary embodiment, the backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, between the +21 nucleotide and the +22 nucleotide, between the +20 nucleotide and +21 nucleotide, and/or between the +19 nucleotide and the +20 nucleotide, of the guide strand, is/are in the *S*p configuration.

In an exemplary embodiment of the first aspect of the invention, the guide strand comprises a PS chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide in the *S*p configuration, between the +21 nucleotide and the +22 nucleotide in the *S*p configuration, between the +20 nucleotide and the +21 nucleotide, and between the +19 nucleotide and the +20 nucleotide in the *S*p configuration, and the passenger strand comprises

a backbone PN chiral center comprising the structure of, e.g.,  (n009) between the +7 nucleotide and the +8 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the guide strand comprises a PS chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide in the *S*p configuration, between the +21 nucleotide and the +22 nucleotide in the *S*p configuration, between the +20 nucleotide and the +21 nucleotide, and between the +19 nucleotide and the +20 nucleotide in the *S*p configuration, and the passenger strand comprises a backbone PN chiral center comprising the structure of, e.g.,  (n039) between the +7 nucleotide and the +8 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises only one PN chiral center comprising the structure of, e.g., n040 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n077 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n082 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n083 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n084 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n086 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n087 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n088 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n089 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n090 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, n091 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide, or n092 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n082 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n082 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand

comprises two PN chiral centers comprising the structure of, e.g., n009 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n009 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n083 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n083 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n033 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n033 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n084 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n084 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

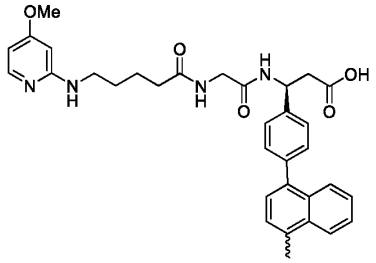
In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n077 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n077 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

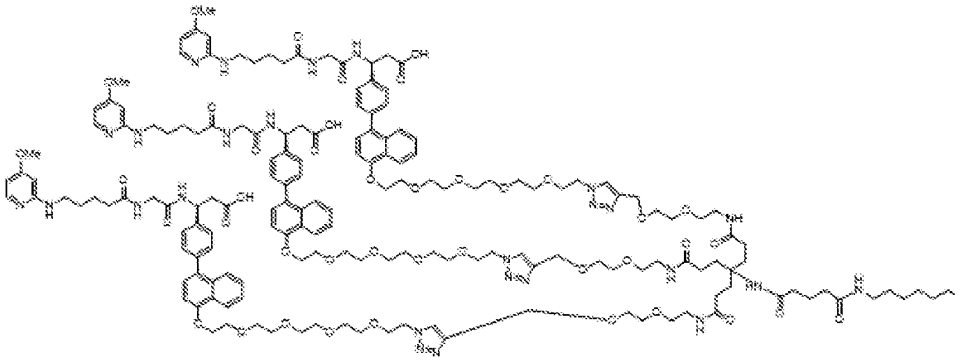
In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n039 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n039 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

In an exemplary embodiment of the first aspect of the invention, the passenger strand comprises two PN chiral centers comprising the structure of, e.g., n003 in the *R*p configuration between the +7 nucleotide and the +8 nucleotide and, e.g., n003 in the *R*p configuration between the +15 nucleotide and the +16 nucleotide.

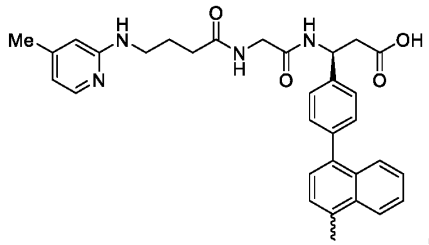
In a second aspect, the invention relates to the dsRNAi agent according to the first aspect, wherein one or both of the guide strand and the passenger strand comprise a non-lipid

ligand, e.g., a carbohydrate, a protein, a peptide, a polyamine, a peptide mimic, a receptor ligand, or a combination thereof, conjugated to the 5'-end and/or the 3'-end, and/or one or more internucleotidic linkages, of one or both of the guide strand and the passenger strand. In an exemplary embodiment, only the passenger strand comprises a non-lipid ligand conjugated to its 5'-end, optionally via a linker comprising, e.g., 6-aminohexanoyl (nC6o) moiety. In an exemplary embodiment, the linker further comprises a C_5 chain.

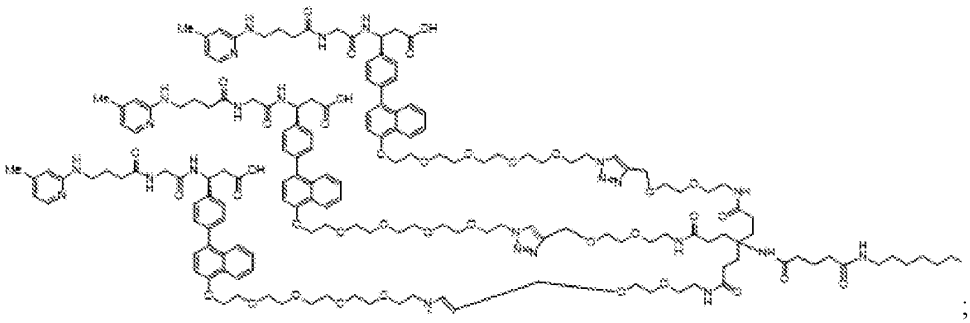
In an exemplary embodiment of the second aspect, the non-lipid ligand is a receptor ligand, e.g., an integrin receptor ligand, e.g.,  (OMe-integrin receptor ligand), e.g., a mono-OMe-integrin receptor ligand, a bis-OMe-integrin receptor ligand, or a tri-OMe-integrin receptor ligand, wherein the tri-OMe-integrin receptor ligand conjugated to, e.g., the passenger strand comprises the structure of, e.g.,



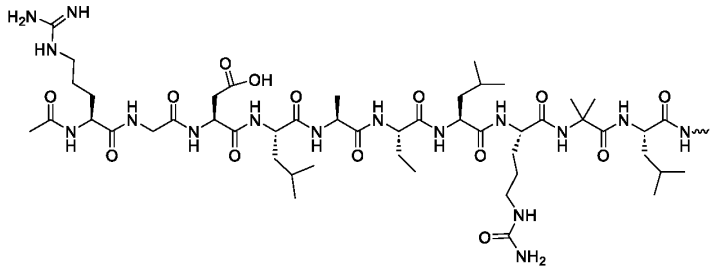
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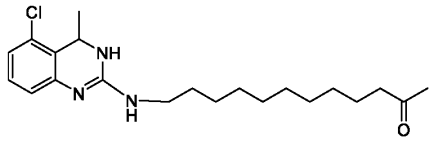
(Me-integrin receptor ligand), e.g., a mono-Me-integrin receptor ligand, a bis-Me-integrin receptor ligand, or a tri-Me-integrin receptor ligand, wherein the tri-Me-integrin receptor ligand conjugated to, e.g., the passenger strand comprises the structure of, e.g.,



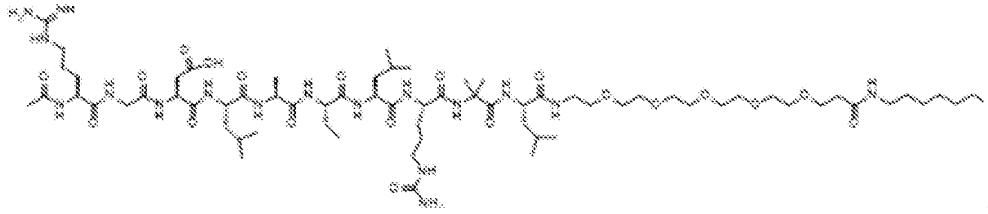
; or



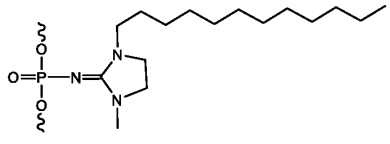
(peptide-integrin receptor ligand). In an exemplary embodiment, the receptor ligand is a serotonin receptor ligand, e.g., a serotonin receptor ligand comprising the structure of, e.g.,



. In an exemplary embodiment, the peptide-integrin receptor ligand conjugated to, e.g., the passenger strand comprises the structure of, e.g.,

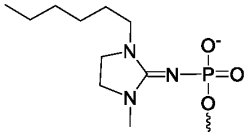


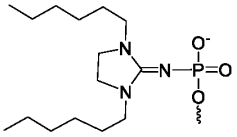
. In an exemplary embodiment, the backbone phosphoryl guanidine (PN) chiral centers, e.g., the backbone PN-lipid ligands, e.g., independently between the +7 nucleotide and the +8 nucleotide, and between the +15 nucleotide and the +16 nucleotide, of the passenger strand, comprise the structure of, e.g.,

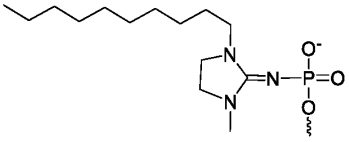


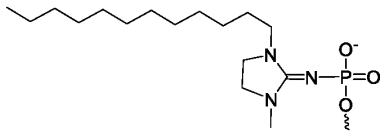
(n009).

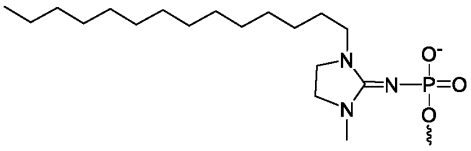
In an exemplary embodiment of the second aspect, the non-lipid ligand is a carbohydrate, e.g., a mono-GalNAc, a bis-GalNAc, a tri-GalNAc, a mannose derivative, a galactose derivative, a glucose sugar derivative, other saccharide derivatives or combinations thereof. In an exemplary embodiment, the carbohydrate is a tri-GalNAc. In an exemplary embodiment, the guide strand comprises a lipid ligand, e.g., a PN-lipid ligand, conjugated to its 5'-end (5'-end PN-lipid ligand) and/or its 3'-end (3'-end PN-lipid ligand), and/or one or more internucleotidic linkages thereof. In an exemplary embodiment, the passenger strand comprises a lipid ligand, e.g., a PN-lipid ligand, conjugated to its 3'-end (3'-end PN-lipid ligand), and/or one or more internucleotidic linkages thereof. In an exemplary embodiment, the guide strand comprises a PN-lipid ligand conjugated to its 5'-end (5'-end PN-lipid ligand). In an exemplary embodiment, the PN-lipid ligand comprises one or two saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain. In an exemplary embodiment, the 5'-end PN-lipid ligand of the guide strand comprises the structure of, e.g.,

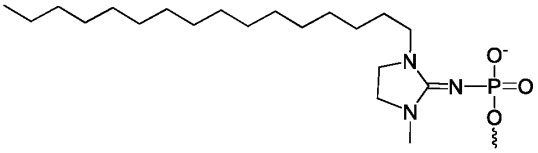

(n031),

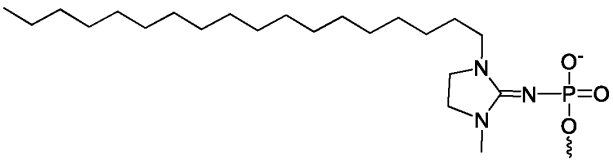

(n037),

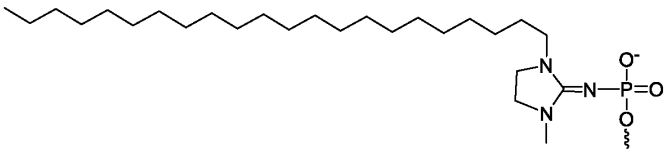

(n082),

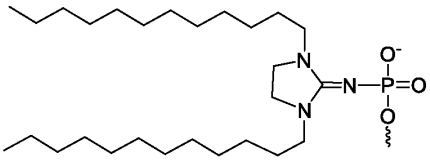

(n009),


(n083),

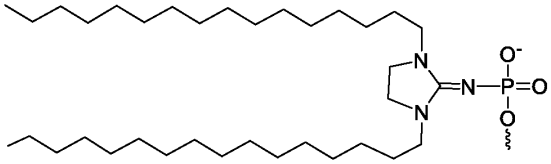

(n033),


(n084),

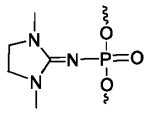

(n077),



(n039), or

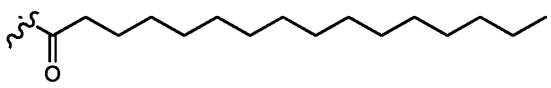


(n040). In an exemplary embodiment, the guide strand further comprises a backbone PN chiral center comprising the structure of, e.g.,

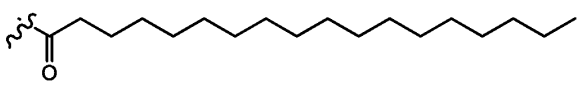


(n001), e.g., between the +10 nucleotide and the +11 nucleotide thereof, e.g., in the *R*p configuration.

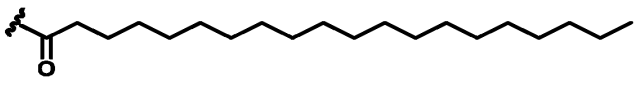
In a third aspect, the invention relates to the dsRNAi agent according to the first aspect, wherein one or both of the guide strand and the passenger strand comprise one or more lipid ligands conjugated to the 5'-end and/or the 3'-end thereof, and/or one or more internucleotidic linkages thereof. In an exemplary embodiment, the lipid ligand is conjugated to the 5'-end and/or the 3'-end of the passenger strand via a linker comprising, e.g., 6-aminohexanol (nC6o). In an exemplary embodiment, the lipid ligand is conjugated to the 5'-end of the passenger strand. In an exemplary embodiment, the lipid ligand comprises a saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain, cholesterol or a lipophilic cholesterol derivative, palmitoyl moiety, octadecanoyl moiety, linoleoyl moiety, turbinaric acid moiety, 2-hexyldecanoyl moiety, 20-oxoicosanoyl moiety, or a combination thereof. In an exemplary embodiment, the lipid comprises the structure of, e.g.,



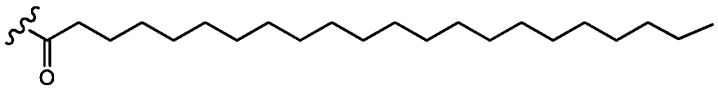
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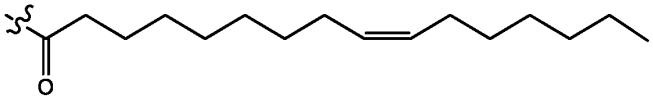


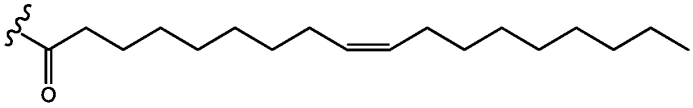
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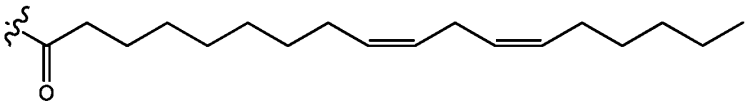


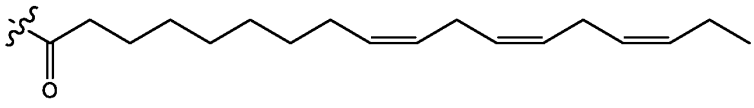
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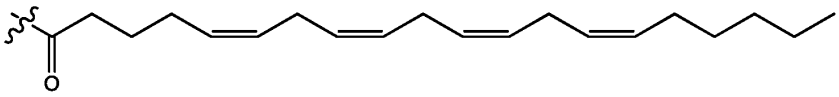

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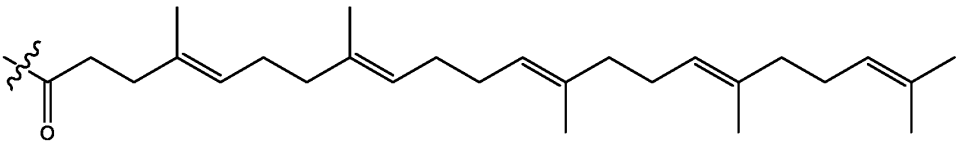

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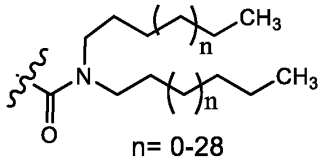

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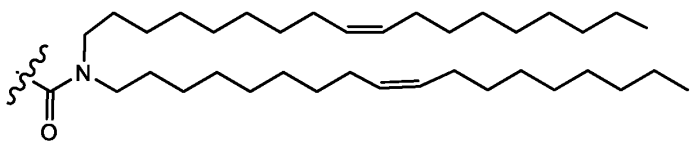

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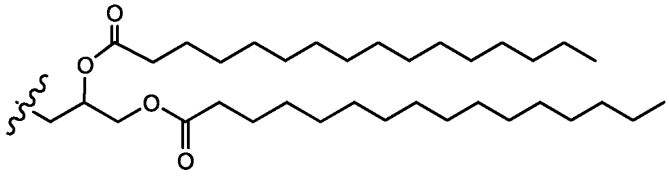

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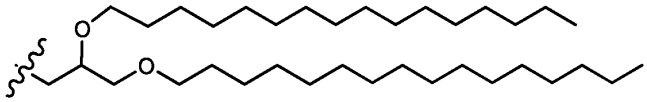

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CH3
n
N
n
CH3
O
n= 0-28
,

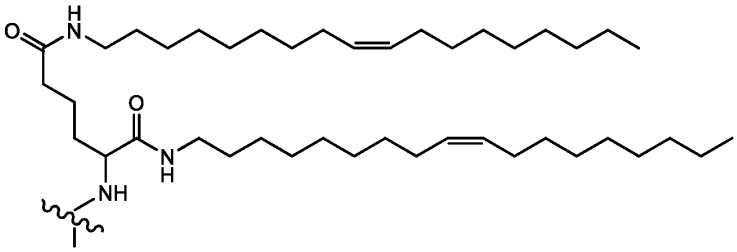

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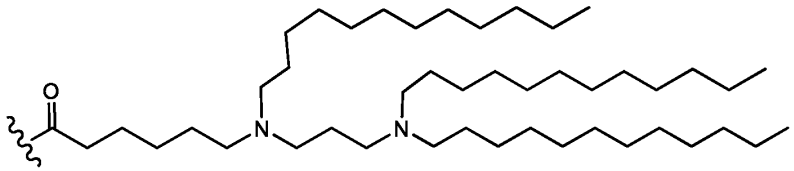
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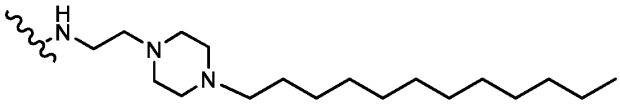
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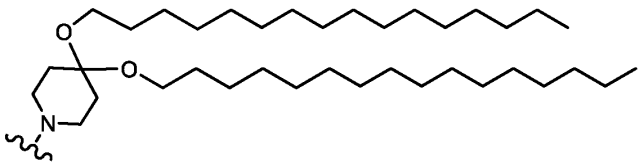
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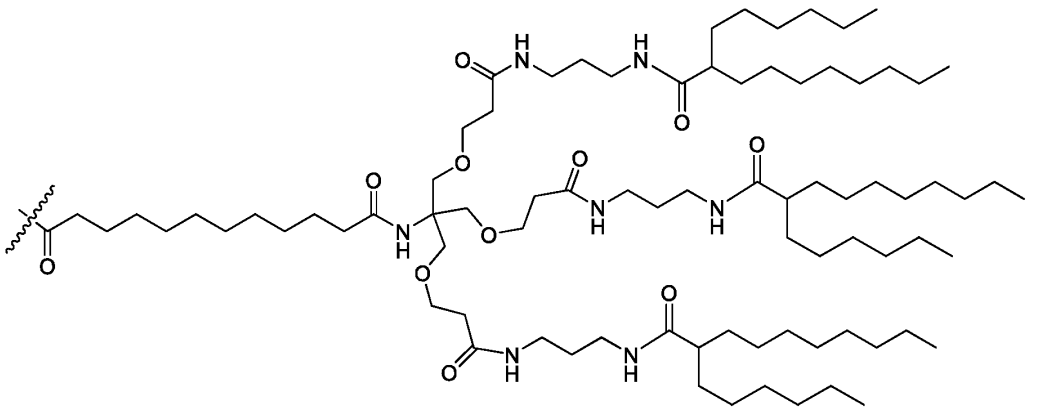
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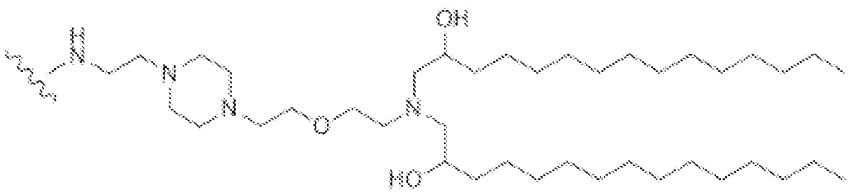


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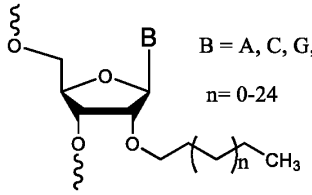
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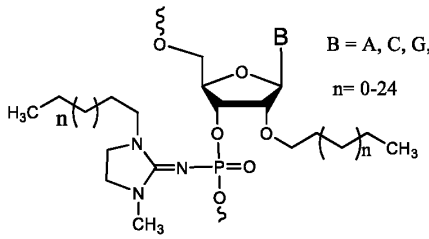


. In an exemplary embodiment, the lipid ligand comprises an octadecanoyl (C18) moiety.

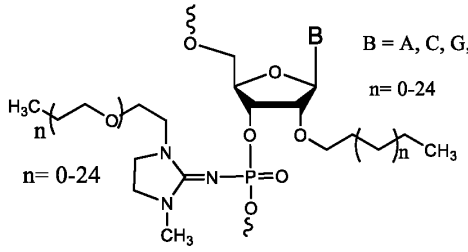
In a fourth aspect, the invention relates to the dsRNAi agent according to the first aspect, wherein one or both of the guide strand and the passenger strand comprise one or more modified sugar moieties, e.g., 2'-modified ribose moiety, at one or more positions 1-7 relative to the 5'-end of, e.g., the passenger strand. In an exemplary embodiment, the modified sugar moiety comprises a 2'-lipid modification, 2'-F modification, 2'-OH modification, 2'-OMe modification, 2'-*O*-alkyl modification (e.g., 2'-*O*-C16 lipid modification or 2'-*O*-C18 lipid modification), 2'-MOE modification, DNA, LNA, UNA, GNA, a homo-DNA, or a combination thereof. In an exemplary embodiment, the 2'-modification is −L−, wherein L connects C2 and C4 of the sugar moiety. In an exemplary embodiment, the modified sugar moiety comprises a 2'-lipid modification, e.g., a 2'-lipid modified ribose moiety, comprising a saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain. In an exemplary embodiment, the 2'-lipid modified ribose moiety comprises the structure of, e.g.,



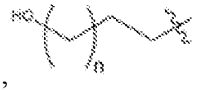
, e.g.,

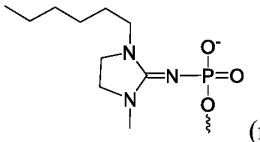
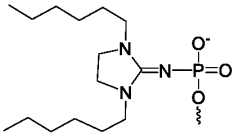
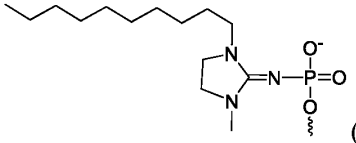
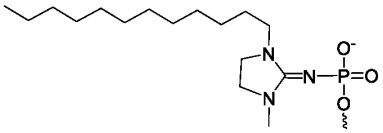
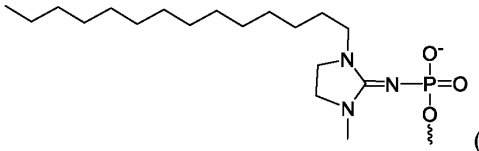
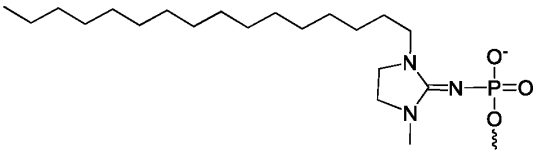
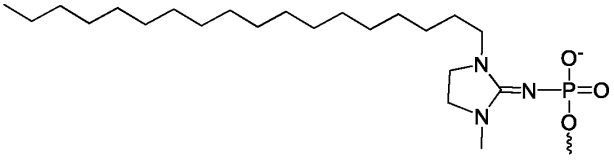
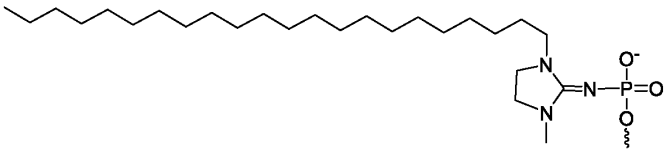
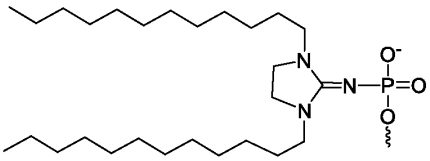
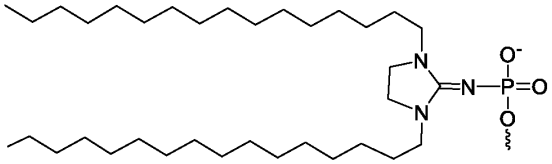


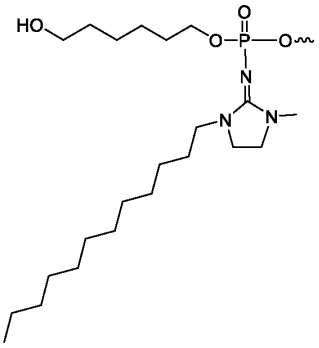
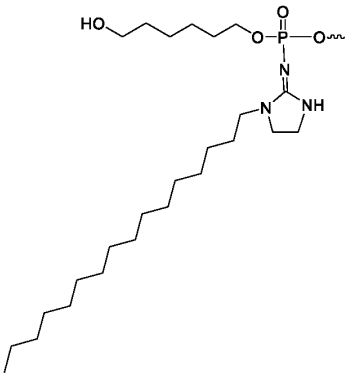
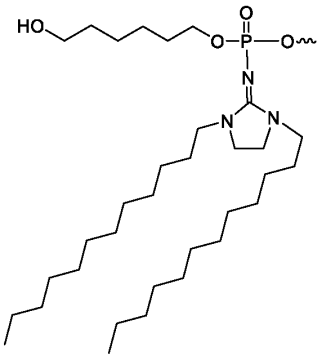
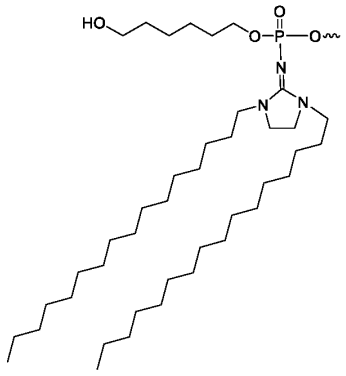
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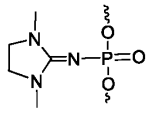
. In an exemplary embodiment, the 2'-lipid modification comprises 2'-*O*-hexadecyl moiety, e.g., at the +7 nucleotide of the passenger. In an exemplary embodiment, the passenger comprises, e.g., n001, n009 or n033 between, e.g., the +7 nucleotide and the +8 nucleotide thereof. In an exemplary embodiment, the passenger comprises, e.g., n009 or n033, e.g., between the +7 nucleotide and the +8 nucleotide thereof, and the 2'-lipid modification, e.g., 2'-*O*-hexadecyl moiety, e.g., at the +7 nucleotide thereof.

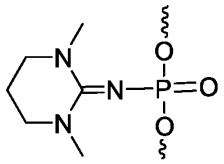
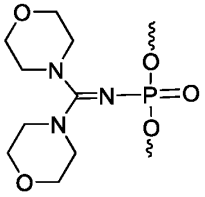
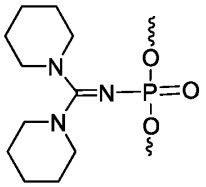
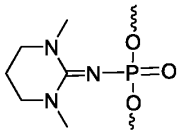
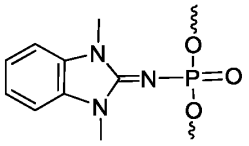
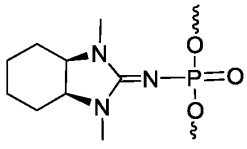
In a fifth aspect, the invention relates to the dsRNAi agent according to the first aspect, wherein one or both of the guide strand and the passenger strand comprise a phosphoryl guanidine-lipid (PN-lipid) ligand at the 5'-end or the 3'-end thereof, wherein the PN-lipid ligand comprises, e.g., one or two saturated or unsaturated C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chains, and wherein the PN-lipid ligand further comprises a non-cleavable linker. In an exemplary embodiment, the PN-lipid ligand comprising the non-cleavable linker is conjugated to the 5'-end of the passenger strand. In an exemplary embodiment, the non-cleavable linker is, e.g., , wherein n = 0-24, or  (oC6o). In an exemplary embodiment, the non-cleavable linker is conjugated to the PN-lipid

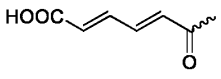
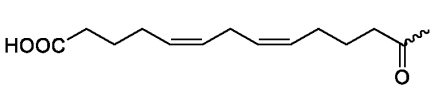
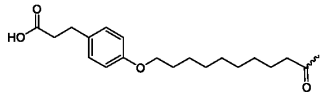
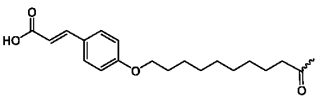
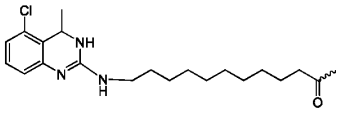
ligand via a phosphoester bond. In an exemplary embodiment, the PN-lipid ligand comprising the non-cleavable linker comprises the structure of, e.g.,  (n031),  (n037),  (n082),  (n009),  (n083),  (n033),  (n084),  (n077),  (n039), or  (n040). In an exemplary embodiment, the PN-lipid ligand comprising the non-cleavable linker comprises the structure of, e.g.,

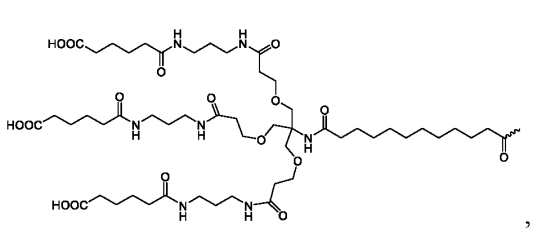
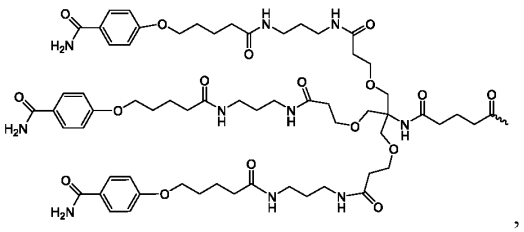
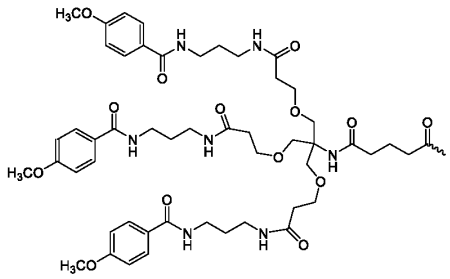
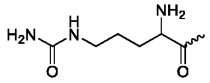
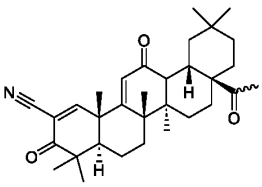
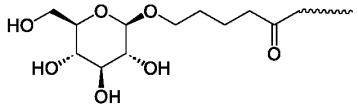
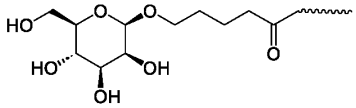
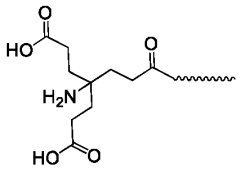





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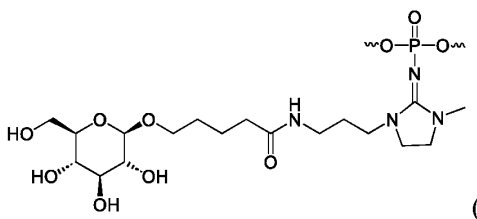
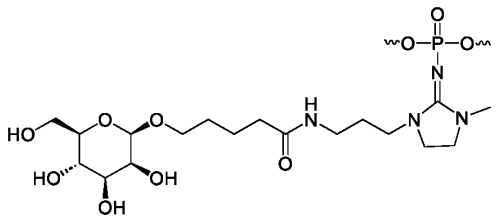
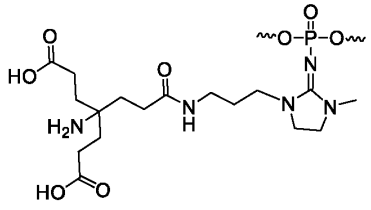
In a sixth aspect, the invention relates to the dsRNAi agent according to the first aspect, wherein one or both of the guide strand and the passenger strand comprise one or more backbone phosphoryl guanidine (PN) chiral centers each independently comprising the structure of  (n001) or a non-lipid variation (non-lipid PN variation) thereof. In an exemplary embodiment, one or both of the guide strand and the passenger strand comprise at least one non-lipid PN variation of n001. In an exemplary embodiment, the guide strand comprises at least one non-lipid PN variation of n001. In an exemplary embodiment, the guide strand further comprises a PN chiral center, e.g., between the +10 nucleotide and the +11 nucleotide thereof, e.g., in the *R*p configuration. In an exemplary embodiment, the guide strand comprises at least one non-lipid PN variation of n001, e.g., independently between the +3 nucleotide and the +4 nucleotide, and between the +10 nucleotide and the +11 nucleotide thereof. In an exemplary embodiment, the guide strand comprises a non-lipid PN variation of n001, e.g., independently between the +3 nucleotide and the +4 nucleotide, and between the +10 nucleotide and the +11 nucleotide thereof. In an exemplary embodiment, the non-lipid

PN-variation of n001 comprises the structure of, e.g.,  (n003),  (n008),  (n078),  (n025),  (n065), or  (n070). In an exemplary embodiment, the passenger strand comprises a backbone PS chiral center, e.g., independently between the +1 nucleotide and the +2 nucleotide, and/or between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide thereof, e.g., in the *S*p configuration. In an exemplary embodiment, the passenger strand comprises backbone PS chiral centers, e.g., independently between the +1 nucleotide and the +2 nucleotide, and between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide thereof, e.g., in the *S*p configuration.

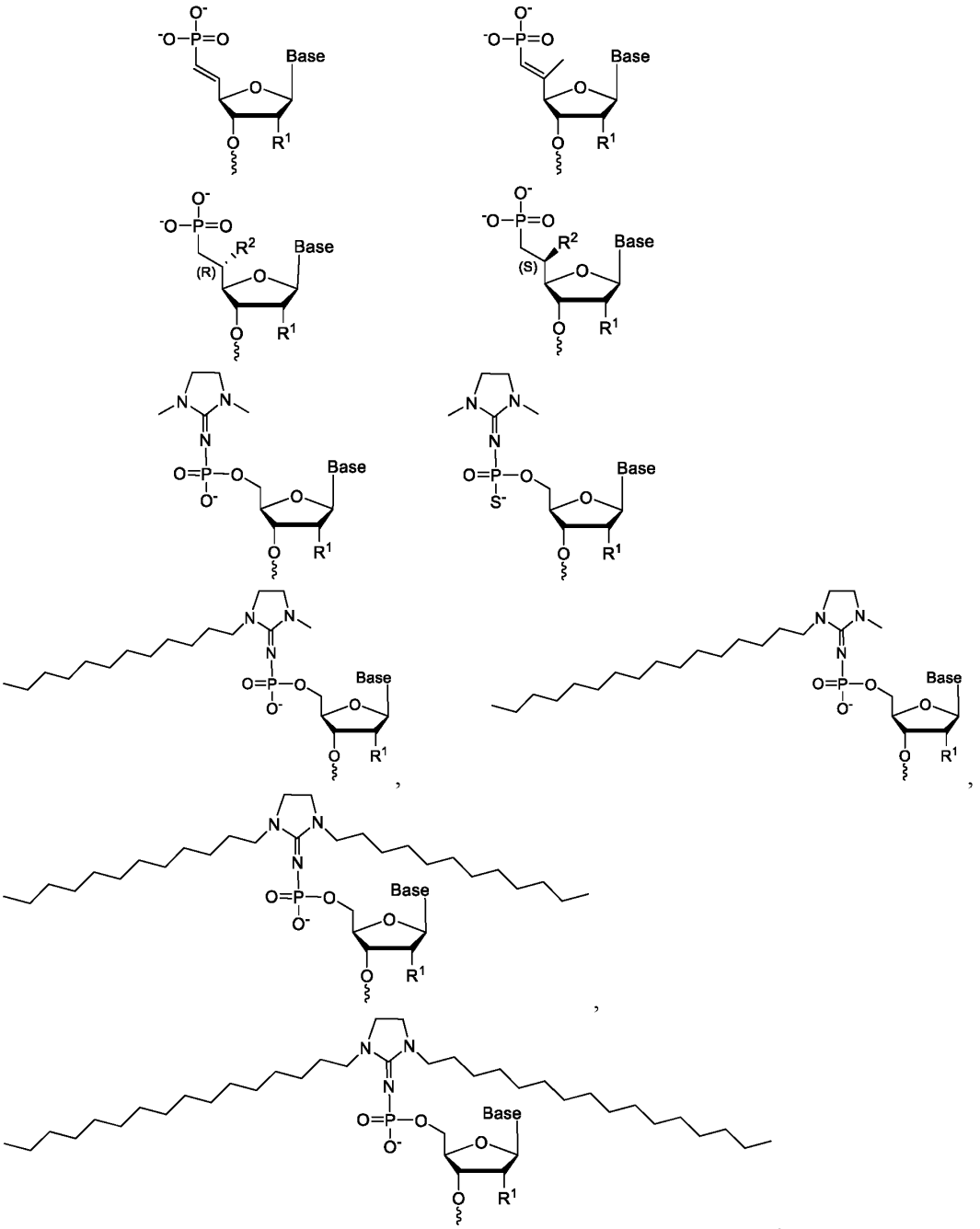
In a seventh aspect, the invention relates to the dsRNAi agent according to the first aspect, wherein one or both of the guide strand and the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to, e.g., the 5'-end and/or the 3'-end thereof, and/or one or more internucleotidic linkages. In an exemplary embodiment, one or both of the guide strand and the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to the 5'-end thereof via a linker. In an exemplary embodiment, the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to its 5'-end via a linker comprising, e.g., 6-aminohexanol (nC6o). In an exemplary embodiment, the hydrophilic or amphiphilic ligand comprises the structure of 20-oxoicosanoyl moiety, , , , , ,

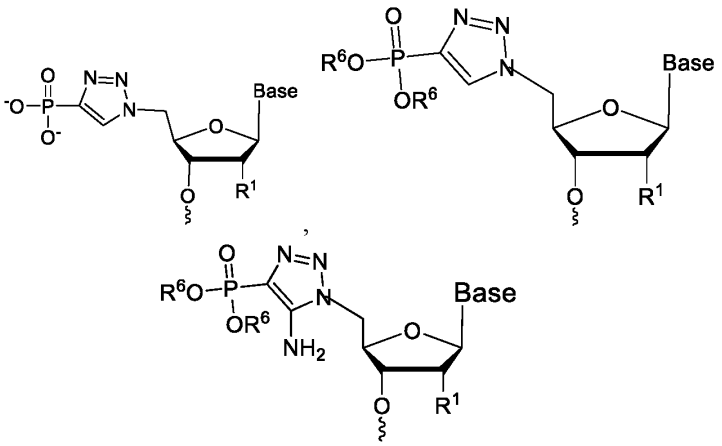

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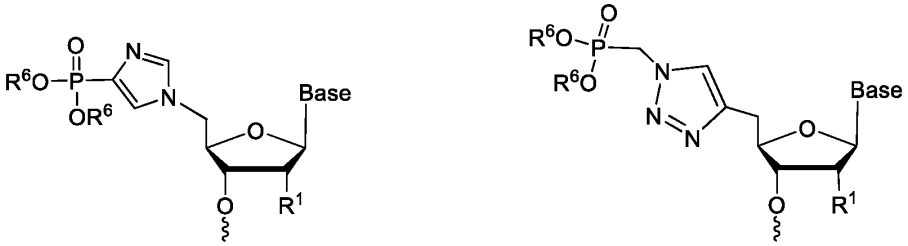
In an eighth aspect, the invention relates to the dsRNAi agent according to the sixth aspect, wherein one or both of the guide strand and the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to a backbone phosphoryl guanidine (PN) chiral center. In an exemplary embodiment, the passenger strand comprises one or more hydrophilic or amphiphilic ligand conjugated to one or more backbone PN chiral center. In an exemplary embodiment, the backbone PN chiral center is, e.g., between the +7 nucleotide and the +8 nucleotide of the passenger strand, e.g., in the *R*p configuration. In an exemplary embodiment, the backbone PN chiral center comprising a hydrophilic or amphiphilic ligand conjugated thereto comprises the structure of, e.g.,

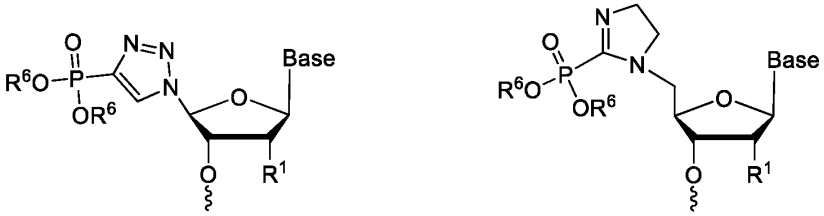

(n079),


(n085), or
(n081).

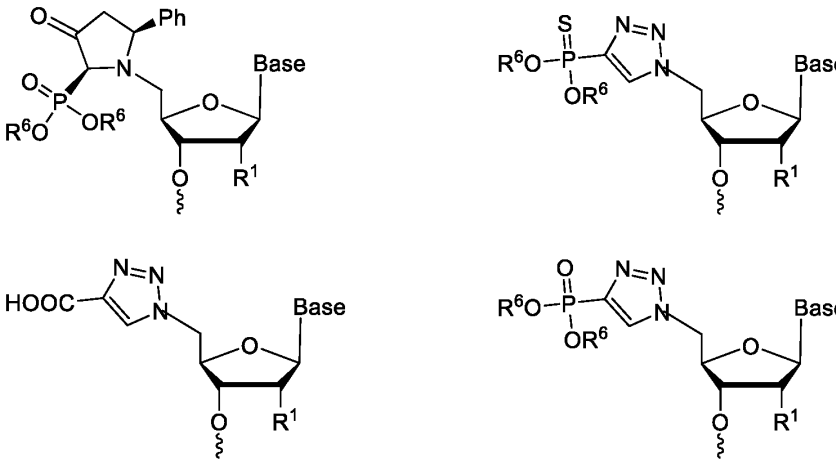
In an exemplary embodiment of the various aspect of the invention (e.g., the first, the second, the third, the fourth, the fifth, the sixth, the seventh, or the eighth aspect of the invention), the guide strand further comprises a 5' terminal modification selected from, e.g., the group consisting of, e.g.:

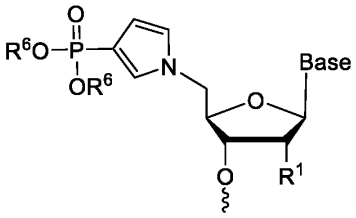
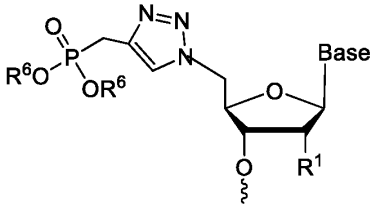
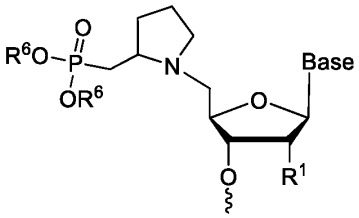
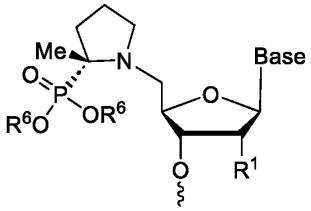
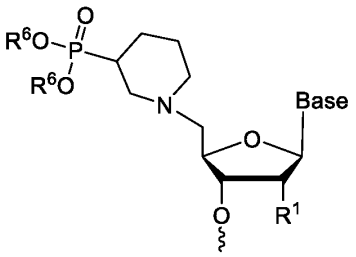
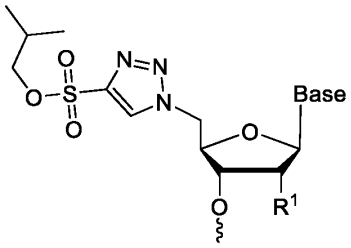
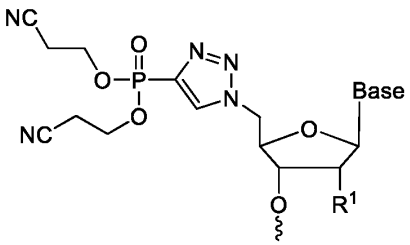
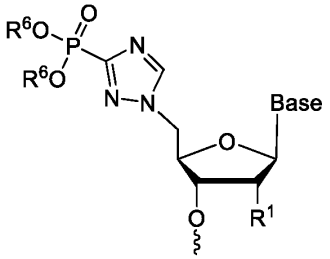
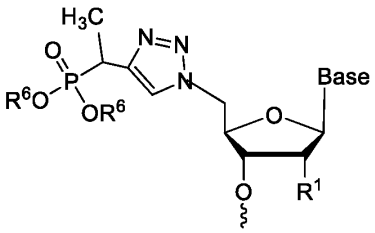
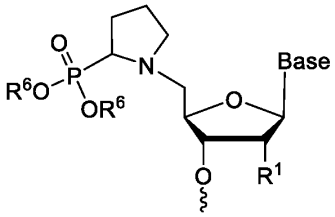
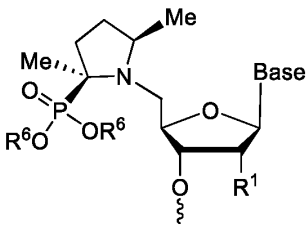
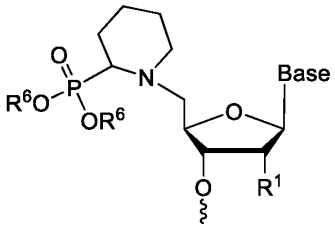


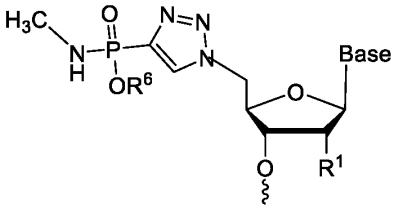
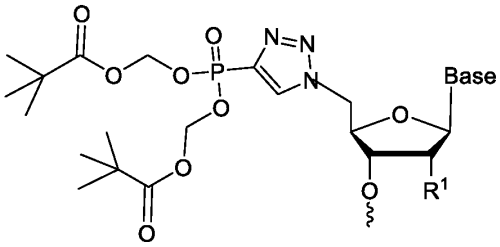
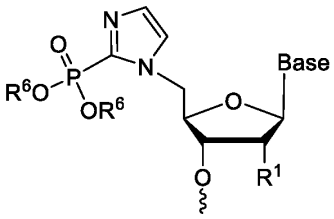
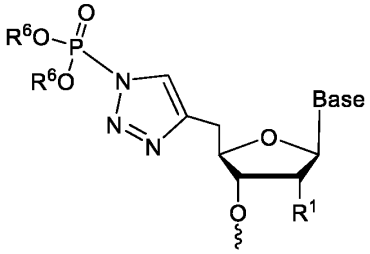
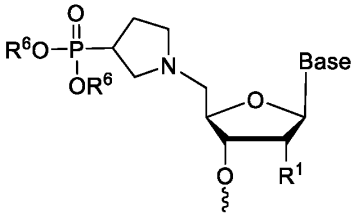
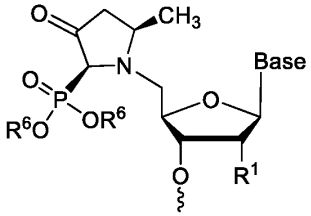
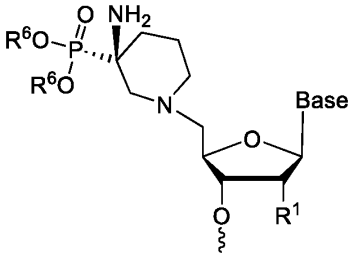
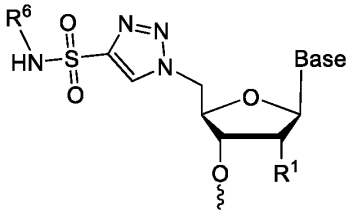
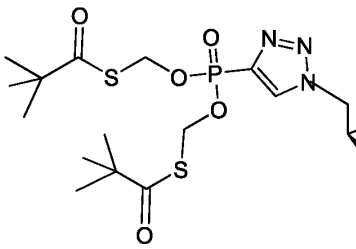


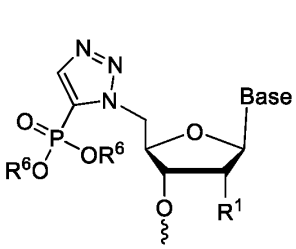






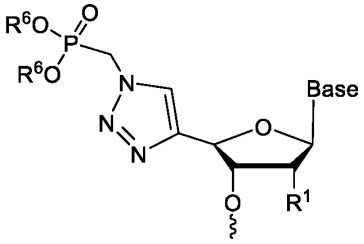













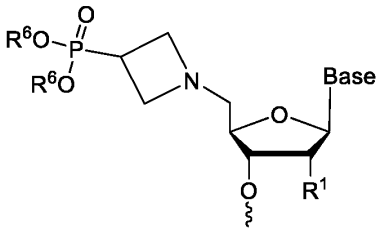










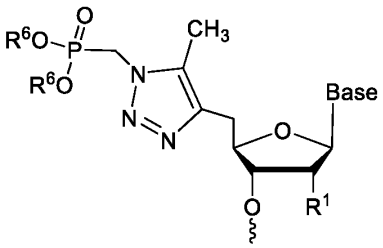


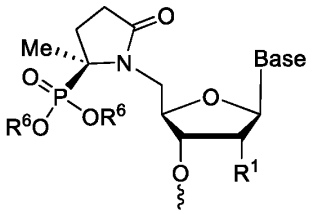
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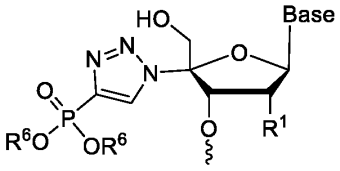
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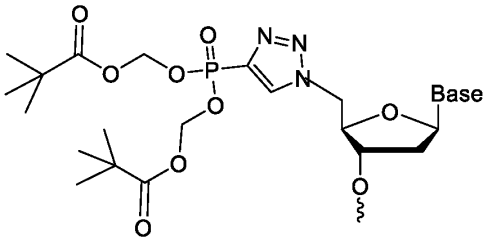


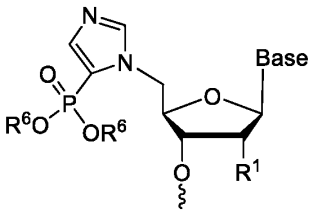


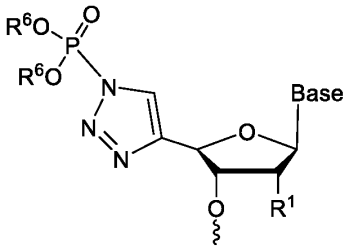


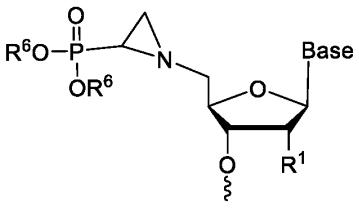


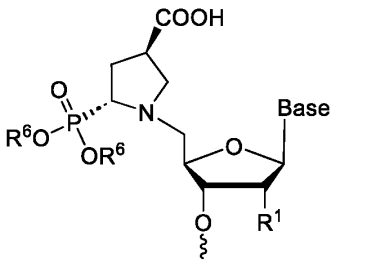


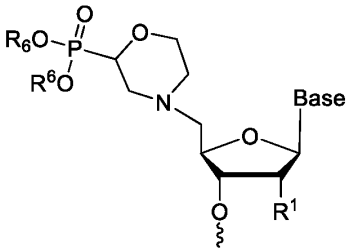


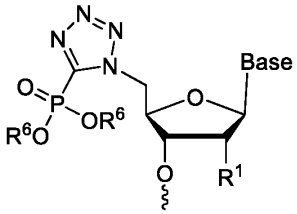


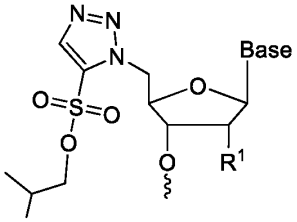


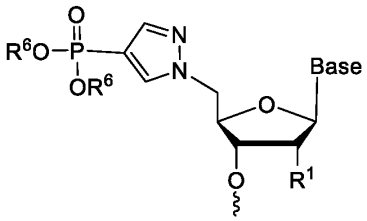


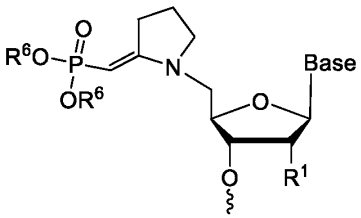


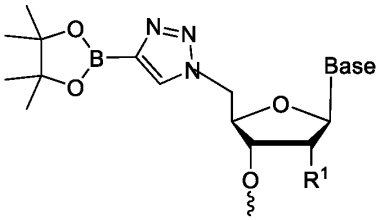

R6O
P
O
R6O
N
O
Base
O
R1


N
N
N
N
O
P
R6O
OR6
Base
O
R1

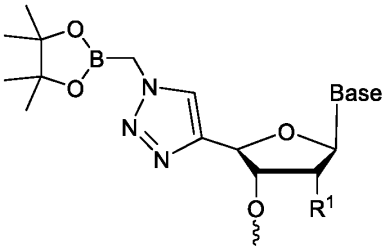

N
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S
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O
Base
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R1

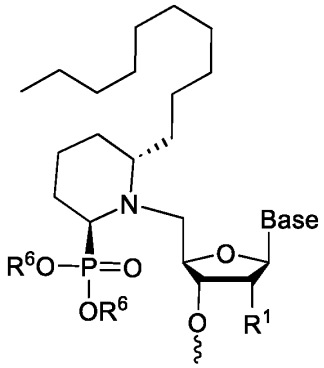

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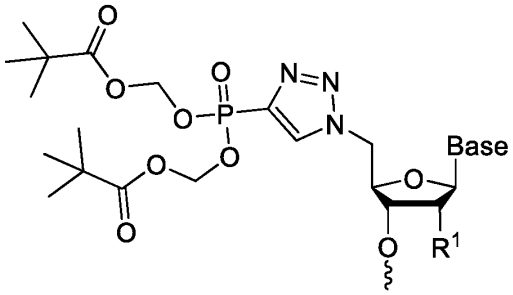

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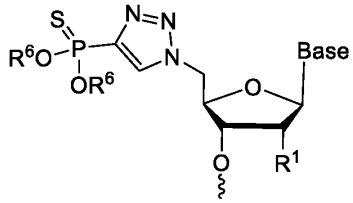

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5

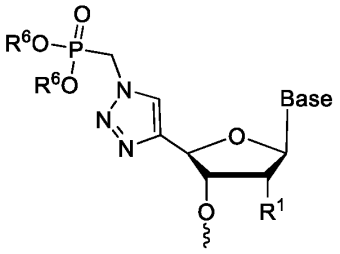

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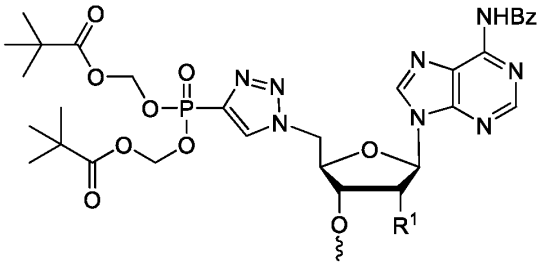

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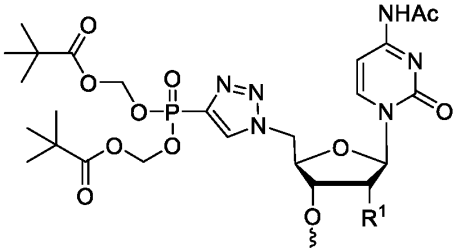

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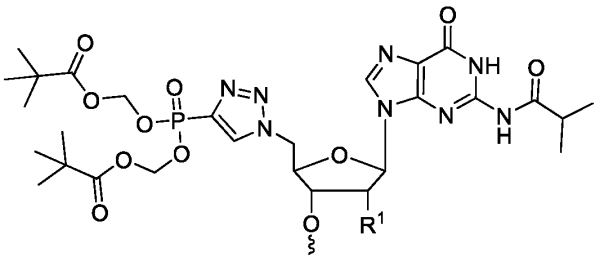

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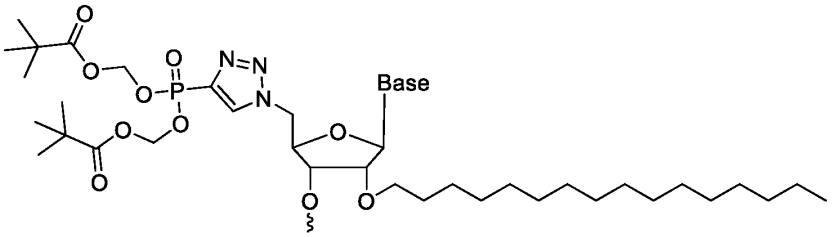
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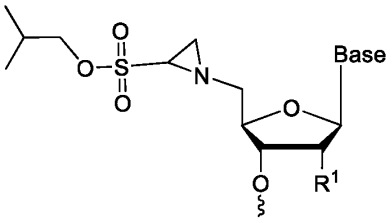


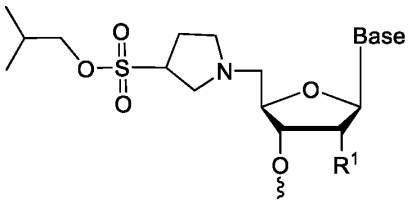


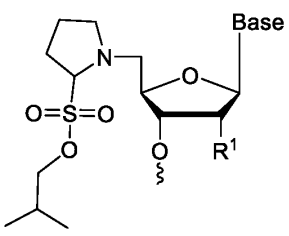


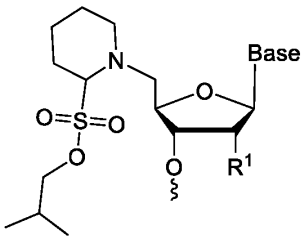


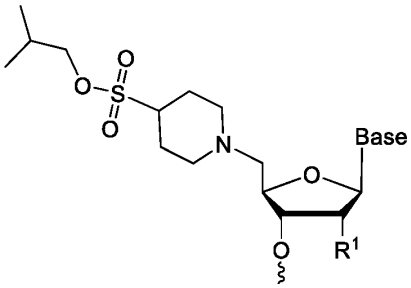
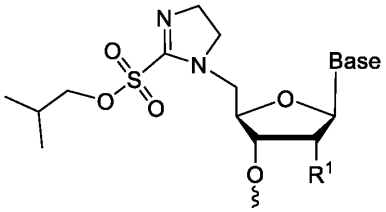
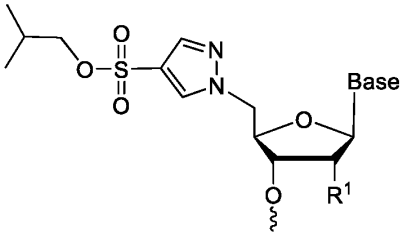
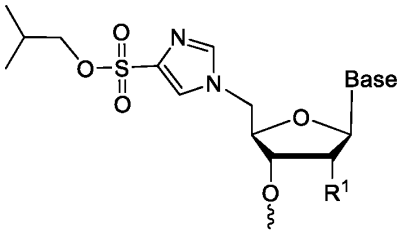
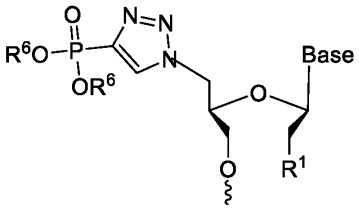
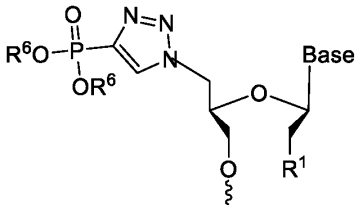
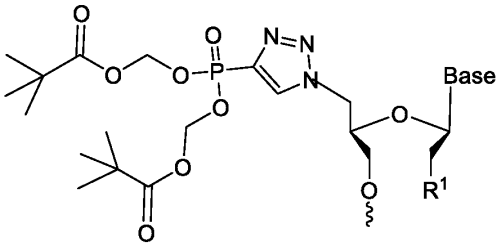
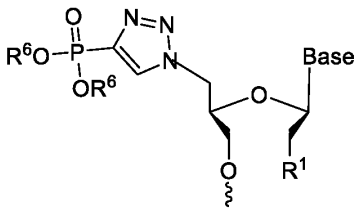
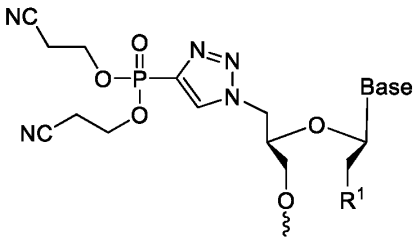
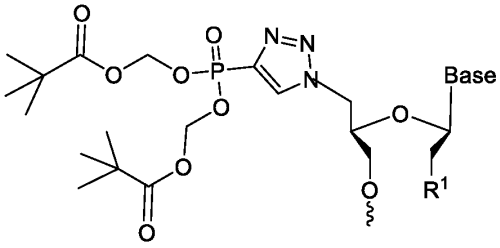


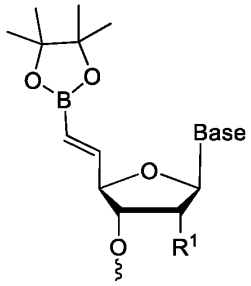










and , wherein the base is A, C, G, T, U, abasic, or a modified nucleobase; R^1 is selected from H, OH, *O*-alkyl, *O*-methyl (O-Me), F, *O*-methoxyethyl (MOE), and 2'-*O*,4'*C*-methylene-bridged or locked nucleic acid (2',4'-BNA or LNA); and R^2 is selected from alkyl, methyl, ethyl, isopropyl, propyl, cyclohexyl, benzyl, phenyl, tolyl, xylyl, aryl, and arene group. In an exemplary embodiment, the 5' terminal modification is triazolyl phosphonate or methyl phosphonate. In an exemplary embodiment, the 5' terminal modification is triazolyl phosphonate.

In certain embodiments, the guide strand comprises a backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction. In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, further comprise one or a plurality of modified sugars.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a modified sugar at: the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, eighth (+8) nucleotide, ninth (+9) nucleotide, tenth (+ 10), twelfth (+12) nucleotide, sixteenth (+16) nucleotide, seventeenth (+17) nucleotide, eighteenth (+18) nucleotide, nineteenth (+19) nucleotide, twentieth (+20) nucleotide, twenty-first (+21) nucleotide, twenty-second (+22), and/or twenty-third (+23), the 3' terminal, nucleotide. In certain embodiments, the modified sugar comprises a 2'-F modification, 2'-H modification, 2'-OH modification, 2'-O-alkyl modification, e.g., 2'-O-methyl (OMe) modification, 2'-methoxyethyl (MOE) modification, 5'-alkyl modification, e.g., 5'-(R)-methyl or 5'-(S)-methyl DNA, locked nucleic acid (LNA), unlocked nucleic acid (UNA), glycol nucleic acid (GNA), or Homo-DNA

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the

immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a 2'-F modification of the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, eighth (+8) nucleotide, ninth (+9) nucleotide, tenth (+ 10), twelfth (+12) nucleotide, sixteenth (+16) nucleotide, seventeenth (+17) nucleotide, eighteenth (+18) nucleotide, nineteenth (+19) nucleotide, twentieth (+20) nucleotide, twenty-first (+21) nucleotide, twenty-second (+22), and/or twenty-third (+23), the 3' terminal, nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a Homo-DNA modification of the 5' terminal (+1) nucleotide, sixth (+6) nucleotide, ninth (+9) nucleotide, tenth (+ 10), twelfth (+12) nucleotide, sixteenth (+16) nucleotide, seventeenth (+17) nucleotide, eighteenth (+18) nucleotide, nineteenth (+19) nucleotide, twentieth (+20) nucleotide, twenty-first (+21) nucleotide, twenty-second (+22), and/or twenty-third (+23), the 3' terminal, nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a LNA modification of the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, and/or eighth (+8) nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a 2'-O-alkyl modification of the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, and/or eighth (+8) nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a 5'-alkyl modification of the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide,

fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, and/or eighth (+8) nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a GNA modification of the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, and/or eighth (+8) nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a (s)-GNA modification of the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, and/or eighth (+8) nucleotide.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, further comprises one or more of:

(1) a guide strand comprising backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream, i.e., in the 5' direction, (N-2) nucleotide;

(2) a guide strand comprising backbone phosphorothioate chiral centers in Rp, Sp, or alternating configurations between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(3) a guide strand comprising one or more backbone phosphorothioate chiral centers upstream, i.e., in the 5' direction, relative to backbone phosphorothioate chiral centers in Sp configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and as between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide, where the upstream backbone phosphorothioate chiral centers are in Rp or Sp configuration;

(4) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide; and between the +2 nucleotide and the immediately downstream (+3) nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration where linkage occurs between any two adjacent nucleotides between the penultimate 3' nucleotide of the guide strand, where N is the 3' terminal nucleotide, and the upstream N-10 nucleotide;

(6) a guide strand comprising one or more backbone phosphoryl guanidine chiral centers in the Sp configuration between the +7 and the immediately downstream (+8), i.e., in the 3' direction.

(7) a guide strand comprising a 5' terminal modification;

(8) a passenger strand in combination with one or more of the aforementioned guide strands, comprising one or more backbone chiral centers in Rp or Sp configuration;

(9) a passenger strand in combination with one or more of the aforementioned guide strands, comprising a non-negatively charged backbone internucleotidic linkage between the +7 nucleotide and the immediately downstream (+8) nucleotide, i.e., in the 3' direction;

(10) a passenger strand in combination with one or more of the aforementioned guide strands, comprising a non-negatively charged backbone internucleotidic linkage between the +15 nucleotide and the immediately downstream (+16) nucleotide, i.e., in the 3' direction; and

(11) a passenger strand in combination with one or more of the aforementioned guide strands, comprising backbone phosphorothioate chiral centers in the Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the 3' terminal nucleotide and the penultimate (N-1) nucleotide;

wherein the ds oligonucleotide further comprises one or more of:

(1) a guide strand where one or both of the 5' and 3' terminal dinucleotides are ***not*** linked by a Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, i.e., the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively

charged internucleotidic linkages downstream, i.e., in the 3' direction, relative to the linkage between the 5' terminal dinucleotide and/or upstream, i.e., in the 5' direction, relative to the linkage between the 3' terminal dinucleotide;

(2) a guide strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide;

(3) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide;

(4) a guide strand where an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between the seventh (+7) and eighth (+8) nucleotides, relative to the 5' terminal nucleotide;

(5) a guide strand comprising one or more backbone phosphorothioate chiral centers in Rp or Sp configuration where linkage occurs between any two adjacent nucleotides between the penultimate 3' nucleotide of the guide strand, where N is the 3' terminal nucleotide, and the upstream N-10 nucleotide;

(6) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand; and

(7) a passenger strand where one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand.

(8) a passenger strand where one or more backbone phosphorothioate chiral centers in Rp or Sp configuration internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand;

(9) a passenger strand where one or more backbone phosphorothioate chiral centers in Rp or Sp configuration internucleotidic linkage internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand; and

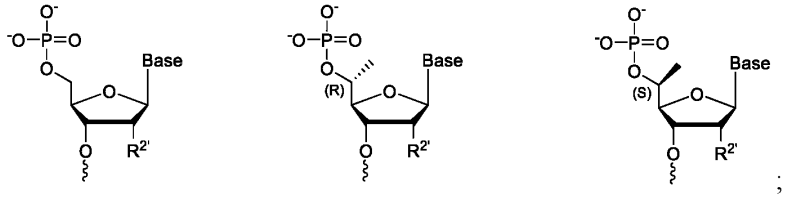
(10) a passenger strand comprising one or more modified sugars, e.g. Homo-DNA, between the 5' terminal (+1) nucleotide and the penultimate (N-1) nucleotide.

In certain embodiments, the ds oligonucleotide further comprises a 2' modification, e.g., a 2' F modification, of the 3' nucleotide of a nucleotide pair linked by a Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage. In certain embodiments the 2' modification is selected from, a 2'-F modification, a 2'-H modification, a 2'-OH modification, and a 2'-O-alkyl modification, e.g., 2'-O-methyl (OMe) modification, a 2'-methoxyethyl (MOE) modification. In certain embodiments, the ds oligonucleotide further comprises a modification selected from 5'-alkyl modifications, e.g., 5'-(R)-methyl or 5'-(S)-methyl DNA, locked nucleic acids (LNA), unlocked nucleic acids (UNA), glycol nucleic acids (GNA), and Homo-DNA. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide or passenger strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage. In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, further comprise one or a plurality of modified sugars. In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, comprise a modified sugar at the 5' terminal (+1) nucleotide, second (+2) nucleotide, third (+3) nucleotide, fourth (+4) nucleotide, fifth (+5) nucleotide, sixth (+6) nucleotide, seventh (+7) nucleotide, eighth (+8), ninth (+9) nucleotide, tenth (+ 10), twelfth (+12) nucleotide, sixteenth (+16) nucleotide, seventeenth (+17) nucleotide, eighteenth (+18) nucleotide, nineteenth (+19) nucleotide, twentieth (+20) nucleotide, twenty-first (+21) nucleotide, twenty-second (+22), and/or twenty-third (+23), the 3' terminal, nucleotide.

In certain embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of chiral centers at a 5' terminal modification of guide strands, can unexpectedly maintain or improve properties of the ds oligonucleotides described herein. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising a guide stranding comprising one or more of: (1) a backbone

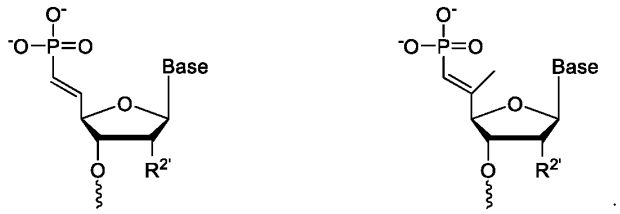
phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide; (2) a phosphorothioate chiral center in Rp or Sp configuration; (3) an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage where the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage comprises a 2' modification, e.g., a 2' F or a 2'-OMe; (4) a modified sugar selected from a 2'-F modification, 2'-H modification, 2'-OH modification, 2'-O-alkyl modification, e.g., 2'-O-methyl (OMe) modification, 2'-methoxyethyl (MOE) modification, 5'-alkyl modification, e.g., 5'-(R)-methyl or 5'-(S)-methyl DNA, locked nucleic acid (LNA), unlocked nucleic acid (UNA), glycol nucleic acid (GNA), or Homo-DNA; and (5) a 5' terminal modification selected from:

(a) 5' PO modifications, such as, but not limited to:



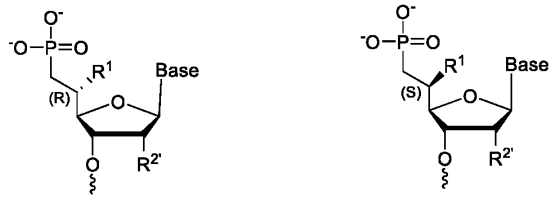
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(b) 5' VP modifications, such as, but not limited to:



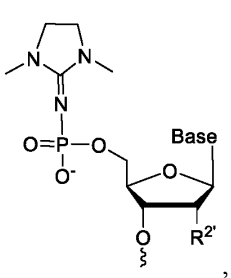
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(c) 5' MeP modifications, such as, but not limited to:

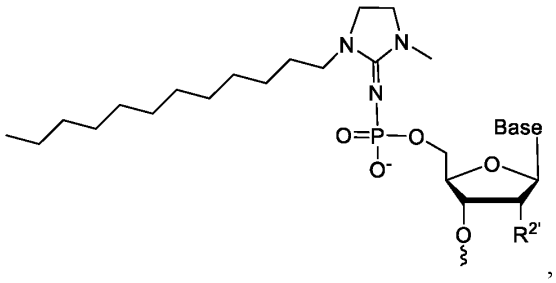


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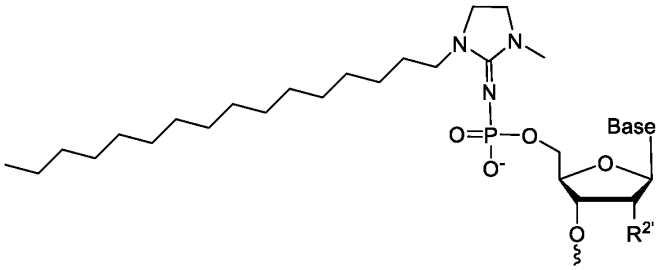
(d) 5' PN and 5' Triazole-P modifications, such as, but not limited to:



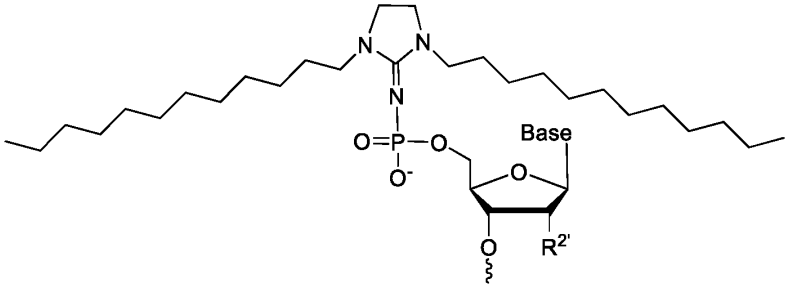
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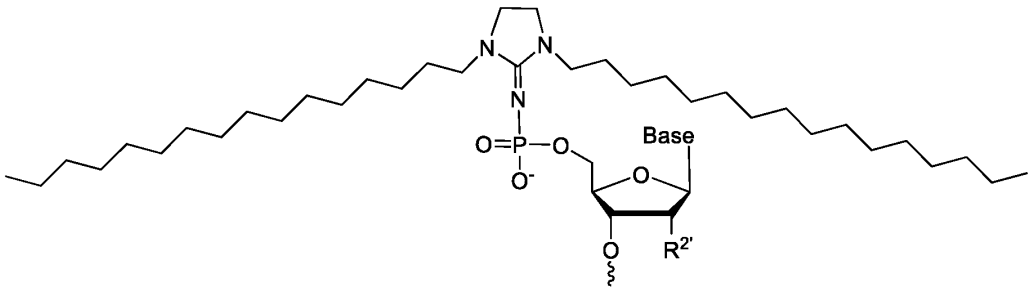
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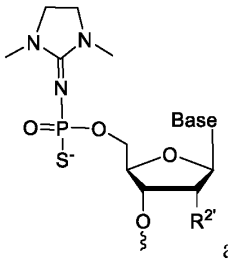


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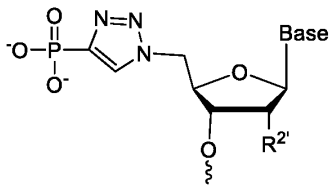


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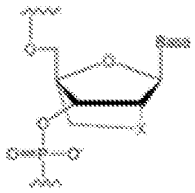
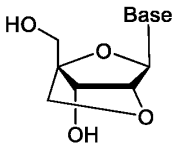


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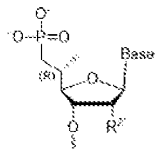
wherein Base is selected from A, C, G, T, U, abasic and modified nucleobases;

R^1 is selected from an alkyl, methyl, ethyl, isopropyl, propyl, cyclohexyl, benzyl, phenyl, tolyl, xylyl, aryl, or arene group.

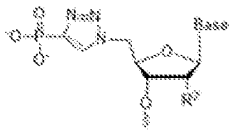
$R^{2'}$ is selected from H, OH, O-alkyl, O-Me, F, MOE, locked nucleic acid (LNA) bridges and bridged nucleic acid (BNA) bridges to the 4' C, such as, but not limited to:

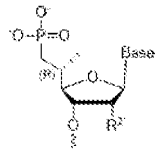

, and


. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the guide strand comprises, a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide. In certain embodiments, the 5' terminal modification is


. In some embodiments, the 5' terminal modification is

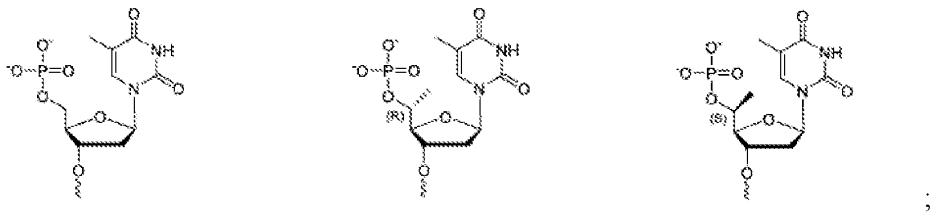
. In certain embodiments, the 5' terminal modification is

. In certain embodiments, the guide strand comprises a 5' terminal modification selected from, but not limited to, 5' MeP modifications and 5' Triazole-P modifications. In certain embodiments, the guide strand comprises the 5'



MeP modification , a backbone phosphorothioate chiral center in Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide, and a backbone phosphorothioate chiral center in the Rp configuration between the +2 nucleotide and the immediately downstream (+3) nucleotide.

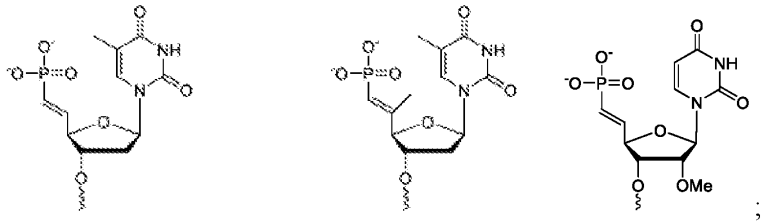
In certain other embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of chiral centers at the 5' terminal nucleotide of guide strands, can unexpectedly maintain or improve properties of ds oligonucleotides wherein the guide strand of the ds oligonucleotide also comprises a phosphorothioate chiral center in Rp or Sp configuration. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising a guide stranding comprising: (1) a phosphorothioate chiral center in Rp or Sp configuration; (2) an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage where the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage comprises a 2' modification, e.g., a 2' F or a 2'-OMe; and (3) a 5' terminal modification selected from:

(a) 5' PO nucleotides, such as, but not limited to:



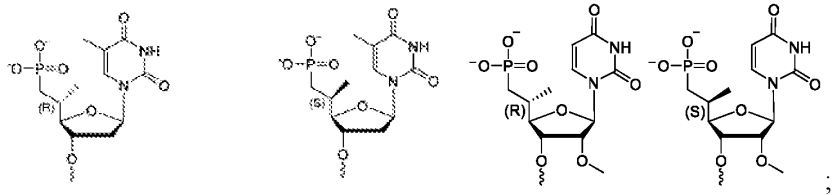
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(b) 5' VP nucleotides, such as, but not limited to:

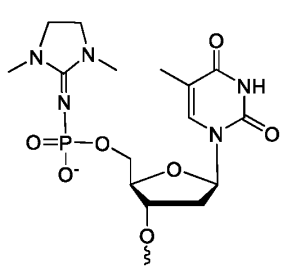


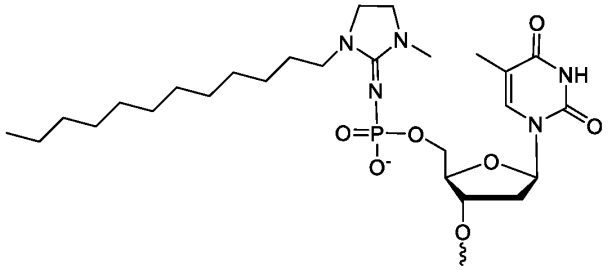
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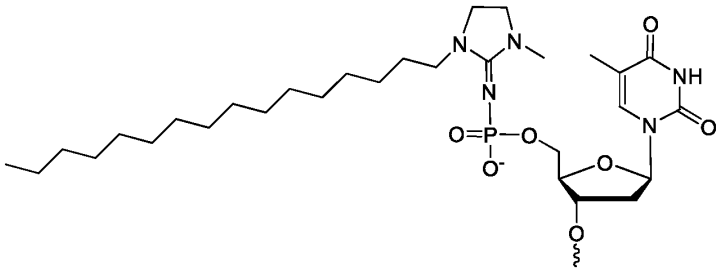
(c) 5' MeP nucleotides, such as, but not limited to:

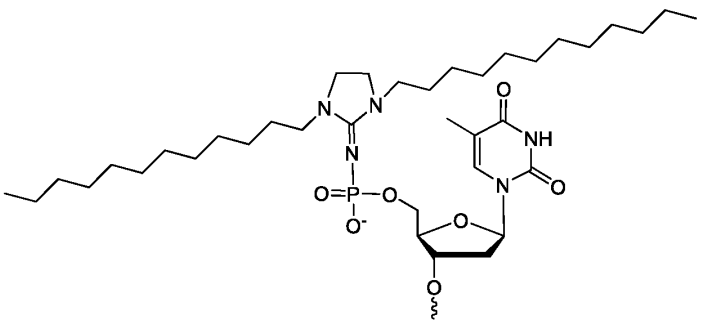

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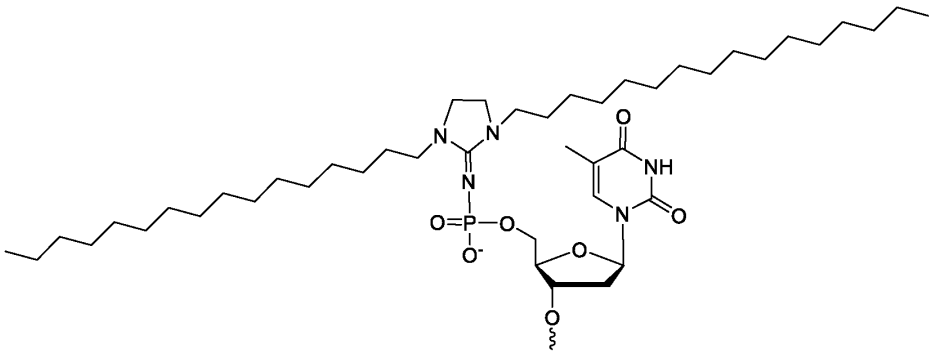
(d) 5' PN and 5' Triazole-P nucleotides, such as, but not limited to:

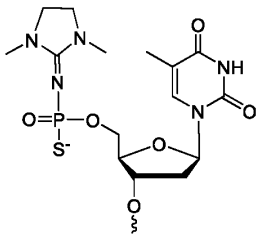
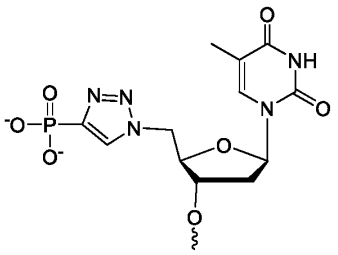
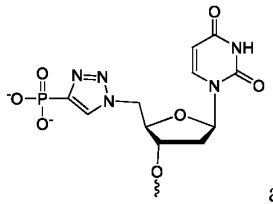
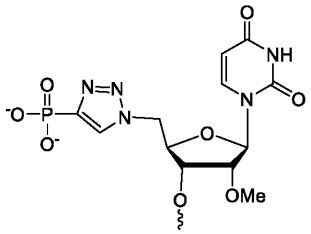

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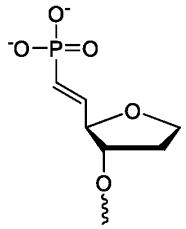
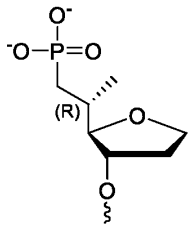

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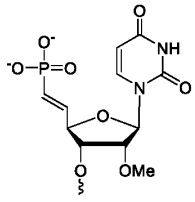



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(e) 5' abasic VP and 5' abasic MeP nucleotides, such as, but not limited to:

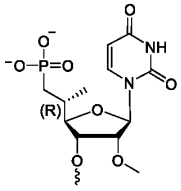

and

. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain other embodiments, the present disclosure encompasses the recognition that stereochemistry, e.g., stereochemistry of chiral centers at the 5' terminal nucleotide of guide strands, can unexpectedly maintain or improve properties of ds oligonucleotides wherein the guide strand of the ds oligonucleotide also comprises a phosphorothioate chiral center in Rp or Sp configuration. For example, but not by way of limitation, the instant disclosure relates, in part, to ds oligonucleotides comprising a guide stranding comprising: (1) a backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide; (2) a backbone phosphoryl guanidine chiral center in the Rp configuration between the +7 nucleotide and the immediately downstream (+8)

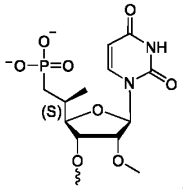
nucleotide; (3) a phosphorothioate chiral center in Rp or Sp configuration; and (4) a protected phosphonate selected from:



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;



; and f; In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage.

In certain embodiments, the present disclosure encompasses the recognition that non-naturally occurring internucleotidic linkages, e.g., neutral internucleotidic linkages, can, in certain embodiments, be used to link one or more molecules to the double-stranded oligonucleotides described herein. In certain embodiments, such linked molecules can facilitate targeting and/or delivery of the double-stranded oligonucleotide. For example, but not limitation, such linked molecules an include lipophilic molecules. In certain embodiments, the linked molecule is a molecule comprising one or more GalNAc moieties. In certain embodiments, the linked molecule is a receptor. In certain embodiments, the linked molecule is a receptor ligand.

In certain embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into ds oligonucleotides. In certain embodiments, the present disclosure provides, for example, reagents and methods for introducing additional chemical moieties through nucleobases (*e.g.*, by covalent linkage, optionally via a linker, to a site on a nucleobase).

In certain embodiments, the present disclosure provides technologies, e.g., ds oligonucleotide compositions and methods thereof, that achieve allele-specific suppression, wherein transcripts from one allele of a particular target gene is selectively knocked down relative to at least one other allele of the same gene.

Among other things, the present disclosure provides structural elements, technologies and/or features that can be incorporated into ds oligonucleotides and can impart or tune one or

more properties thereof (*e.g.*, relative to an otherwise identical ds oligonucleotide lacking the relevant technology or feature). In certain embodiments, the present disclosure documents that one or more provided technologies and/or features can usefully be incorporated into ds oligonucleotides of various sequences.

In certain embodiments, the present disclosure demonstrates that certain provided structural elements, technologies and/or features are particularly useful for ds oligonucleotides that participate in and/or direct RNAi mechanisms (*e.g.*, RNAi agents). Regardless, however, the teachings of the present disclosure are not limited to ds oligonucleotides that participate in or operate via any particular mechanism. In certain embodiments, the present disclosure pertains to any ds oligonucleotide, useful for any purpose, which operates through any mechanism, and which comprises any sequence, structure or format (or portion thereof) described herein. In certain embodiments, the present disclosure provides a ds oligonucleotide, useful for any purpose, which operates through any mechanism, and which comprises any sequence, structure or format (or portion thereof) described herein, comprising a guide strand comprising backbone phosphoryl guanidine chiral centers in Sp configuration.

In certain embodiments, the guide strand comprises a backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction.

In certain embodiments, the ds oligonucleotides comprising a guide strand backbone phosphoryl guanidine chiral center in the Sp configuration between the +3 nucleotide and the immediately downstream (+4) nucleotide, i.e., in the 3' direction, further comprise a phosphoryl guanidine chiral center in the Sp configuration between the +7 and the immediately downstream (+8) nucleotide, between the +10 nucleotide and the immediately downstream (+11) nucleotide, between the +18 nucleotide and the immediately downstream (+19) nucleotide, or combinations thereof.

In certain embodiments, the provided ds oligonucleotides may participate in (*e.g.*, direct) RNAi mechanisms. In certain embodiments, provided ds oligonucleotides may participate in RNase H (ribonuclease H) mechanisms. In certain embodiments, provided ds oligonucleotides may act as translational inhibitors (*e.g.*, may provide steric blocks of translation).

In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage incorporated into the guide strand is an Rp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or

stereorandom non-negatively charged internucleotidic linkage is an Sp non-negatively charged internucleotidic linkage. In certain embodiments, the one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage is a stereorandom non-negatively charged internucleotidic linkage. In certain further embodiments, the passenger strand comprises an Sp backbone phosphorothioate chiral center between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide and an Sp backbone phosphorothioate chiral center between the penultimate (N-1) nucleotide and the 3' terminal (N) nucleotide.

Unless otherwise noted, all sequences (including, but not limited to base sequences and patterns of chemistry, modification, and/or stereochemistry) are presented in 5' to 3' order, with the 5' terminal nucleotide identified as the "+1" position and the 3' terminal nucleotide identified either by the number of nucleotides of the full sequence or by "N", with the penultimate nucleotide identified, e.g., as "N-1", and so on.

In certain embodiments, the present disclosure provides compositions and methods related to an oligonucleotide which is specific to a target and which has any format, structural element or base sequence of any oligonucleotide disclosed herein.

In certain embodiments, the present disclosure provides compositions and methods related to an oligonucleotide which is specific to a target and which has or comprises the base sequence of any oligonucleotide disclosed herein, or a region of at least 15 contiguous nucleotides of the base sequence of any oligonucleotide disclosed herein, wherein the first nucleotide of the base sequence or the first nucleotide of the at least 15 contiguous nucleotides can be optionally replaced by T or DNA T.

In certain embodiments, the present disclosure provides compositions and methods for RNA interference directed by a RNAi agent (also referred to as a RNAi oligonucleotides). In certain embodiments, oligonucleotides of such compositions can have a format, structural element or base sequence of an oligonucleotide disclosed herein.

In certain embodiments, the present disclosure provides compositions and methods for RNase H-mediated knockdown of a target gene RNA directed by an oligonucleotide (*e.g.*, an antisense oligonucleotide).

Provided oligonucleotides and oligonucleotide compositions can have any format, structural element or base sequence of any oligonucleotide disclosed herein. In certain embodiments, a structural element is a 5'-end structure, 5'-end region, 5'-nucleotide, seed region, post-seed region, 3'-end region, 3'-terminal dinucleotide, 3'-end cap, or any portion of any of these structures, GC content, long GC stretch, and/or any modification, chemistry,

stereochemistry, pattern of modification, chemistry or stereochemistry, or a chemical moiety (*e.g.*, including but not limited to, a targeting moiety, a lipid moiety, a GalNAc moiety, a carbohydrate moiety, etc.), any component, or any combination of any of the above.

In certain embodiments, the present disclosure provides compositions and methods of use of an oligonucleotide.

In certain embodiments, an oligonucleotide directing a particular event or activity participates in the particular event or activity, e.g., a decrease in the expression, level or activity of a target gene or a gene product thereof. In certain embodiments, an oligonucleotide is deemed to "direct" a particular event or activity when presence of the oligonucleotide in a system in which the event or activity can occur correlates with increased detectable incidence, frequency, intensity and/or level of the event or activity.

In certain embodiments, provided ds oligonucleotides, compositions and methods can be delivered to the endocrine, respiratory, circulatory, or urinary system, = In certain embodiments, provided ds oligonucleotides, compositions and methods can be delivered to various regions of the endocrine, respiratory, circulatory, or urinary system without conjugation to a targeting ligand (e.g., peptide, sugar, etc.), without a delivery system (e.g., lipid nanoparticles, etc.), or combinations thereof.

In certain embodiments, a provided oligonucleotide comprises any one or more structural elements of an oligonucleotide as described herein, *e.g.*, a base sequence (or a portion thereof of at least 15 contiguous bases); a pattern of internucleotidic linkages (or a portion thereof of at least 5 contiguous internucleotidic linkage); a pattern of stereochemistry of internucleotidic linkages (or a portion thereof of at least 5 contiguous internucleotidic linkages); a 5'-end structure; a 5'-end region; a first region; a second region; and a 3'-end region (which can be a 3'-terminal dinucleotide and/or a 3'-end cap); and an optional additional chemical moiety; and, in certain embodiments, at least one structural element comprises a chirally controlled chiral center. In certain embodiments, a 3'-terminal dinucleotide can comprise two total nucleotides. In certain embodiments, an oligonucleotide further comprises a chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, a lipid moiety, and any other chemical moiety described herein or known in the art. In certain embodiments, a moiety that binds APGR is a moiety of GalNAc, or a variant, derivative or modified version thereof, as described herein and/or known in the art. In certain embodiments, an oligonucleotide is a RNAi agent. In certain embodiments, a first region is a seed region. In certain embodiments, a second region is a post-seed region.

In certain embodiments, a provided oligonucleotide comprises any one or more

structural elements of a RNAi agent as described herein, *e.g.*, a 5'-end structure; a 5'-end region; a seed region; a post-seed region (the region between the seed region and the 3'-end region); and a 3'-end region (which can be a 3'-terminal dinucleotide and/or a 3'-end cap); and an optional additional chemical moiety; and, in certain embodiments, at least one structural element comprises a chirally controlled chiral center. In certain embodiments, a 3'-terminal dinucleotide can comprise two total nucleotides. In certain embodiments, an oligonucleotide further comprises a chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, and a lipid moiety. In certain embodiments, a moiety that binds APGR is any GalNAc, or variant, derivative or modification thereof, as described herein or known in the art.

In certain embodiments, a provided oligonucleotide comprises any one or more structural elements of an oligonucleotide as described herein, *e.g.*, a 5'-end structure, a 5'-end region, a first region, a second region, a 3'-end region, and an optional additional chemical moiety, wherein at least one structural element comprises a chirally controlled chiral center. In certain embodiments, the oligonucleotide comprises a span of at least 5 total nucleotides without 2'-modifications. In certain embodiments, the oligonucleotide further comprises an additional chemical moiety selected from, as non-limiting examples, a targeting moiety, a carbohydrate moiety, a GalNAc moiety, and a lipid moiety. In certain embodiments, a provided oligonucleotide is capable of directing RNA interference. In certain embodiments, a provided oligonucleotide is capable of directing RNase H-mediated knockdown. In certain embodiments, a provided oligonucleotide is capable of directing both RNA interference and RNase H-mediated knockdown. In certain embodiments, a first region is a seed region. In certain embodiments, a second region is a post-seed region.

In certain embodiments, a nucleotide is a natural nucleotide. In certain embodiments, a nucleotide is a modified nucleotide. In certain embodiments, a nucleotide is a nucleotide analog. In certain embodiments, a base is a modified base. In certain embodiments, a base is protected nucleobase, such as a protected nucleobase used in oligonucleotide synthesis. In certain embodiments, a base is a base analog. In certain embodiments, a sugar is a modified sugar. In certain embodiments, a sugar is a sugar analog. In certain embodiments, an internucleotidic linkage is a modified internucleotidic linkage. In certain embodiments, a nucleotide comprises a base, a sugar, and an internucleotidic linkage, wherein each of the base, the sugar, and the internucleotidic linkage is independently and optionally naturally-occurring or non-naturally occurring. In certain embodiments, a nucleoside comprises a base and a sugar, wherein each of the base and the sugar is independently and optionally naturally-occurring or

non-naturally occurring. Non-limiting examples of nucleotides include DNA (2'-deoxy) and RNA (2'-OH) nucleotides; and those which comprise one or more modifications at the base, sugar and/or internucleotidic linkage. Non-limiting examples of sugars include ribose and deoxyribose; ribose and deoxyribose with 2'-modifications, including but not limited to 2'-F, LNA, 2'-OMe, 2'-O-C16 lipid, and 2'-MOE modifications; and ribose and deoxyribose with 5'-modifications, including, but not limited to 5'-alkyl modifications. In certain embodiments, an internucleotidic linkage is a moiety which does not a comprise a phosphorus but serves to link two natural or non-natural sugars.

In certain embodiments, the present disclosure provides an oligonucleotide composition comprising a first plurality of oligonucleotides which share:

1) a common base sequence;

2) a common pattern of backbone linkages;

3) common stereochemistry independently at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, or 50 chiral internucleotidic linkages ("chirally controlled internucleotidic linkages"); which composition is chirally controlled in that level of the first plurality of oligonucleotides in the composition is predetermined.

II. DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Technologies of the present disclosure may be understood more readily by reference to the following detailed description of certain embodiments.

Definitions

As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

As used herein, the terms "aliphatic", "alkenyl", "alkyl", "alkynyl", "analog", "animal", "aryl", "chiral control", "chirally controlled oligonucleotide composition", "cycloaliphatic," "heteroaliphatic", "heteroalkyl", "heteroaryl", "heteroatom", "heterocycle", "identity", "internucleotidic linkage", "in vitro", "in vivo", "ligand", "linkage phosphorus", "lipid" "modified nucleobase", "modified base", "modified nucleoside", "modified

nucleotide", "modified sugar", "nucleic acid", "nucleobase", "nucleoside", "nucleotide", "oligonucleotide", "oligonucleotide type", "substituted", "optionally substituted", "stable", "P-modification", "partially unsaturated", "pharmaceutical composition", "pharmaceutically acceptable", "pharmaceutically acceptable carrier", "pharmaceutically acceptable salt", "predetermined", "protecting group", "subject", "test subject", "substantially", "sugar", "susceptible to", "therapeutic agent", "therapeutically effective amount", "treatment", "treating", and "unsaturated", "wild-type" have their art-understood meaning as would be appreciated by those of ordinary skill in the art, and as specifically defined in WO 2024/182749, at pages 147-179, the contents of which are incorporated herein by reference in their entirety.

As those skilled in the art will appreciate, methods and compositions described herein relating to provided compounds (e.g., oligonucleotides) generally also apply to pharmaceutically acceptable salts of such compounds.

1. Description of Certain Embodiments

As examples, certain dsRNAi oligonucleotides comprising certain example base sequences, nucleobase modifications and patterns thereof, sugar modifications and patterns thereof, internucleotidic linkages and patterns thereof, linkage phosphorus stereochemistry and patterns thereof, linkers, and/or additional chemical moieties are presented in Table 1 (e.g., Tables 1B, 1C, 1D, and 1E), below. Among other things, ds oligonucleotides, e.g., those in Table 1, may be utilized to target a transcript, e.g., to reduce the level of a transcript and/or a product thereof.

Table 1B. Example Oligonucleotides that target TTR

ID	HELM	Base Sequence
SSR-0106266	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106267	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0106268	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106269	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106270	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106271	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106272	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106273	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)[n001S].m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106274	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)[n001S].[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106275	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106276	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106277	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)[n001S].m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106278	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106279	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)	UUAUAGAGCAAGAACACUGUUUU

	p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	
SSR-0106280	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].m(G)[n001S].m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106281	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)[n001S].[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106282	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106283	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)[n001S].m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106284	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)[n001S].m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106285	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)[n001S].m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106286	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)[n001S].m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106287	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)p.[fl2r](A)[n001S].m(C)p.[fl2r](A)[n001S].m(C)p.m(U)[n001S].m(G)p.m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106288	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)p.m(C)[n001S].[fl2r](A)p.m(C)[n001S].m(U)p.m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106289	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].[fl2r](A)p.[fl2r](A)[n001S].[fl2r](C)p.[fl2r](A)[n001S].[fl2r](C)p.m(U)[n001S].[fl2r](G)p.m(U)[n001S].[fl2r](U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106290	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)p.m(C)[n001S].[fl2r](A)p.m(C)[n001S].[fl2r](U)p.m(G)[n001S].[fl2r](U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0106291	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106292	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106293	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106294	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106295	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106296	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106297	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106298	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106299	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106300	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106301	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106302	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S	UUAUAGAGCAAGAACACUGUUUU

	].[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	
SSR-0106303	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].[fl2r](C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106304	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].[fl2r](C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106305	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].[fl2r](U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106306	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].[fl2r](G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0104474	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106307	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)[n001S].[fl2r](U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0104475	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0104720	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0101599	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$V2.	AACAGUGUUCUUGCUCUAUAA
SSR-0101596	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0101630	RNA1{p.m(U)[sp].m(G)p.m(G)p.m(U)p.m(A)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(G)p.m(U)p.m(C)[sp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-	UGGUAUCAAAACCUCAUGUCA

	1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	
SSR-0101695	RNA1{p.m(U)[Ssp].m(G)p.m(G)p.m(U)p.m(A)p.m(U)p.[fl2r](C)p.m(A)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(C)p.m(U)p.m(C)p.m(A)p.m(U)p.m(G)p.m(U)p.m(C)[Ssp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	UGGUAUCAAAACCUCAUGUCA
SSR-0105101	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.[fl2r](C)p.m(A)p.[fl2r](U)p.m(G)p.m(A)p.m(G)p.m(G)p.[fl2r](U)p.m(U)p.m(U)p.[fl2r](U)p.m(G)p.[fl2r](A)p.m(U)p.m(A)p.m(C)p.m(C)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGACAUGAGGUUUUGAUACCAUU
SSR-0106582	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

Table 1C. Example Oligonucleotides

ID	HELM	Base Sequence
SSR-0101596	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0101599	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0104021	RNA1{m(A)[Ssp].m(G)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](C)[n001R].m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)[n001R].m(A)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](U)[Ssp].m(A)[Ssp].m(A)}$$$$V2.0	AGAUGCCUGAACUUGAAUUAA
SSR-0104022	RNA1{m(A)[Ssp].m(G)[Ssp].m(A)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](C)[n001R].m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(G)[n001R].m(A)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)[Ssp].m(A)[Ssp].m(A)}$$$$V2.0	AGAUGCCUGAACUUGAAUUAA
SSR-0104024	RNA1{m(A)[sp].m(G)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](U)p.m(A)[sp].[fl2r](A)}$$$$V2.0	AGAUGCCUGAACUUGAAUUAA
SSR-0104025	RNA1{m(A)[sp].m(G)p.m(A)p.m(U)p.m(G)p.m(C)p.[fl2r](C)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(U)p.m(U)p.m(G)p.m(A)p.m(A)p.m(U)p.m(U)p.m(A)[sp].m(A)}$$$$V2.0	AGAUGCCUGAACUUGAAUUAA
SSR-0104026	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)[Ssp]	CUGUGCUGUAACACAAGUAGA

	.[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	
SSR-0104027	RNA1{m(C)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)[n001R].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0104028	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0104029	RNA1{m(C)[sp].m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)p.m(A)p.m(G)p.m(U)p.m(A)p.m(G)[sp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0104030	RNA1{m(G)[Ssp].m(G)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(A)[Ssp].[fl2r](U)[n001R].m(U)p.[fl2r](G)p.[fl2r](U)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](A)[n001R].m(A)[Ssp].[fl2r](U)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].m(A)}$$$$V2.0	GGAUGAUUGUACAGAAUCAUA
SSR-0104031	RNA1{m(U)[Rsp].[fl2r](A)[Ssp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)[n001S].[fl2r](A)p.m(U)p.[fl2r](A)p.m(G)p.m(U)p.m(G)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[n001S].m(G)[Ssp].[fl2r](A)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAAUGCAUAGUGAUCAGGAAUU
SSR-0104035	RNA1{m(U)[Rsp].[fl2r](A)[Ssp].m(U)[n001S].[fl2r](G)p.m(A)p.[fl2r](U)p.m(U)[n001S].[fl2r](C)p.m(U)p.[fl2r](G)p.m(U)p.m(A)p.m(C)[Ssp].[fl2r](A)[Ssp].m(A)[Ssp].[fl2r](U)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(U)[Ssp].[fl2r](C)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAUGAUUCUGUACAAUCAUCCUU
SSR-0104036	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](U)p.m(G)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(U)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](C)[n001S].m(A)[Ssp].[fl2r](G)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCAUGUUGAGUUUACCACAGAUU
SSR-0104037	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0104038	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001R].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0104039	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU

SSR-0104043	RNA1{m(U)[Rsp].[fl2r](G)[Ssp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)[n001S].[fl2r](C)p.m(U)p.[fl2r](A)p.m(U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](U)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104044	RNA1{m(U)[Rsp].[fl2r](G)[Ssp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(A)[n001R].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(U)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104045	RNA1{m(U)[Rsp].[fl2r](G)[Ssp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(A)[n001S].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(U)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104052	RNA1{m(U)[Rsp].[fl2r](U)[Ssp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)[n001S].[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(U)[Ssp].[fl2r](C)[Ssp].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104053	RNA1{m(U)[Rsp].[fl2r](U)[Ssp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)[n001R].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(U)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104054	RNA1{m(U)[Rsp].[fl2r](U)[Ssp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(U)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104061	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)[n001S].[fl2r](A)p.m(U)p.[fl2r](A)p.m(G)p.m(U)p.m(G)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[n001S].m(G)[Ssp].[fl2r](A)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAAAUGCAUAGUGAUCAGGAAUU
SSR-0104065	RNA1{m(U)[Ssp].[fl2r](A)[Rsp].m(U)[n001S].[fl2r](G)p.m(A)p.[fl2r](U)p.m(U)[n001S].[fl2r](C)p.m(U)p.[fl2r](G)p.m(U)p.m(A)p.m(C)[Ssp].[fl2r](A)[Ssp].m(A)[Ssp].[fl2r](U)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(U)[Ssp].[fl2r](C)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAUGAUUCUGUACAAUCAUCCUU
SSR-0104066	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(A)[n001S].[fl2r](U)p.m(G)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(U)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](C)[n001S].m(A)[Ssp].[fl2r](G)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCAUGUUGAGUUUACCACAGAUU
SSR-0104067	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU

SSR-0104068	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001R].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0104069	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0104073	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)[n001S].[fl2r](C)p.m(U)p.[fl2r](A)p.m(U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](U)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104074	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(A)[n001R].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(U)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104075	RNA1{m(U)[Ssp].[fl2r](G)[Rsp].m(A)[n001S].[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(A)[n001S].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(U)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104082	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)[n001S].[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(U)[Ssp].[fl2r](C)[Ssp].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104083	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)[n001R].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(U)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104084	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(U)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104092	RNA1{m(U)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001R].m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(U)p.[fl2r](A)p.m(G)p.[fl2r](A)[n001R].m(U)[Ssp].[fl2r](U)[Ssp].m(C)[Ssp].[fl2r](U)[Ssp].m(C)[Ssp].m(A)}$$$$V2.0	UAGUGCAUGAAUAGAUUCUCA
SSR-0104094	RNA1{m(U)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](A)[n001R].m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(A)p.m(G)p.m(A)[n001R].m(U)[Ssp].m(U)[Ssp].m(C)[Ssp].m(U)[Ssp].m(C)[Ssp].m(A)}$$$$V2.0	UAGUGCAUGAAUAGAUUCUCA

SSR-0104097	RNA1{m(U)[Ssp].m(C)[Ssp].[fl2r](U)[Ssp].m(G)[Ssp].[fl2r](U)[Ssp].m(G)[Ssp].[fl2r](G)[n001R].m(U)p.[fl2r](A)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(C)p.[fl2r](A)[n001R].m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](U)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	UCUGUGGUAAACUCAACAUGA
SSR-0104099	RNA1{m(U)[Ssp].m(U)[Ssp].[fl2r](C)[Ssp].m(C)[Ssp].[fl2r](U)[Ssp].m(G)[Ssp].[fl2r](A)[n001R].m(U)p.[fl2r](C)p.[fl2r](A)p.[fl2r](C)p.m(U)p.[fl2r](A)p.m(U)p.[fl2r](G)[n001R].m(C)[Ssp].[fl2r](A)[Ssp].m(U)[Ssp].[fl2r](U)[Ssp].m(U)[Ssp].m(A)}$$$$V2.0	UUCCUGAUCACUAUGCAUUUA
SSR-0104100	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0104101	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.m(A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.m(A)p.m(C)p.m(A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0104102	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.[fl2r](G)p.m(A)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(U)p.[fl2r](A)p.m(U)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104103	RNA1{m(U)[sp].[fl2r](G)[sp].m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(U)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](G)p.m(C)p.m(A)p.m(C)p.m(U)p.m(A)[sp].m(U)[sp].m(U)}$$$$V2.0	UGAGAAUCUAUUCAUGCACUAUU
SSR-0104104	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104105	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(A)p.m(U)p.[fl2r](U)p.m(C)p.m(A)p.m(A)p.m(G)p.m(U)p.m(U)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(C)p.m(A)p.m(U)p.m(C)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAAUUCAAGUUCAGGCAUCUUU
SSR-0104106	RNA1{m(U)[sp].m(A)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(U)p.[fl2r](A)p.m(G)p.[fl2r](A)p.m(U)p.[fl2r](U)p.m(C)p.[fl2r](U)p.m(C)[sp].[fl2r](A)}$$$$V2.0	UAGUGCAUGAAUAGAUUCUCA
SSR-0104107	RNA1{m(U)[sp].m(A)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](A)p.m(U)p.[fl2r](G)p.[fl2r](A)p.[fl2r](A)p.m(U)p.m(A)p.m(G)p.m(A)p.m(U)p.m(U)p.m(C)p.m(U)p.m(C)[sp].m(A)}$$$$V2.0	UAGUGCAUGAAUAGAUUCUCA
SSR-0104474	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0104475	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0104720	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.m(U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.m(A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106170	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106171	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)[n001S].m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106172	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106173	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106174	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106175	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)[n001S].m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106176	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106177	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106178	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU

SSR-0106179	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106180	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)[n001S].m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106181	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106182	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106183	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106184	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106185	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)[n001S].m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106186	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106187	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106188	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU

SSR-0106189	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)[n001S].m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106190	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106191	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106192	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106193	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106194	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106195	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)[n001S].m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106196	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106197	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.m(G)p.m(U)p.m(G)[n001S].[fl2r](U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[n001S].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[n001S].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106206	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA

SSR-0106207	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106208	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106209	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106210	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)[Ssp].[fl2r](U)[Ssp].[fl2r](A)[Ssp].[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106211	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)[Ssp].[fl2r](U)[Ssp].[fl2r](A)[Ssp].[fl2r](A)p.m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106212	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)[Ssp].[fl2r](U)[Ssp].[fl2r](A)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106213	RNA1{m(C)[Ssp].m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)[n001R].m(A)p.m(G)p.m(U)p.m(A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106214	RNA1{m(C)[Ssp].m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)[n001R].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106215	RNA1{m(C)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)[n001R].m(A)p.m(G)p.m(U)p.m(A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106216	RNA1{m(C)[Ssp].m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[n001R].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106217	RNA1{m(C)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)[Ssp].[fl2r](U)[Ssp].[fl2r](A)[Ssp].[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)[n001R].m(A)p.m(G)p.m(U)p.m(A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUG UAACACAA GUAGA
SSR-0106218	RNA1{m(C)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)[Ssp].[fl2r](U)[Ssp].[fl2r](A)[Ssp].[fl2r](A)p.m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[n001R]	CUGUGCUG UAACACAA GUAGA

	.m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	
SSR-0106219	RNA1{m(C)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(G)[Ssp].m(C)[Ssp].[fl2r](U)[n001R].m(G)[Ssp].[fl2r](U)[Ssp].[fl2r](A)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].m(A)[Ssp].m(C)[Ssp].m(A)[n001R].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106220	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106221	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106222	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106223	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106224	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106225	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106266	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106267	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106268	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0106269	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106270	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106271	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106272	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106273	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)[n001S].m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106274	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)[n001S].[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106275	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106276	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106277	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)[n001S].m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106278	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106279	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106280	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].m(G)[n001S].m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU

SSR-0106281	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)[n001S].[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106282	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106283	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)[n001S].m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106284	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)[n001S].m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106285	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)[n001S].m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106286	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)[n001S].m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106287	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)p.[fl2r](A)[n001S].m(C)p.[fl2r](A)[n001S].m(C)p.m(U)[n001S].m(G)p.m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106288	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)p.m(C)[n001S].[fl2r](A)p.m(C)[n001S].m(U)p.m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106289	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].[fl2r](A)p.[fl2r](A)[n001S].[fl2r](C)p.[fl2r](A)[n001S].[fl2r](C)p.m(U)[n001S].[fl2r](G)p.m(U)[n001S].[fl2r](U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106290	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)p.m(C)[n001S].[fl2r](A)p.m(C)[n001S].[fl2r](U)p.m(G)[n001S].[fl2r](U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0106291	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)[n001S].m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106292	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)[n001S].[fl2r](A)p.m(C)p.m(U)[n001S].m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106293	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106294	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106295	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106296	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)[n001S].[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106297	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106298	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106299	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106300	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)[n001S].m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106301	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)[n001S].m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106302	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)[n001S].[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU

SSR-0106303	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)[n001S].[fl2r](C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106304	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001S].[fl2r](C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106305	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)[n001S].[fl2r](U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106306	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)[n001S].[fl2r](G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106307	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)[n001S].[fl2r](U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106445	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106446	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n033R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106447	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106448	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n033R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106449	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106450	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n033R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106451	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA

SSR-0106452	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n033R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106479	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n065S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n065S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n065S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106480	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n070S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n070S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n070S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106481	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n071S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n071S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n071S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106482	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n065S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n065S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n065S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106483	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n070S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n070S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n070S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106484	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n071S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n071S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n071S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0106487	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n069R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n069R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106517	RNA1{[vped5m](U)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU

Table 1D. Example Guide Strand Oligonucleotides

ID	HELM	Base Sequence

SSR-0104100	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)p.[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0104186	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](U)[Ssp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0104189	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0104473	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0104475	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0104717	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0105217	RNA1{m(U)[Ssp].[fl2r](C)[Rsp].m(C)[n001S].[fl2r](U)p.m(U)p.[fl2r](C)p.m(C)p.m(C)p.m(U)p.m(G)[n001R].[fl2r](A)p.m(A)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](U)p.m(C)p.m(C)p.m(U)p.m(C)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCCUUCCCU GAAGGUUC CUCCUU
SSR-0105245	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106183	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106224	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106453	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[thpyr](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106454	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.[thpyr](A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU

SSR-0106455	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.[thpyr](A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106456	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.[thpyr](A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106457	RNA1{d([3nU])[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106512	RNA1{m(U)[Rsp].[fl2r](C)[Ssp].m(U)[n029S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n029S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n029S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106514	RNA1{[d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106515	RNA1{[d5m](U)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106516	RNA1{[vped5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106517	RNA1{[vped5m](U)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106518	RNA1{[d25r](T)[Ssp].[fl2r](C)[Ssp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n001S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	TCUACUUG UGUUACAG CACAGUU
SSR-0106519	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(U)[n029S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n029S].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](A)[n029S].m(C)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU

SSR-0106520	RNA1{m(U)[sp].[fl2r](U)[sp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.[thpyr](A)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[sp].m(U)[sp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106521	RNA1{[thpyr](T)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	TUAUAGAG CAAGAACA CUGUUUU
SSR-0106522	RNA1{m(U)[Ssp].[thpyr](T)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UTAUAGAG CAAGAACA CUGUUUU
SSR-0106523	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[thpyr](T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAG CAAGAACA CUGUUUU
SSR-0106524	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[thpyr](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106525	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.[thpyr](G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106526	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.[thpyr](C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106527	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[thpyr](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106528	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.[thpyr](G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106529	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.[thpyr](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106530	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[thpyr](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106531	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.[thpyr](C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU

SSR-0106532	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[thpyr](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106533	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.[thpyr](C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106534	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[thpyr](T)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CTGUUUU
SSR-0106535	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.[thpyr](G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106536	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.[thpyr](T)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGTUUU
SSR-0106537	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.[thpyr](T)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUTUU
SSR-0106538	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].[thpyr](T)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUTU
SSR-0106539	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].[thpyr](T)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUT
SSR-0106584	RNA1{m(U)[sp].[fl2r](C)[sp].m(U)[n001].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001].[fl2r](G)p.m(U)p.[fl2r](G)p.m(U)p.m(U)p.m(A)[sp].[fl2r](C)[sp].m(A)[sp].[fl2r](G)[sp].m(C)[sp].[fl2r](A)[n001].m(C)[sp].[fl2r](A)[sp].m(G)[sp].m(U)[sp].m(U)}$$$$V2.0	UCUACUUG UGUUACAG CACAGUU
SSR-0106587	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Rsp].m(C)[n001S].[fl2r](U)p.m(U)p.[fl2r](C)p.m(C)[n001S].[fl2r](C)p.m(U)p.[fl2r](G)p.m(A)p.m(A)p.m(G)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](U)[Ssp].m(C)[Ssp].[fl2r](C)[n001S].m(U)[Ssp].[fl2r](C)[Ssp].m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCCUUCCCU GAAGGUUC CUCCUU
SSR-0106620	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU
SSR-0106621	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](U)[Ssp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAG CAAGAACA CUGUUUU

SSR-0106625	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[thpyr](A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106626	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[thpyr](T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAGCAAGAACACUGUUUU
SSR-0106627	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.[thpyr](A)p.[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106628	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)p.[thpyr](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107427	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](U)[Ssp].m(U)[n001S].[fl2r](A)p.m(G)p.[fl2r](A)p.m(G)[n001S].[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)[Ssp].[fl2r](U)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(A)[Ssp].m(A)[n001S].m(A)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUAGAGUGAGGAUUAAAAUGUU
SSR-0107428	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](U)[Ssp].m(U)[n001S].[fl2r](A)p.m(G)p.[fl2r](A)p.m(G)[n001S].[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(A)[n001S].m(A)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUAGAGUGAGGAUUAAAAUGUU
SSR-0108082	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](A)[Ssp].m(G)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)[n001S].[fl2r](U)p.[fl2r](A)p.m(A)p.m(A)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(C)[Ssp].[fl2r](G)[Ssp].m(A)[Ssp].m(G)[n001S].m(G)[Ssp].m(A)[Ssp].m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAGACAAUAAAUACCGAGGAAUU
SSR-0108084	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](A)[Ssp].m(G)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)[n001S].[fl2r](U)p.[fl2r](A)p.m(A)p.m(A)p.m(U)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](G)p.m(A)p.m(G)[n001S].m(G)p.m(A)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAGACAAUAAAUACCGAGGAAUU
SSR-0108085	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](A)[Ssp].m(G)[n001S].[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)[n001S].[fl2r](U)p.[fl2r](A)p.m(A)p.m(A)p.m(U)p.m(A)p.[fl2r](C)p.m(C)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.m(A)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UAGACAAUAAAUACCGAGGAAUU
SSR-0107358	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107359	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Rm5m](A)p.[Rm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107360	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Sm5m](A)p.[Sm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.	UUAUAGAGCAAGAACACUGUUUU

	m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	
SSR-0106644	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[Rm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106645	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[Sm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106646	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Rm5m](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106648	RNA1{m(U)[Ssp].[fl2r](U)[Ssp].[Rm5m](A)[n001S].[Rm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106649	RNA1{m(U)[Ssp].[fl2r](U)[Ssp].[Sm5m](A)[n001S].[Sm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106650	RNA1{m(U)[Ssp].[fl2r](U)[Ssp].m(A)[n001S].[Sgna](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107361	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.[Sgna](G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107362	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.[Sgna](A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107363	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[Sgna](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107364	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.[Sgna](A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107416	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[Sgna](T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAGCAAGAACACUGUUUU

SSR-0107366	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Sgna](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106578	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[oylZ58C13oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106579	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Srl1C11oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0107358	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)p.[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107359	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Rm5m](A)p.[Rm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107360	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Sm5m](A)p.[Sm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106644	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[Rm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106645	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[Sm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106646	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Rm5m](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106648	RNA1{m(U)[Ssp].[fl2r](U)[Ssp].[Rm5m](A)[n001S].[Rm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0106649	RNA1{m(U)[Ssp].[fl2r](U)[Ssp].[Sm5m](A)[n001S].[Sm5fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0106650	RNA1{m(U)[Ssp].[fl2r](U)[Ssp].m(A)[n001S].[Sgna](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107361	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.[Sgna](G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107362	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.[Sgna](A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107363	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[Sgna](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107364	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.[Sgna](A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107416	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[Sgna](T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAGCAAGAACACUGUUUU
SSR-0107366	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[Sgna](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107417	RNA1{m(U)[Ssp].[Sgna](T)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UTAUAGAGCAAGAACACUGUUUU
SSR-0107418	RNA1{[Sgna](T)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	TUAUAGAGCAAGAACACUGUUUU
SSR-0107369	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.d(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107370	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.d(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107371	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.d(G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[f	UUAUAGAGCAAGAACACUGUUUU

	l2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	
SSR-0107372	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.d(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107373	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].d(T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAGCAAGAACACUGUUUU
SSR-0107374	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].d(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107375	RNA1{m(U)[Ssp].d(T)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UTAUAGAGCAAGAACACUGUUUU
SSR-0107376	RNA1{d(T)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	TUAUAGAGCAAGAACACUGUUUU
SSR-0107377	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.[moe](G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107378	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.[moe](A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107379	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[moe](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107380	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.[moe](A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107381	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[moe](T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAGCAAGAACACUGUUUU
SSR-0107382	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[moe](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0107383	RNA1{m(U)[Ssp].[moe](T)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UTAUAGAGCAAGAACACUGUUUU
SSR-0107384	RNA1{[moe](T)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	TUAUAGAGCAAGAACACUGUUUU
SSR-0107385	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.[lr](G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107386	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.[lr](A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107387	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[lr](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107388	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.[lr](A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107389	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[lr](T)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUATAGAGCAAGAACACUGUUUU
SSR-0107390	RNA1{m(U)[Ssp].[fl2r](U)[Rsp].[lr](A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0107391	RNA1{m(U)[Ssp].[lr](T)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UTAUAGAGCAAGAACACUGUUUU
SSR-0107392	RNA1{[lr](T)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001S].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	TUAUAGAGCAAGAACACUGUUUU
SSR-0108193	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0108328	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](C)[Ssp].m(C)[n001S].[fl2r](U)p.m(U)p.[fl2r](C)p.m(C)[n001S].[fl2r](C)p.[fl2r](U)p.m(G)p.m(A)p.m(A)p.m(G)p.[fl2r](G)p.m(U)p.[fl2r](U)p.m(C)p.m(C)[n001S].m(U)p.m(C)p.m(C)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCCUUCCCUGAAGGUUCCUCCUU
SSR-0108348	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(U)[n001S].[fl2r](A)p.m(G)p.[fl2r](A)p.m(G)[n001S].[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(A)[n001S].m(A)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUUAGAGUGAGGAUUAAAAUGUU
SSR-0108432	RNA1{[d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[n001S].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0108436	RNA1{[d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.m(A)[n001S].m(C)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0108201	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(A)[Ssp].[fl2r](C)[Ssp].m(A)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].m(A)[n001S].m(C)[Ssp].m(A)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0108209	RNA1{p.[Rm5d5m](U)[Ssp].[fl2r](C)[Rsp].m(U)[n001S].[fl2r](A)p.m(C)p.[fl2r](U)p.m(U)[n001S].[fl2r](G)p.[fl2r](U)p.m(G)p.m(U)p.m(U)p.m(A)p.[fl2r](C)p.m(A)p.[fl2r](G)p.m(C)p.m(A)[n001S].m(C)p.m(A)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UCUACUUGUGUUACAGCACAGUU
SSR-0108298	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](U)[Ssp].m(U)[n001S].[fl2r](A)p.m(G)p.[fl2r](A)p.m(G)[n001S].[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(A)[n001S].m(A)[Ssp].m(U)[Ssp].m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUAGAGUGAGGAUUAAAAUGUU
SSR-0108216	RNA1{p.[Rm5d5m](U)[Rsp].[fl2r](U)[Ssp].m(U)[n001S].[fl2r](A)p.m(G)p.[fl2r](A)p.m(G)[n001S].[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUUAGAGUGAGGAUUAAAAUGUU
SSR-0107991	RNA1{[vped5m](U)[sp].[fl2r](U)[sp].m(U)p.m(A)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)[sp].m(A)[sp].m(G)}$$$$V2.0	UUUAGAGUGAGGAUUAAAAUGAG
SSR-0107992	RNA1{[vped5m](U)[Ssp].[fl2r](U)[Ssp].m(U)p.m(A)p.m(G)p.[fl2r](A)p.m(G)p.[fl2r](U)p.[fl2r](G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](U)p.m(U)p.[fl2r](A)p.m(A)p.m(A)p.m(A)p.m(U)p.m(G)[Ssp].m(A)[Ssp].m(G)}$$$$V2.0	UUUAGAGUGAGGAUUAAAAUGAG
SSR-0108842	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n003S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(	UUAUAGAGCAAGAACACUGUUUU

	U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	
SSR-0108843	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n003R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108844	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n003S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n003R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108845	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n008S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108846	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n008R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108847	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n008S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n008R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108848	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n078S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108849	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n078R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108850	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n078S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n078R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108851	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n025S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

SSR-0108852	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n025R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108853	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n025S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n025R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108854	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n065S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108855	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n065R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108856	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n065S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n065R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108857	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n070S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108858	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n070R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108859	RNA1{[d5m](U)[Ssp].[fl2r](U)[Rsp].m(A)[n070S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n070R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}|CHEM1{[ptz]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108896	RNA1{[n003].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108897	RNA1{[n031].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)	UUAUAGAGCAAGAACACUGUUUU

	p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	
SSR-0108898	RNA1{[n037].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108899	RNA1{[n082].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108900	RNA1{[n009].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108901	RNA1{[n040].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108902	RNA1{[n033].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108903	RNA1{[n084].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108904	RNA1{[n077].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108905	RNA1{[n039].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU
SSR-0108906	RNA1{[n083].m(U)[Ssp].[fl2r](U)[Rsp].m(A)[n001S].[fl2r](U)p.m(A)p.[fl2r](G)p.m(A)p.m(G)p.m(C)p.m(A)[n001R].[fl2r](A)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.m(U)p.m(G)p.m(U)p.m(U)[Ssp].m(U)[Ssp].m(U)}$$$$V2.0	UUAUAGAGCAAGAACACUGUUUU

Table 1E. Example Passenger Strand Oligonucleotides

ID	HELM	Base Sequence
SSR-0101596	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[sp].m(A)}|CHEM1{[	AACAGUGUUCUUGCUCUAUAA

	GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	
SSR-0101599	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0105234	RNA1{p.m(G)[Ssp].m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](A)p.m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(G)p.m(G)p.m(A)p.m(A)p.m(G)p.m(G)[Ssp].m(A)}|CHEM1{[GalNAc3C12oyl]}|CHEM2{[nC6o]}$CHEM2,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R2-1:R1$$$V2.0	GGAGGAACCUUCAGGGAAGGA
SSR-0106206	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106503	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106506	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106507	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106508	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106509	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106510	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[hexdec2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106511	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n029R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n029R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106513	RNA1{m(C)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](G)[Ssp].m(C)[Ssp].[fl2r](U)[n029R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n029R].m(A)[Ssp].[fl2r](G)[Ssp].m(U)[Ssp].[fl2r](A)[Ssp].m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA

SSR-0106563	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106564	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}$CHEM1,RNA1,1:R1-1:R1$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106565	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[C16oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106566	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[C18oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106568	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[lin]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106569	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[turb]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106570	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[chol3o]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106571	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[2hexC10oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106573	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Hexa3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106575	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G	CUGUGCUGUAACACAAGUAGA

	)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Bam3C5oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	
SSR-0106576	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[oylC20oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106577	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Muco]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106578	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[oylZ58C13oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106579	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Srl1C11oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106580	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Citr]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106652	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Phodec]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106653	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[EPhodec]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106660	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[Bardoyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106679	RNA1{p.m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}|CHEM1{[nC6o]}|CHEM2{[anis3C5oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CUGUGCUGUAACACAAGUAGA

SSR-0106589	RNA1{m(G)[Ssp].m(G)p.[fl2r](A)p.m(G)p.[fl2r](G)p.m(A)p.[fl2r](A)[n001R].m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(C)p.[fl2r](A)p.m(G)p.[fl2r](G)[n001R].m(G)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(G)[Ssp].m(A)}$$$$V2.0	GGAGGAACCUUCAGGGAAGGA
SSR-0106597	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)p.m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106598	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106599	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106600	RNA1{m(C)[sp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n033R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[sp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106601	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106602	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[hexdec2r](U)[n033R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106603	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n031R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106604	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n037R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106605	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n046R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106606	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n047R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106607	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n043R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA

SSR-0106629	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].[thpyr](A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0106630	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.[thpyr](A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0106631	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.[thpyr](T)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUATAA
SSR-0106632	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.[thpyr](A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0106633	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.[thpyr](T)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCTAUAA
SSR-0106634	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.[thpyr](C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0106635	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.[thpyr](T)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCTCUAUAA
SSR-0106637	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.[thpyr](G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0106638	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.[thpyr](T)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUTGCUCUAUAA
SSR-0106640	RNA1{p.m(A)[Ssp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.[thpyr](C)p.m(U)p.m(A)p.m(U)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA

SSR-0106643	RNA1{p.m(A)[sp].m(A)p.m(C)p.m(A)p.m(G)p.m(U)p.[fl2r](G)p.m(U)p.[fl2r](U)p.[fl2r](C)p.[fl2r](U)p.m(U)p.m(G)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(U)p.[thpyr](A)[sp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	AACAGUGUUCUUGCUCUAUAA
SSR-0106661	RNA1{[oC6o][n009].m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106662	RNA1{[oC6o][n033].m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106663	RNA1{[oC6o][n039].m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106664	RNA1{[oC6o][n040].m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106665	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n039R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0106666	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n040R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0107400	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n001R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107412	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107413	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107414	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107415	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n039R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m	CAUUUUAAUCCUCACUCUAAA

	(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	
SSR-0107419	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n001R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107420	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n033R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n001R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107421	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n033R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108086	RNA1{m(U)[Ssp].m(U)p.m(C)p.m(C)p.m(U)p.m(C)p.[fl2r](G)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](U)p.m(U)p.m(U)p.m(A)p.m(U)[n009R].m(U)p.m(G)p.m(U)p.m(C)p.m(U)[Ssp].m(A)}$$$$V2.0	UUCCUCGGUAUUUAUUGUCUA
SSR-0108089	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n001R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108090	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[GalNAc3C12oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM1,CHEM2,1:R2-1:R1$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108093	RNA1{[GalNAc1pyr]p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n001R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108094	RNA1{[GalNAc1pyr]p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0106485	RNA1{m(C)[Ssp].m(U)p.[fl2r](G)p.m(U)p.[fl2r](G)p.m(C)p.[fl2r](U)[n001R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.[fl2r](A)p.m(C)p.[fl2r](A)[n001R].m(A)p.[fl2r](G)p.m(U)p.[fl2r](A)p.m(G)[Ssp].[fl2r](A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0107403	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)[n001R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n001R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107405	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)[n001R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107422	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n077R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m	CAUUUUAAUCCUCACUC

	(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	UAAA
SSR-0107993	RNA1{m(C)[sp].m(A)[sp].m(U)p.m(U)p.m(U)p.[hexdec2r](U)p.[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)[sp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107994	RNA1{m(C)[sp].m(A)[sp].m(U)p.m(U)p.m(U)p.m(U)[n001R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)[sp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107995	RNA1{m(C)[sp].m(A)[sp].m(U)p.m(U)p.m(U)p.m(U)[n009R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)[sp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107996	RNA1{m(C)[Ssp].m(A)[Ssp].m(U)p.m(U)p.m(U)p.m(U)[n009R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[Ssp].m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0107997	RNA1{m(C)[Ssp].m(A)[Ssp].m(U)p.m(U)p.m(U)p.m(U)[n001R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[Ssp].m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108004	RNA1{m(C)[sp].m(A)[sp].m(U)p.m(U)p.m(U)p.m(U)[n033R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[sp].m(A)[sp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108005	RNA1{m(C)[Ssp].m(A)[Ssp].m(U)p.m(U)p.m(U)p.m(U)[n033R].[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)[Ssp].m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108195	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)p.m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108331	RNA1{m(G)[Ssp].m(G)p.m(A)p.m(G)p.m(G)p.m(A)p.[fl2r](A)[n009R].m(C)p.[fl2r](C)p.[fl2r](U)p.[fl2r](U)p.m(C)p.m(A)p.m(G)p.m(G)[n009R].m(G)p.m(A)p.m(A)p.m(G)p.m(G)[Ssp].m(A)}$$$$V2.0	GGAGGAACCUUCAGGGAAGGA
SSR-0108343	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[Intlpep]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108344	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[Mucin3C5oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108441	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n079R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$	CAUUUUAAUCCUCACUCUAAA

	$V2.0	
SSR-0108442	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n081R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108471	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[Int3C5oyl_1]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108472	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n009R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n009R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[Alkyn3C5oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108725	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n085R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108728	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[Glu1C5oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108729	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[bMan1C5oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108730	RNA1{p.m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n001R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}|CHEM1{[nC6o]}|CHEM2{[AmheptC3oyl]}$CHEM1,RNA1,1:R1-1:R1|CHEM2,CHEM1,1:R1-1:R2$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108818	RNA1{m(C)[Ssp].m(U)p.m(G)p.m(U)p.m(G)p.m(C)p.[fl2r](U)[n009R].m(G)p.[fl2r](U)p.[fl2r](A)p.[fl2r](A)p.m(C)p.m(A)p.m(C)p.m(A)[n009R].m(A)p.m(G)p.m(U)p.m(A)p.m(G)[Ssp].m(A)}$$$$V2.0	CUGUGCUGUAACACAAGUAGA
SSR-0108819	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n082R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108820	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n083R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108821	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n084R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA

SSR-0108822	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n040R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108837	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n086R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108838	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n087R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108839	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n088R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108827	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n077R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)[n077R].m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108872	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n089R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108873	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n090R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108874	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n091R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA
SSR-0108875	RNA1{m(C)[Ssp].m(A)p.m(U)p.m(U)p.m(U)p.m(U)p.[fl2r](A)[n092R].m(A)p.[fl2r](U)p.[fl2r](C)p.[fl2r](C)p.m(U)p.m(C)p.m(A)p.m(C)p.m(U)p.m(C)p.m(U)p.m(A)p.m(A)[Ssp].m(A)}$$$$V2.0	CAUUUUAAUCCUCACUCUAAA

Table 1F. Example Oligonucleotides

Duplex	Guide	Passenger
DSR-0101651	SSR-0104720	SSR-0101596
DSR-0102161	SSR-0104474	SSR-0101599
DSR-0102524	SSR-0104475	SSR-0101599
DSR-0102630	SSR-0104036	SSR-0104097
DSR-0102631	SSR-0104066	SSR-0104097
DSR-0102632	SSR-0104052	SSR-0104021
DSR-0102633	SSR-0104082	SSR-0104021
DSR-0102634	SSR-0104031	SSR-0104099

Duplex	Guide	Passenger
DSR-0102635	SSR-0104061	SSR-0104099
DSR-0102636	SSR-0104037	SSR-0104026
DSR-0102637	SSR-0104067	SSR-0104026
DSR-0102638	SSR-0104035	SSR-0104030
DSR-0102639	SSR-0104065	SSR-0104030
DSR-0102640	SSR-0104043	SSR-0104092
DSR-0102641	SSR-0104073	SSR-0104092
DSR-0102661	SSR-0104054	SSR-0104022
DSR-0102662	SSR-0104084	SSR-0104022
DSR-0102663	SSR-0104053	SSR-0104022
DSR-0102664	SSR-0104083	SSR-0104022
DSR-0102665	SSR-0104039	SSR-0104027
DSR-0102666	SSR-0104069	SSR-0104027
DSR-0102667	SSR-0104038	SSR-0104027
DSR-0102668	SSR-0104068	SSR-0104027
DSR-0102669	SSR-0104045	SSR-0104094
DSR-0102670	SSR-0104075	SSR-0104094
DSR-0102671	SSR-0104044	SSR-0104094
DSR-0102672	SSR-0104074	SSR-0104094
DSR-0103133	SSR-0106188	SSR-0104027
DSR-0103134	SSR-0106190	SSR-0104027
DSR-0103135	SSR-0106180	SSR-0104027
DSR-0103136	SSR-0106181	SSR-0104027
DSR-0103137	SSR-0104101	SSR-0104029
DSR-0103138	SSR-0106185	SSR-0104026
DSR-0103139	SSR-0106189	SSR-0104026
DSR-0103140	SSR-0106195	SSR-0104026
DSR-0103141	SSR-0106172	SSR-0104026
DSR-0103142	SSR-0106184	SSR-0104026
DSR-0103143	SSR-0106189	SSR-0104027
DSR-0103144	SSR-0106170	SSR-0104027
DSR-0103145	SSR-0106172	SSR-0104027
DSR-0103146	SSR-0106178	SSR-0104027
DSR-0103147	SSR-0106194	SSR-0104026
DSR-0103148	SSR-0106178	SSR-0104026
DSR-0103149	SSR-0106181	SSR-0104026
DSR-0103150	SSR-0106187	SSR-0104027
DSR-0103151	SSR-0106197	SSR-0104027
DSR-0103152	SSR-0106174	SSR-0104027
DSR-0103153	SSR-0106191	SSR-0104026
DSR-0103154	SSR-0106179	SSR-0104026
DSR-0103155	SSR-0106182	SSR-0104026
DSR-0103156	SSR-0106186	SSR-0104027
DSR-0103157	SSR-0106173	SSR-0104027
DSR-0103158	SSR-0106176	SSR-0104027
DSR-0103159	SSR-0106184	SSR-0104027
DSR-0103160	SSR-0106187	SSR-0104026

Duplex	Guide	Passenger
DSR-0103161	SSR-0106188	SSR-0104026
DSR-0103162	SSR-0106176	SSR-0104026
DSR-0103163	SSR-0106177	SSR-0104026
DSR-0103164	SSR-0106183	SSR-0104026
DSR-0103165	SSR-0106185	SSR-0104027
DSR-0103166	SSR-0106193	SSR-0104027
DSR-0103167	SSR-0106175	SSR-0104027
DSR-0103168	SSR-0106186	SSR-0104026
DSR-0103169	SSR-0106190	SSR-0104026
DSR-0103170	SSR-0106192	SSR-0104026
DSR-0103171	SSR-0106175	SSR-0104026
DSR-0103172	SSR-0104039	SSR-0104026
DSR-0103173	SSR-0106180	SSR-0104026
DSR-0103174	SSR-0106192	SSR-0104027
DSR-0103175	SSR-0106195	SSR-0104027
DSR-0103176	SSR-0106171	SSR-0104027
DSR-0103177	SSR-0106179	SSR-0104027
DSR-0103178	SSR-0106197	SSR-0104026
DSR-0103179	SSR-0106171	SSR-0104026
DSR-0103180	SSR-0106174	SSR-0104026
DSR-0103181	SSR-0106194	SSR-0104027
DSR-0103182	SSR-0106196	SSR-0104027
DSR-0103183	SSR-0106182	SSR-0104027
DSR-0103184	SSR-0106193	SSR-0104026
DSR-0103185	SSR-0106170	SSR-0104026
DSR-0103186	SSR-0106191	SSR-0104027
DSR-0103187	SSR-0106177	SSR-0104027
DSR-0103188	SSR-0106183	SSR-0104027
DSR-0103189	SSR-0104037	SSR-0104027
DSR-0103190	SSR-0104100	SSR-0104028
DSR-0103191	SSR-0106196	SSR-0104026
DSR-0103192	SSR-0106173	SSR-0104026
DSR-0103199	SSR-0106222	SSR-0104026
DSR-0103200	SSR-0106225	SSR-0104026
DSR-0103201	SSR-0106188	SSR-0106208
DSR-0103202	SSR-0106188	SSR-0106210
DSR-0103203	SSR-0106188	SSR-0106212
DSR-0103204	SSR-0106188	SSR-0106218
DSR-0103205	SSR-0106224	SSR-0104026
DSR-0103206	SSR-0106183	SSR-0106447
DSR-0103207	SSR-0106188	SSR-0106211
DSR-0103208	SSR-0106188	SSR-0106215
DSR-0103209	SSR-0106188	SSR-0106217
DSR-0103210	SSR-0104100	SSR-0106445
DSR-0103211	SSR-0104100	SSR-0106446
DSR-0103212	SSR-0106188	SSR-0106207
DSR-0103213	SSR-0106188	SSR-0106213

Duplex	Guide	Passenger
DSR-0103214	SSR-0106188	SSR-0106214
DSR-0103215	SSR-0106188	SSR-0106219
DSR-0103216	SSR-0106223	SSR-0104026
DSR-0103217	SSR-0106183	SSR-0106448
DSR-0103218	SSR-0106183	SSR-0106452
DSR-0103219	SSR-0106188	SSR-0106206
DSR-0103220	SSR-0106188	SSR-0106216
DSR-0103221	SSR-0106220	SSR-0104026
DSR-0103222	SSR-0106221	SSR-0104026
DSR-0103223	SSR-0106183	SSR-0106449
DSR-0103224	SSR-0106183	SSR-0106450
DSR-0103225	SSR-0106183	SSR-0106451
DSR-0103226	SSR-0106188	SSR-0106209
DSR-0103227	SSR-0106266	SSR-0101599
DSR-0103228	SSR-0106267	SSR-0101599
DSR-0103229	SSR-0106268	SSR-0101599
DSR-0103230	SSR-0106269	SSR-0101599
DSR-0103231	SSR-0106270	SSR-0101599
DSR-0103232	SSR-0106271	SSR-0101599
DSR-0103233	SSR-0106272	SSR-0101599
DSR-0103234	SSR-0106273	SSR-0101599
DSR-0103235	SSR-0106274	SSR-0101599
DSR-0103236	SSR-0106275	SSR-0101599
DSR-0103237	SSR-0106276	SSR-0101599
DSR-0103238	SSR-0106277	SSR-0101599
DSR-0103239	SSR-0106278	SSR-0101599
DSR-0103240	SSR-0106279	SSR-0101599
DSR-0103241	SSR-0106280	SSR-0101599
DSR-0103242	SSR-0106281	SSR-0101599
DSR-0103243	SSR-0106282	SSR-0101599
DSR-0103244	SSR-0106283	SSR-0101599
DSR-0103245	SSR-0106284	SSR-0101599
DSR-0103246	SSR-0106285	SSR-0101599
DSR-0103247	SSR-0106286	SSR-0101599
DSR-0103248	SSR-0106287	SSR-0101599
DSR-0103249	SSR-0106288	SSR-0101599
DSR-0103250	SSR-0106289	SSR-0101599
DSR-0103251	SSR-0106290	SSR-0101599
DSR-0103252	SSR-0106291	SSR-0101599
DSR-0103253	SSR-0106292	SSR-0101599
DSR-0103254	SSR-0106293	SSR-0101599
DSR-0103255	SSR-0106294	SSR-0101599
DSR-0103256	SSR-0106295	SSR-0101599
DSR-0103257	SSR-0106296	SSR-0101599
DSR-0103258	SSR-0106297	SSR-0101599
DSR-0103259	SSR-0106298	SSR-0101599
DSR-0103260	SSR-0106299	SSR-0101599

Duplex	Guide	Passenger
DSR-0103261	SSR-0106300	SSR-0101599
DSR-0103262	SSR-0106301	SSR-0101599
DSR-0103263	SSR-0106302	SSR-0101599
DSR-0103264	SSR-0106303	SSR-0101599
DSR-0103265	SSR-0106304	SSR-0101599
DSR-0103266	SSR-0106305	SSR-0101599
DSR-0103267	SSR-0106306	SSR-0101599
DSR-0103268	SSR-0106307	SSR-0101599
DSR-0103275	SSR-0106183	SSR-0106206
DSR-0103276	SSR-0106183	SSR-0106209
DSR-0103299	SSR-0106222	SSR-0106206
DSR-0103300	SSR-0106222	SSR-0106209
DSR-0103301	SSR-0106222	SSR-0106447
DSR-0103319	SSR-0106480	SSR-0106206
DSR-0103320	SSR-0106481	SSR-0106206
DSR-0103321	SSR-0106482	SSR-0106206
DSR-0103322	SSR-0106483	SSR-0106206
DSR-0103323	SSR-0106484	SSR-0106206
DSR-0103324	SSR-0106487	SSR-0106206
DSR-0103325	SSR-0104037	SSR-0106206
DSR-0103326	SSR-0106479	SSR-0106206
DSR-0103337	SSR-0104103	SSR-0104107
DSR-0103338	SSR-0104104	SSR-0104024
DSR-0103339	SSR-0104102	SSR-0104106
DSR-0103340	SSR-0104105	SSR-0104025
DSR-0102626	SSR-0104473	SSR-0101599
DSR-0102657	SSR-0105217	SSR-0105234
DSR-0103028	SSR-0104717	SSR-0101596
DSR-0103099	SSR-0105245	SSR-0101599
DSR-0103327	SSR-0106453	SSR-0101599
DSR-0103328	SSR-0106454	SSR-0101599
DSR-0103329	SSR-0106455	SSR-0101599
DSR-0103330	SSR-0106456	SSR-0101599
DSR-0103331	SSR-0106457	SSR-0101599
DSR-0103342	SSR-0106584	SSR-0106563
DSR-0103343	SSR-0104100	SSR-0106563
DSR-0103359	SSR-0104186	SSR-0101599
DSR-0103360	SSR-0106620	SSR-0101599
DSR-0103361	SSR-0104189	SSR-0101599
DSR-0103362	SSR-0106621	SSR-0101599
DSR-0103363	SSR-0106530	SSR-0101599
DSR-0103364	SSR-0104475	SSR-0106630
DSR-0103365	SSR-0106527	SSR-0101599
DSR-0103366	SSR-0106528	SSR-0101599
DSR-0103367	SSR-0106533	SSR-0101599
DSR-0103368	SSR-0106536	SSR-0101599

Duplex	Guide	Passenger
DSR-0103369	SSR-0106625	SSR-0101599
DSR-0103370	SSR-0106520	SSR-0101596
DSR-0103371	SSR-0104475	SSR-0106629
DSR-0103372	SSR-0106532	SSR-0101599
DSR-0103373	SSR-0104475	SSR-0106640
DSR-0103374	SSR-0104475	SSR-0106637
DSR-0103375	SSR-0104475	SSR-0106638
DSR-0103376	SSR-0106522	SSR-0101599
DSR-0103377	SSR-0106523	SSR-0101599
DSR-0103378	SSR-0106524	SSR-0101599
DSR-0103379	SSR-0106526	SSR-0101599
DSR-0103380	SSR-0106534	SSR-0101599
DSR-0103381	SSR-0106627	SSR-0101599
DSR-0103382	SSR-0104475	SSR-0106632
DSR-0103383	SSR-0104475	SSR-0106633
DSR-0103384	SSR-0104475	SSR-0106634
DSR-0103385	SSR-0104717	SSR-0106643
DSR-0103386	SSR-0106626	SSR-0101599
DSR-0103387	SSR-0106628	SSR-0101599
DSR-0103388	SSR-0104475	SSR-0106635
DSR-0103389	SSR-0106525	SSR-0101599
DSR-0103390	SSR-0106535	SSR-0101599
DSR-0103391	SSR-0106537	SSR-0101599
DSR-0103392	SSR-0106538	SSR-0101599
DSR-0103393	SSR-0106539	SSR-0101599
DSR-0103394	SSR-0104475	SSR-0106631
DSR-0103395	SSR-0106521	SSR-0101599
DSR-0103396	SSR-0106529	SSR-0101599
DSR-0103397	SSR-0106531	SSR-0101599
DSR-0103404	SSR-0106183	SSR-0106603
DSR-0103408	SSR-0106183	SSR-0106510
DSR-0103409	SSR-0106183	SSR-0106604
DSR-0103411	SSR-0106183	SSR-0106506
DSR-0103412	SSR-0106183	SSR-0106511
DSR-0103414	SSR-0106183	SSR-0106508
DSR-0103415	SSR-0106183	SSR-0106513
DSR-0103416	SSR-0106183	SSR-0106503
DSR-0103418	SSR-0106183	SSR-0106598
DSR-0103419	SSR-0106183	SSR-0106600
DSR-0103420	SSR-0106183	SSR-0106602
DSR-0103424	SSR-0106183	SSR-0106509
DSR-0103425	SSR-0106183	SSR-0106601
DSR-0103426	SSR-0106183	SSR-0106605
DSR-0103427	SSR-0106183	SSR-0106606

Duplex	Guide	Passenger
DSR-0103428	SSR-0106183	SSR-0106607
DSR-0103429	SSR-0106183	SSR-0106507
DSR-0103430	SSR-0106183	SSR-0106597
DSR-0103431	SSR-0106183	SSR-0106599
DSR-0103432	SSR-0106587	SSR-0106589
DSR-0103712	SSR-0106224	SSR-0106206
DSR-0103713	SSR-0106516	SSR-0106206
DSR-0103714	SSR-0106517	SSR-0106206
DSR-0103715	SSR-0106514	SSR-0106206
DSR-0103716	SSR-0106515	SSR-0106206
DSR-0103717	SSR-0106518	SSR-0106206
DSR-0103718	SSR-0106512	SSR-0106206
DSR-0103719	SSR-0106519	SSR-0106206
DSR-0103966	SSR-0107427	SSR-0107400
DSR-0103967	SSR-0107427	SSR-0107419
DSR-0103968	SSR-0107427	SSR-0107420
DSR-0103969	SSR-0107427	SSR-0107412
DSR-0103970	SSR-0107427	SSR-0107413
DSR-0103971	SSR-0107427	SSR-0107414
DSR-0103972	SSR-0107427	SSR-0107421
DSR-0103973	SSR-0107427	SSR-0107415
DSR-0104104	SSR-0107428	SSR-0107412
DSR-0104105	SSR-0108082	SSR-0108086
DSR-0104106	SSR-0108084	SSR-0108086
DSR-0104107	SSR-0108085	SSR-0108086
DSR-0104147	SSR-0107428	SSR-0107400
DSR-0104167	SSR-0108193	SSR-0101599
DSR-0104213	SSR-0106222	SSR-0106485
DSR-0104214	SSR-0106222	SSR-0106564
DSR-0104215	SSR-0106222	SSR-0106565
DSR-0104216	SSR-0106222	SSR-0106566
DSR-0104217	SSR-0106222	SSR-0106568
DSR-0104218	SSR-0106222	SSR-0106569
DSR-0104219	SSR-0106222	SSR-0106570
DSR-0104220	SSR-0106222	SSR-0106571
DSR-0104221	SSR-0106222	SSR-0106576
DSR-0104222	SSR-0106222	SSR-0106577
DSR-0104223	SSR-0106222	SSR-0106578
DSR-0104224	SSR-0106222	SSR-0106652
DSR-0104225	SSR-0106222	SSR-0106653
DSR-0104226	SSR-0106222	SSR-0106579
DSR-0104227	SSR-0106222	SSR-0106573
DSR-0104228	SSR-0106222	SSR-0106575

Duplex	Guide	Passenger
DSR-0104229	SSR-0106222	SSR-0106679
DSR-0104230	SSR-0106222	SSR-0106580
DSR-0104231	SSR-0106222	SSR-0106660
DSR-0104232	SSR-0106222	SSR-0106503
DSR-0104233	SSR-0106222	SSR-0106507
DSR-0104234	SSR-0106222	SSR-0106665
DSR-0104235	SSR-0106222	SSR-0106666
DSR-0104236	SSR-0106222	SSR-0106601
DSR-0104237	SSR-0106222	SSR-0106602
DSR-0104238	SSR-0106222	SSR-0106661
DSR-0104239	SSR-0106222	SSR-0106662
DSR-0104240	SSR-0106222	SSR-0106663
DSR-0104241	SSR-0106222	SSR-0106664
DSR-0104305	SSR-0108328	SSR-0108331
DSR-0104456	SSR-0107428	SSR-0108472
DSR-0104457	SSR-0107428	SSR-0108471
DSR-0104458	SSR-0107428	SSR-0108344
DSR-0104459	SSR-0107428	SSR-0108343
DSR-0104460	SSR-0108348	SSR-0107412
DSR-0104461	SSR-0108432	SSR-0106447
DSR-0104462	SSR-0108436	SSR-0106447
DSR-0104463	SSR-0108201	SSR-0106447
DSR-0104464	SSR-0108209	SSR-0106447
DSR-0104465	SSR-0108298	SSR-0107412
DSR-0104466	SSR-0108216	SSR-0107412
DSR-0104467	SSR-0108298	SSR-0107400
DSR-0104468	SSR-0108216	SSR-0107400
DSR-0104469	SSR-0108298	SSR-0107413
DSR-0104470	SSR-0108298	SSR-0108195
DSR-0104477	SSR-0107991	SSR-0107413
DSR-0104478	SSR-0107991	SSR-0107414
DSR-0104479	SSR-0107991	SSR-0107421
DSR-0104480	SSR-0107992	SSR-0107413
DSR-0104481	SSR-0107992	SSR-0107414
DSR-0104482	SSR-0107992	SSR-0107421
DSR-0104483	SSR-0107427	SSR-0107993
DSR-0104484	SSR-0107427	SSR-0108004
DSR-0104485	SSR-0107427	SSR-0108005
DSR-0104486	SSR-0107427	SSR-0107995
DSR-0104487	SSR-0107427	SSR-0107996
DSR-0104488	SSR-0107427	SSR-0107994
DSR-0104489	SSR-0107427	SSR-0107997
DSR-0104490	SSR-0107427	SSR-0107403
DSR-0104491	SSR-0107427	SSR-0107405

Duplex	Guide	Passenger
DSR-0104510	SSR-0108432	SSR-0106213
DSR-0104511	SSR-0108432	SSR-0108818
DSR-0104512	SSR-0108436	SSR-0106213
DSR-0104513	SSR-0108436	SSR-0108818
DSR-0104514	SSR-0107428	SSR-0107413
DSR-0104515	SSR-0107428	SSR-0107414
DSR-0104516	SSR-0107428	SSR-0108441
DSR-0104517	SSR-0107428	SSR-0108725
DSR-0104518	SSR-0107428	SSR-0108442
DSR-0104519	SSR-0107428	SSR-0108728
DSR-0104520	SSR-0107428	SSR-0108729
DSR-0104521	SSR-0107428	SSR-0108730
DSR-0104527	SSR-0108432	SSR-0106565
DSR-0104528	SSR-0108432	SSR-0106566
DSR-0104529	SSR-0108432	SSR-0106568
DSR-0104530	SSR-0108432	SSR-0106569
DSR-0104531	SSR-0108432	SSR-0106571
DSR-0104532	SSR-0108432	SSR-0106576
DSR-0104533	SSR-0108432	SSR-0106503
DSR-0104539	SSR-0108432	SSR-0106506
DSR-0104540	SSR-0108432	SSR-0106507
DSR-0104541	SSR-0108432	SSR-0106508
DSR-0104542	SSR-0108432	SSR-0106509
DSR-0104543	SSR-0108432	SSR-0106601
DSR-0104544	SSR-0108432	SSR-0106602
DSR-0104545	SSR-0108432	SSR-0106665
DSR-0104546	SSR-0108432	SSR-0106666
DSR-0104547	SSR-0108432	SSR-0106661
DSR-0104548	SSR-0108432	SSR-0106662
DSR-0104549	SSR-0108432	SSR-0106663
DSR-0104550	SSR-0108432	SSR-0106664
DSR-0104559	SSR-0108432	SSR-0106485
DSR-0104560	SSR-0108432	SSR-0106448
DSR-0104561	SSR-0108432	SSR-0106449
DSR-0104562	SSR-0108432	SSR-0106450
DSR-0104563	SSR-0108348	SSR-0107413
DSR-0104564	SSR-0108348	SSR-0108819
DSR-0104565	SSR-0108348	SSR-0107414
DSR-0104566	SSR-0108348	SSR-0108820
DSR-0104567	SSR-0108348	SSR-0107421
DSR-0104568	SSR-0108348	SSR-0108821
DSR-0104569	SSR-0108348	SSR-0107422
DSR-0104570	SSR-0108348	SSR-0107415
DSR-0104571	SSR-0108348	SSR-0108822

Duplex	Guide	Passenger
DSR-0104572	SSR-0108348	SSR-0108837
DSR-0104573	SSR-0108348	SSR-0108839
DSR-0104624	SSR-0108348	SSR-0108471
DSR-0104625	SSR-0108348	SSR-0108344
DSR-0104626	SSR-0108348	SSR-0108343
DSR-0104627	SSR-0108842	SSR-0101599
DSR-0104628	SSR-0108843	SSR-0101599
DSR-0104629	SSR-0108844	SSR-0101599
DSR-0104630	SSR-0108845	SSR-0101599
DSR-0104631	SSR-0108846	SSR-0101599
DSR-0104632	SSR-0108847	SSR-0101599
DSR-0104633	SSR-0108848	SSR-0101599
DSR-0104634	SSR-0108849	SSR-0101599
DSR-0104635	SSR-0108850	SSR-0101599
DSR-0104636	SSR-0108851	SSR-0101599
DSR-0104637	SSR-0108852	SSR-0101599
DSR-0104638	SSR-0108853	SSR-0101599
DSR-0104639	SSR-0108854	SSR-0101599
DSR-0104640	SSR-0108855	SSR-0101599
DSR-0104641	SSR-0108856	SSR-0101599
DSR-0104642	SSR-0108857	SSR-0101599
DSR-0104643	SSR-0108858	SSR-0101599
DSR-0104644	SSR-0108859	SSR-0101599
DSR-0104645	SSR-0108896	SSR-0101599
DSR-0104646	SSR-0108897	SSR-0101599
DSR-0104647	SSR-0108898	SSR-0101599
DSR-0104648	SSR-0108899	SSR-0101599
DSR-0104649	SSR-0108900	SSR-0101599
DSR-0104650	SSR-0108901	SSR-0101599
DSR-0104651	SSR-0108902	SSR-0101599
DSR-0104652	SSR-0108903	SSR-0101599
DSR-0104653	SSR-0108904	SSR-0101599
DSR-0104654	SSR-0108905	SSR-0101599
DSR-0104655	SSR-0108906	SSR-0101599
DSR-0105668	SSR-0108348	SSR-0108827
DSR-0105688	SSR-0108298	SSR-0107414
DSR-0105689	SSR-0108298	SSR-0107415
DSR-0105659	SSR-0108348	SSR-0108838
DSR-0105660	SSR-0108348	SSR-0108872
DSR-0105661	SSR-0108348	SSR-0108873
DSR-0105662	SSR-0108348	SSR-0108874
DSR-0105663	SSR-0108348	SSR-0108875
DSR-0105658	SSR-0108348	SSR-0107400
DSR-0105664	SSR-0108348	SSR-0108823

Duplex	Guide	Passenger
DSR-0105665	SSR-0108348	SSR-0108824
DSR-0105666	SSR-0108348	SSR-0108825
DSR-0105667	SSR-0108348	SSR-0108826
DSR-0105669	SSR-0108348	SSR-0108828
DSR-0105671	SSR-0108348	SSR-0108726
DSR-0105672	SSR-0108348	SSR-0108727
DSR-0105788	SSR-0108348	SSR-0111131
DSR-0105789	SSR-0108348	SSR-0111132
DSR-0105791	SSR-0108348	SSR-0111136
DSR-0105792	SSR-0108348	SSR-0111137

Table 1H

GUIDE SEQUENCE	MW (calculated)	MW (ESI-MS)
SSR-0104474	7905.44	7906.3
SSR-0104037	7922.77	7922.9
SSR-0106188	7935.73	7936.9
SSR-0106183	8014.81	8013.3
SSR-0106222	8014.81	8012.1
SSR-0106225	7935.73	7936.4
SSR-0106224	8014.81	8013.3
SSR-0106223	7935.73	7934.4
SSR-0106220	8014.81	8015.2
SSR-0106221	7935.73	7936.2
SSR-0106266	8012.62	8013.3
SSR-0106267	8012.62	8013.1
SSR-0106268	8012.62	8013.5
SSR-0106269	8012.62	8013.5
SSR-0106270	8012.62	8013.1
SSR-0106271	8012.62	8013.3
SSR-0106272	8012.62	8013.1
SSR-0106273	8012.62	8013.1
SSR-0106274	8107.77	8108.6
SSR-0106275	8107.77	8108.8
SSR-0106276	8107.77	8108.6
SSR-0106277	8107.77	8108.7
SSR-0106278	8107.77	8108.7
SSR-0106279	8107.77	8108.6
SSR-0106280	8107.77	8108.5
SSR-0106281	8202.92	8203.2
SSR-0106282	8202.92	8203.5

SSR-0106283	8202.92	8203.9
SSR-0106284	8202.92	8203.2
SSR-0106285	8202.92	8203.5
SSR-0106286	8202.92	8203.5
SSR-0106287	8298.07	8299.0
SSR-0106288	8202.92	8203.7
SSR-0106289	8237.92	8238.0
SSR-0106290	8178.86	8179.4
SSR-0106291	8202.92	8203.6
SSR-0106292	8202.92	8203.9
SSR-0106293	7917.47	7918.1
SSR-0106294	7917.47	7918.2
SSR-0106295	7917.47	7918.2
SSR-0106296	7917.47	7918.3
SSR-0106297	7917.47	7918.3
SSR-0106298	7917.47	7918.1
SSR-0106299	7917.47	7918.1
SSR-0106300	7917.47	7918.3
SSR-0106301	7917.47	7918.2
SSR-0106302	7905.44	7906.5
SSR-0106303	7905.44	7906.5
SSR-0106304	7905.44	7906.7
SSR-0106305	7905.44	7906.5
SSR-0106306	7905.44	7906.2
SSR-0106307	7905.44	7906.4
SSR-0106480	8177.08	8175.8
SSR-0106481	8177.08	8176.3
SSR-0106482	8066.89	8065.7
SSR-0106483	8085.04	8084.4
SSR-0106484	8085.04	8084.1
SSR-0106487	7190.80	7189.7
SSR-0106479	8158.93	8157.9
SSR-0104473	7822.32	7824.1
SSR-0105217	7639.10	7640.7
SSR-0106453	7806.32	7804.1
SSR-0106454	7806.32	7804.2
SSR-0106455	7806.32	7804.2
SSR-0106456	7806.32	7803.7
SSR-0106457	7792.30	7790.2
SSR-0106584	7922.77	7921.9
SSR-0104186	7914.36	7912.4

SSR-0106620	7914.36	7912.9
SSR-0104189	7914.36	7913.1
SSR-0106621	7914.36	7913.0
SSR-0106530	7818.35	7818.3
SSR-0106527	7818.35	7818.4
SSR-0106528	7806.32	7806.6
SSR-0106533	7806.32	7806.6
SSR-0106536	7820.35	7820.9
SSR-0106625	7616.02	7615.7
SSR-0106520	7616.02	7616.1
SSR-0106532	7818.35	7818.3
SSR-0106522	7832.38	7832.6
SSR-0106523	7832.38	7832.7
SSR-0106524	7818.35	7818.3
SSR-0106526	7806.32	7806.5
SSR-0106534	7820.35	7820.5
SSR-0106627	7616.02	7615.8
SSR-0106626	7642.08	7642.1
SSR-0106628	7628.05	7628.3
SSR-0106525	7806.32	7806.6
SSR-0106535	7806.32	7806.6
SSR-0106537	7820.35	7821.0
SSR-0106538	7820.35	7821.2
SSR-0106539	7820.35	7820.9
SSR-0106521	7820.35	7820.3
SSR-0106529	7806.32	7806.7
SSR-0106531	7806.32	7806.6
SSR-0106587	7902.69	7902.3
SSR-0106516	7998.76	7996.4
SSR-0106517	7998.76	7996.5
SSR-0106514	8053.8	8051.6
SSR-0106515	8053.8	8051.8
SSR-0106518	8037.81	8035.3
SSR-0106512	8178.22	8176
SSR-0106519	8270.26	8268.1
SSR-0107427	8191.02	8190.2
SSR-0107428	8078.53	8080.3
SSR-0108082	8179.09	8180.5
SSR-0108084	8066.60	8069.6
SSR-0108085	7971.45	7973.6
SSR-0108193	7953.35	7955.3

SSR-0108328	7814.26	7812.5
SSR-0108348	8117.52	8116.2
SSR-0108432	8077.86	8077.1
SSR-0108436	7965.37	7965.0
SSR-0108201	8038.87	8037.3
SSR-0108209	7926.38	7924.8
SSR-0108298	8110.67	8109.2
SSR-0108216	7983.38	7982.0
SSR-0107991	7851.14	7851.8
SSR-0107992	7851.14	7852.3
SSR-0108842	7955.36	7954.5
SSR-0108843	7955.36	7954.6
SSR-0108844	7957.37	7956.6
SSR-0108845	8039.44	8039.0
SSR-0108846	8039.44	8039.2
SSR-0108847	8125.53	8124.7
SSR-0108848	8035.49	8034.4
SSR-0108849	8035.49	8034.5
SSR-0108850	8117.63	8117.3
SSR-0108851	7967.37	7966.3
SSR-0108852	7967.37	7966.4
SSR-0108853	7981.39	7980.4
SSR-0108854	8001.39	8001.4
SSR-0108855	8001.39	8000.4
SSR-0108856	8049.43	8048.8
SSR-0108857	8007.44	8006.8
SSR-0108858	8007.44	8007.8
SSR-0108859	8061.53	8060.5
SSR-0108896	7999.46	8000.3
SSR-0108897	8067.58	8068.4
SSR-0108898	8137.72	8138.6
SSR-0108899	8123.69	8124.4
SSR-0108900	8151.75	8153.1
SSR-0108901	8418.24	8418.9
SSR-0108902	8207.85	8209.5
SSR-0108903	8235.91	8237.2
SSR-0108904	8292.00	8293.7
SSR-0108905	8306.03	8307.4
SSR-0108906	8179.80	8181.4

Table 1I

PASSENGER SEQUENCE	MW (calculated)	MW (ESI-MS)
SSR-0101599	8686.45	8686.3
SSR-0104026	7261.32	7258.9
SSR-0106208	7197.04	7197.7
SSR-0106210	7245.25	7245.6
SSR-0106212	7373.81	7374.4
SSR-0106218	7429.92	7430.9
SSR-0106447	7163.81	7162.3
SSR-0106211	7357.74	7359.2
SSR-0106215	7269.22	7269.6
SSR-0106217	7317.43	7318.4
SSR-0106445	7163.81	7164.3
SSR-0106446	7219.91	7220.2
SSR-0106207	7180.97	7181.8
SSR-0106213	7188.87	7187.2
SSR-0106214	7253.15	7253.4
SSR-0106219	7445.99	7446.5
SSR-0106448	7219.91	7220.9
SSR-0106452	7471.72	7472.1
SSR-0106206	7116.69	7115.6
SSR-0106216	7301.36	7301.6
SSR-0106449	7258.96	7259.5
SSR-0106450	7315.06	7315.4
SSR-0106451	7415.62	7416.5
SSR-0106209	7229.18	7227.7
SSR-0105234	8944.72	8947.3
SSR-0106563	7116.69	7115.3
SSR-0106630	8670.45	8670.1
SSR-0106629	8670.45	8670.3
SSR-0106640	8670.45	8670.1
SSR-0106637	8670.45	8670.3
SSR-0106638	8684.48	8683.5
SSR-0106632	8670.45	8670.6
SSR-0106633	8684.48	8683.5
SSR-0106634	8670.45	8670.3
SSR-0106643	8670.45	8670.4
SSR-0106635	8684.48	8684.0
SSR-0106631	8684.48	8684.0
SSR-0106603	7079.64	7078.7
SSR-0106510	7483.75	7480.8

SSR-0106604	7149.78	7149.0
SSR-0106506	7136.79	7134.7
SSR-0106511	7274.96	7273.1
SSR-0106508	7231.94	7230.0
SSR-0106513	7431.62	7429.4
SSR-0106503	7009.51	7007.6
SSR-0106598	7231.94	7231.5
SSR-0106600	7442.34	7441.4
SSR-0106602	7442.34	7441.3
SSR-0106509	7327.09	7325.3
SSR-0106601	7386.24	7385.1
SSR-0106605	7117.69	7116.2
SSR-0106606	7117.69	7116.4
SSR-0106607	7097.61	7097.3
SSR-0106507	7231.94	7230.4
SSR-0106597	7136.79	7136.5
SSR-0106599	7386.24	7384.9
SSR-0106589	7273.84	7273.0
SSR-0107400	6991.69	6992.0
SSR-0107419	7145.99	7147.1
SSR-0107420	7202.09	7202.1
SSR-0107412	7300.29	7300.5
SSR-0107413	6896.54	6897.0
SSR-0107414	7050.84	7051.5
SSR-0107421	7106.94	7107.5
SSR-0107415	7205.12	7205.8
SSR-0108086	7327.23	7329.5
SSR-0106485	7104.66	7105.9
SSR-0106564	7283.82	7281.7
SSR-0106565	7522.23	7522.8
SSR-0106566	7550.28	7549.5
SSR-0106568	7546.25	7545.6
SSR-0106569	7666.44	7665.6
SSR-0106570	7696.47	7696.2
SSR-0106571	7522.23	7522.0
SSR-0106576	7608.32	7607.9
SSR-0106577	7407.91	7408.2
SSR-0106578	7506.10	7505.6
SSR-0106652	7602.23	7601.1
SSR-0106653	7600.21	7600.7
SSR-0106579	7645.73	7645.7

SSR-0106573	8368.12	8367.6
SSR-0106575	8543.26	8543.0
SSR-0106679	8287.95	8287.9
SSR-0106580	7440.99	7440.7
SSR-0106660	7757.46	7757.8
SSR-0106665	7318.09	7319.2
SSR-0106666	7430.30	7430.8
SSR-0106661	7534.25	7535
SSR-0106662	7590.35	7590.9
SSR-0106663	7688.53	7689.2
SSR-0106664	7800.74	7801.7
SSR-0108331	7654.62	7653.4
SSR-0108472	8198.29	8196.7
SSR-0108471	10646.07	10644.5
SSR-0108344	10555.99	10554.1
SSR-0108343	8879.10	8877.5
SSR-0108195	6801.39	6800.2
SSR-0107993	7043.93	7045.2
SSR-0108004	7139.08	7140.1
SSR-0108005	7139.08	7140.1
SSR-0107995	7082.98	7084.1
SSR-0107996	7082.98	7084.0
SSR-0107994	6928.68	6930.2
SSR-0107403	6991.69	6992.8
SSR-0107405	6896.54	6896.6
SSR-0108818	7497.47	7496.0
SSR-0108441	7201.87	7200.2
SSR-0108725	7201.87	7200.6
SSR-0108442	7168.84	7168.3
SSR-0108728	7337.96	7337.0
SSR-0108729	7337.96	7336.9
SSR-0108730	7304.93	7304.1
SSR-0108819	7022.78	7022.8
SSR-0108820	7078.89	7079.1
SSR-0108821	7135.00	7134.7
SSR-0107422	7191.09	7191.1
SSR-0108822	7317.33	7317.0
SSR-0108837	7202.04	7201.7
SSR-0108839	7204.06	7203.9
SSR-0108827	7580.79	7580.2
SSR-0108838	7178.02	7178.6

SSR-0108872	7206.08	7207.3
SSR-0108873	7176.01	7177.2
SSR-0108874	7178.02	7179.8
SSR-0108875	7322.24	7323.6
SSR-0108823	7244.17	7243.8
SSR-0108824	7356.39	7355.7
SSR-0108825	7412.49	7411.4
SSR-0108826	7468.61	7468.6
SSR-0108828	7608.85	7608.5
SSR-0108726	6995.71	6994.9
SSR-0108727	7161.99	7160.8
SSR-0111131	7342.16	7340.1
SSR-0111132	7398.27	7395.9
SSR-0111136	7437.31	7435.3
SSR-0111137	7493.42	7491.7

Notes:

HELM Description and Base Sequence, due to their length, may be divided into multiple lines in Table 1 (e.g., Tables 1A, 1B, 1C, and 1D). Unless otherwise specified, all oligonucleotides in Table 1 are single-stranded. As appreciated by those skilled in the art, nucleoside units are unmodified and contain unmodified nucleobases and 2'-deoxy sugars unless otherwise indicated (e.g., with m, [fl2r], etc.); linkages, unless otherwise indicated, are natural phosphate linkages; and acidic/basic groups may independently exist in their salt forms. If a sugar is not specified, the sugar is a natural DNA sugar; and if an internucleotidic linkage is not specified, the internucleotidic linkage is a natural phosphate linkage. A natural DNA sugar may also be indicated with "d" as in d(G), d(A), d(C), d(T), etc., and a natural phosphate linkage may be indicated with "p" in Table (e.g., Tables 1B 1C,1D, and 1E). Oligonucleotides in Table 1 are described using the Hierarchical Editing Language for Macromolecules (HELM), which is described in, e.g., Zhang, T. et al. J Chem Inf Model. 2012 Oct 22;52(10):2796-806 and Milton, J. et al. J Chem Inf Model. 2017 Jun 26;57(6):1233-1239, which are incorporated herein by reference. As described in Zhang et al., 2012 and Milton et al., 2017, connections between oligonucleotides, linker moieties, GalNAc moieties, etc. may be indicated in HELM, for example, as the following: CHEM1,RNA1,1:R1-1:R1, wherein CHEM1 is, e.g., a first linker or moiety, RNA1 is an oligonucleotide, and 1:R1-1:R1 indicates that CHEM1 is linked via a first attachment point to a first attachment point on a first monomer of RNA1, as described herein (see, e.g., below). A double-stranded oligonucleotide may be indicated in HELM, for

example, as the following: RNA1, wherein RNA1 is, e.g., a first oligonucleotide strand of a double-stranded oligonucleotide, and RNA2, wherein RNA2 is, e.g., a second oligonucleotide strand of the double-stranded oligonucleotide. Various moieties and modifications (e.g., internucleotidic linkages, sugars, nucleobases, etc.) are described in the present disclosure including the below:

m: 2'-OMe or 2-*O*-methylribose;

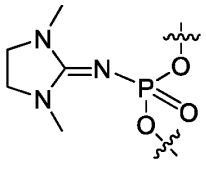
[fl2r]: 2'-F or 2-fluororibose;

PO or p: phosphodiester (phosphate);

PS or [sp]: phosphorothioate;

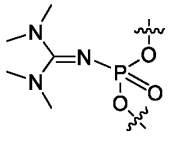
*R*p or [Rsp]: phosphorothioate in the *R*p configuration;

*S*p or [Ssp]: phosphorothioate or phosphoryl guanidine in the *S*p configuration;

n001:  or *N*-(1,3-dimethylimidazolidin-2-ylidene)phosphoramidate;

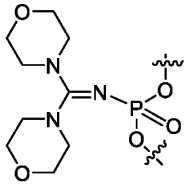
[n001R]: n001 in *R*p configuration;

[n001S]: n001 in *S*p configuration;

n003:  or *N*-(1,3-dimethylimidazolidin-2-ylidene)phosphoramidate;

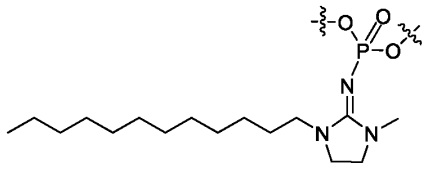
[n003R]: n003 in *R*p configuration;

[n003S]: n003 in *S*p configuration;

n008:  or *N*-(di(morpholin-1-yl)methylene)phosphoramidate;

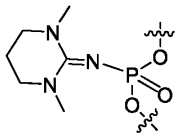
[n008R]: n008 in *R*p configuration;

[n008S]: n008 in *S*p configuration;

n009:  or *N*-(1-docecyl-3-methylimidazolidin-2-ylidene)phosphoramidate;

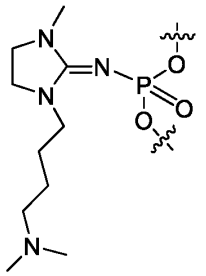
[n009R]: n009 in *R*p configuration;

[n009S]: n009 in *S*p configuration;

n025:  or *N*-(1,3-dimethyltetrahydropyrimidin-2(1H)-ylidene)phosphoramidate;

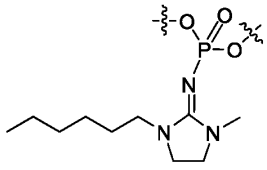
[n025R]: n025 in *R*p configuration;

[n025S]: n025 in *S*p configuration;

n029:  or *N*-(1-(4-dimethylamino-butyl)-3-methylimidazolidin-2-ylidene)phosphoramidate;

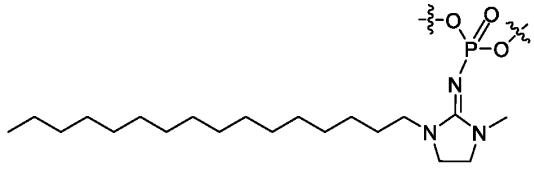
[n029R]: n029 in *R*p configuration;

[n029S]: n029 in *S*p configuration;

n031:  or *N*-(1-hexyl-3-methylimidazolidin-2-ylidene)phosphoramidate;

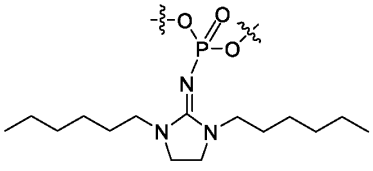
[n031R]: n031 in *R*p configuration;

[n031S]: n031 in *S*p configuration;

n033:  or *N*-(1-hexadecyl-3-methylimidazolidin-2-ylidene)phosphoramidate;

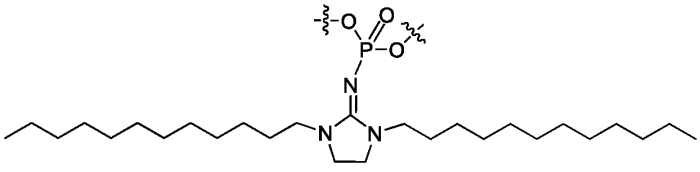
[n033R]: n033in *R*p configuration;

[n033S]: n033 in *S*p configuration;

n037:  or *N*,*N*-(1,3-dihexylimidazolidin-2-ylidene)phosphoramidate;

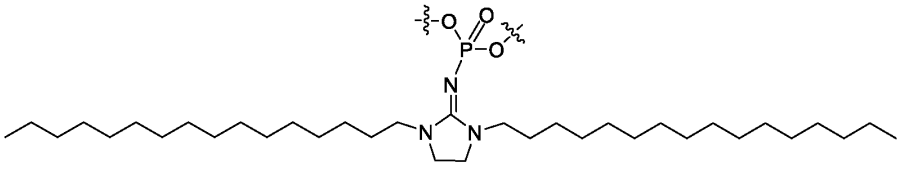
[n037R]: n037in *R*p configuration;

[n037S]: n037 in *S*p configuration;

n039:  or *N*,*N*-(1,3-didodecylimidazolidin-2-ylidene)phosphoramidate;

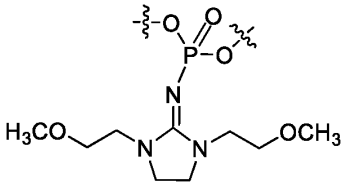
[n039R]: n039 in *R*p configuration;

[n039S]: n039 in *S*p configuration;

n040:  or *N*-(1,3-dihexadecylimidazolidin-2-ylidene)phosphoramidate;

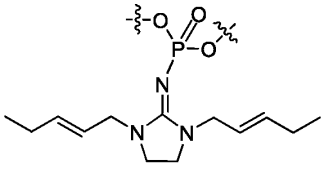
[n040R]: n040in *R*p configuration;

[n040S]: n040 in *S*p configuration;

n043:  or *N*-(1,3-di(2-methoxyethyl)imidazolidin-2-ylidene)phosphoramidate;

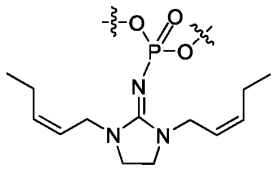
[n043R]: n043 in *R*p configuration;

[n043S]: n043 in *S*p configuration;

n046:  or *N*,*N*-(1,3-di[(2*E*)-pent-2-en-1-yl]imidazolidin-2-ylidene)phosphoramidate;

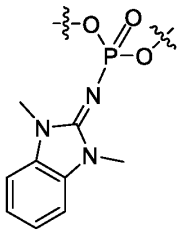
[n046R]: n046in *R*p configuration;

[n046S]: n046 in *S*p configuration;

n047:  or *N*,*N*-(1,3-di[(2*Z*)-pent-2-en-1-yl]imidazolidin-2-ylidene)phosphoramidate;

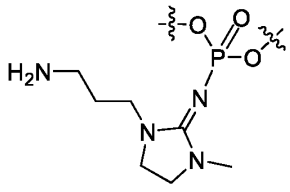
[n047R]: n047in *R*p configuration;

[n047S]: n047 in *S*p configuration;

n065:  or *N*,*N*-(1,3-dimethyl-1,3-dihydro-2*H*-benzo[d]imidazol-2-ylidene)phosphoramidate;

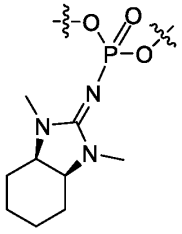
[n065R]: n065 in *R*p configuration;

[n065S]: n065 in *S*p configuration;

n069:  or *N*,*N*-(1-(3-aminopropyl)-3-methylimidazolidin-2-ylidene)phosphoramidate;

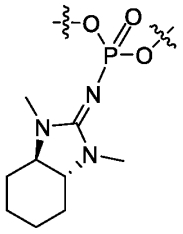
[n069R]: n069 in *R*p configuration;

[n069S]: n069 in *S*p configuration;

n070:  or *N*,*N*-(3a*R*,7a*S*-1,3,dimethyloctahydro-2*H*-benzo[d]imidazol-2ylidene)phosphoramidate;

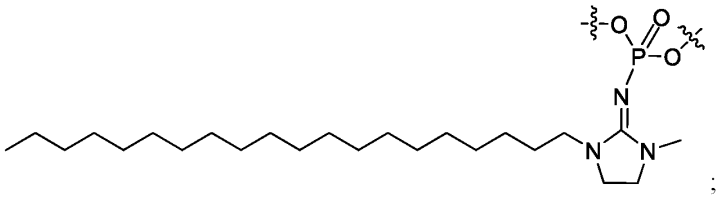
[n070R]: n070 in *R*p configuration;

[n070S]: n070 in *S*p configuration;

n071:  or *N*,*N*-(3a*R*,7a*R*-1,3,dimethyloctahydro-2*H*-benzo[d]imidazol-2ylidene)phosphoramidate;

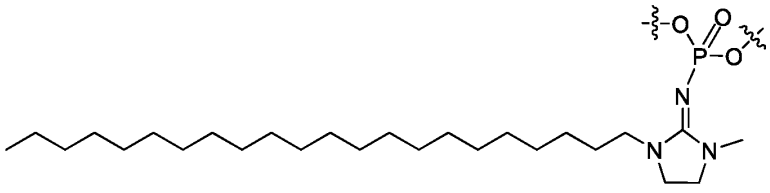
[n071R]: n071 in *R*p configuration;

[n071S]: n071 in *S*p configuration;

n076:  ;

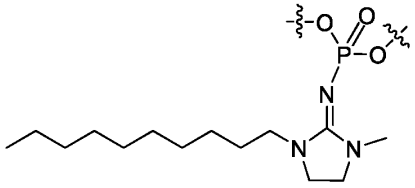
[n076R]: n076in *R*p configuration;

[n076S]: n076 in *S*p configuration;

n077:  or *N*-(1,3-dimethylimidazolidin-2-ylidene)phosphoramidate;

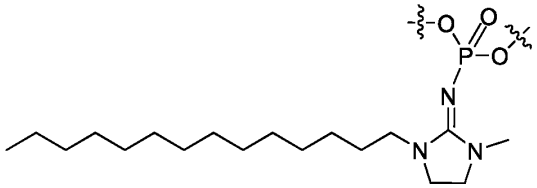
[n077R]: n077in *R*p configuration;

[n077S]: n077 in *S*p configuration;

n082:  or (2*Z*)-*N*-(disub phosphoryl)-1-decyl-3-methylimidazolidin-2-imine;

[n082R]: n082in *R*p configuration;

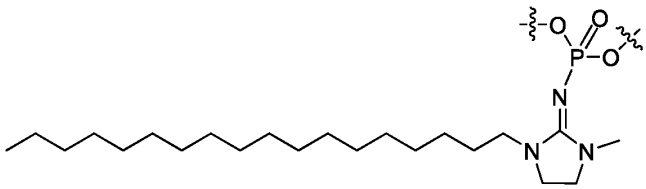
[n082S]: n082 in *S*p configuration;

n083:  or (2*Z*)-*N*-(disub phosphoryl)-1-

tetradecyl-3-methylimidazolidin-2-imine;

[n083R]: n083in *R*p configuration;

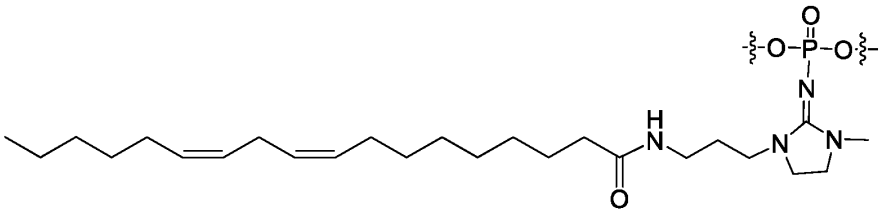
[n083S]: n083 in *S*p configuration;

n084:  or (2*Z*)-*N*-(disub

phosphoryl)-1-octadecyl-3-methylimidazolidin-2-imine;

[n084R]: n084in *R*p configuration;

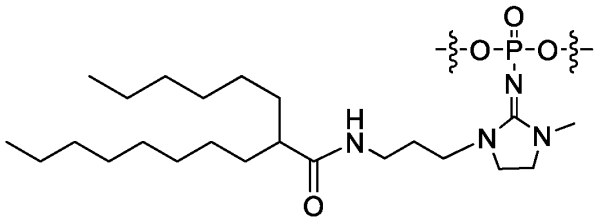
[n084S]: n084 in *S*p configuration;

n086:  or PN

linoleic acid;

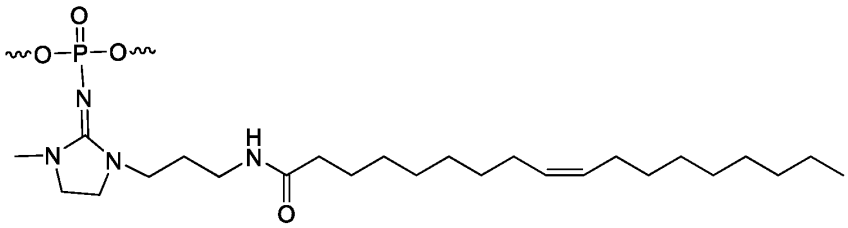
[n086R]: n086 in *R*p configuration;

[n086S]: n086 in *S*p configuration;

n087:  or PN hexyldecanoic acid;

[n087R]: n087 in *R*p configuration;

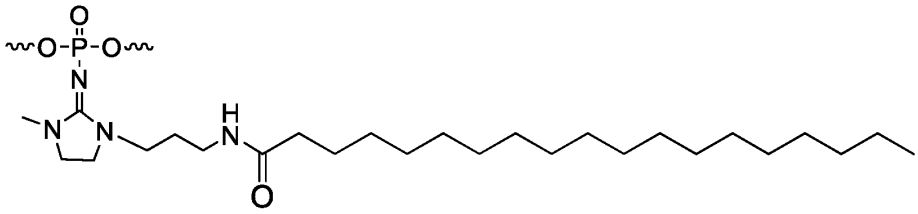
[n087S]: n087 in *S*p configuration;

n088:  or PN

oleic acid;

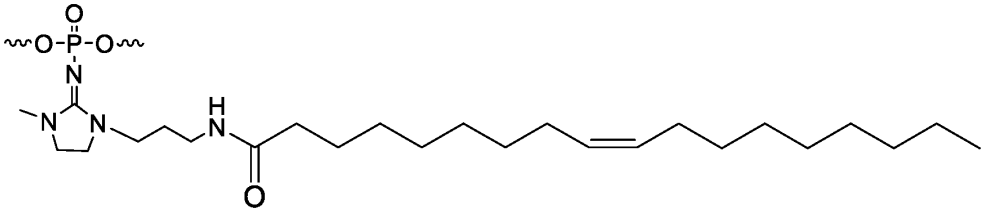
[n088R]: n088 in *R*p configuration;

[n088S]: n088 in *S*p configuration;

n089:  or *N*-(1-(3-stearamidopropyl)-methyl-3-methylimidazolidin-2-ylidene)phosphoramidate;

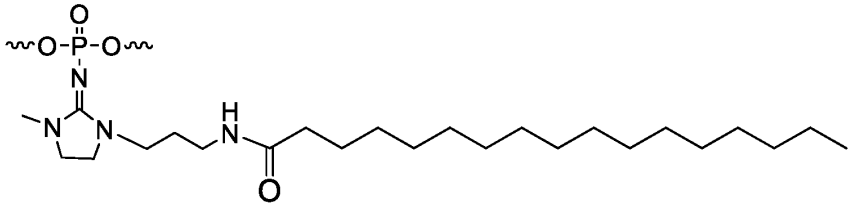
[n089R]: n089 in *R*p configuration;

[n089S]: n089 in *S*p configuration;

n090:  or *N*-(1-(3-palmitoleamidopropyl)-methyl-3-methylimidazolidin-2-ylidene)phosphoramidate;

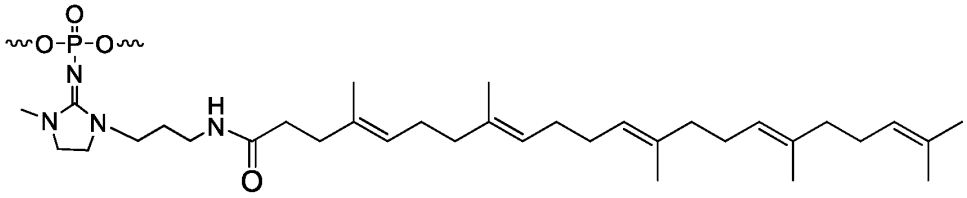
[n090R]: n090 in *R*p configuration;

[n090S]: n090 in *S*p configuration;

n091:  or *N*-(1-(3-palmitamidopropyl)-methyl-3-methylimidazolidin-2-ylidene)phosphoramidate;

[n091R]: n091 in *R*p configuration;

[n091S]: n091 in *S*p configuration;

n092:  or *N*-(1-(3-turbinaramidopropyl)-methyl-3-methylimidazolidin-2-ylidene)phosphoramid;

[n092R]: n092 in *R*p configuration;

[n092S]: n092 in *S*p configuration;

[ptz]: (1*H*-1,2,3-triazol-4-yl)phosphonate;

[Rm5d5m]: 5-(*R*)-methyl-5-deoxy-2-*O*-methylribose;

[vped5m]: 5-(*E*)-vinylphosphonate-5-deoxy-2-methylribose;

[d25r]: 2,5-deoxyribose;

[Rm5m]: 5-(*R*)-methyl-2-*O*-methylribose;

[Rm5fl2r]: 5-(*R*)-methyl-2-fluororibose;

[Sm5fl2r]: 5-(*S*)-methyl-2-fluororibose;

[Sgna]: *S*-propanetriol;

[Mucin3C5oyl]: triantennary mucin 5 AC inhibitor with a C5 linker;

[hexdec2r]: 2-*O*-hexadecylribose;

[C16oyl]: palmitic acid;

[C18oyl]: octadecanoic acid (stearic acid);

[lin]: linoleic acid;

[turb]: turbinaric acid;

[chol3o]: cholesterol-3-ester;

[2hexC10oyl]: 2-hexyldecanoic acid;

[Hexa3C12oyl]: triantennary hexanoic acid with C12 linker;

[Bam3C5oyl]: triantennary benzamide with C5 linker;

[oylC20oyl]: 20-oxoicosanoic acid;

[Muco]: E,E-muconic acid;

[oylZ58C13oyl]: *Z*,*Z*-tridec-5,8-dienedioic acid;

[Srl1C11oyl]: 5-chloro-1,4-dihydro-4-methyl-2-quinazolinamine, C11oyl linker;

[Citr]: L-citruline;

[Phodec]: 10-(4-(2-carboxyethyl)phenoxy)decanoic acid;

[EPhodec]: (*E*)-10-(4-(2-carboxyvinyl)phenoxy)decanoic acid;

[Bardoyl]: bardoxolone (acid-linked);

[anis3C5oyl]: *R*-*N*-(1,3-dimethylimidazolidin-2-ylidene)phosphoramidate;

[thpyr]: 2,3-dideoxy-beta-D-glucopyranose;

[Int3C5oyl_1]: trientenary AVB6 (integrin) receptor ligand-1 with C5 linker;

[Alkyn3C5oyl]: triantennary alkyne v2 with C5 linker;

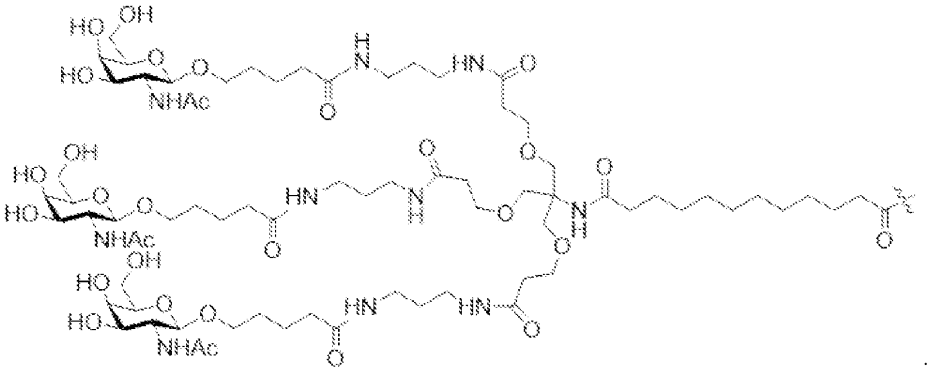
[Glu1C5oyl]: mono glucose, C5oyl linker;

[bMan1C5oyl]: mono beta mannose, C5oyl linker;

[AmheptC3oyl]: aminoheptanedioic acid with a C3 linker;

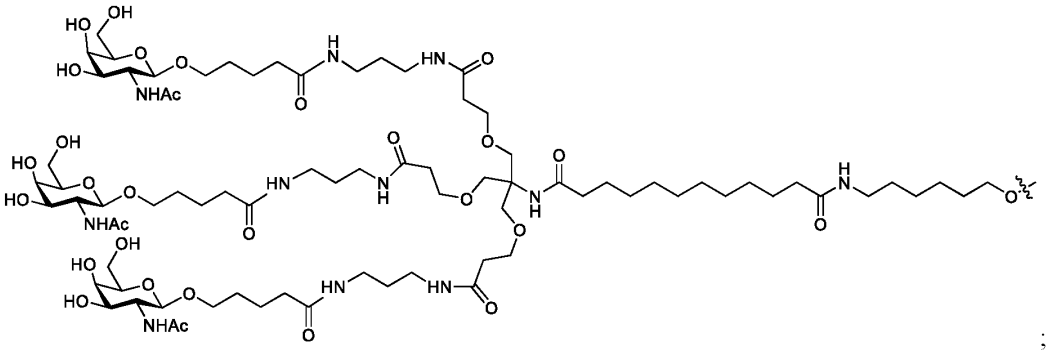
[GalNAc1pyr]: mono GalNAc C5-amino-C6-pyrrolidine

[GalNAc3C12oyl]: triantennary GalNAc with C12 linker or



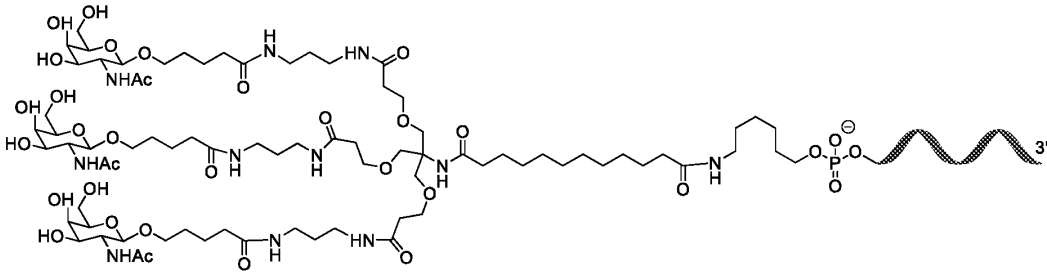
;

[GalNAc3C12oyl][nC6o]:



;

[GalNAc3C12oyl][nC6o] conjugated to the 5'-end of an oligonucleotide:



 = oligonucleotide chain

nC6o or [nC6o]: $-NH-(CH_2)_6-$ linker (C6 linker, C6 amine linker or C6 amino linker), connected to one moiety, e.g., CHEM2, through −NH− (e.g., forming an amide group −C(O)−NH−), and, in various cases, the 5'-end of the oligonucleotide chain through a linkage (e.g., if the 5'-end of an oligonucleotide contains p, through a phosphate linkage (PO or p); if

the 5'-end of an oligonucleotide contains [sp], through a phosphorothioate linkage (PS or [sp]), e.g., [nC6o]: 6-aminohexanol or $-NH-(CH_2)_6-$ linker (C6 linker, C6 amine linker or C6 amino linker), connected to, e.g., the 5'-end of the oligonucleotide chain through a phosphate linkage as the chemical structure above for [GalNAc3C12oyl][nC6o] indicates.

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Double Stranded Oligonucleotide Lengths

As appreciated by those skilled in the art, ds oligonucleotides can be of various lengths to provide desired properties and/or activities for various uses. Many technologies for assessing, selecting and/or optimizing ds oligonucleotide length are available in the art and can be utilized in accordance with the present disclosure. As demonstrated herein, in certain embodiments, dsRNAi oligonucleotides are of suitable lengths to hybridize with their targets and reduce levels of their targets and/or an encoded product thereof. In certain embodiments, a ds oligonucleotide is long enough to recognize a target nucleic acid (e.g., a target mRNA). In certain embodiments, a ds oligonucleotide is sufficiently long to distinguish between a target nucleic acid and other nucleic acids (e.g., a nucleic acid having a base sequence which is not a target sequence) to reduce off-target effects. In certain embodiments, a dsRNAi oligonucleotide is sufficiently short to reduce complexity of manufacture or production and to reduce cost of products.

Internucleotidic Linkages

In certain embodiments, ds oligonucleotides comprise base modifications, sugar modifications, and/or internucleotidic linkage modifications. Various internucleotidic linkages can be utilized in accordance with the present disclosure to link units comprising nucleobases, e.g., nucleosides. In certain embodiments, provided ds oligonucleotides comprise both one or more modified internucleotidic linkages and one or more natural phosphate linkages. As widely known by those skilled in the art, natural phosphate linkages are widely found in natural DNA and RNA molecules; they have the structure of $-OP(O)(OH)O-$, connect sugars in the nucleosides in DNA and RNA, and may be in various salt forms, for example, at physiological pH (about 7.4), natural phosphate linkages are predominantly exist in salt forms with the anion being $-OP(O)(O^-)O-$. A modified internucleotidic linkage, or a non-natural phosphate linkage, is an internucleotidic linkage that is not natural phosphate linkage or a salt form thereof. Modified internucleotidic linkages, depending on their structures, may also be in their salt forms. For example, as appreciated by those skilled in the art, phosphorothioate internucleotidic

linkages which have the structure of −OP(O)(SH)O− may be in various salt forms, e.g., at physiological pH (about 7.4) with the anion being −OP(O)(S^-)O−.

Without wishing to be bound by any particular theory, the present disclosure notes that a neutral internucleotidic linkage can be more hydrophobic than a phosphorothioate internucleotidic linkage (PS), which can be more hydrophobic than a natural phosphate linkage (PO). Typically, unlike a PS or PO, a neutral internucleotidic linkage bears less charge. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages into a ds oligonucleotide may increase the ds oligonucleotides' ability to be taken up by a cell and/or to escape from endosomes. Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more neutral internucleotidic linkages can be utilized to modulate melting temperature of duplexes formed between a ds oligonucleotide and its target nucleic acid.

Without wishing to be bound by any particular theory, the present disclosure notes that incorporation of one or more non-negatively charged internucleotidic linkages, e.g., neutral internucleotidic linkages, into a ds oligonucleotide may be able to increase the ds oligonucleotide's ability to mediate a function such as target adenosine editing.

In some embodiments, an oligonucleotide comprises a modified internucleotidic linkage (e.g., a modified internucleotidic linkage having the structure of Formula **I**, **I-a**, **I-b**, or **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc., or a salt form thereof) as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612 the internucleotidic linkages (e.g., those of Formula **I**, **I-a**, **I-b**, or **I-c**, **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc.,) of each of which are independently incorporated herein by reference. In some embodiments, a modified internucleotidic linkage is a non-negatively charged internucleotidic linkage. In some embodiments, provided oligonucleotides comprise one or more non-negatively charged internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic linkage is a positively charged internucleotidic linkage. In some embodiments, a non-negatively charged internucleotidic linkage is a neutral internucleotidic linkage. In some embodiments, the present disclosure provides oligonucleotides comprising one or more neutral internucleotidic linkages. In some embodiments, a non-negatively charged internucleotidic

linkage or a neutral internucleotidic linkage (e.g., one of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc.) is as described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612. In some embodiments, a non-negatively charged internucleotidic linkage or neutral internucleotidic linkage is one of Formula **I-n-1**, **I-n-2**, **I-n-3**, **I-n-4**, **II**, **II-a-1**, **II-a-2**, **II-b-1**, **II-b-2**, **II-c-1**, **II-c-2**, **II-d-1**, **II-d-2**, etc. as described in WO 2018/223056, WO 2019/032607, WO 2019/075357, WO 2019/032607, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, such internucleotidic linkages of each of which are independently incorporated herein by reference.

As appreciated by those skilled in the art, many other types of internucleotidic linkages may be utilized in accordance with the present disclosure, for example, those described in U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,177,195; 5,023,243; 5,034,506; 5,166,315; 5,185,444; 5,188,897; 5,214,134; 5,216,141; 5,235,033; 5,264,423; 5,264,564; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,938; 5,405,939; 5,434,257; 5,453,496; 5,455,233; 5,466,677; 5,466,677; 5,470,967; 5,476,925; 5,489,677; 5,519,126; 5,536,821; 5,541,307; 5,541,316; 5,550,111; 5,561,225; 5,563,253; 5,571,799; 5,587,361; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,625,050; 5,633,360; 5,64,562; 5,663,312; 5,677,437; 5,677,439; 6,160,109; 6,239,265; 6,028,188; 6,124,445; 6,169,170; 6,172,209; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; or RE39464. In certain embodiments, a modified internucleotidic linkage is one described in US 9982257, US 20170037399, US 20180216108, WO 2017192664, WO 2017015575, WO2017062862, WO 2018067973, WO 2017160741, WO 2017192679, WO 2017210647, WO 2018098264, PCT/US18/35687, PCT/US18/38835, or PCT/US18/51398, the nucleobases, sugars, internucleotidic linkages, chiral auxiliaries/reagents, and technologies for oligonucleotide synthesis (reagents, conditions, cycles, etc.) of each of which is independently incorporated herein by reference.

In certain embodiments, a ds oligonucleotide comprises one or more internucleotidic linkages that improve one or more pharmaceutical properties and/or activities of the oligonucleotide. It is well documented in the art that certain oligonucleotides are rapidly

degraded by nucleases and exhibit poor cellular uptake through the cytoplasmic cell membrane (Poijarvi-Virta et al., Curr. Med. Chem. (2006), 13(28);3441-65; Wagner et al., Med. Res. Rev. (2000), 20(6):417-51; Peyrottes et al., Mini Rev. Med. Chem. (2004), 4(4):395-408; Gosselin et al., (1996), 43(1):196-208; Bologna et al., (2002), Antisense & Nucleic Acid Drug Development 12:33-41). Vives et al. (Nucleic Acids Research (1999), 27(20):4071-76) reported that tert-butyl SATE pro-oligonucleotides displayed markedly increased cellular penetration compared to the parent oligonucleotide under certain conditions.

Various types of internucleotidic linkages may be utilized in combination of other structural elements, e.g., sugars, to achieve desired ds oligonucleotide properties and/or activities. For example, the present disclosure routinely utilizes modified internucleotidic linkages and modified sugars, optionally with natural phosphate linkages and natural sugars, in designing ds oligonucleotides. In certain embodiments, the present disclosure provides a ds oligonucleotide comprising one or more modified sugars. In certain embodiments, the present disclosure provides a ds oligonucleotide comprising one or more modified sugars and one or more modified internucleotidic linkages, one or more of which are natural phosphate linkages.

Double Stranded Oligonucleotide Compositions

Among other things, the present disclosure provides various ds oligonucleotide compositions. In certain embodiments, the present disclosure provides ds oligonucleotide compositions of ds oligonucleotides described herein. In certain embodiments, a ds oligonucleotide composition, e.g., a dsRNAi oligonucleotide composition, comprises a plurality of a ds oligonucleotide described in the present disclosure. In certain embodiments, a ds oligonucleotide composition, e.g., a dsRNAi oligonucleotide composition, is chirally controlled. In certain embodiments, a ds oligonucleotide composition, e.g., a dsRNAi oligonucleotide composition, is not chirally controlled (stereorandom).

In certain embodiments, the present disclosure encompasses technologies for designing and preparing chirally controlled ds oligonucleotide compositions. In certain embodiments, a chirally controlled ds oligonucleotide composition comprises a controlled/pre-determined (not random as in stereorandom compositions) level of a plurality of ds oligonucleotides, wherein the ds oligonucleotides share the same linkage phosphorus stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages). In certain embodiments, ds oligonucleotides of a plurality share the same pattern of backbone chiral centers (stereochemistry of linkage phosphorus). In certain embodiments, a pattern of backbone chiral centers is as described in the present disclosure. In certain embodiments, ds

oligonucleotides of a plurality share a common constitution. In certain embodiments, they are structurally identical.

For example, in certain embodiments, the present disclosure provides a ds oligonucleotide composition comprising a plurality of ds oligonucleotides, wherein ds oligonucleotides of the plurality share:

1) a common base sequence, and

2) the same linkage phosphorus stereochemistry independently at one or more (e.g., about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 5-50, 5-40, 5-30, 5-25, 5-20, 5-15, 5-10, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more) chiral internucleotidic linkages ("chirally controlled internucleotidic linkages"); wherein level of ds oligonucleotides of the plurality in the composition is non-random (e.g., controlled/pre-determined as described herein).

Common patterns of backbone chiral centers, as appreciated by those skilled in the art, comprise at least one *R*p or at least one *S*p. Certain patterns of backbone chiral centers are illustrated in, e.g., Table 1.

In certain embodiments, a chirally controlled ds oligonucleotide composition is enriched, relative to a substantially racemic preparation of ds oligonucleotides share the same common base sequence and a common pattern of backbone linkages, for ds oligonucleotides of the particular ds oligonucleotide type.

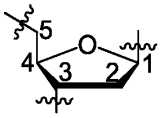
In certain embodiments, ds oligonucleotides of a plurality, e.g., a particular ds oligonucleotide type, have a common pattern of backbone phosphorus modifications and a common pattern of nucleoside modifications. In certain embodiments, ds oligonucleotides of a plurality have a common pattern of sugar modifications. In certain embodiments, ds oligonucleotides of a plurality have a common pattern of base modifications. In certain embodiments, ds oligonucleotides of a plurality have a common pattern of nucleoside modifications. In certain embodiments, ds oligonucleotides of a plurality have the same constitution. In certain embodiments, ds oligonucleotides of a plurality are identical. In certain embodiments, ds oligonucleotides of a plurality are of the same ds oligonucleotide (as those skilled in the art will appreciate, such ds oligonucleotides may each independently exist in one of the various forms of the ds oligonucleotide, and may be the same, or different forms of the ds oligonucleotide). In certain embodiments, ds oligonucleotides of a plurality are each independently of the same ds oligonucleotide or a pharmaceutically acceptable salt thereof.

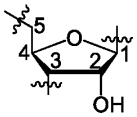
In certain embodiments, a chirally controlled ds oligonucleotide composition is chirally pure (or stereopure, stereochemically pure) ds oligonucleotide composition, wherein the ds

oligonucleotide composition comprises a plurality of ds oligonucleotides, wherein the ds oligonucleotides are independently of the same stereoisomer (including that each chiral element of the ds oligonucleotides, including each chiral linkage phosphorus, is independently defined (stereodefined)). A chirally pure (or stereopure, stereochemically pure) ds oligonucleotide composition of a ds oligonucleotide stereoisomer does not contain other stereoisomers (as appreciated by those skilled in the art, one or more unintended stereoisomers may exist as impurities from, e.g., preparation, storage, etc.).

Sugars

Various sugars, including modified sugars, can be utilized in accordance with the present disclosure. In certain embodiments, the present disclosure provides sugar modifications and patterns thereof optionally in combination with other structural elements (e.g., internucleotidic linkage modifications and patterns thereof, pattern of backbone chiral centers thereof, etc.) that when incorporated into oligonucleotides can provide improved properties and/or activities.

The most common naturally occurring nucleosides comprise ribose sugars (e.g., in RNA) or deoxyribose sugars (e.g., in DNA) linked to the nucleobases adenosine (A), cytosine (C), guanine (G), thymine (T) or uracil (U). In certain embodiments, a sugar, e.g., various sugars in many oligonucleotides in Table 1 (unless otherwise notes), is a natural DNA sugar (in DNA nucleic acids or oligonucleotides, having the structure of 

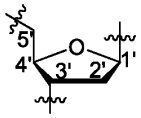
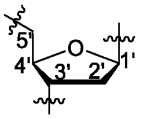
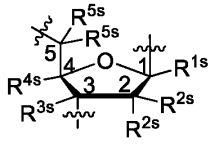
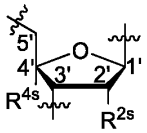
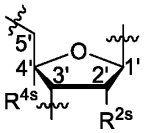
, wherein a nucleobase is attached to the 1' position, and the 3' and 5' positions are connected to internucleotidic linkages (as appreciated by those skilled in the art, if at the 5'-end of a ds oligonucleotide, the 5' position may be connected to a 5'-end group (e.g., −OH), and if at the 3'-end of a ds oligonucleotide, the 3' position may be connected to a 3'-end group (e.g., −OH). In certain embodiments, a sugar is a natural RNA sugar (in RNA nucleic acids or oligonucleotides, having the structure of 

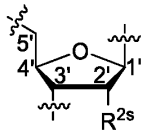
, wherein a nucleobase is attached to the 1' position, and the 3' and 5' positions are connected to internucleotidic linkages (as appreciated by those skilled in the art, if at the 5'-end of a ds oligonucleotide, the 5' position may be connected to a 5'-end group (e.g., −OH), and if at the 3'-end of a ds oligonucleotide, the 3' position may be connected to a 3'-end group (e.g., −OH). In certain embodiments, a sugar is a modified sugar in that it is not a natural DNA sugar or a natural RNA sugar. Among

other things, modified sugars may provide improved stability. In certain embodiments, modified sugars can be utilized to alter and/or optimize one or more hybridization characteristics. In certain embodiments, modified sugars can be utilized to alter and/or optimize target recognition. In certain embodiments, modified sugars can be utilized to optimize Tm. In certain embodiments, modified sugars can be utilized to improve oligonucleotide activities.

Sugars can be bonded to internucleotidic linkages at various positions. As non-limiting examples, internucleotidic linkages can be bonded to the 2', 3', 4' or 5' positions of sugars. In certain embodiments, as most commonly in natural nucleic acids, an internucleotidic linkage connects with one sugar at the 5' position and another sugar at the 3' position unless otherwise indicated.

In certain embodiments, a sugar is an optionally substituted natural DNA or RNA sugar.

In certain embodiments, a sugar is optionally substituted . In certain embodiments, the 2' position is optionally substituted. In certain embodiments, a sugar is . In certain embodiments, a sugar has the structure of  or , wherein each of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s} is independently −H, a suitable substituent or suitable sugar modification (e.g., those described in US 9394333, US 9744183, US 9605019, US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019/032612, WO 2019/055951, and/or WO 2019/075357, the substituents, sugar modifications, descriptions of R^{1s}, R^{2s}, R^{3s}, R^{4s}, and R^{5s}, and modified sugars of each of which are independently incorporated herein by reference). In certain embodiments, a sugar has the structure of . In certain embodiments, R^{4s} is

−H. In certain embodiments, a sugar has the structure of 

, wherein R^{2s} is −H, halogen, or −OR, wherein R is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^{2s} is −H. In certain embodiments, R^{2s} is −F. In certain embodiments, R^{2s} is −OMe. In certain embodiments, R^{2s} is $-OCH_2CH_2OMe$.

Various additional sugars useful for preparing oligonucleotides or analogs thereof are known in the art and may be utilized in accordance with the present disclosure.

Nucleobases

Various nucleobases may be utilized in provided ds oligonucleotides in accordance with the present disclosure. In certain embodiments, a nucleobase is a natural nucleobase, the most commonly occurring ones being A, T, C, G and U. In certain embodiments, a nucleobase is a modified nucleobase in that it is not A, T, C, G or U. In certain embodiments, a nucleobase is optionally substituted A, T, C, G or U, or a substituted tautomer of A T, C, G or U. In certain embodiments, a nucleobase is optionally substituted A, T, C, G or U, e.g., 5mC, 5-hydroxymethyl C, etc. In certain embodiments, a nucleobase is alkyl-substituted A, T, C, G or U. In certain embodiments, a nucleobase is A. In certain embodiments, a nucleobase is T. In certain embodiments, a nucleobase is C. In certain embodiments, a nucleobase is G. In certain embodiments, a nucleobase is U. In certain embodiments, a nucleobase is 5mC. In certain embodiments, a nucleobase is substituted A, T, C, G or U. In certain embodiments, a nucleobase is a substituted tautomer of A, T, C, G or U. In certain embodiments, substitution protects certain functional groups in nucleobases to minimize undesired reactions during oligonucleotide synthesis. Suitable technologies for nucleobase protection in oligonucleotide synthesis are widely known in the art and may be utilized in accordance with the present disclosure. In certain embodiments, modified nucleobases improves properties and/or activities of ds oligonucleotides. For example, in many cases, 5mC may be utilized in place of C to modulate certain undesired biological effects, e.g., immune responses. In certain embodiments, when determining sequence identity, a substituted nucleobase having the same hydrogen-bonding pattern is treated as the same as the unsubstituted nucleobase, e.g., 5mC may be treated the same as C [e.g., a ds oligonucleotide having 5mC in place of C (e.g., AT5mCG) is considered to have the same base sequence as a ds oligonucleotide having C at the corresponding location(s) (e.g., ATCG)].

In certain embodiments, a modified nucleobase is a modified nucleobase known in the art, e.g., WO2017/210647. In certain embodiments, modified nucleobases are expanded-size nucleobases in which one or more aryl and/or heteroaryl rings, such as phenyl rings, have been added.

In certain embodiments, a nucleobase is one described in US 9394333, US 9744183, US 9605019, US 9598458, US 9982257, US 10160969, US 10479995, US 2020/0056173, US 2018/0216107, US 2019/0127733, US 10450568, US 2019/0077817, US 2019/0249173, US 2019/0375774, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the nucleobases of each of which is incorporated herein by reference.

Additional Chemical Moieties

In certain embodiments, a ds oligonucleotide comprises one or more additional chemical moieties. Various additional chemical moieties, e.g., targeting moieties, carbohydrate moieties, lipid moieties, etc. are known in the art and can be utilized in accordance with the present disclosure to modulate properties and/or activities of provided oligonucleotides, e.g., stability, half-life, activities, delivery, pharmacodynamics properties, pharmacokinetic properties, etc. In certain embodiments, certain additional chemical moieties facilitate delivery of oligonucleotides to desired cells, tissues and/or organs. In certain embodiments, certain additional chemical moieties facilitate internalization of oligonucleotides. In certain embodiments, certain additional chemical moieties increase oligonucleotide stability. In certain embodiments, the present disclosure provides technologies for incorporating various additional chemical moieties into oligonucleotides.

In certain embodiments, a ds oligonucleotide comprises an additional chemical moiety demonstrates increased delivery to and/or activity in a tissue compared to a reference oligonucleotide, e.g., a reference oligonucleotide which does not have the additional chemical moiety but is otherwise identical.

In certain embodiments, non-limiting examples of additional chemical moieties include carbohydrate moieties, targeting moieties, etc., which, when incorporated into oligonucleotides, can improve one or more properties. In certain embodiments, an additional chemical moiety is selected from: glucose, GluNAc (N-acetyl amine glucosamine) and anisamide moieties. In certain embodiments, a provided ds oligonucleotide can comprise two or more additional chemical moieties, wherein the additional chemical moieties are identical

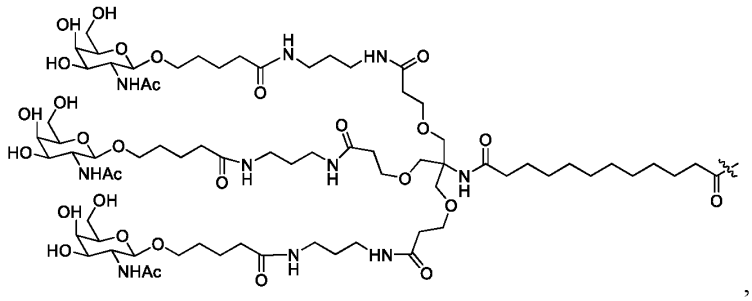
or non-identical, or are of the same category (e.g., carbohydrate moiety, sugar moiety, targeting moiety, etc.) or not of the same category.

In certain embodiments, an additional chemical moiety is a targeting moiety. In certain embodiments, an additional chemical moiety is or comprises a carbohydrate moiety. In certain embodiments, an additional chemical moiety is or comprises a lipid moiety. In certain embodiments, an additional chemical moiety is or comprises a ligand moiety for, e.g., cell receptors such as a sigma receptor, an asialoglycoprotein receptor, etc. In certain embodiments, a ligand moiety is or comprises an anisamide moiety, which may be a ligand moiety for a sigma receptor. In certain embodiments, a ligand moiety is or comprises a GalNAc moiety, which may be a ligand moiety for an asialoglycoprotein receptor. In certain embodiments, an additional chemical moiety facilitates delivery to liver.

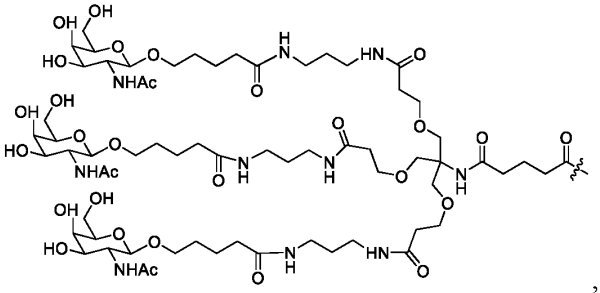
In certain embodiments, a provided ds oligonucleotide can comprise one or more linkers and additional chemical moieties (e.g., targeting moieties), and/or can be chirally controlled or not chirally controlled, and/or have a bases sequence and/or one or more modifications and/or formats as described herein.

Various linkers, carbohydrate moieties and targeting moieties, including many known in the art, can be utilized in accordance with the present disclosure. In certain embodiments, a carbohydrate moiety is a targeting moiety. In certain embodiments, a targeting moiety is a carbohydrate moiety.

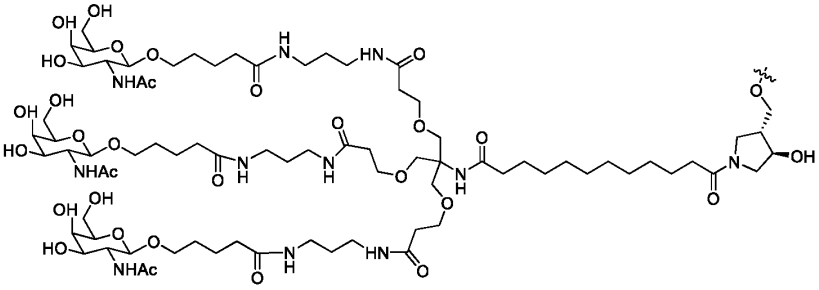
In particular embodiments, an additional chemical moiety is or comprises a tri-antennary ASGPR ligand with three such moieties. In certain embodiments a tri-antennary ASGPR ligand comprises:



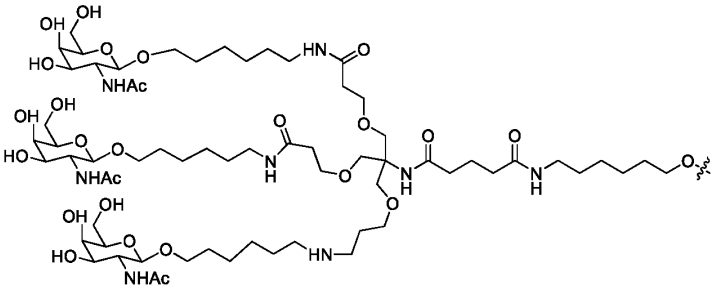
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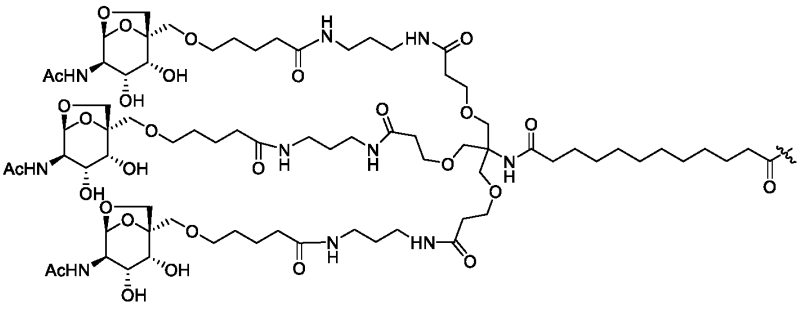
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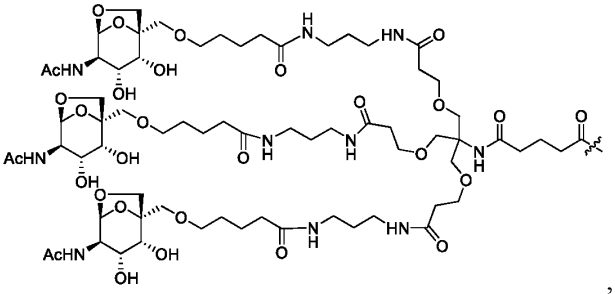
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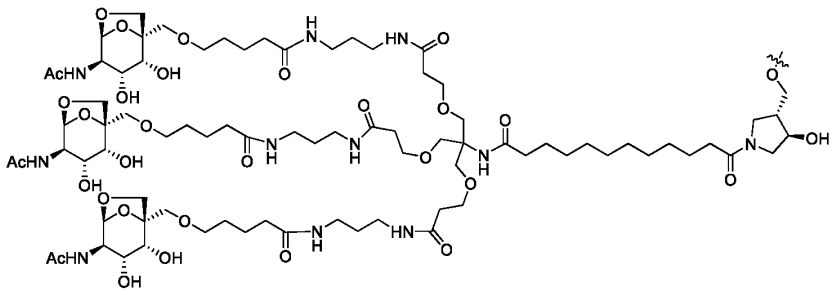
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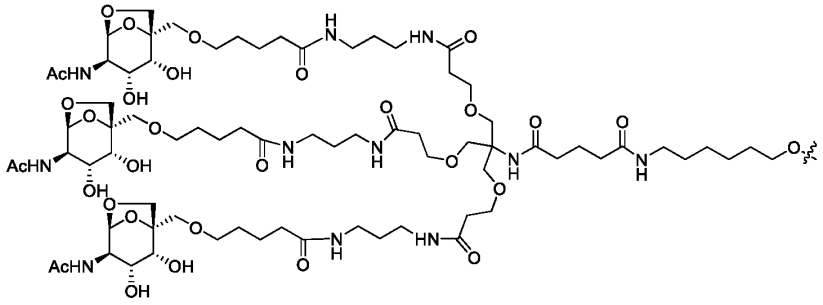
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, or



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Certain additional chemical moieties (e.g., lipid moieties, targeting moieties, carbohydrate moieties), and various linkers for connecting additional chemical moieties to ds oligonucleotide chains, are described in WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO2019032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the additional chemical moieties and linkers of each of which are independently incorporated herein by reference, and can be utilized in accordance with the present disclosure. In certain embodiments, an additional chemical moiety is digoxigenin or biotin or a derivative thereof.

In certain embodiments, an additional chemical moiety is one described in WO 2012/030683. In certain embodiments, a provided ds oligonucleotide comprise a chemical structure (e.g., a linker, lipid, solubilizing group, and/or targeting ligand) described in WO 2012/030683.

In certain embodiments, a provided ds oligonucleotide comprises an additional chemical moiety and/or a modification (e.g., of nucleobase, sugar, internucleotidic linkage, etc.) described in: U.S. Pat. Nos. 5,688,941; 6,294,664; 6,320,017; 6,576,752; 5,258,506; 5,591,584; 4,958,013; 5,082,830; 5,118,802; 5,138,045; 6,783,931; 5,254,469; 5,414,077; 5,486,603; 5,112,963; 5,599,928; 6,900,297; 5,214,136; 5,109,124; 5,512,439; 4,667,025; 5,525,465; 5,514,785; 5,565,552; 5,541,313; 5,545,730; 4,835,263; 4,876,335; 5,578,717;

5,580,731; 5,451,463; 5,510,475; 4,904,582; 5,082,830; 4,762,779; 4,789,737; 4,824,941; 4,828,979; 5,595,726; 5,214,136; 5,245,022; 5,317,098; 5,371,241; 5,391,723; 4,948,882; 5,218,105; 5,112,963; 5,567,810; 5,574,142; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 5,585,481; 5,292,873; 5,552,538; 5,512,667; 5,597,696; 5,599,923; 7,037,646; 5,587,371; 5,416,203; 5,262,536; 5,272,250; or 8,106,022.

In certain embodiments, an additional chemical moiety, e.g., a Mod, is connected via a linker. Various linkers are available in the art and may be utilized in accordance with the present disclosure, for example, those utilized for conjugation of various moieties with proteins (e.g., with antibodies to form antibody-drug conjugates), nucleic acids, etc. Certain useful linkers are described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/223056, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, and/or WO 2019/032612, the linker moieties of each which are independently incorporated herein by reference.

Pharmaceutical Compositions

When used as therapeutics, a provided ds oligonucleotide, e.g., a dsRNAi oligonucleotide, or ds oligonucleotide composition thereof is typically administered as a pharmaceutical composition. In certain embodiments, the present disclosure provides pharmaceutical compositions comprising a provided compound, e.g., a ds oligonucleotide, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier. In certain embodiments, for therapeutic and clinical purposes, ds oligonucleotides of the present disclosure are provided as pharmaceutical compositions. As appreciated by those skilled in the art, ds oligonucleotides of the present disclosure can be provided in their acid, base or salt forms. In certain embodiments, ds oligonucleotides can be in acid forms, e.g., for natural phosphate linkages, in the form of −OP(O)(OH)O−; for phosphorothioate internucleotidic linkages, in the form of −OP(O)(SH)O−; etc. In certain embodiments, dsRNAi oligonucleotides can be in salt forms, e.g., for natural phosphate linkages, in the form of −OP(O)(ONa)O− in sodium salts; for phosphorothioate internucleotidic linkages, in the form of −OP(O)(SNa)O− in sodium salts; etc. Unless otherwise noted, ds oligonucleotides of the present disclosure can exist in acid, base and/or salt forms.

In certain embodiments, the present disclosure provides salts of ds oligonucleotides and pharmaceutical compositions thereof. In certain embodiments, a salt is a pharmaceutically

acceptable salt. In certain embodiments, a pharmaceutical composition comprises a ds oligonucleotide, optionally in its salt form, and a sodium salt. In certain embodiments, a pharmaceutical composition comprises a ds oligonucleotide, optionally in its salt form, and sodium chloride. In certain embodiments, each hydrogen ion of a ds oligonucleotide that may be donated to a base (e.g., under conditions of an aqueous solution, a pharmaceutical composition, etc.) is replaced by a non-H^+ cation. For example, in certain embodiments, a pharmaceutically acceptable salt of a ds oligonucleotide is an all-metal ion salt, wherein each hydrogen ion (for example, of −OH, −SH, etc.) of each internucleotidic linkage (e.g., a natural phosphate linkage, a phosphoryl guanidine internucleotidic linkage, a phosphorothioate internucleotidic linkage, etc.) is replaced by a metal ion. Various suitable metal salts for pharmaceutical compositions are widely known in the art and can be utilized in accordance with the present disclosure. In certain embodiments, a pharmaceutically acceptable salt is a sodium salt. In certain embodiments, a pharmaceutically acceptable salt is magnesium salt. In certain embodiments, a pharmaceutically acceptable salt is a calcium salt. In certain embodiments, a pharmaceutically acceptable salt is a potassium salt. In certain embodiments, a pharmaceutically acceptable salt is an ammonium salt (cation $N(R)_4^+$). In certain embodiments, a pharmaceutically acceptable salt comprises one and no more than one types of cation. In certain embodiments, a pharmaceutically acceptable salt comprises two or more types of cation. In certain embodiments, a cation is Li^+, Na^+, K^+, Mg^{2+} or Ca^{2+}. In certain embodiments, a pharmaceutically acceptable salt is an all-sodium salt. In certain embodiments, a pharmaceutically acceptable salt is an all-sodium salt, wherein each internucleotidic linkage which is a natural phosphate linkage (acid form −O−P(O)(OH)−O−), if any, exists as its sodium salt form (−O−P(O)(ONa)−O−), and each internucleotidic linkage which is a phosphorothioate or a phosphoryl guanidine internucleotidic linkage (acid form −O−P(O)(SH)−O−), if any, exists as its sodium salt form (−O−P(O)(SNa)−O−).

In certain embodiments, dsRNAi oligonucleotides are formulated in pharmaceutical compositions described in WO 2005/060697, WO 2011/076807 or WO 2014/136086.

In certain embodiments, a composition comprising a ds oligonucleotide is lyophilized. In certain embodiments, a composition comprising a ds oligonucleotide is lyophilized, and the lyophilized ds oligonucleotide is in a vial. In certain embodiments, the vial is back filled with nitrogen. In certain embodiments, the lyophilized ds oligonucleotide composition is reconstituted prior to administration. In certain embodiments, the lyophilized ds oligonucleotide composition is reconstituted with a sodium chloride solution prior to administration. In certain embodiments, the lyophilized ds oligonucleotide composition is

reconstituted with a 0.9% sodium chloride solution prior to administration. In certain embodiments, reconstitution occurs at the clinical site for administration. In certain embodiments, in a lyophilized composition, a ds oligonucleotide composition is chirally controlled or comprises at least one chirally controlled internucleotidic linkage and/or the ds oligonucleotide targets.

III. EXEMPLIFICATION

Various technologies can be utilized to assess properties and activities of the provided oligonucleotides and compositions thereof. Some such technologies are described in this Example. Those skilled in the art appreciate that many other technologies can be readily utilized.

EXAMPLE 1. Oligonucleotide Synthesis

Various technologies for preparing oligonucleotides and oligonucleotide compositions (both stereorandom and chirally controlled) can be utilized in accordance with the present disclosure, including, for example, methods and reagents described in U.S. 9,394,333, U.S. 9,744,183, U.S. 9,605,019, U.S. 9,598,458, U.S. 9,982,257, U.S. 10,160,969, U.S. 10,479,995, U.S. 2020/0056173, U.S. 2018/0216107, U.S. 2019/0127733, U.S. 10,450,568, U.S. 2019/0077817, U.S. 2019/0249173, U.S. 2019/0375774, U.S. 2017/0037399, U.S. 2018/0216108, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, WO 2021/071858, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2022/099159, WO2023/201095, and WO 2024/182749. The methods and reagents of each of which are incorporated herein by reference. Stereorandom and chirally controlled guide strand sequences were prepared utilizing the synthetic procedures as exemplified in above mentioned disclosures. Respective passenger strands were designed to have covalently linked GalNAc moiety as delivery vehicle at either end of sequences. Oligonucleotides with 5'-GalNAc modifications were synthesized by coupling C6-amino modifier linker at the 5'-end of sequence. Oligonucleotides with 3'-GalNAc moiety as delivery vehicle were synthesized by utilizing 3'-C6 amino modified support. The single strand was cleaved from CPG by using deprotection condition as exemplified in earlier disclosures. The resulting amino group containing crude oligonucleotide was purified by ion exchange chromatography on AKTA pure system using a sodium chloride gradient. Desired product was

desalted and further used for conjugation with GalNAc acid. After conjugation reaction was found to be complete the material was further purified by ion exchange chromatography and desalted to achieve desired material. For introduction of PN linkages in guide and passenger strands, specific PN coupling cycles were introduced at desired positions in oligonucleotide sequence utilizing the conditions as exemplified in WO2019/200185.

In certain embodiments, oligonucleotides were prepared using suitable chiral auxiliaries, e.g., DPSE and PSM chiral auxiliaries. Various oligonucleotides, e.g., those in Table 1 and Table 1f, and compositions thereof, were prepared in accordance with the present disclosure.

Various technologies can be utilized to assess properties and/or activities of provided oligonucleotides and compositions thereof. Some such technologies are described in this Example. Those skilled in the art appreciate that many other technologies can be readily utilized. As demonstrated herein, provided oligonucleotides and compositions, among other things, can be highly active, e.g., in reducing levels of their target nucleic acids.

Abbreviation

1X reagent: TEA-3HF : TEA : H_2O : DMSO = 5.0 : 1.8 : 15.5 : 77.7 (v/v/v/v)

ADIH: 2-azido-1,3-dimethylimidazolium hexafluorophosphate

CMIMT: *N*-cyanomethylimidazolium triflate

CPG: controlled pore glass

DCM: dichloromethane, CH_2Cl_2

DIPEA: diisopropylethylamine

DMSO: dimethylsulfoxide

DMTr: 4,4′-dimethoxytrityl

GalNAc: *N*-acetylgalactosamine

HF: hydrogen fluoride

HATU: 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

IBN: isobutyronitrile

MeCN: acetonitrile

MeIm: *N*-methylimidazole

TCA: trichloroacetic acid

TEA: triethylamine

XH: xanthane hydride

General procedure for the synthesis of chiral-oligos (25 μmol scale):

The automated solid-phase synthesis of chiral-oligos was performed according to the cycles shown in Table 2 (regular amidite cycle, for PO linkages), Table 3 (regular amidite cycle, for stereo-random PS linkages), Table 4 (DPSE amidite cycle, for chiral PS linkages), and Table 5 (PSM amidite cycle, for chiral PN linkages).

Table 2. Regular Amidite Synthetic Cycle for PO linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	oxidation	50mM I_2 / pyridine-H_2O (9:1, v/v)	2.0 mL	1 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 3. Regular Amidite Synthetic Cycle for stereo-random PS linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
4	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 4. DPSE Amidite Synthetic Cycle for chiral PS linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min

4	sulfurization	0.2M XH / pyridine	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

Table 5. PSM Amidite Synthetic Cycle for chiral PN linkages

step	operation	reagents and solvent	volume	waiting time
1	detritylation	3% TCA / DCM	10 mL	65 s
2	coupling	0.2M monomer / 20% IBN-MeCN 0.5M CMIMT / MeCN	0.5 mL 1.0 mL	8 min
3	cap-1	20% Ac_2O, 30% 2,6-lutidine / MeCN	2.0 mL	2 min
4	imidation	0.5M ADIH reagent / MeCN	2.0 mL	6 min
5	cap-2	20% Ac_2O, 30% 2,6-lutidine / MeCN 20% MeIm / MeCN	1.0 mL 1.0 mL	45 s

General procedure for the C&D conditions (25 μmol scale):

After completion of the synthesis, the CPG solid support was dried and transferred into 50 mL plastic tube. The CPG was treated with 1X reagent (2.5 mL; 100 μL/umol) for 3 h at 28°C, then added conc. NH_3 (5.0 mL; 200 μL/umol) for 24 h at 37°C. The reaction mixture was cooled to room temperature and the CPG was separated by membrane filtration, washed with 15 mL of H_2O. The crude material (filtrate) was analyzed by LTQ and RP-UPLC.

General procedure for the purification conditions:

The crude sense and antisense strands were purified separately by AEX chromatography. The purification run was performed using sodium hydroxide eluents. A sodium chloride gradient was used to elute the oligonucleotide from the column. The elution profile was monitored by UV spectrophotometry, and the selected fraction pool (sense or antisense strand) was then concentrated and diafiltered against purified water to remove the purification buffer by TFF. The UF/DF process proceeded as follows, the selected pool of fractions was neutralized with sodium phosphate monobasic solution and then concentrated to a target concentration. The concentrated oligonucleotide was diafiltered against purified water before final concentration to the target concentration and collected.

General procedure for the annealing to form duplex:

The duplex was formed by combining equal molar quantities of the sense and antisense strands with mixing in an appropriately sized vessel. The formation of the duplex was confirmed by UPLC that there was no excess of single strands. The duplex oligonucleotide solution was filtered through a 0.2-micron filter and then placed in freeze drying tray for lyophilization. After lyophilization, the duplex was isolated as a white to off-white solid powder.

General procedure for the GalNAc conjugation conditions (1 μmol scale):

Into a plastic tube, tri-GalNAc (2.0 eq.), HATU (1.9 eq.), and DIPEA (10 eq.) were dissolved in anhydrous MeCN (0.5 mL). The mixture was stirred for 10 min at room temperature, then the mixture was added into the amino-oligo (1 μmol) in H_2O (1 mL) and stirred for 1 h at 37 °C. The reaction was monitored by LC-MS and RP-UPLC. After the reaction was completed, the resultant GalNAc-conjugated oligo was treated with conc. NH_3 (2 mL) for 1 h at 37 °C. The solution was concentrated under vacuum to remove MeCN and conc. NH_3. The residue was then dissolved in H_2O (10 mL) for reversed phase purification.

While various embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described in the present disclosure, and each of such variations and/or modifications is deemed to be included. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be example and that the actual parameters, dimensions, materials, and/or configurations may depend upon the specific application or applications for which the teachings of the present disclosure is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments of the present disclosure. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, claimed technologies may be practiced otherwise than as specifically described and claimed. In addition, any combination of two or more features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present disclosure.

In some embodiments, preparations include one or more DPSE and/or PSM cycles.

A number of oligonucleotide compositions were synthesized and assessed, including, e.g., those in the Tables.

As described and confirmed herein, technologies of the present disclosure are useful for preparing various compositions of oligonucleotides comprising various structural features at various scales (e.g., 1 umol, 5 umol, or 50 umol). It is understood that certain parameters will be modified based on the scale, e.g., volumes or equivalents.

The resulting oligonucleotides can undergo an annealing step to form a duplex.

Example 1B. Example procedure for preparation of oligonucleotide compositions (1 μmol scale)

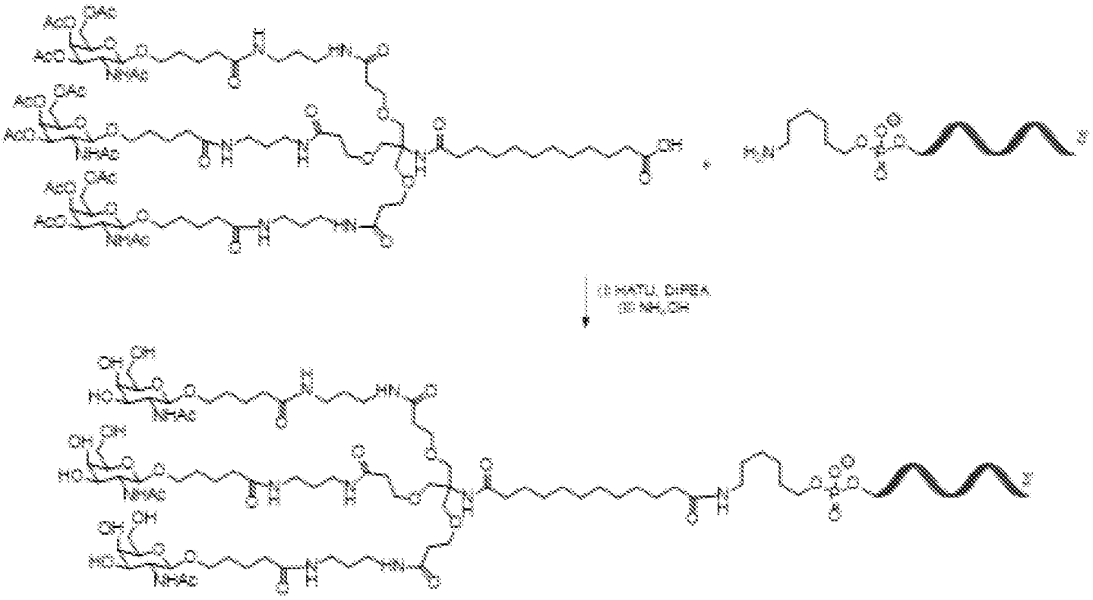
Certain stereopure oligonucleotides were synthesized at 1 μmol scale using a MerMade192 synthesizer and universal CPG. In some embodiments, an amidite approach was used to incorporate GalNAc on the 5' end. Generally, cyanoethyl amidites were used to prepare the PO linkages, DPSE amidites for the PS linkages, and PSM amidites for the PN linkages. A typical MerMade192, 1 μmol cycle is outlined in the table below:

Step	Operation	Reagents and Solvent	Volume	Approx. Total Time
1	Detritylation	3% dichloroacetic acid in toluene	5 x 225 μL	6.5 min
2	Double Coupling	0.1M phosphoramidite in combinations of ACN/IBN/PC/DMF and 0.5M CMIMT in ACN	95 μL / 110 μL (per coupling)	6 min (per coupling)
3	Cap 1	80% THF / 10% 2,6-lutidine / 10% acetic anhydride	200 μL	1.5 min
4	Oxidation (PO)	0.02M iodine in 70% THF / 20% pyridine / 10% water	200 μL	1.5 min
	Sulfurization (PS)	0.1M xanthane hydride in 50% pyridine / 50% ACN	200 μL	6.5 min
	PN	0.3M ADIH in ACN	200 μL	7 min
5	Cap 2	80% THF / 10% 2,6-lutidine / 10% acetic anhydride and 16% n-methylimidazole in THF	100 μL / 100 μL	1.5 min

The first step of deprotection was performed on the synthesizer. 200 μL of 20% diethylamine in ACN was added to the column for 3 x 6 min followed by washing with ACN and drying. CPG was transferred to a container and 250 μL of fluoride solution was added. The fluoride solution consisted of dimethylformamide, water, triethylamine trihydrofluoride, and triethylamine (15.5/3.1/1.0/1.8 volume ratio). After about 4 hours at room temperature, approximately 375 μL of 30% ammonium hydroxide was added, and the reaction incubated at 37 °C overnight. The CPG was filtered and washed with water and the filtrate collected.

The oligonucleotides were purified by anion exchange purification at room temperature. The oligonucleotide was loaded onto a column packed with Source Q15 resin after equilibration with a 20 mM sodium hydroxide in 20% acetonitrile mobile phase. The purified oligonucleotide was eluted using a mobile phase of 20 mM sodium hydroxide and 2.5 M sodium chloride in 20% acetonitrile. The desired fraction was desalted using a G-25 Sephadex column against water for injection. Desalted samples were dried, reconstituted and analyzed.

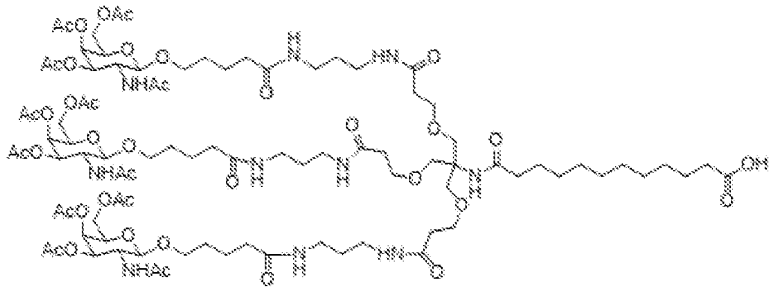
A useful protocol for GalNAc conjugation is described below as an example.



For example, pre-conjugation oligo sequence can be represented by the following structure.



The tri-antennary GalNAc acid (hydroxyl groups protected as −OAc) can be represented by the following structure



The tri-antennary GalNAc acid (hydroxyl groups protected as –OAc) and HATU were weighed out in a 50 mL plastic tube and dissolved in anhydrous acetonitrile then DIEA was added into the tube. The resulting mixture was stirred for 10 min at 37 °C. Lyophilized pre-conjugation oligo sequence was reconstituted in water in a separate tube and the GalNAc mixture was added to the oligonucleotide solution and stirred for 60 min at 37 °C. The reaction was monitored by RP-UPLC. Reaction was complete in 1 hr. The reaction mixture was concentrated under vacuum to remove the acetonitrile and the resultant GalNAc-conjugated oligonucleotides is treated with conc. ammonia for 2 hr at 37°C. The formation of final product was confirmed by mass spectrometry and RP-UPLC. The conjugated material was purified by anion exchange chromatography and desalted using tangential flow filtration (TFF) to obtain the final product.

Additional chemical moieties can also be installed by coupling with phosphoramidites comprising such additional chemical moieties (and optional linkers), e.g., phosphoramidites comprising GalNAc such as those described in Example 1C. Additional technologies for preparing oligonucleotides are illustrated below as examples.

Example 1C. Example procedure for preparation of oligonucleotide compositions (50 µmol scale)

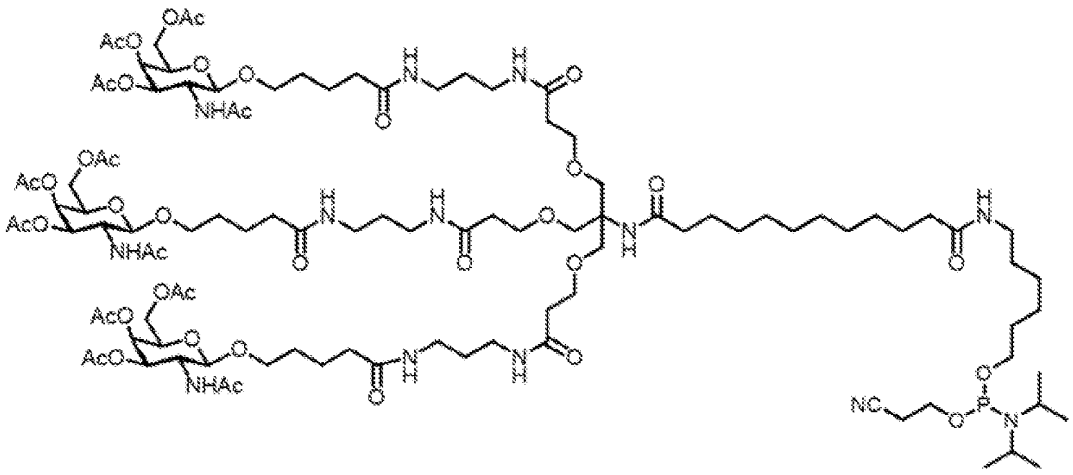
Certain stereopure oligonucleotides were synthesized at 50 µmol scale using a MerMade12 synthesizer and standard CPG. In some embodiments, an amidite approach was used to incorporate GalNAc on the 5' end. Generally, cyanoethyl amidites were used to prepare the PO linkages, DPSE amidites for the PS linkages and PSM amidites for the PN linkages. A typical MerMade12, 50 µmol cycle is outlined in the table below:

Step	Operation	Reagents and Solvent	Volume	Approx. Total Time
1	Detritylation	3% dichloroacetic acid in toluene	4 x 4.5 mL	4-5 min
2	Single	0.15M phosphoramidite in combinations of	1.5 mL /	6-12 min

	Coupling	ACN/IBN/PC and 0.5M CMIMT in ACN	2.25 mL	
3	Cap 1	80% THF / 10% 2,6-lutidine / 10% acetic anhydride	5 mL	1-1.5 min
4	Oxidation (PO)	0.02M iodine in 70% THF / 20% pyridine / 10% water	6 mL	2-4 min
	Sulfurization (PS)	0.1M xanthane hydride in 50% pyridine / 50% ACN	6 mL	6 min
	PN	0.3M ADIH in ACN	6 mL	10 min
5	Cap 2	80% THF / 10% 2,6-lutidine / 10% acetic anhydride and 16% n-methylimidazole in THF	2.5 mL / 2.5 mL	1-1.5 min

CMIMT: N-cyanomethylimidazolium triflate; ACN: acetonitrile; IBN: isobutyronitrile; ADIH: 2-azido-4,5-dihydro-1,3-dimethyl-1H-imidazolium hexafluorophosphate; THF: tetrahydrofuran; PC: propylene carbonate. The cycles were performed multiple times until the desired length was achieved.

In some embodiments, an amidite approach was used to incorporate GalNAc on the 5' end. The GalNAc amidite, or , or tri-antennary GalNAc-acetyl derivative C6 phosphoramidite, can be represented by the following structure. The synthesis is disclosed in WO2023201095 (Paragraph [001468])



The GalNAc amidite was coupled either as a single 10-15 min or a two x 10 min procedure. For each coupling, 1.5 mL of 0.2M GalNAc amidite and 3 mL of CMIMT in ACN were added.

The first step of deprotection was performed on the synthesizer. 6 mL of 20% diethylamine in ACN was added to the column for 10 min followed by washing with ACN and drying. CPG was transferred to a tube and 5 mL of fluoride solution was added. The fluoride solution consisted of dimethylsulfoxide, water, triethylamine trihydrofluoride, and triethylamine (15.5/3.1/1.0/1.8 volume ratio). After about 1 hour at room temperature,

approximately 10 mL of 30% ammonium hydroxide was added, and the reaction incubated at 37°C overnight. The CPG was filtered off and washed with water and the filtrate collected.

The oligonucleotides were purified by anion exchange purification at room temperature. The oligonucleotide was loaded onto a column packed with Source Q15 resin after equilibration with a 20 mM sodium hydroxide in water or 20 mM sodium hydroxide with 20% acetonitrile in water mobile phase. The purified oligonucleotide was eluted as fractions by gradient elution with a mobile phase of 20 mM sodium hydroxide and 2.5 M sodium chloride in water or 20 mM sodium hydroxide and 2.5 M sodium chloride with 20% acetonitrile in water. Fractions were analyzed, pooled to the desired purity and desalted using a G-25 Sephadex column against water for injection. Desalted samples were dried, reconstituted and sterile filtered prior to final analysis including UPLC, LC-MS and UV-Vis.

EXAMPLE 2. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. Male 8-9 weeks of age C57BL/6 mice underwent surgery for the implantation of intracerebroventricular cannulas. At 10-11 weeks of age the same mice were dosed 100 μg on Day 0 by intracerebroventricular injection. After 8 weeks animals in groups 1-5 were euthanized by CO_2 asphyxiation followed by thoracotomy. After cardiac perfusion with PBS brain samples were taken from both hemispheres (cortex, striatum, hippocampus, cerebellum, and brain stem) and flash frozen on dry ice. After 12 weeks animals in groups 6-10 were euthanized by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS brain samples were taken from both hemispheres (cortex, striatum, hippocampus, cerebellum, brain stem, and spinal cord) and flash frozen on dry ice. After 16 weeks animals in groups 11-15 were euthanized by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS brain samples were taken from both hemispheres (cortex, striatum, hippocampus, cerebellum, brain stem, and spinal cord) and flash frozen on dry ice. One animals from each group had the right hemisphere of their brain placed in buffered 10% formalin. Total RNA from different CNS regions was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse APP mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Mm01344172_m1. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse

5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3'. Thermofisher Taqman qPCR assay ID for Calb1: Mm00486647_m1, Grid2: Mm00515047_m1, Pcp2: Mm00435514_m1, Gfap: Mm01253033_m1, Aif1: Mm00479862_g1. Thermofisher Taqman qPCR assay ID Mouse Tubb3 which was used as normalizer: Mm00727586_s1. Oligonucleotide accumulation in CNS regions was determined by sandwich ELISA.

To evaluate the safety of siRNAs used , serum NfL levels were measured at 4-, 6-, and 8-weeks following administration. Monoclonal antibody UD1 (Uman Diagnostics) was covalently coupled to MagPlex-C Microspheres #12 (MC10012-01, Luminex) using xMAP Antibody Coupling Kit (#40-50016, Luminex). Serum samples from mice were diluted as 1:4 with Specimen Diluent Buffer (Quidel #A3670) and incubated with UD1 coupled microspheres (2500 beads/well) in a 96-well plate for 18-20 hours at 4C on an orbital plated shaker. Following three washes with Wash Buffer (EMD Millipore #L-WB), the wells were subjected to an incubation step with 25uL of Detection antibody (1:500, UD3, Uman Diagnostics) on a plate shaker for 2 hours at ambient temperature. 25uL of Streptavidin-Phycoerthrin (EMD Millipore #LB-SAPE10) was introduced into each well, followed by an incubation period of 30 minutes with continuous agitation. Following three rounds of washing, 150 microliters of Sheath Fluid PLUS (EMD Millipore #40-50021) was introduced, and subsequently, the beads were resuspended on a plate shaker for a duration of 5 minutes. The fluorescence intensity signal of the beads was measured using FLEXMAP 3D (Luminex) instrument with xPONENT software (Luminex). The analyses were conducted in duplicate to ensure accuracy and reliability. The standard NfL protein (Progen # RPC20469) was used to prepare five standards at the concentration from 30 to 200,000 pg/ml in Assay buffer (EMD Millipore #L-AB) Unspiked assay buffer was used as blank. Standard curves were fitted using 5-Parameter Logistic regression analysis by XPONENT software. Average NfL concentration of each group was calculated and plotted using GraphPad Prism. Minimal changes in the serum levels of NfL were observed in the mice treated with siRNA, in comparison to the group treated with PBS. There was no statistically significant difference observed between the groups.

Cerebellum total RNA extracted from mice treated with PBS, DSR-0103432, DSR-0103299, DSR-0103300, and DSR-0103301 (3 animals from each group) were RNA-sequenced and Fastq's were obtained from Novogene. nf-core/rnaseq (version 3.10.1) pipeline was used to process the data, with the specific packages following. Adapters were trimmed using Trim Galore! (Version 0.6.7 & cutadapt version 3.4) then aligned using STAR (version 2.7.9a) and transcript counts quantified using Salmon (version 1.9.0). Aligned bam files were

processed using R (version 4.3.0) and differential expression results calculated using DEseq2 (version 1.40.2) and plotted using EnhancedVolcano (version 1.18.0) with cutoffs greater than |log2foldChange| > 1 and padj (Benjamini-Hochberg) less than 0.01.

Ago2 immunoprecipitation assay: Tissues were lysed in lysis buffer 50 mM Tris-HCl at pH 7.5, 200mM NaCl, 0.5% Triton X-100, 2 mM EDTA, 1 mg/mL heparin) with protease inhibitor (Sigma-Aldrich). Lysate concentration was measured with a protein BCA kit (Pierce BCA protein assay kit or Bradford protein assay kit). Anti-Ago2 antibody was purchased from Wako Chemicals. Control mouse IgG was from eBioscience. Dynabeads (Invitrogen) were used to precipitate antibodies. Ago2-associated siRNA and endogenous miR-124 were measured by Stem-Loop RT followed by TaqMan PCR analysis using Taqman miRNA and siRNA assay kit (Thermo Fisher) based on manufacturer's methods.

The contents of Tables 27, 28, and 29 of WO 2021/234459, and Tables 8-126R and 127-183 of WO 2024/182749, along with the corresponding experimental protocol descriptions, are incorporated herein by reference in their entirety.

Table 6. shows Ago 2 loading of guide strand relative to miR-124 in cortex 8 weeks, 12 weeks and 16 weeks post dose. N=3.

	Week 8				
	Ct: mAPP/Ago2	Ct: miR-124/Ago2	Ct: mAPP/IgG	Ct: miR-124/IgG	Relative mAPP/miR-124
PBS-1	36.87	31.83	35.7	40	0.001543
PBS-2	34.16	29.97	34.59	35.6	0.027205
PBS-3	34.89	30.5	35.18	39.79	0.001953
DSR-0103299-1	24.10	30.89	30.89	40	0.200267
DSR-0103299-2	24.14	31.45	30.16	40	0.173139
DSR-0103299-3	24.51	31.46	30.29	36.67	1.484524
DSR-0103300-1	24.27	31.51	29.74	38.23	0.420448
DSR-0103300-2	24.97	32.15	30.11	40	0.15283
DSR-0103300-3	23.47	32.67	28.23	40	0.168404
DSR-0103301-1	24.33	33.12	29.57	40	0.320856
DSR-0103301-2	24.15	33.66	30.05	40	0.737135
DSR-0103301-3	22.12	33.92	28.13	40	0.952638
	Week 12				
	Ct: mAPP/Ago2	Ct: miR-124/Ago2	Ct: mAPP/IgG	Ct: miR-124/IgG	Relative mAPP/miR-124
DSR-0103299-1	24.45	32.38	29.24	40	0.140632
DSR-0103299-2	24.59	31.47	30.02	40	0.116629

DSR-0103299-3	24.35	32.16	29.54	40	0.15932
DSR-0103300-1	24.64	31.5	30.15	40	0.125869
DSR-0103300-2	24.66	32.26	29.51	39.03	0.264255
DSR-0103300-3	27.14	32.65	30.78	40	0.076415
DSR-0103301-1	23.24	32.73	28.97	40	0.343885
DSR-0103301-2	23.69	32.19	29.27	40	0.213159
DSR-0103301-3	22.95	32.37	29.16	37.01	2.969047
	Week 16				
	Ct: mAPP/Ago2	Ct: miR-124/Ago2	Ct: mAPP/IgG	Ct: miR-124/IgG	Relative mAPP/miR-124
DSR-0103299-1	24.82	32.25	30.7	40	0.273573
DSR-0103299-2	24.98	31.46	30.07	40	0.091505
DSR-0103299-3	26	31.41	30.97	40	0.081334
DSR-0103300-1	24.46	31.92	29.29	40	0.105112
DSR-0103300-2	24.79	32.04	30.2	40	0.170755
DSR-0103300-3	26.65	32.36	31.97	40	0.200267
DSR-0103301-1	24.96	32.66	31.39	37.05	4.112455
DSR-0103301-2	23.51	32.94	29.74	40	0.562529
DSR-0103301-3	25.05	33.41	31.2	40	0.737135

EXAMPLE 3. Provided Oligonucleotides and Compositions Are Active *in vitro*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and liver exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0 by subcutaneous administration. Animals were euthanized on Day 14 or 28 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse SOD1 mRNA, the following qPCR assay were utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (Forward 5'CAAACTTTGCTTTCCCTGGTT3', Reverse 5'TGGCCTGTATCCAACACTTC3', Probe 5'/5HEX/ACCAGCAAG/Zen/CTTGCAACCTTAACC/3IABkFQ/3'. Oligonucleotide accumulation was determined by sandwich ELISA.

Table 7. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	86.84	79.21	45.93	83.23	91.92	75.91	47.84
	2	108.08	84.01	45.30	87.83	83.14	68.41	70.58
	3	105.11	80.79	62.26	86.19	96.84	83.32	65.84
	4	103.56	79.54	58.67	94.29	97.10	91.72	52.08
	5	96.41	74.33	56.04	97.03	87.01	97.07	70.50
	Mean	100.00	79.57	53.64	89.71	91.20	83.29	61.37
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	111.15	70.77	70.97	93.40	88.26	62.18	57.84
	2	103.02	70.95	50.30	86.90	96.69	70.84	74.93
	3	99.79	77.69	55.86	91.85	92.30	72.82	82.75
	4	85.23	77.10	51.08	97.32	90.96	72.86	83.29
	5	100.81	72.94	47.42	91.33	105.05	80.55	82.14
	Mean	100.00	73.89	55.12	92.16	94.65	71.85	76.19

Table 8. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	177.81	51.92	9.49	3.24	3.65	8.43	4.29
	2	81.73	34.98	17.15	2.40	3.52	8.25	3.95
	3	77.70	50.60	16.34	3.42	2.72	7.58	12.40
	4	83.56	52.58	16.03	3.03	2.29	8.44	4.08
	5	79.20	48.48	14.77	2.61	2.86	7.04	9.05
	Mean	100.00	47.71	14.76	2.94	3.01	7.95	6.75
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	157.96	73.37	27.46	4.57	4.56	8.95	5.81
	2	79.83	61.20	15.28	3.58	2.97	8.67	4.41
	3	90.47	88.59	20.59	3.30	3.14	13.13	4.63
	4	84.56	104.51	15.36	3.50	3.26	10.26	4.31

	5	87.17	72.76	19.72	3.09	4.55	14.96	7.85
	Mean	100.00	80.09	19.68	3.61	3.70	11.19	5.40

Table 9. shows % mouse SOD1 mRNA remaining relative to PBS control in the brown adipose 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	83.19	73.28	13.93	43.59	35.37	45.64	9.75
	2	92.06	66.65	31.73	71.33	21.54	62.58	21.80
	3	91.27	81.79	15.01	89.37	44.64	44.21	20.50
	4	102.89	59.71	33.72	70.69	18.71	69.60	10.25
	5	130.58	70.80	31.37	64.22	45.91	59.75	23.40
	Mean	100.00	70.45	25.15	67.84	33.23	56.36	17.14
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	96.21	103.83	40.60	74.09	36.70	78.66	10.97
	2	111.48	112.23	30.69	61.86	21.00	70.69	14.42
	3	113.60	52.41	23.08	76.18	49.36	43.21	16.43
	4	105.93	47.70	8.27	69.07	14.44	67.33	20.79
	5	72.78	100.07	18.66	90.04	41.12	70.38	17.19
	Mean	100.00	83.25	24.26	74.25	32.53	66.05	15.96

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Table 10. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose 2- and 4-weeks post dosing. N = 5. N.D.: Not determined.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	90.40	84.07	31.98	140.95	68.74	116.30	30.70
	2	122.45	99.34	23.77	129.21	61.86	118.11	47.42
	3	68.91	106.53	97.21	121.04	79.58	150.83	40.79
	4	100.08	92.74	35.00	107.29	94.19	97.90	45.30
	5	118.15	81.82	48.41	142.18	92.94	115.92	25.06
	Mean	100.00	92.90	47.27	128.14	79.46	119.81	37.85
4 weeks	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	97.33	68.57	58.67	66.31	55.13	70.67	35.34

post dosing	2	111.57	143.97	74.53	128.37	52.42	69.30	30.61
	3	122.36	113.83	21.12	N.D	52.38	121.74	71.27
	4	95.62	65.48	145.12	127.61	85.79	78.64	46.26
	5	73.13	98.89	49.60	100.09	54.94	81.31	42.68
	Mean	100.00	98.15	69.81	105.60	60.13	84.33	45.23

Table 11. shows % mouse SOD1 mRNA remaining relative to PBS control in the lung 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	81.77	91.82	71.71	103.31	78.09	110.97	87.34
	2	95.69	87.81	86.07	110.59	81.03	106.11	83.59
	3	94.24	95.69	89.16	88.32	85.83	117.20	112.04
	4	137.87	104.41	80.62	111.43	101.85	133.12	88.03
	5	90.42	98.66	95.78	86.01	117.72	106.58	110.77
	Mean	100.00	95.68	84.67	99.93	92.90	114.79	96.35
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	80.08	80.32	84.14	75.91	47.56	39.29	49.83
	2	128.88	106.53	49.17	87.05	41.63	33.44	82.13
	3	79.05	56.13	83.16	72.85	87.01	51.25	44.49
	4	101.22	57.88	62.80	38.05	85.09	126.84	111.92
	5	110.77	110.84	104.98	74.11	37.18	62.10	84.48
	Mean	100.00	82.34	76.85	69.59	59.69	62.58	74.57

Table 12. shows % mouse SOD1 mRNA remaining relative to PBS control in the diaphragm 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	79.75	111.97	81.87	120.81	71.59	78.49	68.13
	2	95.72	90.40	108.73	107.33	66.82	73.27	54.35
	3	83.51	45.83	50.03	122.88	62.39	71.66	52.49
	4	133.71	92.09	86.03	121.69	73.79	68.31	41.31
	5	107.31	69.99	56.91	83.80	82.74	65.99	40.80
	Mean	100.00	82.05	76.72	111.30	71.47	71.54	51.41

	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
4 weeks post dosing	1	83.54	110.41	32.06	38.92	37.95	57.44	15.53
	2	85.19	85.93	54.80	57.01	28.77	23.63	18.09
	3	128.61	51.21	53.63	38.23	31.48	38.18	19.27
	4	101.53	67.05	18.78	23.00	18.76	23.10	17.48
	5	101.13	57.79	18.22	15.70	27.68	40.36	25.05
	Mean	100.00	74.48	35.50	34.57	28.93	36.54	19.08

Table 13. shows % mouse SOD1 mRNA remaining relative to PBS control in the heart 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	80.40	98.06	32.37	57.06	31.31	46.92	23.46
	2	91.50	89.85	24.48	56.43	22.51	46.27	18.76
	3	122.18	77.78	20.58	61.84	29.17	43.14	18.12
	4	100.86	39.68	29.75	68.17	33.59	45.41	17.10
	5	105.06	75.23	29.59	45.91	31.55	43.92	18.19
	Mean	100.00	76.12	27.35	57.88	29.63	45.13	19.12
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	55.94	139.81	35.59	98.91	59.05	55.27	25.72
	2	94.89	142.12	27.02	122.92	79.02	68.07	29.41
	3	119.49	126.03	74.22	111.32	78.90	74.56	19.14
	4	104.94	148.84	51.13	112.68	36.99	85.04	24.10
	5	124.74	139.91	57.74	130.29	60.46	72.54	21.06
	Mean	100.00	139.34	49.14	115.22	62.88	71.10	23.89

Table 14. shows % mouse SOD1 mRNA remaining relative to PBS control in the kidney 2- and 4-weeks post dosing. N = 5.

		% remaining of mSOD1 mRNA						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	98.12	123.25	91.52	112.27	89.45	54.10	38.58
	2	67.04	100.72	55.92	93.10	102.07	47.66	45.51
	3	75.18	104.75	87.05	57.31	71.10	52.43	40.19

	4	140.21	56.29	106.41	140.46	85.42	50.85	38.20
	5	119.46	45.01	45.24	42.01	41.89	46.62	33.89
	Mean	100.00	86.00	77.23	89.03	77.99	50.33	39.28
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	56.93	68.49	63.71	53.47	54.62	35.97	31.10
	2	52.64	74.06	50.41	47.02	49.35	60.33	33.36
	3	123.70	36.04	51.02	48.42	53.78	37.12	32.92
	4	140.61	63.58	59.69	39.66	73.29	59.74	31.08
	5	126.12	65.77	55.41	50.51	39.76	48.61	44.49
	Mean	100.00	61.59	56.05	47.82	54.16	48.36	34.59

Table 15. shows the accumulation of antisense strand in the liver at 2 weeks and 4 weeks post dosing. N = 5.

		Liver Guide Strand PK (ug oligo/g tissue)						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	0.00	0.62	6.56	10.24	10.30	1.62	5.91
	2	0.00	0.71	6.06	10.88	11.00	1.50	6.96
	3	0.00	0.60	6.27	11.44	11.98	1.57	8.01
	4	0.00	0.56	6.56	11.00	10.37	1.79	8.87
	5	0.00	0.68	7.99	11.60	12.08	1.78	8.00
	Mean	0.00	0.63	6.69	11.03	11.14	1.65	7.55
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	0.00	0.32	1.10	6.51	9.96	1.20	5.99
	2	0.00	0.32	1.80	7.30	11.16	1.18	5.21
	3	0.00	0.33	1.80	8.58	12.08	1.17	6.58
	4	0.00	0.38	2.89	8.55	10.40	1.11	6.40
	5	0.00	0.38	2.26	8.95	11.50	1.34	5.33
	Mean	0.00	0.35	1.97	7.98	11.02	1.20	5.90

Table 16 shows the accumulation of antisense strand in the white adipose at 2 weeks and 4 weeks post dosing. N = 5.

		White adipose Guide Strand PK (ug oligo/g tissue)						
2 weeks	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151

post dosing	1	0.00	0.01	0.07	0.01	0.02	0.01	0.05
	2	0.00	0.01	0.11	0.01	0.13	0.02	0.11
	3	0.00	0.02	0.13	0.01	0.04	0.02	0.06
	4	0.00	0.02	0.11	0.01	0.04	0.01	0.11
	5	0.00	0.05	0.13	0.02	0.03	0.02	0.10
	Mean	0.00	0.02	0.11	0.01	0.05	0.02	0.08
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	0.00	0.01	0.02	0.01	0.02	0.01	0.04
	2	0.00	0.01	0.05	0.01	0.02	0.01	0.03
	3	0.00	0.01	0.03	0.01	0.02	0.01	0.03
	4	0.00	0.01	0.05	0.01	0.02	0.01	0.03
	5	0.00	0.01	0.05	0.01	0.01	0.01	0.05
	Mean	0.00	0.01	0.04	0.01	0.02	0.01	0.04

Table 17. shows the accumulation of antisense strand in the brown adipose at 2 weeks and 4 weeks post dosing. N = 5.

		Brown adipose Guide Strand PK (ug oligo/g tissue)						
2 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	0.00	0.21	2.25	0.49	1.55	0.28	1.51
	2	0.00	0.10	1.34	0.30	2.21	0.21	2.27
	3	0.00	0.11	1.61	0.11	2.31	0.49	1.24
	4	0.00	0.32	1.90	0.35	3.28	0.11	3.60
	5	0.00	0.14	1.36	1.18	0.66	0.72	1.32
	Mean	0.00	0.18	1.69	0.49	2.00	0.36	1.99
4 weeks post dosing	animal No.	PBS	DSR-0104147	DSR-0104104	DSR-0104148	DSR-0104149	DSR-0104150	DSR-0104151
	1	0.00	0.09	0.70	0.32	2.06	0.10	0.66
	2	0.00	0.10	1.18	0.26	1.07	0.09	0.71
	3	0.00	0.10	1.08	0.20	0.20	0.10	0.89
	4	0.00	0.11	1.51	0.11	1.38	0.11	0.62
	5	0.00	0.10	1.25	0.29	0.47	0.11	0.99
	Mean	0.00	0.10	1.14	0.24	1.04	0.11	0.77

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EXAMPLE 4. Provided Oligonucleotides and Compositions Are Active *in vitro* in

Mouse Primary Hepatocytes

Various siRNAs for mouse TTR were designed and constructed. A number of siRNAs were tested *in vitro* in mouse primary hepatocytes at one or a range of concentrations. Example protocol for *in vitro* determination of siRNA activity in mouse primary hepatocytes: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to mouse primary hepatocytes plated at 96-well plates, with 10,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse TTR mRNA, the following qPCR assay was utilized: IDT PrimeTime predesigned qPCR Assay Mm.PT.58.11922308. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 18. shows % mouse TTR mRNA remaining (at 500, 150 and 50 pM siRNA treatment) in primary mouse hepatocytes relative to mouse HPRT control. N = 2.

	500 pM			150 pM		
siRNA	%remaining mRNA (mTTR/ mHPRT)- 1	%remaining mRNA (mTTR/ mHPRT)-2	Mean	%remaining mRNA (mTTR/ mHPRT)- 1	%remaining mRNA (mTTR/ mHPRT)-2	Mean
DSR-0102626	11.88	7.31	9.60	32.21	32.07	32.14
DSR-0104167	11.02	7.84	9.43	34.57	35.56	35.07
DSR-0104655	37.86	32.63	35.25	63.95	63.89	63.92
DSR-0104654	81.80	82.33	82.07	93.90	94.26	94.08
DSR-0104653	94.52	93.41	93.97	93.11	94.88	93.99
DSR-0104652	79.83	77.03	78.43	88.29	83.89	86.09
DSR-0104651	46.03	45.78	45.91	76.19	70.40	73.29
DSR-0104650	27.09	26.69	26.89	53.88	51.54	52.71
DSR-0104649	25.50	21.10	23.30	49.68	45.24	47.46
DSR-0104648	17.54	16.77	17.16	43.09	44.60	43.84
DSR-	11.79	11.75	11.77	41.57	44.74	43.15

0104647						
DSR-0104646	8.94	9.01	8.97	32.84	34.42	33.63
DSR-0104645	10.42	10.49	10.46	30.44	30.74	30.59

	50 pM		
siRNA	%remaining mRNA (mTTR/ mHPRT)- 1	%remaining mRNA (mTTR/ mHPRT)-2	Mean
DSR-0102626	41.41	47.12	44.26
DSR-0104167	52.35	52.36	52.35
DSR-0104655	94.91	73.09	84.00
DSR-0104654	132.67	101.68	117.17
DSR-0104653	118.51	94.36	106.44
DSR-0104652	125.33	103.54	114.44
DSR-0104651	96.89	97.13	97.01
DSR-0104650	58.14	63.51	60.82
DSR-0104649	58.19	69.32	63.75
DSR-0104648	50.89	58.68	54.79
DSR-0104647	63.30	65.73	64.51
DSR-0104646	64.59	74.08	69.33
DSR-0104645	75.87	59.29	67.58

Table 19. shows % mouse TTR mRNA remaining (at 500pM, 150pM and 50pM siRNA treatment) in primary mouse hepatocyte relative to mouse HPRT control. N = 2.

	500pM			150pM		
siRNA	% remaining mRNA (mTTR/ mHPRT)-1	% remaining mRNA (mTTR/ mHPRT)-2	Mean	% remaining mRNA (mTTR/ mHPRT)-1	% remaining mRNA (mTTR/ mHPRT)-2	Mean
DSR-0102626	11.88	7.31	9.60	32.21	32.07	32.14
DSR-	11.02	7.84	9.43	34.57	35.56	35.07

0104167						
DSR-0104644	11.84	10.50	11.17	30.49	24.96	27.72
DSR-0104643	10.47	9.78	10.13	29.10	29.36	29.23
DSR-0104642	11.27	9.11	10.19	33.88	27.88	30.88
DSR-0104641	14.83	16.69	15.76	41.73	38.23	39.98
DSR-0104640	11.77	12.70	12.24	34.15	29.80	31.97
DSR-0104639	8.72	10.44	9.58	30.59	27.03	28.81
DSR-0104638	6.42	8.30	7.36	27.38	18.74	23.06
DSR-0104637	7.56	9.28	8.42	31.77	27.30	29.53
DSR-0104636	6.59	8.94	7.76	27.12	27.91	27.52
DSR-0104635	9.02	13.90	11.46	37.98	46.55	42.26
DSR-0104634	5.52	8.35	6.94	31.49	31.39	31.44
DSR-0104633	8.02	11.38	9.70	33.30	26.78	30.04
DSR-0104632	6.99	7.20	7.10	25.55	17.58	21.57
DSR-0104631	6.66	8.43	7.54	39.85	21.79	30.82
DSR-0104630	8.16	11.70	9.93	31.03	28.78	29.90
DSR-0104629	9.72	14.72	12.22	29.89	27.93	28.91
DSR-0104628	9.64	12.46	11.05	28.09	25.91	27.00
DSR-0104627	6.96	8.10	7.53	23.72	23.69	23.71

	50pM		
siRNA	% remaining mRNA (mTTR/ mHPRT)-1	% remaining mRNA (mTTR/ mHPRT)-2	Mean
DSR-0102626	41.41	47.12	44.26
DSR-0104167	52.35	52.36	52.35
DSR-0104644	59.37	57.43	58.40
DSR-	67.57	62.38	64.97

0104643			
DSR-0104642	64.52	70.77	67.65
DSR-0104641	67.79	85.60	76.69
DSR-0104640	66.21	88.01	77.11
DSR-0104639	70.00	88.21	79.11
DSR-0104638	31.69	54.55	43.12
DSR-0104637	53.13	58.39	55.76
DSR-0104636	49.54	54.12	51.83
DSR-0104635	67.58	80.94	74.26
DSR-0104634	58.36	66.31	62.34
DSR-0104633	49.35	49.45	49.40
DSR-0104632	42.31	42.33	42.32
DSR-0104631	58.14	49.27	53.70
DSR-0104630	57.52	57.30	57.41
DSR-0104629	60.73	60.90	60.81
DSR-0104628	68.80	54.25	61.52
DSR-0104627	52.63	46.86	49.75

EXAMPLE 5. Provided Oligonucleotides and Compositions Are Active *in vitro* in human iCell GABA neurons

Various siRNAs for human APP were designed and constructed. A number of siRNAs were tested *in vitro* in human iCell GABA neurons at one or a range of concentrations.

Example protocol for in vitro determination of siRNA activity in human iCell GABA neurons: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to human iCell GABA neurons plated at 96-well plates, with 40,000 cells/well. Following 5 days treatment, total RNA was extracted using SV96 Total RNA

Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human APP mRNA, the following qPCR assay was utilized: Thermofisher Taqman qPCR assay ID Hs00169098_m1. Human SFRS9 was used as normalizer (Forward, 5'-TGGAATATGCCCTGCGTAAA-3'; Reverse, 5'- TGGTGCTTCTCTCAGGATAAAC-3', Probe, 5'- TGGATGACACCAAATTCCGCTCTCA-3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 20. shows % human APP mRNA remaining (at 3 and 1 uM siRNA treatment) in iCell GABA neurons relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104213	15.80	13.20	14.50	26.70	21.60	24.15
DSR-0104223	19.60	18.70	19.15	34.90	42.60	38.75
DSR-0104222	18.30	17.90	18.10	31.10	30.80	30.95
DSR-0104221	64.10	62.10	63.10	79.00	74.00	76.5
DSR-0104220	39.40	37.80	38.60	81.70	65.70	73.70
DSR-0104219	28.70	32.10	30.40	55.70	58.80	57.25
DSR-0104218	52.20	61.80	57.00	74.30	78.00	76.15
DSR-0104217	40.40	40.10	40.25	66.40	63.50	64.95
DSR-0104216	51.20	57.10	54.15	60.10	63.10	61.6
DSR-0104215	43.40	42.10	42.75	65.90	54.90	60.40
DSR-0104214	19.60	19.40	19.50	34.60	31.00	32.80

Table 21. shows % human APP mRNA remaining (at 3 and 1 uM siRNA treatment) in iCell GABA neurons relative to human SFRS9 control. N = 2.

	3 uM	1 uM

siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104213	15.80	13.20	14.50	26.70	21.60	24.15
DSR-0104231	9.20	9.10	9.15	27.00	8.30	17.65
DSR-0104230	18.90	18.90	18.90	32.20	32.60	32.40
DSR-0104229	13.80	11.70	12.75	31.70	31.10	31.40
DSR-0104228	12.20	12.70	12.45	26.10	25.60	25.85
DSR-0104227	19.20	20.60	19.90	36.80	39.90	38.35
DSR-0104226	13.30	12.80	13.05	30.00	27.40	28.70
DSR-0104225	32.30	34.70	33.50	57.60	56.80	57.20
DSR-0104224	55.10	62.80	58.95	65.60	81.40	73.50

Table 22. shows % human APP mRNA remaining (at 3 and 1 uM siRNA treatment) in iCell GABA neurons relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104213	15.80	13.20	14.50	26.70	21.60	24.15
DSR-0104233	18.30	18.70	18.50	43.40	51.00	47.20
DSR-0104232	15.70	15.50	15.60	21.70	28.10	24.90
DSR-0103301	11.70	10.90	11.30	28.10	27.90	28.00
DSR-0104241	32.10	31.20	31.65	62.90	57.10	60.00
DSR-0104240	50.50	47.30	48.90	64.70	76.10	70.40
DSR-0104239	38.60	39.40	39.00	55.00	61.80	58.40
DSR-0104238	25.80	26.30	26.05	55.70	56.70	56.20
DSR-	25.40	21.50	23.45	50.20	55.20	52.70

0104237						
DSR-0104236	24.80	24.80	24.80	61.40	66.70	64.05
DSR-0104235	29.00	28.60	28.80	58.60	62.70	60.65
DSR-0104234	21.70	23.70	22.70	51.90	59.60	55.75

Table 23. shows % IC50 of knocking down human APP mRNA in human iCell GABA neurons.

siRNA	IC50 (uM)	95% CI
DSR-0104461	0.23	0.16 to 0.35
DSR-0104462	0.18	0.11 to 0.30
DSR-0104463	0.21	0.14 to 0.31
DSR-0104464	0.11	0.08 to 0.16

EXAMPLE 6. Provided Oligonucleotides and Compositions Are Active in vitro in Normal Human Bronchial Epithelium Cells

Various siRNAs for human APP were designed and constructed. A number of siRNAs were tested *in vitro* in human bronchial epithelium (NHBE) cells at a range of concentrations.

Example protocol for *in vitro* determination of siRNA activity in human NHBE cells: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to NHBE cells plated at 96-well plates, with 5,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human APP mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Hs00169098_m1. Human hSFRS9 was used as normalizer (Forward 5' TGGAATATGCCCTGCGTAAA', Reverse 5' TGGTGCTTCTCTCAGGATAAAC 3', Probe 5'/5HEX/TGGATGACA/Zen/CCAAATTCCGCTCTCA/3IABkFQ/3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 24. shows % human APP mRNA remaining (at 30, 10, 3 and 1 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2.

	30 uM			10 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-010330	58.19	21.23	39.71	35.26	37.14	36.20
DSR-0104214	47.19	51.82	49.50	63.00	49.15	56.07
DSR-0104215	4.41	3.44	3.92	6.34	6.89	6.61
	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0103301	49.80	49.60	49.70	69.96	53.43	61.70
DSR-0104214	74.54	68.30	71.42	73.10	70.08	71.59
DSR-0104215	15.24	16.32	15.78	41.15	29.07	35.11

Table 25. shows % human APP mRNA remaining (at 10, 3, 1, and 0.3 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2.

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104513	42.55	52.23	47.39	54.57	56.82	55.70
DSR-0104512	39.76	52.28	46.02	62.78	61.38	62.08
DSR-0104511	37.01	25.62	31.31	41.01	38.90	39.95
DSR-0104510	44.61	59.35	51.98	62.94	68.69	65.81
DSR-0104215	12.19	8.20	10.20	17.78	17.61	17.69
DSR-0104214	48.57	60.18	54.37	58.09	68.35	63.22
DSR-	36.29	33.71	35.00	99.90	38.18	69.04

0103301						

	1 uM			0.3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104513	60.33	67.26	63.79	70.75	69.10	69.93
DSR-0104512	64.44	61.81	63.12	83.15	86.80	84.97
DSR-0104511	59.76	48.67	54.21	67.25	74.12	70.69
DSR-0104510	61.97	64.84	63.40	66.60	78.60	72.60
DSR-0104215	27.55	28.29	27.92	47.92	53.17	50.54
DSR-0104214	65.75	59.63	62.69	62.70	77.72	70.21
DSR-0103301	49.09	42.50	45.79	54.44	59.60	57.02

Table 26. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2. N.D.: Not determined

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104461	25.56	N.D.	25.56	32.27	62.16	47.22
DSR-0104559	82.67	156.43	119.55	49.40	85.06	67.23
DSR-0104533	44.42	N.D.	44.42	42.99	57.62	50.30
DSR-0104511	47.56	22.88	35.22	33.30	54.81	44.06
DSR-0104510	N.D.	19.01	19.01	29.60	46.75	38.18

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	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-	41.84	46.73	44.28

0104461			
DSR-0104559	61.60	79.85	70.72
DSR-0104533	49.82	72.96	61.39
DSR-0104511	41.63	47.51	44.57
DSR-0104510	56.67	77.22	66.95

Table 27. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2. N.D.: Not determined

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104532	34.22	57.40	45.81	42.72	61.53	52.13
DSR-0104531	97.53	132.96	115.25	45.74	69.02	57.38
DSR-0104530	12.34	19.65	15.99	11.00	17.35	14.17
DSR-0104529	46.73	48.31	47.52	17.40	33.29	25.34
DSR-0104528	9.22	4.54	6.88	7.64	14.26	10.95
DSR-0104527	20.14	4.34	12.24	14.13	23.05	18.59
DSR-0104461	25.56	N.D.	25.56	32.27	62.16	47.22
DSR-0104559	82.67	156.43	119.55	49.40	85.06	67.23
DSR-0104533	44.42	N.D.	44.42	42.99	57.62	50.30

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104532	38.19	71.07	54.63
DSR-0104531	48.25	64.32	56.29
DSR-	18.28	31.72	25.00

0104530			
DSR-0104529	37.56	48.03	42.79
DSR-0104528	14.56	16.14	15.35
DSR-0104527	25.90	39.55	32.73
DSR-0104461	41.84	46.73	44.28
DSR-0104559	61.60	79.85	70.72
DSR-0104533	49.82	72.96	61.39

Table 28. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2. N.D.: Not determined

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104546	3.57	4.92	4.25	12.66	65.20	38.93
DSR-0104545	10.49	16.54	13.51	21.60	46.18	33.89
DSR-0104562	46.61	71.12	58.86	27.29	44.53	35.91
DSR-0104561	46.67	97.50	72.08	38.16	54.51	46.34
DSR-0104560	22.76	39.91	31.33	31.10	41.76	36.43
DSR-0104461	25.56	N.D.	25.56	32.27	62.16	47.22
DSR-0104559	82.67	156.43	119.5	49.40	85.06	67.23
DSR-0104533	44.42	N.D.	44.42	42.99	57.62	50.31

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104546	37.46	47.46	42.46
DSR-0104545	29.03	65.02	47.03

DSR-0104562	37.04	49.96	43.50
DSR-0104561	38.63	58.20	48.41
DSR-0104560	46.13	52.33	49.23
DSR-0104461	41.84	46.73	44.28
DSR-0104559	61.60	79.85	70.72
DSR-0104533	49.82	72.96	61.39

Table 29. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2. N.D.: Not determined

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104544	4.15	5.87	5.01	16.82	16.22	16.52
DSR-0104543	5.48	11.50	8.49	12.66	30.31	21.48
DSR-0104542	33.17	38.05	35.61	34.84	44.40	39.62
DSR-0104541	64.39	N.D.	64.39	33.78	47.58	40.68
DSR-0104540	24.09	25.97	25.03	32.16	45.27	38.72
DSR-0104539	22.74	38.88	30.81	29.06	46.35	37.70
DSR-0104461	25.56	N.D.	25.56	32.27	62.16	47.22
DSR-0104559	82.67	156.43	119.55	49.40	85.06	67.23
DSR-0104533	44.42	N.D.	44.42	42.99	57.62	50.30

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104544	52.71	74.32	63.51

DSR-0104543	32.83	68.05	50.44
DSR-0104542	45.29	52.96	49.12
DSR-0104541	39.29	52.08	45.69
DSR-0104540	35.24	58.44	46.84
DSR-0104539	34.58	49.98	42.28
DSR-0104461	41.84	46.73	44.28
DSR-0104559	61.60	79.85	70.72
DSR-0104533	49.82	72.96	61.39

Table 30. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in NHBE cells relative to human SFRS9 control. N = 2. N.D.: Not determined

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104550	3.43	7.51	5.47	17.46	65.27	41.36
DSR-0104549	32.29	28.52	30.40	27.79	42.11	34.95
DSR-0104548	63.22	N.D.	63.22	44.97	21.43	33.20
DSR-0104547	73.08	56.49	64.78	39.66	39.16	39.41
DSR-0104461	25.56	N.D.	25.56	32.27	62.16	47.22
DSR-0104559	82.67	156.43	119.55	49.40	85.06	67.23
DSR-0104533	44.42	N.D.	44.42	42.99	57.62	50.31

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104550	41.53	56.58	49.06

DSR-0104549	51.67	119.80	85.73
DSR-0104548	56.85	59.28	58.06
DSR-0104547	50.80	74.46	62.63
DSR-0104461	41.84	46.73	44.28
DSR-0104559	61.60	79.85	70.72
DSR-0104533	49.82	72.96	61.39

Table 31. shows % IC50 of knocking down human APP mRNA in normal human bronchial epithelia cells. N.D.: Not determined

siRNA	IC50 (uM)	95% CI
DSR-0104533	N.D.	N.D.
DSR-0104461	N.D.	N.D.
DSR-0104527	0.59	0.31 to 1.16
DSR-0104528	0.24	0.19 to 0.31
DSR-0104530	0.70	0.45 to 1.07
DSR-0104560	0.38	0.23 to 0.63
DSR-0104546	1.01	0.55 to 1.89
DSR-0104539	0.63	0.37 to 1.06
DSR-0104544	0.92	0.58 to 1.46
DSR-0104550	0.8804	0.62 to 1.26

EXAMPLE 7. Provided Oligonucleotides and Compositions Are Active in vitro in HEK293T Cells

Various siRNAs for human APP were designed and constructed. A number of siRNAs were tested *in vitro* in HEK293T cells at a range of concentrations.

Example protocol for in vitro determination of siRNA activity in human HEK293T: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to Human HEK293T cells plated at 96-well plates, with 30,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human APP mRNA, the following qPCR assay was utilized: Thermofisher Taqman qPCR assay ID Hs00169098_m1. Human SFRS9 was used as normalizer (Forward, 5'-TGGAATATGCCCTGCGTAAA-3'; Reverse, 5'- TGGTGCTTCTCTCAGGATAAAC-3', Probe, 5'- TGGATGACACCAAATTCCGCTCTCA-3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 32. shows % human APP mRNA remaining (at 30, 10, 3 and 1 uM siRNA treatment) in HEK293T cells relative to human SFRS9 control. N = 2.

	30 uM			10 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0103301-015-001	18.86	19.15	19.01	32.10	29.67	30.88
DSR-0104214-002-001	23.68	24.92	24.30	38.20	37.14	37.67
DSR-0104215-002-001	11.92	11.85	11.89	20.10	20.67	20.39
	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0103301-015-001	39.05	34.35	36.70	54.06	47.72	50.89
DSR-0104214-002-001	47.13	49.99	48.56	67.41	66.38	66.89
DSR-0104215-	40.68	42.88	41.78	65.20	63.65	64.43

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EXAMPLE 8. Provided Oligonucleotides and Compositions Are Active in vitro in 3T3-L1 Cells

Various siRNAs for mouse APP were designed and constructed. A number of siRNAs were tested *in vitro* in 3T3-L1 cells at a range of concentrations.

Example protocol for in vitro determination of siRNA activity in 3T3-L1 cells: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to mouse 3T3-L1 s plated at 96-well plates, with 3,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse APP mRNA, the following qPCR assay was utilized: Thermofisher Taqman qPCR assay ID Mm01344172_m1. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 33. shows % mouse APP mRNA remaining (at 30, 10, 3 and 1 uM siRNA treatment) in 3T3-L1 cells relative to mouse HPRT control. N = 2.

	30 uM			10 uM		
siRNA	%remaining mRNA (mAPP/ mHPRT)- 1	%remaining mRNA (mAPP/ mHPRT)-2	Mean	%remaining mRNA (mAPP/ mHPRT)- 1	%remaining mRNA (mAPP/ mHPRT)-2	Mean
DSR-0103301	59.73	47.75	53.74	47.47	43.75	45.61
DSR-0104214	29.99	33.04	31.51	44.31	42.92	43.62
DSR-0104215	8.70	7.40	8.05	24.67	26.24	25.46
	3 uM			1 uM		
siRNA	%remaining mRNA (mAPP/ mHPRT)- 1	%remaining mRNA (mAPP/ mHPRT)-2	Mean	%remaining mRNA (mAPP/ mHPRT)- 1	%remaining mRNA (mAPP/ mHPRT)-2	
DSR-0103301	51.28	39.66	45.47	44.66	45.28	44.97
DSR-0104214	60.57	57.37	58.97	64.30	68.31	66.30

DSR-0104215	42.90	42.01	42.46	50.64	55.97	53.31

EXAMPLE 9. Provided Oligonucleotides and Compositions Are Active in vitro in Human Renal Proximal Tubule Cells

Various siRNAs for human APP were designed and constructed. A number of siRNAs were tested *in vitro* in human renal proximal tubule cells at a range of concentrations.

Example protocol for in vitro determination of siRNA activity in human renal proximal convoluted tubule: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to Human renal proximal convoluted tubule cells plated at 96-well plates, with 10,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human APP mRNA, the following qPCR assay were utilized: Thermofisher Taqman qPCR assay ID Hs00169098_m1. Human SFRS9 was used as normalizer (Forward, 5'- TGGAATATGCCCTGCGTAAA-3'; Reverse, 5'-TGGTGCTTCTCTCAGGATAAAC-3', Probe, 5'-TGGATGACACCAAATTCCGCTCTCA-3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 34. shows % human APP mRNA remaining (at 30, 10, 3 and 1 uM siRNA treatment) in human renal proximal tubule cells relative to human SFRS9 control. N = 2.

	30 uM			10 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0103301-015-001	51.75	51.17	51.46	70.98	61.69	66.34
DSR-0104214-002-001	69.49	77.03	73.26	91.01	89.62	90.32
DSR-0104215-002-001	20.98	23.10	22.04	33.08	34.79	33.94
	3 uM			1 uM		

siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0103301-015-001	83.99	81.97	82.98	84.33	84.26	84.30
DSR-0104214-002-001	109.40	99.35	104.38	107.10	98.54	102.82
DSR-0104215-002-001	55.49	55.22	55.36	78.90	68.87	73.89

EXAMPLE 10. Provided Oligonucleotides and Compositions Are Active in vitro in Human Adipocytes

Various siRNAs for human APP were designed and constructed. A number of siRNAs were tested *in vitro* in Human adipocytes at a range of concentrations.

Example protocol for in vitro determination of siRNA activity in human adipocytes: Preadipocyte was plated at 96-well plates with 10,000 cells/well for differentiation. For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to human adipocyte 6 days after differentiation initiation. Following 5 days treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human APP mRNA, the following qPCR assay was utilized: Thermofisher Taqman qPCR assay ID Hs00169098_m1. Human SFRS9 was used as normalizer (Forward, 5'- TGGAATATGCCCTGCGTAAA-3'; Reverse, 5'-TGGTGCTTCTCTCAGGATAAAC-3', Probe, 5'-TGGATGACACCAAATTCCGCTCTCA-3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 35. shows % human APP mRNA remaining (at 30, 10, 3 and 1 uM siRNA treatment) in human adipocytes relative to human SFRS9 control. N = 2.

	30 uM			10 uM		
siRNA	%remaining mRNA (hAPP/	%remaining mRNA (hAPP/	Mean	%remaining mRNA (hAPP/	%remaining mRNA (hAPP/	Mean

	hSFRS9)- 1	hSFRS9)-2		hSFRS9)- 1	hSFRS9)-2	
DSR-0103301	8.24	7.30	7.77	17.74	15.59	16.66
DSR-0104214	14.59	16.08	15.33	31.20	30.41	30.80
DSR-0104215	3.61	4.27	3.94	16.55	15.18	15.86
	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0103301	26.71	22.56	24.63	35.01	33.10	34.05
DSR-0104214	48.57	51.94	50.26	69.42	64.40	66.91
DSR-0104215	41.87	39.78	40.82	63.82	65.60	64.71

Table 36. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in human adipocytes relative to human SFRS9 control. N = 2.

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104461	11.78	12.40	12.09	15.12	14.89	15.00
DSR-0104559	16.59	21.16	18.88	27.97	32.48	30.23
DSR-0104533	22.12	27.73	24.93	32.00	40.60	36.30
DSR-0104511	15.33	11.83	13.58	22.99	16.92	19.96
DSR-0104510	19.24	16.50	17.87	23.85	18.16	21.01

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104461	24.49	24.63	24.56
DSR-0104559	47.60	62.86	55.23
DSR-0104533	46.95	69.08	58.02

DSR-0104511	34.86	27.92	31.39
DSR-0104510	44.61	31.97	38.29

Table 37. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in human adipocytes relative to human SFRS9 control. N = 2.

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104532	25.74	31.99	28.86	33.06	53.85	43.46
DSR-0104531	17.41	24.52	20.97	27.43	38.13	32.78
DSR-0104530	17.84	24.09	20.97	35.56	46.77	41.16
DSR-0104529	9.18	11.99	10.59	20.47	27.39	23.93
DSR-0104528	9.93	11.15	10.54	29.84	36.54	33.19
DSR-0104527	8.51	10.94	9.73	16.72	22.28	19.50
DSR-0104461	11.78	12.40	12.09	15.12	14.89	15.00
DSR-0104559	16.59	21.16	18.88	27.97	32.48	30.23
DSR-0104533	22.12	27.73	24.93	32.00	40.60	36.30

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104532	52.89	75.96	64.43
DSR-0104531	47.03	69.10	58.06
DSR-0104530	46.56	73.10	59.83
DSR-0104529	44.94	59.16	52.05
DSR-0104528	48.33	57.52	52.93
DSR-0104527	35.67	43.20	39.43
DSR-	24.49	24.63	24.56

0104461			
DSR-0104559	47.60	62.86	55.23
DSR-0104533	46.95	69.08	58.02

Table 38. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in human adipocytes relative to human SFRS9 control. N = 2.

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104546	9.26	9.19	9.22	21.70	21.18	21.44
DSR-0104545	9.74	8.35	9.05	19.74	17.07	18.41
DSR-0104562	12.56	12.39	12.47	17.00	20.48	18.74
DSR-0104561	17.47	17.41	17.44	24.05	24.30	24.17
DSR-0104560	11.01	10.32	10.66	18.40	19.54	18.97
DSR-0104461	11.78	12.40	12.09	15.12	14.89	15.00
DSR-0104559	16.59	21.16	18.88	27.97	32.48	30.23
DSR-0104533	22.12	27.73	24.93	32.00	40.60	36.30

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104546	49.43	52.82	51.13
DSR-0104545	32.21	32.80	32.51
DSR-0104562	33.76	34.56	34.16
DSR-0104561	38.57	36.72	37.64
DSR-0104560	32.49	30.52	31.51
DSR-0104461	24.49	24.63	24.56

DSR-0104559	47.60	62.86	55.23
DSR-0104533	46.95	69.08	58.02

Table 39. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in human adipocytes relative to human SFRS9 control. N = 2.

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104544	20.16	15.07	17.62	31.61	26.29	28.95
DSR-0104543	10.01	9.94	9.98	13.92	13.69	13.81
DSR-0104542	13.13	12.62	12.87	19.24	18.01	18.63
DSR-0104541	17.37	17.69	17.53	24.48	25.59	25.04
DSR-0104540	15.50	17.19	16.35	22.82	26.15	24.48
DSR-0104539	17.07	17.41	17.24	24.21	27.74	25.97
DSR-0104461	11.78	12.40	12.09	15.12	14.89	15.00
DSR-0104559	16.59	21.16	18.88	27.97	32.48	30.23
DSR-0104533	22.12	27.73	24.93	32.00	40.60	36.30

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104544	55.61	53.65	54.63
DSR-0104543	28.17	28.04	28.11
DSR-0104542	35.95	32.84	34.40
DSR-0104541	47.62	47.32	47.47
DSR-0104540	43.55	40.68	42.12
DSR-0104539	40.79	45.24	43.02

DSR-0104461	24.49	24.63	24.56
DSR-0104559	47.60	62.86	55.23
DSR-0104533	46.95	69.08	58.02

Table 40. shows % human APP mRNA remaining (at 10, 3 and 1 uM siRNA treatment) in human adipocytes relative to human SFRS9 control. N = 2.

	10 uM			3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104550	5.22	4.81	5.01	19.75	16.40	18.07
DSR-0104549	22.90	25.95	24.42	43.30	38.02	40.66
DSR-0104548	19.11	20.88	19.99	35.84	35.89	35.87
DSR-0104547	14.75	14.36	14.56	21.88	24.11	23.00
DSR-0104461	11.78	12.40	12.09	15.12	14.89	15.00
DSR-0104559	16.59	21.16	18.88	27.97	32.48	30.23
DSR-0104533	22.12	27.73	24.93	32.00	40.60	36.30

	1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104550	60.97	57.96	59.46
DSR-0104549	68.61	68.59	68.60
DSR-0104548	54.80	53.56	54.18
DSR-0104547	48.44	43.31	45.88
DSR-0104461	24.49	24.63	24.56
DSR-0104559	47.60	62.86	55.23
DSR-0104533	46.95	69.08	58.02

EXAMPLE 11. Provided Oligonucleotides and Compositions Are Active in vitro in Human Primary Hepatocytes

Various siRNAs for human APP were designed and constructed. A number of siRNAs were tested *in vitro* in human primary hepatocytes at one or a range of concentrations.

Example protocol for *in vitro* determination of siRNA activity in human primary hepatocytes: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to primary hepatocytes plated at 96-well plates, with 10,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For human APP mRNA, the following qPCR assay was utilized: Thermofisher Taqman qPCR assay ID Hs00169098_m1. Human hSFRS9 was used as normalizer (Forward 5' TGGAATATGCCCTGCGTAAA', Reverse 5' TGGTGCTTCTCTCAGGATAAAC 3', Probe 5'/5HEX/TGGATGACA/Zen/CCAAATTCCGCTCTCA/3IABkFQ/3'. mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 41. Shows % human APP mRNA remaining (at 3,1, and 0.3 uM siRNA treatment) in primary human hepatocyte relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104461	10.22	9.85	10.03	15.95	16.95	16.45
DSR-0104559	19.60	18.95	19.27	23.21	23.78	23.49
DSR-0104533	18.91	18.73	18.82	28.52	23.76	26.14
DSR-0104511	7.27	9.01	8.14	15.28	13.05	14.17
DSR-0104510	22.85	22.32	22.59	33.67	31.54	32.60

0.3 uM

siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104461	28.01	24.35	26.18
DSR-0104559	41.30	38.00	39.65
DSR-0104533	37.85	35.29	36.57
DSR-0104511	30.30	25.97	28.14
DSR-0104510	50.40	44.79	47.59

Table 42. Shows % human APP mRNA remaining (at 3,1, and 0.3 uM siRNA treatment) in primary human hepatocyte relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104532	46.30	35.35	40.82	44.70	44.40	44.55
DSR-0104531	18.18	18.19	18.18	29.39	24.62	27.01
DSR-0104530	8.90	8.94	8.92	16.95	12.69	14.82
DSR-0104529	11.29	12.26	11.78	18.59	14.12	16.35
DSR-0104528	10.03	7.61	8.82	15.45	13.01	14.23
DSR-0104527	9.49	11.09	10.29	15.04	17.23	16.13
DSR-0104461	10.22	9.85	10.03	15.95	16.95	16.45
DSR-0104559	19.60	18.95	19.27	23.21	23.78	23.49
DSR-0104533	18.91	18.73	18.82	28.52	23.76	26.14

	0.3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean

DSR-0104532	60.70	56.44	58.57
DSR-0104531	40.61	42.96	41.78
DSR-0104530	32.76	26.56	29.66
DSR-0104529	31.35	29.75	30.55
DSR-0104528	30.53	23.70	27.12
DSR-0104527	31.72	30.55	31.14
DSR-0104461	28.01	24.35	26.18
DSR-0104559	41.30	38.00	39.65
DSR-0104533	37.85	35.29	36.57

Table 43. Shows % human APP mRNA remaining (at 3,1, and 0.3 uM siRNA treatment) in primary human hepatocyte relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104546	7.30	4.75	6.02	12.15	10.36	11.25
DSR-0104545	7.22	5.66	6.44	12.13	11.67	11.90
DSR-0104562	8.33	5.18	6.75	12.54	9.77	11.15
DSR-0104561	9.61	8.22	8.91	15.13	14.19	14.66
DSR-0104560	8.08	6.67	7.37	14.03	9.77	11.90
DSR-0104461	10.22	9.85	10.03	15.95	16.95	16.45
DSR-0104559	19.60	18.95	19.27	23.21	23.78	23.49
DSR-0104533	18.91	18.73	18.82	28.52	23.76	26.14

	0.3 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)-2	%remaining mRNA (hAPP/ hSFRS9)-2	Mean

DSR-0104546	35.76	29.56	32.66
DSR-0104545	25.31	22.98	24.15
DSR-0104562	20.18	18.35	19.26
DSR-0104561	28.06	20.85	24.45
DSR-0104560	20.54	19.70	20.12
DSR-0104461	28.01	24.35	26.18
DSR-0104559	41.30	38.00	39.65
DSR-0104533	37.85	35.29	36.57

Table 44. Shows % human APP mRNA remaining (at 3,1, and 0.3 uM siRNA treatment) in primary human hepatocyte relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104544	8.66	6.36	7.51	14.02	11.60	12.81
DSR-0104543	5.59	6.39	5.99	12.79	12.02	12.41
DSR-0104542	6.62	6.62	6.62	11.57	10.71	11.14
DSR-0104541	7.39	6.74	7.07	14.01	15.54	14.78
DSR-0104540	6.34	5.82	6.08	12.87	10.82	11.85
DSR-0104539	7.33	7.10	7.22	15.45	14.51	14.98
DSR-0104461	10.22	9.85	10.03	15.95	16.95	16.45
DSR-0104559	19.60	18.95	19.27	23.21	23.78	23.49
DSR-0104533	18.91	18.73	18.82	28.52	23.76	26.14

	0.3 uM		
siRNA	%remaining mRNA (hAPP/	%remaining mRNA (hAPP/	Mean

	hSFRS9)- 1	hSFRS9)-2	
DSR-0104544	35.82	29.21	32.51
DSR-0104543	30.94	25.61	28.28
DSR-0104542	21.50	20.84	21.17
DSR-0104541	25.99	27.66	26.82
DSR-0104540	21.02	23.32	22.17
DSR-0104539	32.10	29.02	30.56
DSR-0104461	28.01	24.35	26.18
DSR-0104559	41.30	38.00	39.65
DSR-0104533	37.85	35.29	36.57

Table 45. Shows % human APP mRNA remaining (at 3,1, and 0.3 uM siRNA treatment) in primary human hepatocyte relative to human SFRS9 control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104550	8.95	9.01	8.98	25.84	30.30	28.07
DSR-0104549	9.68	10.01	9.84	22.86	33.22	28.04
DSR-0104548	13.01	11.29	12.15	25.35	25.13	25.24
DSR-0104547	8.30	7.94	8.12	18.35	16.62	17.49
DSR-0104461	10.22	9.85	10.03	15.95	16.95	16.45
DSR-0104559	19.60	18.95	19.27	23.21	23.78	23.49
DSR-0104533	18.91	18.73	18.82	28.52	23.76	26.14

0.3 uM

siRNA	%remaining mRNA (hAPP/ hSFRS9)- 1	%remaining mRNA (hAPP/ hSFRS9)-2	Mean
DSR-0104550	50.70	47.31	49.00
DSR-0104549	46.39	50.83	48.61
DSR-0104548	46.61	50.61	48.61
DSR-0104547	29.61	32.85	31.23
DSR-0104461	28.01	24.35	26.18
DSR-0104559	41.30	38.00	39.65
DSR-0104533	37.85	35.29	36.57

EXAMPLE 12. Provided Oligonucleotides and Compositions Are Active *in vitro* in Mouse Primary Hepatocytes

Various siRNAs for mouse SOD1 were designed and constructed. A number of siRNAs were tested *in vitro* in mouse primary hepatocytes at one or a range of concentrations. Some siRNAs were also tested in mice (e.g., C57BL6 wild type mice).

Example protocol for *in vitro* determination of siRNA activity in mouse primary hepatocytes: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to mouse primary hepatocytes plated at 96-well plates, with 10,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse SOD1 mRNA, the following qPCR assay was utilized: IDT PrimeTime predesigned qPCR Assay Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 46. shows % mouse SOD1 mRNA remaining (at 0.1, 0.03 and 0.01 uM siRNA treatment) in primary mouse hepatocytes relative to mouse HPRT control. N = 2.

	0.1 uM			0.03 uM		
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0103970	22.66	26.19	24.43	45.68	39.27	42.47
DSR-0104477	60.62	59.89	60.26	92.47	74.61	83.54
DSR-0104480	39.53	38.00	38.76	64.70	71.27	67.98
DSR-0103971	39.79	32.14	35.97	51.84	48.03	49.94
DSR-0104478	18.41	20.13	19.27	26.32	28.69	27.51
DSR-0104481	32.06	32.41	32.23	34.30	49.11	41.71
DSR-0103972	35.68	23.57	29.63	48.72	46.42	47.57
DSR-0104479	18.04	12.44	15.24	26.34	20.16	23.25
DSR-0104482	13.35	11.99	12.67	27.10	30.22	28.66

0.01 uM			
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0103970	61.43	64.72	63.07
DSR-0104477	97.83	90.45	94.14
DSR-0104480	82.18	90.14	86.16
DSR-0103971	77.05	68.52	72.78
DSR-0104478	49.05	56.68	52.86
DSR-0104481	38.33	40.87	39.60
DSR-0103972	70.94	63.65	67.30
DSR-0104479	52.97	46.36	49.66
DSR-0104482	43.57	35.75	39.66

Table 47. shows % mouse SOD1 mRNA remaining (at 0.1, 0.03 and 0.01 uM siRNA treatment) in primary mouse hepatocytes relative to mouse HPRT control. N = 2.

	0.1 uM			0.03 uM		
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0103970	22.66	26.19	24.43	45.68	39.27	42.47
DSR-0104491	29.10	28.31	28.70	59.17	45.25	52.21
DSR-0104490	15.78	18.09	16.93	30.77	33.18	31.98
DSR-0104489	41.21	48.36	44.79	34.85	49.37	42.11
DSR-0104488	19.53	16.08	17.80	36.09	28.77	32.43
DSR-0103971	39.79	32.14	35.97	51.84	48.03	49.94
DSR-0104487	31.35	24.94	28.15	39.66	49.84	44.75
DSR-0104486	25.69	22.03	23.86	25.49	24.97	25.23
DSR-0103972	35.68	23.57	29.63	48.72	46.42	47.57
DSR-0104485	38.80	26.60	32.70	37.96	27.29	32.62
DSR-0104484	34.99	18.51	26.75	32.57	27.96	30.26
DSR-0104483	32.27	33.64	32.95	58.66	28.92	43.79

0.01 uM			
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0103970	61.43	64.72	63.07
DSR-0104491	83.63	64.38	74.01
DSR-0104490	79.23	43.30	61.26
DSR-0104489	62.08	69.73	65.91
DSR-0104488	55.31	47.22	51.27

DSR-0103971	77.05	68.52	72.78
DSR-0104487	78.73	65.47	72.10
DSR-0104486	55.32	47.58	51.45
DSR-0103972	70.94	63.65	67.30
DSR-0104485	60.51	52.42	56.46
DSR-0104484	41.51	44.19	42.85
DSR-0104483	59.70	54.72	57.21

Table 48. shows % IC50 of knocking down mouse SOD1 mRNA in primary mouse hepatocytes

siRNA	IC50 (uM)	95% CI
DSR-0104460	0.01	0.01 to 0.02
DSR-0104104	0.03	0.02 to 0.03

Table 49. shows % mouse SOD1 mRNA remaining (at 0.3, 0.1 and 0.03 uM siRNA treatment) in primary mouse hepatocytes relative to mouse HPRT control. N = 2.

	0.3 uM			0.1 uM		
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0104521	21.06	21.53	21.29	35.03	31.69	33.36
DSR-0104520	18.89	20.32	19.61	33.13	26.16	29.64
DSR-0104519	18.70	23.65	21.18	33.63	27.83	30.73
DSR-0104518	17.49	22.95	20.22	32.88	25.26	29.07
DSR-0104517	20.18	25.51	22.84	33.49	30.51	32.00
DSR-0104516	20.18	21.72	20.95	35.23	27.42	31.33
DSR-0104515	20.18	N.D.	20.18	28.86	25.27	27.07

DSR-0104514	20.18	50.33	35.26	28.90	32.68	30.79

0.03 uM			
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0104521	70.65	43.11	56.88
DSR-0104520	44.84	34.96	39.90
DSR-0104519	58.02	37.76	47.89
DSR-0104518	54.04	40.01	47.03
DSR-0104517	59.73	45.14	52.44
DSR-0104516	48.87	46.08	47.47
DSR-0104515	54.20	54.05	54.12
DSR-0104514	45.40	56.51	50.96

Table 50. shows % mouse SOD1 mRNA remaining (at 0.1, 0.03 and 0.01 uM siRNA treatment) in primary mouse hepatocytes relative to mouse HPRT control. N = 2

	0.1 uM			0.03 uM		
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0104573	9.14	12.70	10.92	17.80	28.42	23.11
DSR-0104572	11.43	11.73	11.58	21.12	21.52	21.32
DSR-0104571	10.28	16.13	13.20	20.25	28.94	24.59
DSR-0104570	7.82	9.30	8.56	20.26	24.50	22.38
DSR-0104569	6.05	11.25	8.65	18.95	25.38	22.16
DSR-0104568	7.53	11.61	9.57	21.36	25.54	23.45
DSR-0104567	8.97	10.91	9.94	18.37	18.25	18.31
DSR-0104566	9.18	12.26	10.72	16.91	16.96	16.93

DSR-0104565	10.63	11.02	10.82	16.35	18.23	17.29
DSR-0104564	16.69	16.45	16.57	28.34	28.55	28.44
DSR-0104563	27.33	27.12	27.23	48.79	44.29	46.54

0.01 uM			
siRNA	%remaining mRNA (mSOD1/ mHPRT)- 1	%remaining mRNA (mSOD1/ mHPRT) -2	Mean
DSR-0104573	46.16	54.61	50.39
DSR-0104572	41.65	51.22	46.43
DSR-0104571	53.24	44.16	48.70
DSR-0104570	59.27	56.21	57.74
DSR-0104569	68.30	61.44	64.87
DSR-0104568	53.15	63.98	58.57
DSR-0104567	58.22	46.84	52.53
DSR-0104566	38.77	39.27	39.02
DSR-0104565	31.64	32.68	32.16
DSR-0104564	43.64	45.45	44.55
DSR-0104563	60.07	64.86	62.46

EXAMPLE 13. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0 by subcutaneous administration. Animals were euthanized on Day 28 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse APP mRNA, the following qPCR assay was utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation was determined by sandwich ELISA.

Table 51. shows % mouse SOD1 mRNA remaining relative to PBS control in the kidney 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	86	77	109	118	109	100
DSR-0103969	89	109	90	80	70	88
DSR-0104465	60	45	51	55	54	53
DSR-0104104	92	59	72	94	74	78
DSR-0104466	74	53	77	49	70	65
DSR-0103966	54	55	58	52	62	56
DSR-0104467	63	46	46	52	52	52
DSR-0104147	107	86	89	76	136	99
DSR-0104468	97	74	75	78	93	83
DSR-	94	94	100	75	83	89

0104469						
DSR-0104470	88	78	97	91	103	92

Table 52. shows the accumulation of antisense strand in the kidney at 28 days post the first dosing. N = 5. N.D.: Not determined

		Kidney Guide Strand PK (ug oligo/g tissue)										
	Animal No.	PBS	DSR-0103969	DSR-0104465	DSR-0104104	DSR-0104466	DSR-0103966	DSR-0104467	DSR-0104147	DSR-0104468	DSR-0104469	DSR-0104470
28 days post dosing	1	0	3.66	2.43	1.79	1.63	0.00	2.00	0.70	0.35	1.84	0.82
	2	0	2.37	2.95	1.83	1.32	4.70	2.03	0.88	N.D.	1.78	0.97
	3	0	3.94	0.18	2.03	N.D.	4.18	1.97	0.78	0.29	1.76	1.02
	4	0	2.98	4.27	2.87	1.85	5.32	2.45	1.02	0.33	2.05	1.07
	5	0	3.78	4.44	2.32	1.42	4.52	2.56	1.68	0.38	2.26	1.27
	Mean	0	3.35	2.85	2.17	1.55	3.75	2.20	1.01	0.34	1.94	1.03

EXAMPLE 14. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0, 2, and 4 by subcutaneous administration. Animals were euthanized on Day14 and 28 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse APP mRNA, the following qPCR assay were utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation was determined by sandwich ELISA.

Table 53. shows % mouse SOD1 mRNA remaining relative to PBS control in the brown adipose tissue 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days	PBS	95	108	64	118	115	100

post dosing	DSR-0104305	119	107	115	114	110	113
	DSR-0104104	21	24	17	26	21	22
	DSR-0104456	22	21	18	25	11	19
	DSR-0104457	13	20	19	18	18	18
	DSR-0104458	12	15	21	18	16	16
	DSR-0104459	17	16	16	12	14	15
28 days post dosing	PBS	97	103	104	106	90	100
	DSR-0104305	86	97	93	86	105	93
	DSR-0104104	18	16	24	53	28	28
	DSR-0104456	18	17	28	20	24	21
	DSR-0104457	20	14	19	21	17	18
	DSR-0104458	10	11	11	15	11	12
	DSR-0104459	10	10	11	11	13	11

Table 54. shows % mouse SOD1 mRNA remaining relative to PBS control in the heart 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	61	95	124	110	109	100
	DSR-0104305	83	65	87	72	79	77
	DSR-0104104	21	28	26	21	15	22
	DSR-0104456	10	11	11	11	9	10
	DSR-0104457	6	6	5	5	8	6
	DSR-0104458	3	4	6	5	4	5
	DSR-0104459	4	4	4	4	5	4
28 days post dosing	PBS	82	130	127	79	83	100
	DSR-0104305	87	92	97	92	105	94

	DSR-0104104	20	16	17	12	16	16
	DSR-0104456	11	15	12	13	13	13
	DSR-0104457	9	8	11	8	12	10
	DSR-0104458	13	10	7	9	8	9
	DSR-0104459	9	7	6	8	8	8

Table 55. shows % mouse SOD1 mRNA remaining relative to PBS control in the pancreas 14 and 28 days post the first dosing. N = 5. N.D.: Not Determined.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	28	26	200	173	72	100
	DSR-0104305	31	77	39	161	182	98
	DSR-0104104	143	115	85	N.D.	25	92
	DSR-0104456	128	4	121	114	153	104
	DSR-0104457	28	16	55	228	135	92
	DSR-0104458	45	17	68	105	128	73
	DSR-0104459	25	40	59	23	75	44
28 days post dosing	PBS	43	80	209	68	N.D.	100
	DSR-0104305	62	46	48	199	101	91
	DSR-0104104	10	19	42	15	N.D.	21
	DSR-0104456	1	3	18	12	47	16
	DSR-0104457	7	1	21	23	N.D.	13
	DSR-0104458	1	2	11	22	28	13
	DSR-0104459	0	1	1	18	13	7

Table 56. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 14 and 28 days post the first dosing. N = 5. N.D.: Not determined

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	96	88	101	103	112	100
	DSR-0104305	174	111	112	123	82	120
	DSR-0104104	29	33	19	15	23	24
	DSR-0104456	32	46	17	22	19	27
	DSR-0104457	22	62	22	15	27	30
	DSR-0104458	16	13	21	20	49	24
	DSR-0104459	27	14	16	19	32	22
28 days post dosing	PBS	110	77	108	102	103	100
	DSR-0104305	125	117	103	94	110	110
	DSR-0104104	8	10	5	8	8	8
	DSR-0104456	7	9	10	5	9	8
	DSR-0104457	7	5	6	9	12	8
	DSR-0104458	6	11	14	7	14	11
	DSR-0104459	9	8	8	12	9	9

Table 57. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	110	86	107	105	91	100
	DSR-0104305	94	88	78	97	111	94
	DSR-0104104	9	10	6	7	6	8

	DSR-0104456	11	9	7	6	6	8
	DSR-0104457	11	8	13	11	9	11
	DSR-0104458	12	30	33	25	25	25
	DSR-0104459	10	10	10	7	8	9
28 days post dosing	PBS	111	90	107	92	100	100
	DSR-0104305	101	110	110	105	121	109
	DSR-0104104	6	6	11	5	5	7
	DSR-0104456	6	7	7	6	8	7
	DSR-0104457	17	11	10	9	18	13
	DSR-0104458	7	21	19	35	19	20
	DSR-0104459	6	7	6	8	8	7

Table 58. shows % mouse SOD1 mRNA remaining relative to PBS control in the diaphragm 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	105	79	100	95	122	100
	DSR-0104305	96	106	87	111	89	98
	DSR-0104104	23	26	18	13	19	20
	DSR-0104456	16	22	27	27	18	22
	DSR-0104457	19	14	14	14	18	16
	DSR-0104458	18	15	11	11	17	14
	DSR-0104459	12	11	17	16	17	15
28 days post dosing	PBS	102	113	80	100	105	100
	DSR-0104305	102	94	102	101	106	101
	DSR-0104104	27	17	30	29	32	27
	DSR-0104456	32	27	29	29	25	29

	DSR-0104457	25	21	27	35	27	27
	DSR-0104458	34	39	42	36	34	37
	DSR-0104459	29	33	39	46	33	36

Table 59. shows % mouse SOD1 mRNA remaining relative to PBS control in the lung 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	117	90	91	88	113	100
	DSR-0104305	84	150	127	199	134	139
	DSR-0104104	95	80	84	81	58	79
	DSR-0104456	99	101	96	79	78	91
	DSR-0104457	65	51	50	62	65	59
	DSR-0104458	94	116	105	87	102	101
	DSR-0104459	78	82	46	84	74	73
28 days post dosing	PBS	155	96	70	82	96	100
	DSR-0104305	86	125	93	105	88	100
	DSR-0104104	59	96	98	69	67	78
	DSR-0104456	86	61	66	67	79	71
	DSR-0104457	81	54	90	60	55	68
	DSR-0104458	43	53	61	74	60	58
	DSR-0104459	61	44	66	63	76	62

Table 60. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 14 and 28 days post the first dosing. N = 5.

		Animal No.	

	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	101	105	92	101	101	100
	DSR-0104305	102	127	118	128	109	117
	DSR-0104104	42	42	53	50	40	45
	DSR-0104456	36	24	57	49	44	42
	DSR-0104457	14	17	16	14	13	15
	DSR-0104458	17	16	18	21	19	18
	DSR-0104459	12	9	8	9	6	9
28 days post dosing	PBS	108	101	99	91	101	100
	DSR-0104305	130	141	112	142	143	134
	DSR-0104104	45	35	67	50	33	46
	DSR-0104456	42	50	54	57	51	51
	DSR-0104457	19	25	29	27	29	26
	DSR-0104458	31	32	48	40	32	37
	DSR-0104459	23	21	29	27	32	26

Table 61. shows % mouse SOD1 mRNA remaining relative to PBS control in the sciatic nerve 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	102	110	111	100	78	100
	DSR-0104305	97	116	176	137	115	128
	DSR-0104104		100	77	95	70	85
	DSR-0104456	92	136	110	124	96	111
	DSR-0104457	67	78	82	78	36	68
	DSR-0104458	52	67	46	72	41	56
	DSR-0104459	38	48	60	17	47	42
28 days	PBS	95	89	93	136	87	100

post dosing	DSR-0104305	105	137	132	95	110	116
	DSR-0104104	112	111	191	76	98	118
	DSR-0104456	85	130	100	195	108	124
	DSR-0104457	83	81	67	77	163	94
	DSR-0104458	106	91	74	89	111	94
	DSR-0104459	81	99	121	64	70	87

Table 62. shows % mouse SOD1 mRNA remaining relative to PBS control in the kidney 14 and 28 days post the first dosing. N = 5.

		Animal No.					
	siRNA	1	2	3	4	5	Mean
14 days post dosing	PBS	94	96	96	107	107	100
	DSR-0104305	105	103	108	111	115	108
	DSR-0104104	38	34	36	27	31	33
	DSR-0104456	33	38	44	38	36	38
	DSR-0104457	58	47	49	53	58	53
	DSR-0104458	62	85	68	81	84	76
	DSR-0104459	36	36	29	35	37	35
28 days post dosing	PBS	82	90	109	124	95	100
	DSR-0104305	134	127	97	104	147	122
	DSR-0104104	56	44	43	37	49	46
	DSR-0104456	56	54	52	45	50	51
	DSR-0104457	75	54	61	43	49	56
	DSR-0104458	103	102	91	92	87	95
	DSR-0104459	48	31	48	42	61	46

Table 63. shows the accumulation of antisense strand in the lung at 14 days and 28 days post the first dosing. N = 5. N.D.: Not determined

		Lung Guide Strand PK (ug oligo/g tissue)						
	animal No.	PBS	DSR-0104305	DSR-0104104	DSR-0104456	DSR-0104457	DSR-0104458	DSR-0104459
14 days post dosing	1	0.00	0.69	1.48	1.05	0.82	0.99	1.49
	2	0.00	1.90	1.91	1.94	0.99	0.80	2.07
	3	0.00	0.76	1.67	1.23	1.24	0.88	1.52
	4	0.00	0.92	2.07	1.50	0.84	0.85	1.72
	5	0.00	1.34	1.67	2.67	0.88	1.20	1.53
	Mean	0.00	1.12	1.76	1.68	0.95	0.94	1.67
28 days post dosing	animal No.	PBS	DSR-0104305	DSR-0104104	DSR-0104456	DSR-0104457	DSR-0104458	DSR-0104459
	1	0.00	0.68	0.93	1.08	0.85	0.40	1.71
	2	0.00	0.67	1.74	1.32	0.67	0.39	0.99
	3	0.00	0.59	1.18	1.24	0.54	0.43	1.41
	4	0.00	1.67	0.82	1.25	0.79	0.27	1.14
	5	0.00	1.44	1.86	1.80	N.D.	0.67	1.32
	Mean	0.00	1.01	1.31	1.34	0.72	0.43	1.31

Table 64. shows the accumulation of antisense strand in the quadriceps at 14 days and 28 days post the first dosing. N = 5. N.D.: Not determined.

		Quadriceps Guide Strand PK (ug oligo/g tissue)						
	animal No.	PBS	DSR-0104305	DSR-0104104	DSR-0104456	DSR-0104457	DSR-0104458	DSR-0104459
14 days post dosing	1	0.00	0.28	0.68	0.58	0.34	0.17	0.64
	2	0.00	0.32	0.51	0.62	0.44	0.19	0.75
	3	0.00	N.D.	0.66	0.63	0.38	0.25	0.52
	4	0.00	0.29	0.77	0.74	0.40	0.23	0.78
	5	0.00	0.29	1.00	0.70	0.50	0.29	0.67
	Mean	0.00	0.29	0.73	0.65	0.41	0.23	0.67
28 days post dosing	animal No.	PBS	DSR-0104305	DSR-0104104	DSR-0104456	DSR-0104457	DSR-0104458	DSR-0104459
	1	0.00	0.22	0.46	0.54	0.40	0.20	0.56
	2	0.00	0.22	0.53	0.52	0.32	0.15	0.59
	3	0.00	0.22	0.32	0.50	0.21	0.25	0.53
	4	0.00	0.21	0.44	0.66	0.37	0.11	0.49

	5	0.00	0.22	0.47	0.48	0.28	0.16	0.47
	Mean	0.00	0.22	0.44	0.54	0.32	0.17	0.53

EXAMPLE 15. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0 by subcutaneous administration. Animals were euthanized on Day 28 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse SOD1 mRNA, the following qPCR assay were utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation was determined by sandwich ELISA.

Table 65. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	100	101	100	101	97	100
DSR-0104563	108	90	87	92	98	95
DSR-0104564	77	79	86	70	74	77
DSR-0104565	83	70	102	70	71	79
DSR-0104566	58	85	46	47	47	57
DSR-0104567	41	49	42	53	38	44
DSR-0104568	30	52	39	52	82	51
DSR-0104569	20	56	32	41	26	35
DSR-	31	28	34	43	36	34

0104570						
DSR-0104571	77	58	43	46	55	56
DSR-0104572	43	49	68	55	43	51
DSR-0104573	26	40	38	45	41	38

Table 66. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 28 days post dosing. N = 5. N.D.: Not determined

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	128	78	126	90	79	100
DSR-0104563	104	78	93	59	94	85
DSR-0104564	49	79	73	76	143	84
DSR-0104565	92	81	101	47	215	107
DSR-0104566	N.D.	91	99	83	47	80
DSR-0104567	22	N.D.	108	114	N.D.	81
DSR-0104568	10	39	11	13	25	19
DSR-0104569	36	13	12	17	11	18
DSR-0104570	45	94	51	52	57	60
DSR-0104571	79	96	76	79	83	82
DSR-0104572	160	30	43	83	66	76
DSR-0104573	162	59	26	25	29	60

Table 67. shows % mouse SOD1 mRNA remaining relative to PBS control in the lung 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	110	75	89	106	119	100
DSR-0104563	69	99	105	175	105	111

DSR-0104564	108	71	82	117	78	91
DSR-0104565	116	125	89	74	158	112
DSR-0104566	89	75	148	142	110	113
DSR-0104567	98	105	137	227	109	135
DSR-0104568	135	129	119	98	61	108
DSR-0104569	89	163	132	203	212	160
DSR-0104570	193	177	157	232	209	194
DSR-0104571	200	115	135	87	159	139
DSR-0104572	113	180	195	277	131	179
DSR-0104573	156	164	165	160	240	177

Table 68. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	102	102	111	90	95	100
DSR-0104563	75	66	77	68	71	72
DSR-0104564	68	63	60	67	62	64
DSR-0104565	57	68	61	59	69	63
DSR-0104566	45	43	65	54	57	53
DSR-0104567	45	29	31	48	32	37
DSR-0104568	40	32	47	24	26	34
DSR-0104569	29	20	21	25	21	23
DSR-0104570	50	46	60	58	56	54
DSR-0104571	79	79	73	95	80	81
DSR-0104572	57	52	46	38	48	48

DSR-0104573	29	35	32	36	44	35

Table 69. shows % mouse SOD1 mRNA remaining relative to PBS control in the heart 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	92	98	105	98	106	100
DSR-0104563	96	98	119	91	107	102
DSR-0104564	87	95	100	72	64	83
DSR-0104565	51	58	55	83	69	63
DSR-0104566	53	50	69	64	40	55
DSR-0104567	25	22	25	27	37	27
DSR-0104568	48	20	21	37	42	33
DSR-0104569	34	16	17	36	16	24
DSR-0104570	61	44	50	51	60	53
DSR-0104571	115	105	113	100	97	106
DSR-0104572	34	54	37	38	61	45
DSR-0104573	50	23	24	27	64	38

Table 70. shows % mouse SOD1 mRNA remaining relative to PBS control in the sciatic nerve 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	154	99	89	77	80	100
DSR-0104563	62	79	78	59	82	72
DSR-0104564	90	77	98	69	66	80
DSR-0104565	71	54	50	56	66	59
DSR-	70	65	75	55	71	67

0104566						
DSR-0104567	71	57	85	60	83	71
DSR-0104568	74	89	77	82	68	78
DSR-0104569	78	84	85	68	81	79
DSR-0104570	94	57	59	55	63	66
DSR-0104571	58	66	81	93	94	78
DSR-0104572	67	68	64	75	120	79
DSR-0104573	91	73	77	95	78	83

Table 71. shows % mouse SOD1 mRNA remaining relative to PBS control in the kidney 28 days post dosing. N = 5.

	Animal No.					
siRNA	1	2	3	4	5	Mean
PBS	75	77	108	116	124	100
DSR-0104563	107	100	82	79	77	89
DSR-0104564	92	78	113	92	86	92
DSR-0104565	65	60	56	94	79	71
DSR-0104566	90	63	104	67	96	84
DSR-0104567	112	91	135	110	101	110
DSR-0104568	105	81	105	81	93	93
DSR-0104569	96	79	78	73	80	81
DSR-0104570	88	82	95	93	89	89
DSR-0104571	96	77	79	63	85	80
DSR-0104572	96	82	95	74	110	91
DSR-0104573	108	89	86	99	90	94

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EXAMPLE 16. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0 and 7 by subcutaneous administration. Animals were euthanized on Day 28 and 56 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse APP mRNA, the following qPCR assay was utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation was determined by sandwich ELISA.

Table 72. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 28 and

56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	101.36	6	21.13	11	27.37	16	37.58
2	91.87	7	11.89	12	13.52	17	53.98
3	93.48	8	19.14	13	22.88	18	42.01
4	102.44	9	18.23	14	25.67	19	39.06
5	110.86	10	14.92	15	20.41	20	40.99
Mean	100.00	Mean	17.06	Mean	21.97	Mean	42.72
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	22.03	26	98.08	31	14.34	36	28.77
22	19.39	27	81.27	32	41.68	37	22.92
23	9.22	28	135.60	33	14.72	38	27.04
24	14.22	29	86.99	34	18.94	39	15.58
25	14.02	30	98.06	35	18.62	40	38.75
Mean	15.78	Mean	100.00	Mean	21.66	Mean	26.61
Day 56							
DSR-0104625		DSR-0104626					
41	64.57	46	49.80				
42	57.61	47	28.31				
43	60.20	48	42.84				
44	64.63	49	19.89				
45	59.17	50	28.17				
Mean	61.23	Mean	33.80				

Table 73. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 28 and 56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	100.74	6	7.20	11	9.68	16	11.91
2	99.75	7	46.25	12	14.20	17	6.62
3	87.13	8	7.05	13	89.05	18	13.31
4	107.12	9	8.92	14	7.51	19	8.80
5	105.25	10	7.05	15	8.54	20	8.73
Mean	100.00	Mean	15.29	Mean	25.80	Mean	9.87
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	6.48	26	64.77	31	N.D.	36	17.96
22	46.05	27	104.12	32	22.88	37	10.90
23	11.27	28	159.35	33	15.02	38	13.31
24	17.16	29	87.92	34	10.75	39	12.04
25	17.08	30	83.85	35	14.26	40	24.58
Mean	19.61	Mean	100.00	Mean	15.73	Mean	15.76
Day 56							
DSR-0104625		DSR-0104626					
41	25.16	46	57.78				
42	18.28	47	47.00				
43	N.D.	48	67.10				
44	25.98	49	24.96				
45	16.98	50	24.46				
Mean	21.60	Mean	44.26				

Table 74. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad tissue 28 and 56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	88.94	6	46.51	11	25.83	16	36.32
2	113.36	7	32.68	12	15.85	17	30.39
3	98.75	8	54.64	13	30.43	18	47.21
4	96.38	9	40.76	14	25.23	19	38.28
5	102.58	10	50.10	15	25.60	20	27.34
Mean	100.00	Mean	44.94	Mean	24.59	Mean	35.91
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	24.69	26	96.16	31	33.75	36	17.20
22	23.37	27	86.33	32	34.77	37	18.91
23	22.93	28	102.18	33	56.44	38	19.28
24	17.36	29	112.84	34	57.81	39	19.81
25	14.86	30	102.50	35	30.91	40	14.60
Mean	20.64	Mean	100.00	Mean	42.74	Mean	17.96
Day 56							
DSR-0104625		DSR-0104626					
41	39.85	46	14.44				
42	11.39	47	18.23				
43	27.62	48	14.06				
44	17.63	49	22.98				
45	23.34	50	12.92				
Mean	23.97	Mean	16.53				

Table 75. shows % mouse SOD1 mRNA remaining relative to PBS control in the diaphragm tissue 28 and 56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	87.85	6	36.82	11	33.34	16	18.03
2	112.16	7	29.77	12	28.73	17	25.95
3	100.18	8	32.49	13	30.55	18	21.21
4	100.12	9	32.19	14	23.62	19	26.08
5	99.69	10	34.84	15	21.28	20	28.62
Mean	100.00	Mean	33.22	Mean	27.50	Mean	23.98
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	29.57	26	78.12	31	17.98	36	25.59
22	30.97	27	107.06	32	26.54	37	22.30
23	38.76	28	111.42	33	29.11	38	20.32
24	19.06	29	82.61	34	23.74	39	20.50
25	14.10	30	120.79	35	18.86	40	26.99
Mean	26.49	Mean	100.00	Mean	23.24	Mean	23.14
Day 56							
DSR-0104625		DSR-0104626					
41	28.04	46	17.20				
42	21.20	47	24.61				
43	30.04	48	22.77				
44	22.06	49	19.23				
45	26.76	50	14.79				
Mean	25.62	Mean	19.72				

Table 76. shows % mouse SOD1 mRNA remaining relative to PBS control in the lung tissue 28 and 56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	71.57	6	58.82	11	96.00	16	51.94
2	121.67	7	N.D.	12	111.49	17	55.83
3	102.28	8	77.90	13	74.93	18	65.80
4	84.03	9	68.51	14	69.31	19	59.41
5	120.45	10	52.85	15	109.97	20	58.82
Mean	100.00	Mean	64.52	Mean	92.34	Mean	58.36
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	75.14	26	N.D.	31	88.98	36	85.79
22	55.00	27	118.38	32	59.63	37	78.41
23	58.72	28	97.40	33	62.52	38	105.24
24	52.24	29	97.69	34	66.96	39	90.68
25	59.49	30	86.54	35	101.21	40	84.04
Mean	60.12	Mean	100.00	Mean	75.86	Mean	88.83
Day 56							
DSR-0104625		DSR-0104626					
41	80.16	46	81.73				
42	85.17	47	88.84				
43	76.01	48	74.41				
44	94.34	49	62.66				
45	102.15	50	74.20				
Mean	87.56	Mean	76.37				

Table 77. shows % mouse SOD1 mRNA remaining relative to PBS control in the sciatic nerve tissue 28 and 56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	107.34	6	61.37	11	72.02	16	60.03
2	96.85	7	105.94	12	69.85	17	84.32
3	111.69	8	91.58	13	66.33	18	90.51
4	94.30	9	81.06	14	74.38	19	60.20
5	89.82	10	68.41	15	66.45	20	85.19
Mean	100.00	Mean	81.67	Mean	69.81	Mean	76.05
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	66.22	26	103.07	31	102.06	36	76.21
22	81.10	27	97.58	32	69.96	37	66.72
23	84.54	28	112.12	33	77.94	38	60.86
24	71.19	29	92.77	34	79.31	39	80.01
25	75.12	30	94.46	35	67.41	40	78.60
Mean	75.63	Mean	100.00	Mean	79.34	Mean	72.48
Day 56							
DSR-0104625		DSR-0104626					
41	106.96	46	59.13				
42	85.67	47	74.83				
43	102.95	48	89.37				
44	82.46	49	61.92				
45	79.82	50	83.66				
Mean	91.57	Mean	73.78				

Table 78. shows % mouse SOD1 mRNA remaining relative to PBS control in the pancreas tissue 28 and 56 days post dosing. N = 5.

Day 28							
PBS		DSR-0104460		DSR-0104624		DSR-0104625	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	115.36	6	82.79	11	111.47	16	126.97
2	71.53	7	46.34	12	72.75	17	53.09
3	85.72	8	83.50	13	N.D.	18	195.62
4	141.38	9	122.94	14	145.12	19	93.27
5	86.01	10	27.49	15	103.81	20	104.41
Mean	100.00	Mean	72.61	Mean	108.29	Mean	114.67
Day 28		Day 56					
DSR-0104626		PBS		DSR-0104460		DSR-0104624	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	107.72	26	100.89	31	99.94	36	98.58
22	107.36	27	56.74	32	108.52	37	63.33
23	116.69	28	130.49	33	99.35	38	163.90
24	120.38	29	117.76	34	98.03	39	61.58
25	141.11	30	94.11	35	86.42	40	65.75
Mean	118.65	Mean	100.00	Mean	98.45	Mean	90.63
Day 56							
DSR-0104625		DSR-0104626					
41	48.04	46	112.45				
42	85.74	47	98.52				
43	92.58	48	102.36				
44	52.64	49	108.05				
45	36.63	50	27.55				
Mean	63.13	Mean	89.79				

EXAMPLE 17. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0 by subcutaneous administration. Animals were euthanized on Day 28, 56, and 84 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse APP mRNA, the following qPCR assay was utilized: mouse

Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation was determined by sandwich ELISA.

Table 79. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	84.49	6	41.63	11	26.73	16	71.75
2	103.06	7	35.66	12	23.10	17	44.18
3	102.87	8	29.72	13	23.79	18	63.20
4	105.09	9	38.39	14	27.36	19	67.83
5	104.49	10	34.34	15	18.09	20	63.16
Mean	100.00	Mean	35.95	Mean	23.81	Mean	62.02

Table 80. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 28 days post dosing. N = 5. N.D.: Not determined

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	103.26	6	74.69	11	14.33	16	N.D.
2	77.60	7	18.04	12	17.20	17	30.39
3	134.93	8	22.36	13	38.80	18	33.39
4	95.97	9	N.D.	14	66.69	19	24.89
5	88.24	10	66.16	15	23.10	20	37.46
Mean	100.00	Mean	45.31	Mean	32.02	Mean	31.53

Table 81. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	95.94	6	52.12	11	27.31	16	88.19
2	90.52	7	54.65	12	35.66	17	49.50
3	96.57	8	37.96	13	32.01	18	59.44
4	104.24	9	44.50	14	29.05	19	74.39
5	112.73	10	50.23	15	41.65	20	48.53
Mean	100.00	Mean	47.89	Mean	33.14	Mean	64.01

Table 82. shows % mouse SOD1 mRNA remaining relative to PBS control in the heart 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	94.12	6	48.56	11	44.70	16	50.94
2	101.03	7	26.11	12	37.34	17	16.22
3	121.75	8	19.85	13	12.98	18	13.75
4	81.59	9	57.76	14	14.18	19	49.07
5	101.52	10	57.85	15	15.90	20	44.94
Mean	100.00	Mean	42.02	Mean	25.02	Mean	34.99

Table 83. shows % mouse SOD1 mRNA remaining relative to PBS control in the diaphragm 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	94.49	6	17.67	11	20.49	16	22.46
2	90.27	7	15.34	12	20.14	17	19.49
3	102.14	8	39.73	13	21.39	18	30.28
4	106.36	9	18.73	14	35.63	19	22.72
5	106.74	10	20.50	15	16.64	20	30.96
Mean	100.00	Mean	22.40	Mean	22.86	Mean	25.18

Table 84. shows % mouse SOD1 mRNA remaining relative to PBS control in the kidney 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	87.71	6	82.04	11	115.11	16	83.19
2	116.01	7	77.66	12	95.98	17	103.43
3	109.77	8	88.64	13	94.06	18	114.70
4	94.98	9	N.D.	14	86.29	19	127.18
5	91.53	10	105.86	15	91.38	20	93.98
Mean	100.00	Mean	88.55	Mean	96.56	Mean	104.50

Table 85. shows % mouse SOD1 mRNA remaining relative to PBS control in the lung 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	85.54	6	107.03	11	208.87	16	109.50
2	102.55	7	87.37	12	260.10	17	71.26
3	105.69	8	116.41	13	78.32	18	131.45
4	117.02	9	67.65	14	99.64	19	118.39
5	89.19	10	122.25	15	114.28	20	125.70
Mean	100.00	Mean	100.14	Mean	152.24	Mean	111.26

Table 86. shows % mouse SOD1 mRNA remaining relative to PBS control in the pancreas 28 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	86.20	6	N.D.	11	151.23	16	109.96
2	112.02	7	101.05	12	164.66	17	138.75
3	123.00	8	102.59	13	146.58	18	95.84
4	113.92	9	128.40	14	151.48	19	137.70
5	64.86	10	138.81	15	148.29	20	88.37
Mean	100.00	Mean	117.72	Mean	152.45	Mean	114.12

Table 87. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 56 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	125.54	6	115.48	11	49.78	16	102.23
2	69.58	7	68.97	12	34.52	17	162.34
3	125.51	8	64.31	13	50.46	18	65.70
4	105.84	9	79.52	14	52.43	19	76.75
5	73.53	10	50.54	15	45.27	20	99.76
Mean	100.00	Mean	75.76	Mean	46.49	Mean	101.36

Table 88. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 56 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	86.39	6	22.45	11	34.38	16	29.67
2	79.21	7	68.71	12	29.64	17	31.28
3	101.91	8	85.30	13	75.96	18	11.98
4	91.39	9	43.94	14	21.33	19	13.14
5	141.11	10	20.56	15	10.26	20	9.27
Mean	100.00	Mean	48.19	Mean	34.32	Mean	19.07

Table 89. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 56 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	73.57	6	47.71	11	32.81	16	28.40
2	98.02	7	45.93	12	33.32	17	55.48
3	80.79	8	48.30	13	31.56	18	64.29
4	125.82	9	49.39	14	19.32	19	40.98
5	121.79	10	41.27	15	32.35	20	73.80
Mean	100.00	Mean	46.52	Mean	29.87	Mean	52.59

Table 90. shows % mouse SOD1 mRNA remaining relative to PBS control in the heart 56 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	89.29	6	56.46	11	57.63	16	70.81
2	94.98	7	25.86	12	18.42	17	15.36
3	116.37	8	44.33	13	25.39	18	21.50
4	102.93	9	25.58	14	51.83	19	27.86
5	96.43	10	24.85	15	22.73	20	61.43
Mean	100.00	Mean	35.42	Mean	35.20	Mean	39.39

Table 91. % mouse SOD1 mRNA remaining relative to PBS control in the diaphragm 56 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	95.28	6	23.60	11	26.19	16	19.11
2	106.10	7	36.19	12	19.90	17	23.80
3	91.66	8	29.78	13	27.19	18	23.75
4	105.84	9	25.49	14	29.71	19	20.05
5	101.11	10	21.18	15	19.41	20	18.12
Mean	100.00	Mean	27.25	Mean	24.48	Mean	20.96

EXAMPLE 18. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 5 mg/kg on Day 0 by subcutaneous administration. Animals were euthanized on Day 28, 56, and 84 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse APP mRNA, the following qPCR assay was utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation

was determined by sandwich ELISA.

Table 92. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 84 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	111.94	6	61.78	11	43.91	16	73.56
2	90.97	7	61.71	12	33.73	17	45.86
3	95.04	8	57.66	13	64.43	18	82.07
4	101.89	9	86.00	14	53.87	19	53.19
5	100.16	10	46.44	15	55.26	20	74.69
Mean	100.00	Mean	62.72	Mean	50.24	Mean	65.87

Table 93. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 84 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	93.25	6	37.80	11	14.96	16	25.27
2	130.70	7	26.01	12	33.69	17	22.45
3	84.36	8	33.74	13	21.47	18	35.35
4	105.32	9	61.59	14	32.11	19	21.98
5	86.38	10	25.01	15	26.55	20	27.72
Mean	100.00	Mean	36.83	Mean	25.75	Mean	26.55

Table 94. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 84 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	99.51	6	61.57	11	39.91	16	71.62
2	95.07	7	69.18	12	33.99	17	81.64
3	105.05	8	49.57	13	39.32	18	69.95
4	103.93	9	47.96	14	46.53	19	53.85
5	96.45	10	41.42	15	44.94	20	62.11
Mean	100.00	Mean	53.94	Mean	40.94	Mean	67.83

Table 95. shows % mouse SOD1 mRNA remaining relative to PBS control in the heart 84 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	112.11	6	101.07	11	73.28	16	80.20
2	88.68	7	80.22	12	N.D.	17	23.59
3	97.99	8	52.34	13	97.40	18	60.98
4	100.49	9	32.52	14	65.42	19	21.76
5	100.74	10	77.68	15	76.63	20	18.94
Mean	100.00	Mean	68.77	Mean	78.18	Mean	41.09

Table 96. shows % mouse SOD1 mRNA remaining relative to PBS control in the diaphragm 84 days post dosing. N = 5.

PBS		DSR-0104568		DSR-0104569		DSR-0105668	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	79.89	6	27.47	11	19.75	16	21.13
2	100.32	7	43.98	12	28.38	17	25.87
3	126.83	8	32.09	13	30.06	18	29.34
4	116.34	9	35.57	14	31.73	19	29.83
5	76.62	10	25.35	15	29.63	20	26.91
Mean	100.00	Mean	32.89	Mean	27.91	Mean	26.62

EXAMPLE 19. Provided Oligonucleotides and Compositions Are Active *in vivo*

All animal procedures were performed under IACUC guidelines. To evaluate the potency and tissue exposure of provided oligonucleotides and compositions, male 8-10 weeks of age C57BL/6 mice were dose at 10 mg/kg on Day 0 by subcutaneous administration. Animals were euthanized on Day 14 and 28 by CO_2 asphyxiation followed by thoracotomy and terminal blood collection. After cardiac perfusion with PBS, various tissue samples were harvested and flash-frozen in dry ice. Total RNA was extracted using RNeasy 96 kit (Qiagen), after tissue lysis with TRIzol and chloroform. cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad for mouse APP mRNA, the following qPCR assay was utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). Oligonucleotide accumulation was determined by sandwich ELISA.

Table 97. shows % mouse SOD1 mRNA remaining relative to PBS control in the sciatic nerve 14 and 28 days post dosing. N = 5.

Day 14							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	96.65	6	81.10	11	71.76	16	76.91
2	81.60	7	78.44	12	78.87	17	75.15
3	98.16	8	114.32	13	78.68	18	83.17
4	106.00	9	82.68	14	74.17	19	85.99
5	117.59	10	70.87	15	80.04	20	88.69
Mean	100.00	Mean	85.48	Mean	76.71	Mean	81.98
Day 28							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	57.10	26	89.55	31	149.59	36	155.87
22	48.13	27	122.36	32	170.92	37	145.41
23	164.54	28	78.99	33	130.86	38	172.28
24	129.90	29	121.97	34	126.77	39	111.90
25	100.33	30	146.34	35	93.11	40	86.53
Mean	100.00	Mean	111.84	Mean	134.25	Mean	134.40

Day 28	
DSR-0105689	
Animal No.	%mRNA remaining of SOD1 mRNA
41	127.63
42	124.70
43	125.98
44	137.14
45	155.16
Mean	134.12

Table 98. shows % mouse SOD1 mRNA remaining relative to PBS control in the liver 14 and 28 days post dosing. N = 5 or 7.

Day 14							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	85.02	6	56.78	11	15.51	16	37.40
2	92.21	7	60.54	12	34.74	17	31.98
3	96.08	8	31.29	13	11.21	18	31.69
4	110.51	9	72.88	14	15.42	19	18.19
5	116.18	10	36.00	15	13.02	20	38.22
Mean	100.00	Mean	51.50	Mean	17.98	Mean	31.50
Day 28							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	92.95	28	47.08	35	42.30	42	33.86
22	93.57	29	50.99	36	39.53	43	35.08
23	95.34	30	56.12	37	40.28	44	32.29
24	107.54	31	35.16	38	50.43	45	26.40
25	102.59	32	109.76	39	42.46	46	27.56
26	105.77	33	40.81	40	45.25	47	34.78
27	102.23	34	59.24	41	32.48	48	32.02
Mean	100.00	Mean	57.02	Mean	41.82	Mean	31.71

Day 28	
DSR-0105689	
Animal No.	%mRNA remaining of SOD1 mRNA
49	30.92
50	34.10
51	33.89
52	36.33
53	31.08
54	25.08
55	33.75

Mean	32.16

Table 99. shows % mouse SOD1 mRNA remaining relative to PBS control in the white adipose tissue 14 and 28 days post dosing. N = 5 or 7.

Day 14							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	89.77	6	75.23	11	22.30	16	52.01
2	108.72	7	33.01	12	69.69	17	55.04
3	91.79	8	24.91	13	24.32	18	19.92
4	109.14	9	29.30	14	32.38	19	26.23
5	100.57	10	37.78	15	14.49	20	42.78
Mean	100.00	Mean	40.05	Mean	32.64	Mean	39.19
Day 28							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	82.51	28	23.39	35	23.69	42	17.48
22	112.68	29	55.49	36	68.09	43	23.13
23	111.83	30	65.48	37	31.49	44	29.47
24	95.23	31	12.75	38	56.61	45	24.63
25	84.11	32	62.02	39	23.45	46	37.59
26	114.70	33	53.22	40	23.55	47	27.50
27	98.94	34	27.43	41	19.40	48	37.18
Mean	100.00	Mean	42.83	Mean	35.18	Mean	28.14

Day 28	
DSR-0105689	
Animal No.	%mRNA remaining of SOD1 mRNA
49	20.51
50	21.96
51	18.60
52	26.78
53	81.88
54	76.85
55	16.28
Mean	37.55

Table 100. shows % mouse SOD1 mRNA remaining relative to PBS control in the quad 14 and 28 days post dosing. N = 5 or 7.

Day 14							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	100.59	6	58.36	11	62.37	16	46.89
2	100.10	7	62.85	12	50.34	17	50.69
3	97.67	8	62.79	13	47.56	18	46.06
4	101.26	9	55.52	14	54.35	19	45.97
5	100.38	10	69.09	15	43.88	20	53.52
Mean	100.00	Mean	61.72	Mean	51.70	Mean	48.62
Day 28							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	92.95	28	47.08	35	42.30	42	33.86
22	93.57	29	50.99	36	39.53	43	35.08
23	95.34	30	56.12	37	40.28	44	32.29
24	107.54	31	35.16	38	50.43	45	26.40
25	102.59	32	109.76	39	42.46	46	27.56
26	105.77	33	40.81	40	45.25	47	34.78
27	102.23	34	59.24	41	32.48	48	32.02
Mean	100.00	Mean	57.02	Mean	41.82	Mean	31.71

Day 28	
DSR-0105689	
Animal No.	%mRNA remaining of SOD1 mRNA
49	30.92
50	34.10
51	33.89
52	36.33
53	31.08
54	25.08
55	33.75
Mean	32.16

Table 101. shows % mouse SOD1 mRNA remaining relative to PBS control in the kidney 14 and 28 days post dosing. N = 5 or 7.

Day 14							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
1	92.84	6	71.27	11	65.07	16	30.57
2	100.97	7	77.86	12	80.50	17	31.76
3	101.76	8	75.63	13	67.01	18	28.85
4	93.22	9	72.63	14	77.91	19	22.58
5	111.21	10	71.74	15	86.11	20	28.71
Mean	100.00	Mean	73.83	Mean	75.32	Mean	28.50
Day 28							
PBS		DSR-0104565		DSR-0104570		DSR-0105688	
Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA	Animal No.	%mRNA remaining of SOD1 mRNA
21	107.45	28	53.89	35	64.39	42	23.97
22	99.20	29	45.56	36	67.15	43	22.99
23	93.13	30	51.59	37	72.96	44	25.05
24	94.17	31	45.80	38	70.34	45	26.15
25	86.40	32	103.66	39	58.53	46	23.33
26	113.74	33	52.06	40	64.75	47	27.82
27	105.91	34	61.49	41	63.44	48	22.48
Mean	100.00	Mean	59.15	Mean	65.94	Mean	24.54

Day 28	
DSR-0105689	
Animal No.	%mRNA remaining of SOD1 mRNA
49	41.36
50	50.91
51	43.89
52	50.24
53	45.92
54	50.98
55	46.36
Mean	47.09

EXAMPLE 20. Provided Oligonucleotides and Compositions Are Active *in vitro* in 3T3-L1 Cells

Various siRNAs for mouse SOD1 were designed and constructed. A number of siRNAs were tested *in vitro* in 3T3-L1 cells at a range of concentrations.

Example protocol for in vitro determination of siRNA activity in 3T3-L1 cells: For determination of siRNAs activity, siRNAs at specific concentration were gymnotically delivered to mouse 3T3-L1 cells plated in 96-well plates, with 3,000 cells/well. Following 48 hours treatment, total RNA was extracted using SV96 Total RNA Isolation kit (Promega). cDNA production from RNA samples were performed using High-Capacity cDNA Reverse Transcription kit (Thermo Fisher) following manufacturer's instructions and qPCR analysis performed in CFX System using iQ Multiplex Powermix (Bio-Rad). For mouse SOD1 mRNA, the following qPCR assay was utilized: mouse Sod1 from IDT (Integrated DNA Technologies) qPCR assay ID Mm.PT.58.12368303. Mouse HPRT was used as normalizer (IDT, Mm.PT.39a.22214828). mRNA knockdown levels were calculated as %mRNA remaining relative to mock treatment.

Table 102. shows % mouse SOD1 mRNA remaining (at 3 and 1 uM siRNA treatment) in 3T3-L1 cells relative to mouse HPRT control. N = 2.

	3 uM			1 uM		
siRNA	%remaining mRNA (mSOD1/ mHPRT)-1	%remaining mRNA (mSOD1/ mHPRT)-2	Mean	%remaining mRNA (mSOD1/ mHPRT)-1	%remaining mRNA (mSOD1/ mHPRT)-2	Mean
DSR-0104563	24.48	33.00	28.74	34.11	43.15	38.63
DSR-0104564	44.15	53.13	48.64	57.08	71.12	64.10
DSR-0104566	26.53	35.10	30.81	32.22	49.54	40.88
DSR-0104568	16.90	22.21	19.55	14.38	25.01	19.70
DSR-0104569	13.15	21.49	17.32	10.93	18.54	14.73
DSR-0104571	7.86	11.99	9.92	10.47	22.81	16.64
DSR-0104572	44.98	58.58	51.78	59.11	75.12	67.12
DSR-0105659	72.48	85.84	79.16	82.26	86.74	84.50
DSR-0105660	60.26	62.16	61.21	72.83	71.82	72.32

DSR-0105661	78.38	73.24	75.81	84.14	83.41	83.77
DSR-0105662	66.72	55.56	61.14	67.07	76.29	71.68
DSR-0105663	37.83	44.92	41.38	43.41	57.94	50.68
DSR-0104573	61.95	63.60	62.77	76.45	73.46	74.96
DSR-0105658	84.88	84.56	84.72	83.46	93.17	88.31
DSR-0105664	33.58	39.44	36.51	33.94	44.69	39.32
DSR-0104460	43.06	61.82	52.44	46.83	58.01	52.42
DSR-0105665	18.82	32.53	25.68	23.63	36.89	30.26
DSR-0105666	34.87	48.18	41.52	49.65	51.78	50.72
DSR-0105667	52.81	65.80	59.30	71.09	71.77	71.43
DSR-0105668	7.55	15.39	11.47	18.20	24.87	21.54
DSR-0105669	9.76	15.59	12.67	23.80	28.00	25.90
DSR-0105671	86.36	84.31	85.33	96.54	89.62	93.08
DSR-0105672	79.46	79.45	79.46	84.07	79.14	81.60
DSR-0105788	55.75	66.69	61.22	72.90	69.28	71.09
DSR-0105789	19.80	29.58	24.69	39.15	51.45	45.30
DSR-0105791	53.45	69.06	61.25	76.12	71.21	73.67
DSR-0105792	14.28	13.70	13.99	22.42	26.02	24.22
DSR-0104569	13.15	21.49	17.32	10.93	18.54	14.73

EXAMPLE 21: Synthesis and deprotection of stereopure oligonucleotide sequences containing 5'-Phosphonate

General procedure for the 5'-phosphonate deprotection conditions (25 µmole):

To prepare TMSI solution for 5'-phosphonate deprotection, pyridine (0.5 mL) was added to DCM (23.9 mL) and the resulting solution was cooled in ice-bath for 15 minutes. After that TMSI reagent (0.6 mL) was added to the mixture to get a bright yellow solution (total volume 25.0 mL). TMSI quenching solution (50 mL) was prepared by adding 2-

Dodecane thiol (12.0 mL) and TEA (18.0 mL) in acetonitrile (18.0 mL).

After completion of the synthesis, the CPG solid support was dried and transferred into 50 mL plastic tube. Minimum amount of DCM was added to 5'-Phosphonate containing oligonucleotide on CPG and the CPG was vortexed to get a homogenous slurry. To this homogenous slurry, the TMSI solution (10.0 mL) was added slowly and mixed well. After the addition of total TMSI solution the color of the reaction mixture turns yellow indicating excess of TMSI solution. The resulting reaction mixture was stirred for 30 minutes at room temperature. After 30 min. the support was promptly washed using excess of acetonitrile followed by addition of quenching solution (10.0 mL) and this process was repeated three times (Total quenching volume 30.0 mL). The total time of exposure was limited to 20 min. The CPG was rinsed thoroughly using acetonitrile and drying under vacuum. Afterwards, CPG was subjected to standard cleavage and deprotection condition.

General procedure for the C&D conditions (25 µmol scale):

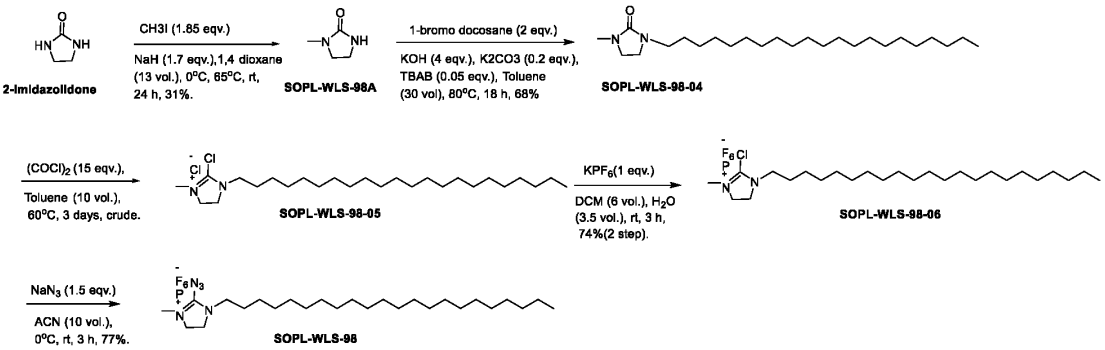
After completion of the synthesis and 5'-phosphonate deprotection, the CPG solid support was dried and transferred into 50 mL plastic tube. The CPG was treated with DS1 reagent (2.5 mL; 100 uL/umol) for 3 h at 27 °C, then added conc. NH_3 (5.0 mL; 200 umol/umol) for 24 h at 37 °C. The reaction mixture was cooled to room temperature and the CPG was separated by membrane filtration, washed with 15 mL of H_2O. The crude material (filtrate) was analyzed by LTQ and RP-UPLC.

	Crude ODs/µmol	**calcd. [M]**	**found [M]**	**UPLC purity**
SSR-0106222	64.94 O.D./µmole	8014.8	8013.2	25.95%
SSR-0106517	34.0 O.D./µmole	7998.8	7998.9	25.60%

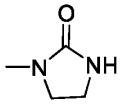
The contents of pages 724-932 of WO 2024/182749 are incorporated herein by reference in their entirety, wherein the synthesis of the following compounds is described:WV-NU-017, WV-NU-010, WV-NU-10-CNE, WV-NU-128, WV-NU-128-CNE, WV-NU-038, WV-NU-037, WV-NU-037A, WV-NU-037, WV-NU-040, WV-NU-042, WV-RA-009, WV-RA-009-CNE, WV-RA-010, WV-RA-010-CNE, 5'-(R)-C-M'-5'-ODMT'-2'-F-dU, 5'-(R)-C-M'-5'-ODMT'-2'-F-dU-CNE phosphoramidite, 5'-(S)-C-Me-5'-ODMTr-2'-F-dU, of 5'-(R)-C-Me-5'-ODMTr-2'-OMe-U, 5'-(S)-C-Me-5'-ODMTr-2'-OMe-U, 5'-(R)-C-Me-5'-ODMTr-dT, 5'-

(S)-C-Me-5'-ODMTr-dT, L-DPSE-Cl, (3'-L-DPSE-WV-NU-010), 3'-L-DPSE-WV-NU-017, 3'-L-DPSE-WV-NU-040, 3'-L-DPSE-WV-NU-037, 3'-L-DPSE-WV-NU-037A, L-DPSE-5'-ODMTr-5'-(R)-Me-2'F-dU amidite, L-DPSE-5'-ODMTr-5'-(S)-Me-2'F-dU amidite, 3'-L-DPSE-WV-RA-009, D-DPSE-Cl, 3'-D-DPSE-5'-ODMTr-5'-(R)-Me-dT amidite, 3'-D-DPSE-5'-ODMTr-5'-(S)-Me-dT amidite, 3'-D-DPSE-5'-ODMTr-5'-(R)-Me-2'F-dU amidite, 3'-D-DPSE-5'-ODMTr-5'-(S)-Me-2'F-dU amidite, 3'-D-DPSE-5'-PO(OEt)2 Vinylphosphonate-dT amidite, 3'-D-DPSE-5'-(R)-Me-PO(OEt)2-dT amidite, 3'-D-DPSE-5'-(S)-Me-PO(OEt)2-dT amidite, WV-NU-231, WV-NU-306, WV-NU-299, WV-NU-301, L-DPSE-2'-OMe-5'-(R)-Me-PO(OEt)2-uridine amidite, L-DPSE-2'-OMe-5'-triazole-PO(OEt)2-uridine amidite, D-DPSE-2'-OMe-5'-triazole-PO(OEt)2-2'OMe-uridine amidite, L-DPSE-2'-OMe-5'-vinyl-PO(OEt)2-uridine amidite, D-DPSE-2'-OMe-5'-vinyl-PO(OEt)2-uridine amidite, L-PSM-2'-O-C16 lipid-5'-ODMTr-uridine amidite, D-PSM-2'-O-C16 lipid-5'-ODMTr-uridine amidite, 5'-(R)-C-Me-5'-ODMTr-2'OMe-A(Bz)-D-PSM, 5'-(S)-C-Me-5'-ODMTr-2'OMe-A(Bz)-D-PSM, 2'O-C16-U-L-PSM, 2'O-C16-U-D-PSM, 2'-OMe-5'-triazole-PO(OEt)2-3'-CNE uridine amidite, 2'-O-C16 lipid-5'-ODMTr-3'-CNE Uridine amidite, 5'-(R)-C-Me-5'-ODMTr-2'OMe-A(Bz)-CNE, 5'-(R)-C-Me-5'-ODMTr-2'Fd-A(Bz)-CNE, 5'-(R)-C-Me-5'-ODMTr-2'Fd-U-CNE, 5'-ODMTr-(S)-GNA-G(iBu)-CNE, 5'-ODMTr-(S)-GNA-T-CNE, 5'-triazole-PO(OEt)2-2'OMe-U-CNE, 2'O-C16-U-CNE, WV-NU-332, WV-NU-306, WV-NU-336, 5'-triazole-PO(OEt)2-2'OMe-U-L-DPSE, 5'-triazole-PO(OEt)2-2'OMe-U-D-DPSE, 5'-vinyl-PO(OEt)2-2'OMe-U-L-DPSE, 5'-vinyl-PO(OEt)2-2'OMe-U-D-DPSE, WV-NU-223, WV-NU-286, WV-NU-287, WV-NU-288, WV-DL-045 (n009), SOPL-WLS-41 (n033), SOPL-WLS-97 (n039), SOPL-WLS-42 (n040), SOPL-WLS-70, SOPL-WLS-96 (n071), SOPL-WLS-95, and SOPL-WLS-94 (n069).

Synthesis SOPL-WLS-98 (n077) Azide.



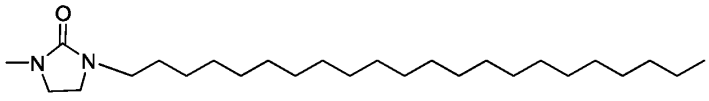
1. Preparation of 1-methylimidazolidin-2-one (SOPL-WLS-98A)



SOPL-WLS-98A

To an ice cool solution of 2-Imidazolidone (25 g, 0.290 mol) in dry 1,4 dioxane (325 mL, 13 vol.) was added sodium hydride (60% dispersion in mineral oil) (19 g, 0.494 mol.) portion-wise over a period of 15 min. then the solution was allowed to heat to 65 °C for 2 h. After that the mixture was again cool to 0°C and methyl iodide (33.49 mL, 0.537 mol) was added dropwise over a period of 30 mins and stirred at rt for 24 h. Progress of the reaction was monitored by TLC. Then reaction mixture was diluted with ice water (100 mL) and extracted with ethyl acetate (2 x 200 mL), washed with brine (1 x 150 mL), dried over Na2SO4 and concentrated under reduced pressure. The crude material was purified by column chromatography over silica-gel (230-400 mesh) eluted in 2% MeOH/DCM afforded SOPL-WLS-98A as a off white solid (9 g, 31%). TLC Mobile phase details: 7% MeOH in DCM.

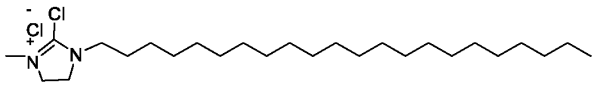
2. ***Preparations of 1-docosyl-3-methylimidazolidin-2-one (SOPL-WLS-98-04)***



SOPL-WLS-98-04

To a stirred solution of (SOPL-WLS-98A) (9 g, 0.0918 mol) in dry toluene (180 mL, 20 vol.) was added KOH powder (20.5 g, 0.3673 mol.), anhydrous free flow K_2CO_3 (2.53 g, 0.0183 mol.), followed by TBAB (1.47 g, 0.0183 mol.) at rt. Then reaction mixture was further stirred at rt for 20 min. Then added 1-bromodocosane (70 mL, 0.183 mol) dropwise over a period of 30 mins at 0oC and further stirred at 80oC for 18 h. Progress of the reaction was monitored by TLC. The crude was diluted ice water (150 mL), extracted with DCM (100 mL x 3), washed with water (80 mL x 1), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH/DCM to get an off white solid (SOPL-WLS-98A) (25.3 g, 68%). TLC Mobile phase details: 7% MeOH in DCM.1H NMR (400 MHz, $CDCl_3$): δ in ppm = 3.27 (s, 4H), 3.16 (t, 2H, J1 = 7.2 Hz), 2.78 (s, 3H), 1.48 (t, 2H, J1 = 6.9 Hz), 1.28-1.25 (m, 42H), 0.88 (t, 3H, J1 = 6.9 Hz). MS: m/z calcd for C26H52N2O, 408.7; found 409.66 $[M+H]^+$.

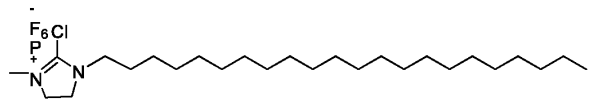
3. ***Preparations of 2-chloro-1-docosyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium chloride (SOPL-WLS-98-05)***



SOPL-WLS-98-05

To a stirred solution of (**SOPL-WLS-98-04)** (20 g, 0.049 mol) in dry toluene (400 mL, 20 vol.) was added Oxalyl chloride (63 mL, 0.735 mol) dropwise over a period for 30 min, at 0°C. Then reaction mixture was further stirred at 60°C for 3days. Progress of the reaction was monitored by TLC. Then reaction mixture was concentrated under reduced pressure. The crude was washed with diethyl ether (100 mL x 2), dried under vacuum afforded a yellowish syrup. **(SOPL-WLS-98-05)** (25 g, crude). TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (400 MHz, $CDCl_3$): δ in ppm = 6.01 (s, 4H), 4.34 (t, 2H, *J1* = 9.6 Hz), 4.25 (t, 2H, *J1* = 10.0 Hz), 3.61 (t, 2H, *J1* = 7.6 Hz), 3.33 (s, 3H), 3.18 (t, 1H, *J1* = 7.2 Hz), 2.81 (s, 1H), 1.66 (s, 2H), 1.47 (t, 1H, *J1* = 7.2 Hz), 1.29-1.26 (m, 51H), 0.86 (t, 4H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{26}H_{52}Cl_2N_2$, 428.2; found 428.87 $[M^+]^+$.

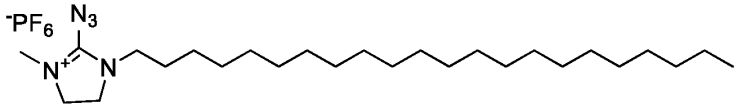
4. Preparations of 2-chloro-1-docosyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium hexafluoro phosphate(V) (SOPL-WLS-98-06)



SOPL-WLS-98-06

To a stirred solution of (**SOPL-WLS-98-05)** (25 g, 0.0539 mol) in DCM (150 mL, 6 vol.) was added a solution of KPF_6 (9.9 g, 0.0539 mol.) in water (87.5 mL, 3.5 vol.) dropwise over a period of 30 mins at 0°C. Above reaction mixture was stirred at rt for 3 h. Progress of the reaction was monitored by TLC. Then the mixture was filtered through a celite bed washed with DCM (2 x 60 mL) and organic layer washed with water (2 x 60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was washed with diethyl ether (100 ml x 3) and dried under vacuum afforded **SOPL-WLS-98-06** as off white solid ((23 g, 74%). TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (400 MHz, $CDCl_3$): δ in ppm = 4.16-4.02 (m, 4H), 3.53 (t, 2H, *J1* = 7.6 Hz), 3.24 (s, 3H), 1.65-1.62 (m, 2H), 1.2 (d, 40H, *J1* = 24.9 Hz), 0.86 (t, 3H, *J1* = 6.8 Hz). MS: *m/z* calcd for $C_{24}H_{52}ClF_6N_2P$, 428.2; found 428.2 [M+].

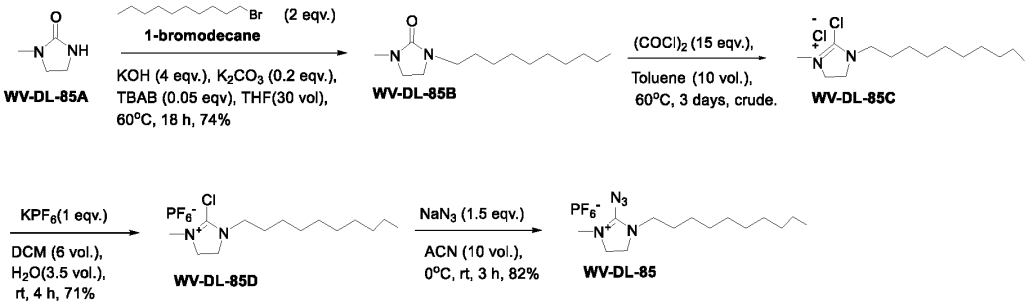
5. Preparations of 2-azido-1-docosyl-3-methyl-4,5-dihydro-1H-imidazol-3-iumhexafluoro phosphate(V)) (SOPL-WLS-98)



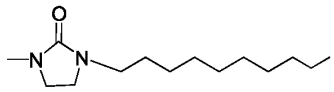
SOPL-WLS-98

To a stirred solution of (**SOPL-WLS-98-06)** (23 g, 0.0401 mol) in dry acetonitrile (230 mL, 10 vol.) was added sodium azide (3.91 g, 0.0602 mol.) portion-wise over a period of 10 mins at 0°C and further stirred at rt for 3 h. Progress of the reaction was monitored by TLC. Then reaction mixture was filtered through a celite bed washed with acetonitrile (2 x 50 mL) and concentrated under reduced pressure. The crude was washed with diethyl ether (100 ml x 2) and dried under vacuum afforded **SOPL-WLS-98** as an off white solid (18 g, 77%). TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (400 MHz, $CDCl_3$): δ in ppm = 3.99-3.84 (m, 4H), 3.40 (t, 2H, *J1* = 7.6 Hz), 3.21 (s, 3H), 1.61 (t, 2H, *J1* = 6.9 Hz), 1.27 (d, 38H, *J1* = 16.9 Hz), 0.88 (t, 3H, *J1* = 6.8 Hz). MS: *m/z* calcd for $C_{26}H_{52}F_6N_5P$; 434.7; found 435.0 $[M+H]^+$. **IR:** 2176.27.

Synthesis of WV-DL-85 (n082) Azide.



1. Preparations of 1-decyl-3-methylimidazolidin-2-one (WV-DL-85B)



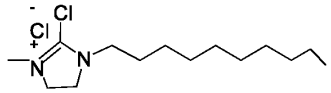
WV-DL-85B

To a stirred solution of (**WV-DL-85A**) (10 g, 0.1 mol) in dry THF (300 mL, 30 vol.) was added KOH powder (22.44 g, 0.4 mol.), K_2CO_3 (2.76 g, 0.02 mol.), followed by TBAB (1.61 g, 0.005 mol) at rt. Then reaction mixture was further stirred at rt for 20 min. Then added 1-bromodecane (41.3 mL, 0.2 mol) dropwise over a period of 30 mins at 0°C and stirred at 65°C for 18 h. Progress of the reaction was monitored by TLC. The crude was diluted with ice water

(100 mL), extracted with EtOAc (100 mL x 2), washed with water (70 mL x 2), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH in DCM concentrated under reduced pressure afforded **WV-DL-85B** as Oily liquid (20 g, 74%). TLC Mobile phase details: 5% MeOH in DCM.

^{1}H NMR (500 MHz, CDCl3): δ in ppm = 3.26 (s, 4H), 3.16 (t, 2H, J1 = 7.6 Hz), 2.77 (s, 3H), 1.48 (q, 2H, J1 = 7.3 Hz), 1.27 (d, 14H, J1= 17.9 Hz), 0.87 (t, 3H, J1 = 6.9 Hz). MS: m/z calcd for $C_{14}H_{28}N_2O$, 240.4; found 241.43 [M+H] +.

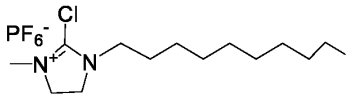
2. ***Preparations of 2-chloro-1-decyl-3-methyl-4,5-dihydro-1H-imidazol-3-iumchloride (WV-DL-85C)***



WV-DL-85C

To a stirred solution of **(WV-DL-85B).)** (18 g, 0.075 mol) in dry toluene (360 mL, 20 vol) was added oxalyl chloride (96 mL, 1.13 mol) dropwise over a period for 30 min, at 0°C. Then reaction mixture was further stirred at 60°C for 3 days. Progress of the reaction was monitored by TLC. Then reaction mixture was concentrated under reduced pressure. The crude was codistilled with toluene (100 ml x 2). The crude was washed with diethyl ether (100 mL x 2), dried under vacuum to give a brown solid **(WV-DL-85C)** (19 g, crude). TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 10.26 (s, 2H), 4.35 (m, 2H), 4.26 (m, 2H), 3.61 (t, 2H, *J1* = 7.6 Hz), 3.34 (s, 3H), 1.68 (s, 2H, J1= 7.2 Hz) , 1.29 (m, 14H), 0.88 (t, 3H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{14}H_{28}Cl_2N_2$, 295.3; found 260.24 [M-Cl].

3. ***Preparations of 2-chloro-1-decyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium hexafluoro phosphate(V) (WV-DL-85D)***

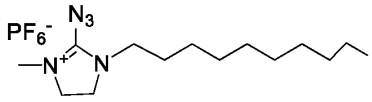


WV-DL-85D

To a stirred solution of crude ***(*WV-DL-85C*)*** (18.5 g, 0.063 mol) in DCM (110 mL, 6 vol) was added a solution of KPF_6 (11.5 g, 0.063 mol.) in water (64.7 mL, 3.5 vol) drop wise over a period of 30 mins at 0°C. Above reaction mixture was stirred at rt for 4 h. Progress of the reaction was monitored by TLC. To the above reaction mixture was added DCM (90 ml) and H_2O (45 ml), separate two layers, organic layer washed with water (2 x 90 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was washed with diethyl ether (90 ml x 3) and dried under vacuum and obtain **WV-DL-85D** an

off white solid (18g, 71%). TLC Mobile phase details: 5% MeOH in DCM. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 4.0 (m, 4H), 3.49 (m, 2H), 3.21 (s, 3H), 1.65 (m, 2H), 1.25 (m, 14H), 0.88 (t, 3H, *J1* = 7.2 Hz). MS: *m/z* calcd for $C_{14}H_{28}ClF_6N_2P$, 404.8; found 259.8 [M+].

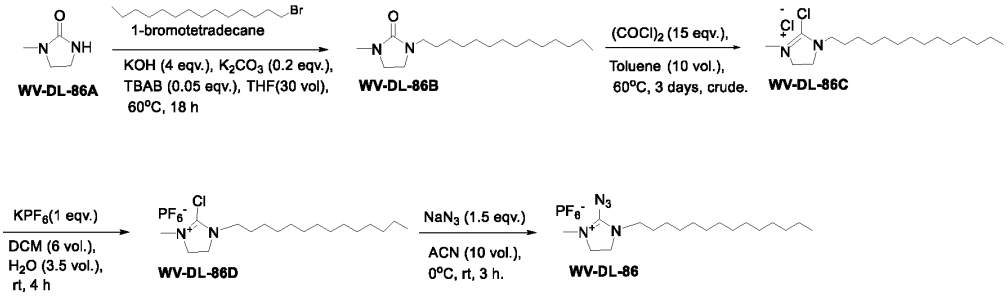
4. ***Preparations of 2-azido-1-decyl-3-methyl-4,5-dihydro-1H-imidazol-3-iumhexafluorophosphate (V) (WV-DL-85)***



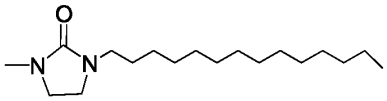
WV-DL-85

To a stirred solution of (**WV-DL-85D)** (19 g, 0.044 mol) in acetonitrile (180 mL, 10 vol) was added sodium azide (4.34 g, 0.066 mol) portion-wise over a period of 20 mins at 0°C and further stirred at rt for 5 h. Progress of the reaction was monitored by TLC. Then reaction mixture was filtered through a celite bed, washed with acetonitrile (2 x 80 mL) and concentrated under reduced pressure to afford a yellowish solid .The solid was washed with diethyl ether (100 ml x 4) and dried under vacuum to give an off white solid (**WV-DL-85)** (16 g, 82%). TLC Mobile phase details: 100% EtOAc. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 3.96 (m, 2H), 3.86 (m, 2H), 3.38 (t, 2H, *J1* = 7.6 Hz), 3.20 (s, 3H), 1.63 (t, 2H, J1 = 7.2 Hz), 1.28 (m, 14H), 0.88 (t, 3H), MS: *m/z* calcd for $C_{14}H_{28}F_6N_5P$; 266.4; found 266.53([M+]).

Synthesis of WV-DL-86 (n083) Azide.



1. ***Preparations of 1-tetradecyl-3-methylimidazolidin-2-one (WV-DL-86B)***

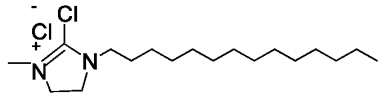


WV-DL-86B

To a stirred solution of (**WV-DL-86A**) (8 g, 0.08 mol) in dry THF (240 mL, 30 vol) was added KOH powder (17.9 g, 0.32 mol), K_2CO_3 (2.2 g, 0.016 mol), followed by TBAB (1.28 g, 0.004

mol) at rt. Then reaction mixture was further stirred at rt for 20 min. Then added 1-bromotetradecane (47.6 mL, 0.16 mol) dropwise over a period of 40 mins at 0°C and stirred at 65°C for 22 h. Progress of the reaction was monitored by TLC. The crude was diluted with ice water (100 mL), extracted with EtOAc (100 mL x 2), washed with water (100 mL x 1), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH in DCM concentrated under reduced pressure afforded **WV-DL-86B** as a liquid (18 g, 76%). TLC Mobile phase details: 5% MeOH in DCM.1H NMR (500 MHz, CDCl3): δ in ppm = 3.25 (s, 4H), 3.14 (t, 2H, J1 = 7.6 Hz), 2.76 (s, 3H), 1.46 (t, 2H, J1 = 6.9 Hz), 1.27 (s, 7H), 1.23 (s, 15H), 0.88 (t, 3H, J1 = 6.9 Hz). MS: m/z calcd for C18H36N2O, 296.5; found 297.56 [M+H]+.

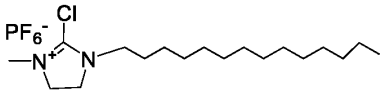
2. ***Preparations of 2-chloro-1-tetradecyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium chloride (WV-DL-86C)***



WV-DL-86C

To a stirred solution of **(WV-DL-86B)** (14 g, 0.047 mol) in dry toluene (280 mL, 20 vol) was added oxalyl chloride (60 mL, 0.71 mol) dropwise over a period for 30 min, at 0°C. Then the reaction mixture was further stirred at 60°C for 80 h. Progress of the reaction was monitored by TLC. Then reaction mixture was concentrated under reduced pressure. The crude was co-distilled with toluene (100 ml x 2). The crude was washed with diethyl ether (100 mL x 2), dried under vacuum to give brown solid **(WV-DL-86C)** (18 g, crude). TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 4.31 (ddd, 4H, *J1* = 44.8 Hz, *J2* = 11.7 Hz), 3.62 (t, 2H, *J1* = 7.6 Hz), 3.35 (s, 3H), 1.69 (d, 2H, J1 = 6.9 Hz) , 1.29 (m, 22H), 0.88 (t, 3H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{18}H_{36}Cl_2N_2$, 351.4; found 316.34 [M-Cl].

3. ***Preparations of 2-chloro-1-tetradecyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium hexafluoro phosphate(V) (WV-DL-86D)***

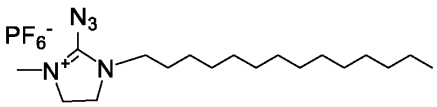


WV-DL-86D

To a stirred solution of crude ***(*WV-DL-86C*)*** (16 g, 0.0455 mol) in DCM (96 mL, 6 vol) was added a solution of KPF_6 (8.3 g, 0.046mol.) in water (56 mL, 3.5 vol.) drop wise over a period of 30 mins at

0°C. Above reaction mixture was stirred at rt for 4 h. Progress of the reaction was monitored by TLC. To the above reaction mixture was added DCM (100 ml) and H_2O (50 ml), separate two layers, organic layer washed with water (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was washed with diethyl ether (100 ml x 3) and dried under vacuum afforded **WV-DL-86D** an off white solid (16g, 76%). TLC Mobile phase details: 5% MeOH in DCM. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 4.10 (m, 4H), 3.53 (t, 2H, *J1* = 7.6 Hz), 3.24 (s, 3H), 1.66 (d, 2H, J1=6.9 Hz), 1.28 (t, 22H, *J1* = 13.4 Hz), 0.88 (t, 3H, *J1* = 7.2 Hz). MS: *m/z* calcd for $C_{18}H_{36}ClF_6N_2P$, 315.9; found 316.37 [M+].

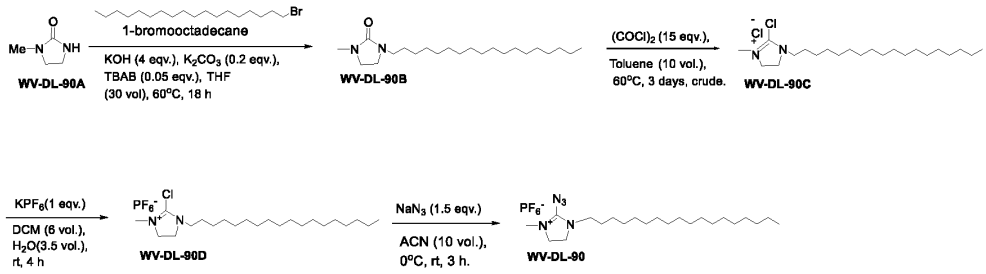
4. ***Preparations of 2-azido-1-tetradecyl-3-methyl-4,5-dihydro-1H-imidazol-3-iumhexafluoro phosphate (V) (WV-DL-86)***



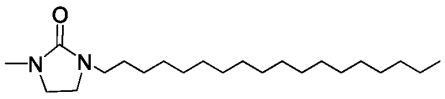
WV-DL-86

To a stirred solution of **(WV-DL-86D)** (16 g, 0.0326 mol) in acetonitrile (160 mL, 10 vol) was added sodium azide (3.37 g, 0.049 mol) portion-wise over a period of 20 mins at 0°C and further stirred at rt for 4 h. Progress of the reaction was monitored by TLC. Then reaction mixture was filtered through a celite bed, washed with acetonitrile (2 x 60 mL) and concentrated under reduced pressure to afford a yellowish solid .The solid was washed with diethyl ether (100 ml x 4) and dried under vacuum to furnish an off white solid. **(WV-DL-86)** (14 g, 86%). TLC Mobile phase details: 100% EtOAc. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 3.96 (m, 2H), 3.86 (m, 2H), 3.39 (t, 2H, *J1* = 7.6 Hz), 3.20 (s, 3H), 1.62 (q, 2H, *J1* = 7.1 Hz), 1.28 (d, 22H), 0.88 (t, 3H, *J1* = 6.9 Hz) MS: *m/z* calcd for $C_{18}H_{36}F_6N_5P$; 322.5; found: 322.74([M+]).

Synthesis of WV-DL-90 (n084) Azide



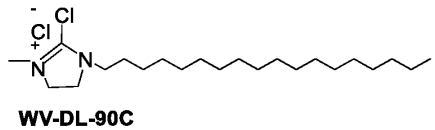
1. ***Preparation of 1-octadecyl-3-methylimidazolidin-2-one (WV-DL-90B)***



WV-DL-90B

To a stirred solution of (**WV-DL-90A**) (10 g, 0.1 mol) in dry THF (300 mL, 30 vol) was added KOH powder (22.4 g, 0.4 mol), K_2CO_3 (2.76 g, 0.02 mol), followed by TBAB (1.61 g, 0.005 mol) at rt. Then the reaction mixture was further stirred at rt for 30 min. after that was added 1-bromooctadecane (68.3 mL, 0.2 mol) dropwise over a period of 30 mins at 0°C and stirred at 65°C for 21 h. Progress of the reaction was monitored by TLC. The crude was diluted with ice water (100 mL), extracted with EtOAc (100 mL x 3), washed with water (80 mL x 2), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH in DCM concentrated under reduced pressure to give **WV-DL-90B** as a liquid material (22 g, 62%). TLC Mobile phase details: 5% MeOH in DCM.1H NMR (400 MHz, CDCl3): δ in ppm = 3.27 (s, 4H), 3.16 (t, 2H, J1 = 7.4 Hz), 2.78 (s, 3H), 1.49 (q, 2H, J1 = 7.0 Hz), 1.27 (d, 30H, J1 = 14.4 Hz), 0.88 (m, 3H). MS: m/z calcd for C22H44N2O, 352.6; found 353.71 [M+H] +.

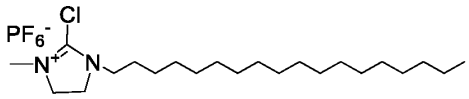
2. ***Preparation of 2-chloro-1-octadecyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium chloride (WV-DL-90C)***



WV-DL-90C

To a stirred solution of (**WV-DL-90B**) (10 g, 0.28 mol) in dry toluene (200 mL, 20 vol) was added oxalyl chloride (36.6 mL, 0.43 mol) dropwise over a period for 30 min, at 0°C. Then reaction mixture was further stirred at 60°C for 3days. Progress of the reaction was monitored by TLC. Then reaction mixture was concentrated under reduced pressure. The crude was co-distilled with toluene (100 ml x2). The crude was washed with diethyl ether (100 mL x 2), dried under vacuum to give **WV-DL-90C** as brown solid (12 g, crude). TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 4.31 (dt, 2H, *J1* = 4.7 Hz), 3.62 (t, 2H, *J1* = 7.6 Hz), 3.35 (s, 3H), 1.67 (s, 2H) , 1.29 (d, 33H, J1= 31.0 Hz), 0.88 (t, 3H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{22}H_{44}Cl_2N_2$, 406.7; found 372.7 [M-Cl].

3. ***Preparation of 2-chloro-1-octadecyl-3-methyl-4,5-dihydro-1H-imidazol-3-ium hexafluoro phosphate(V) (WV-DL-90D)***

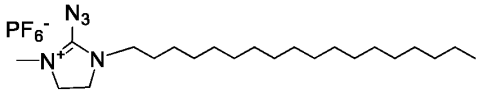


WV-DL-90D

To a stirred solution of *(***WV-DL-89C***)* (12 g, 0.029 mol) in DCM (72 mL, 6 vol) was added a solution

of KPF_6 (5.4 g, 0.029 mol) in water (42 mL, 3.5 vol) drop wise over a period of 30 mins at 0°C. Above reaction mixture was stirred at rt for 4 h. Progress of the reaction was monitored by TLC. To the above reaction mixture added DCM (100 ml) and H_2O (50 ml), separate two layers, organic layer washed with water (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was washed with diethyl ether (100 ml x 3) and dried under vacuum to afforded **WV-DL-89D** as off white solid (11 g, 79%). TLC Mobile phase details: 5% MeOH in DCM. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 4.10 (m, 4H), 3.52 (t, 2H, *J1* = 7.6 Hz), 3.24 (s, 3H), 1.65 (t, 2H, J1=6.9 Hz), 1.28 (t, 30H, *J1* = 13.8 Hz), 0.88 (t, 3H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{22}H_{44}ClF_6N_2P$, 372.1; found 372.45 [M+].

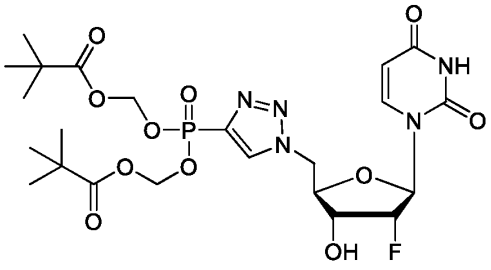
4. ***Preparation of 2-azido-1-hexadecyl-3-methyl-4,5-dihydro-1H-imidazol-3-iumhexafluo rophosphate (V) (WV-DL-90)***



WV-DL-90

To a stirred solution of (**WV-DL-89D)** (11 g, 0.021 mol) in acetonitrile (110 mL, 10 vol) was added sodium azide (2.1 g, 0.032 mol) portion-wise over a period of 20 mins at 0°C and further stirred at rt for 4 h. Progress of the reaction was monitored by TLC. Then reaction mixture was filtered through a celite bed washed with acetonitrile (2 x 100 mL) and concentrated under reduced pressure to afford a light yellow solid. The solid was washed with diethyl ether (100 ml x 4) and dried under vacuum to give **WV-DL-89** as an off white solid (10 g, 89%). TLC Mobile phase details: 100% EtoAc. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 3.96 (m, 2H), 3.86 (m, 2H), 3.39 (t, 2H, *J1* = 7.6 Hz), 3.20 (s, 3H), 1.61 (t, 2H, *J1* = 7.6 Hz), 1.28 (m, 30H), 0.88 (t, 3H, J1 = 6.9 Hz), MS: *m/z* calcd for $C_{22}H_{44}F_6N_5P$; 378.6; found 379.05([M+]).

EXAMPLE 22. Synthesis of WV-NU-347

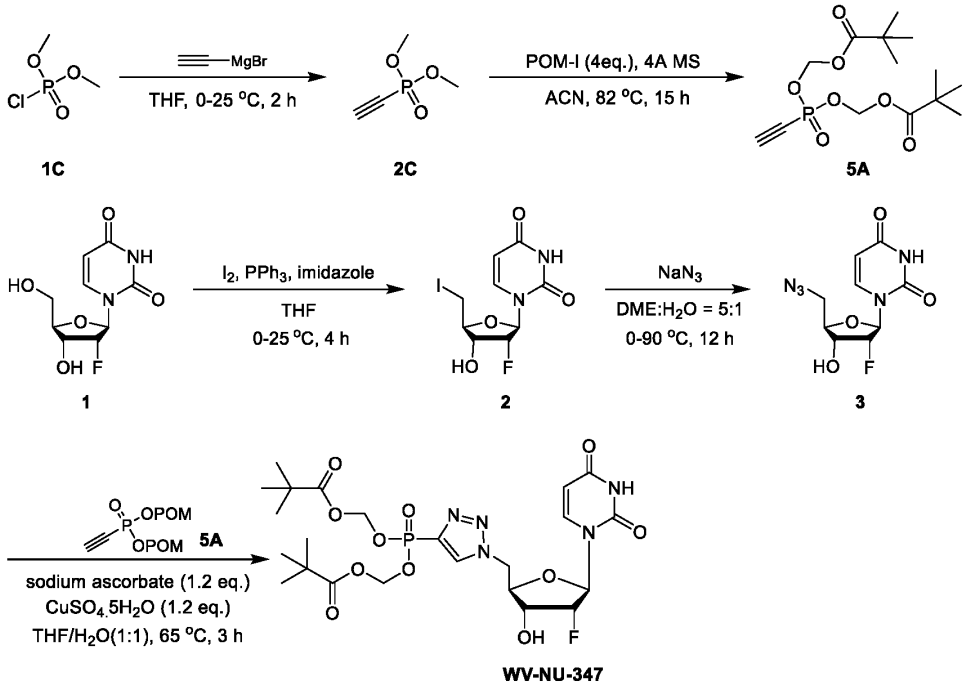


WV-NU-347

2'-Fluoro-5'-PO(POM)$_2$-Triazolyl Phosphonate Uridine (**WV-NU-347**)

(((1-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)

General Scheme:

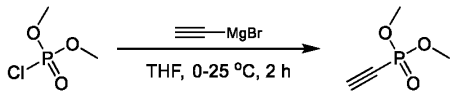


WV-NU-347

2'-Fluoro-5'-PO(POM)$_2$-Triazolyl Phosphonate Uridine (**WV-NU-347**)

Experimental Procedure:

1. ***Preparation of compound 2C :***

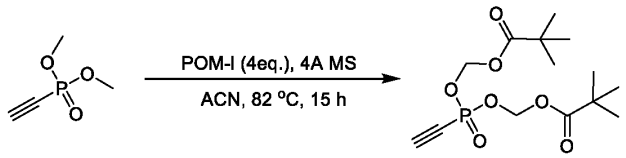


1C 2C

For three batches: To a solution of compound **1C** (36 g, 249.15 mmol) in THF (400 mL) was added bromo(ethynyl)magnesium (0.5 M, 498.29 mL) under N_2. The mixture was stirred at 0-25 °C for 2 hr. TLC indicated compound **1C** was consumed completely and one new spot formed. Each reaction mixture was quenched by addition NH_4Cl 100mL at 0 °C, and then diluted with water 300 mL and extracted with EtOAc (100 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10: 1 to 0:1). Compound **2C** (28.5 g, 28.44% yield) was obtained as a yellow oil.

TLC: Petroleum ether : Ethyl acetate = 0:1, Rf = 0.35

2. Preparation of compound 5A :



2C 5A

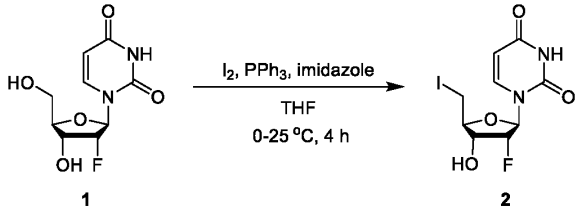
For three batches: To a solution of compound **2C** (9.5 g, 70.86 mmol) in ACN (500 mL) was added 4A MS (3 g, 70.86 mmol), iodomethyl 2,2-dimethylpropanoate (68.61 g, 283.43 mmol). The mixture was stirred at 82 °C for 15 hr. TLC indicated Reactant 1 was consumed completely and two new spots formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10:1 to1:1). Compound **5A** (45 g, 63.32% yield) was obtained as a colorless oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.72 (d, J = 1.2 Hz, 2H), 5.68 (s, 2H), 3.04 (d, J = 14.3 Hz, 1H), 1.22 (s, 18H)

31P NMR (162 MHz, CHLOROFORM-d) δ = -10.36 (s, 1P)

TLC: Petroleum ether : Ethyl acetate = 3:1, Rf = 0.38

3. Preparation of compound 2:



1 2

For three batches. To a solution of compound **1** (15 g, 60.93 mmol) in THF (210 mL) was added imidazole (10.78 g, 158.41 mmol), I_2 (24.74 g, 97.48 mmol) and PPh_3 (25.57 g, 97.48 mmol) at 0 °C. The mixture was stirred at 25 °C for 4 hr. LCMS showed compound **1** was consumed completely and the desired mass was detected. Three batches with together. The reaction was quenched by 10% aqueous sodium thiosulfate solution (100 ml). After removing the solvent and volatiles under reduced pressure, the residue was extracted into EtOAc (50 mL * 5) and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1 to Dichloromethane: Methanol =1: 0 to 3: 1). The crude product was purified by re-crystallization from Ethyl acetate (100 mL) and Methanol (10 mL) at 15 °C. Compound **2** (43 g (total three batches), 66.15% yield,) was obtained as a yellow solid.

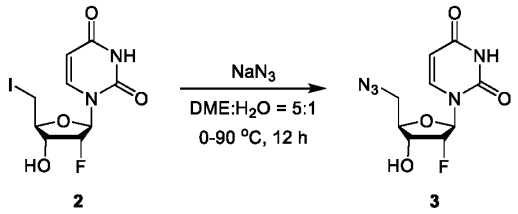
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.46 (br s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 5.94 - 5.79 (m, 2H), 5.66 (d, J = 8.0 Hz, 1H), 5.33 - 5.13 (m, 1H), 4.10 - 3.98 (m, 1H), 3.77 (dt, J = 3.4, 7.2 Hz, 1H), 3.60 (dd, J = 3.6, 11.0 Hz, 1H), 3.41 (dd, J = 6.8, 11.0 Hz, 1H)

19F NMR (376 MHz, DMSO-d6) δ = -199.11 (s, 1F)

LCMS (M+H+): 356.9, purity: 95.16%

TLC: Dichloromethane: Methanol = 10:1 Rf =0.45

4. Preparation of compound 3:



2 3

For two batches. To a solution of compound **2** (10 g, 28.08 mmol) in 1, 2-dimethoxyethane

(100 mL) and H_2O (20 mL) was added NaN_3 (1.83 g, 28.08 mmol) at 0 °C under N_2. The mixture was stirred at 90 °C for 12 hr. LCMS showed compound **2** was remained and the desired mass was detected. Two batches with together. The reaction was quenched by H_2O (50 mL), and extracted with Ethyl acetate (100 mL*3). The combined organic layers were washed with saturated aqueous NaCl 50 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). The crude product was purified by re-crystallization from Ethyl acetate (100 mL) at 20 °C. Compound **3** (28 g, 85.63% yield) was obtained as a white solid.

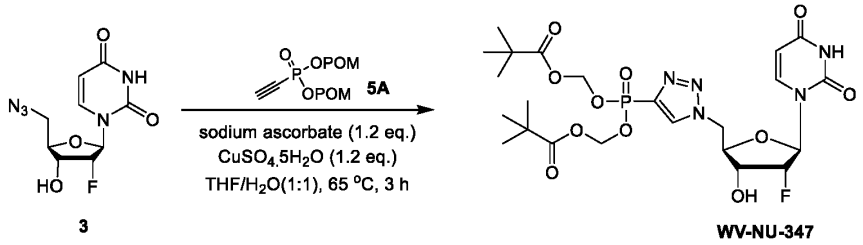
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.45 (br s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 5.90 - 5.81 (m, 1H), 5.75 (br s, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.29 - 5.10 (m, 1H), 4.31 - 4.17 (m, 1H), 3.94-3.93 (m, 1H), 3.79 - 3.48 (m, 2H)

19F NMR (376 MHz, DMSO-d6) δ = -198.74 (s, 1F)

LCMS: (M+H+): 272.0, purity: 92.29%

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.45

5. Preparation of WV-NU-347:



2'-Fluoro-5'-(POM)$_2$-Triazolyl Phosphonate Uridine (WV-NU-347)

For two batches. To a solution of compound **3** (5 g, 18.44 mmol) and compound **5A** (7.40 g, 22.12 mmol) in H_2O (25 mL) and THF (25 mL) was degassed and purged with N_2 for 3 times, $CuSO_4.5H_2O$ (5.52 g, 22.12 mmol), sodium ascorbate (4.38 g, 22.12 mmol) was added. The mixture was stirred at 65 °C for 3 hr under N_2 atmosphere. LCMS showed compound **3** was consumed completely and the desired mass was detected. Two batches with together. The reaction mixture was extracted with Ethyl acetate (30mL*3). The combined organic layers were washed with saturated aqueous NaCl 20 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography

(SiO_2, Petroleum ether: Ethyl acetate=1:0 to 0:1 to Ethyl acetate: Methanol=1:0 to 2:1). Compound **WV-NU-347** (14.5 g, 65.91% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.42 (d, J = 1.6 Hz, 1H), 8.71 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 5.91 (d, J = 6.0 Hz, 1H), 5.87 - 5.78 (m, 1H), 5.69 (d, J = 13.8 Hz, 4H), 5.62 (dd, J = 2.0, 8.1 Hz, 1H), 5.31 - 5.09 (m, 1H), 4.91 - 4.71 (m, 2H), 4.30 - 4.16 (m, 2H), 1.08 (s, 18H)

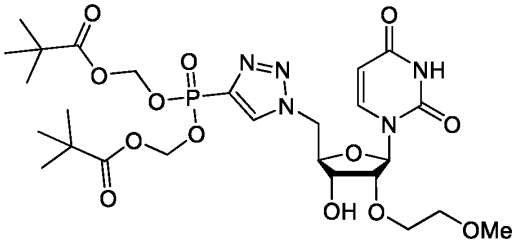
^{31}P NMR (162 MHz, DMSO-d6) δ = 7.04 (s, 1P)

^{19}F NMR (376 MHz, DMSO-d6) δ = -199.16 (s, 1F)

LCMS (M+H+): 606.2, purity: 98.32%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.55

EXAMPLE 23. Synthesis of WV-NU-348

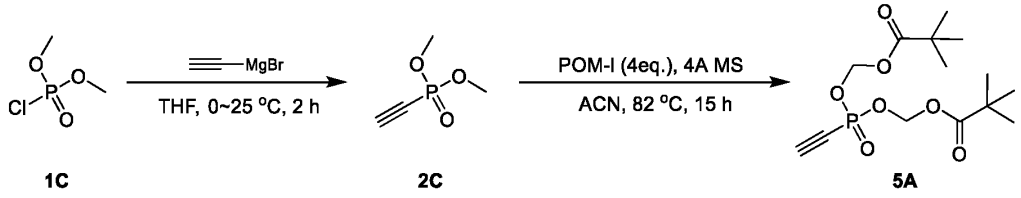


WV-NU-348

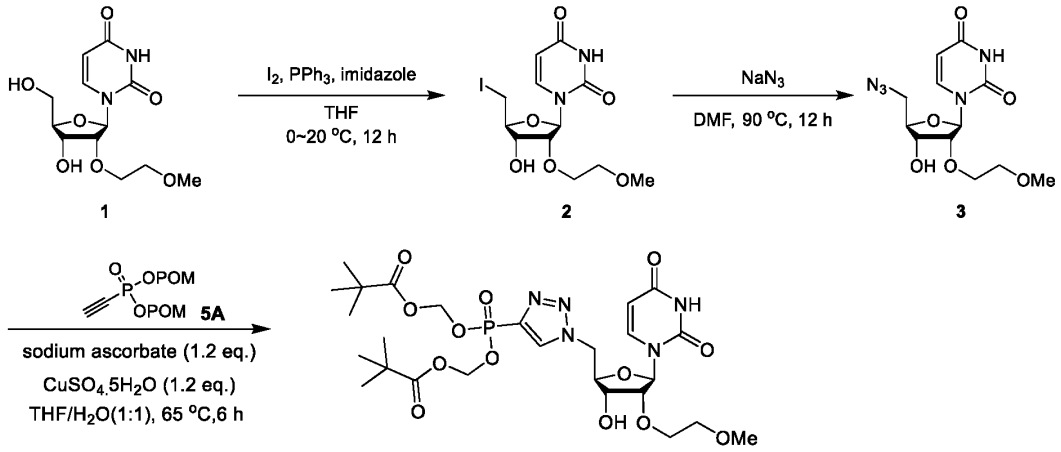
2'-OMOE-5'-PO(POM)$_2$-Triazolyl Phosphonate Uridine (**WV-NU-348**)

(((1-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-hydroxy-4-(2-methoxyethoxy)tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) (**WV-NU-348**)

General Scheme:

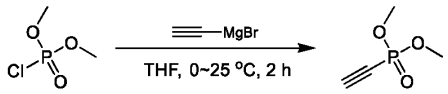


1C **2C** **5A**



Experimental Procedure:

1. ***Preparation of compound 2C :***



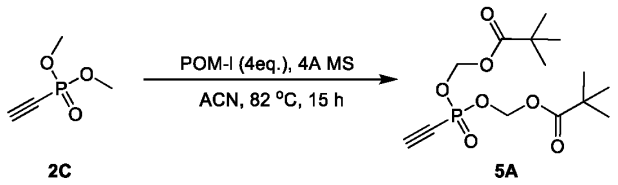
For four batches: To a solution of compound **1C** (36 g, 249.15 mmol, 26.87 mL) in THF (400 mL) was added bromo(ethynyl)magnesium (0.5 M, 498.29 mL) under N_2. The mixture was stirred at 0 ~ 25 °C for 2 h. TLC indicated compound **1C** was consumed completely and one new spot formed. Four batches with together, the each reaction mixture was quenched by addition NH_4Cl 100 mL at 0 °C, and then diluted with water 300 mL and extracted with EtOAc (100 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10: 1 to 0: 1). Compound **2C** (23 g, 17.21% yield) was obtained as a yellow oil

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 3.82 (s, 3H), 3.80 (s, 3H), 2.96 (d, J = 13.4 Hz, 1H)

^{31}P NMR (162 MHz, CHLOROFORM-d) δ = -5.07 - -5.22 (m, 1P)

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.31

2. ***Preparation of compound 5A :***



2C 5A

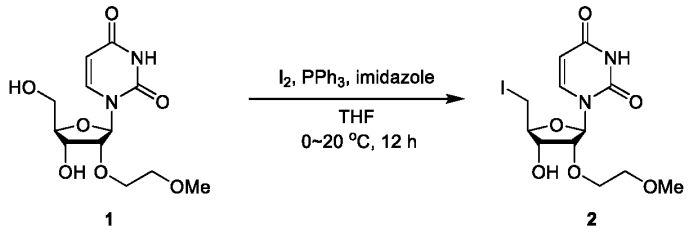
For two batches: To a solution of compound **2C** (11.5 g, 85.78 mmol) in ACN (500 mL) was added 4A MS (5 g, 85.78 mmol), iodomethyl 2,2-dimethylpropanoate (83.05 g, 343.10 mmol). The mixture was stirred at 82 °C for 15h. TLC indicated compound **2C** was consumed completely and two new spots formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10: 1 to 0: 1). Compound **5A** (33 g, 57.89% yield) was obtained as a colorless liquid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.70 (d, J = 1.5 Hz, 2H), 5.66 (d, J = 0.8 Hz, 2H), 3.06 (d, J = 14.3 Hz, 1H), 1.20 (s, 18H)

31P NMR (162 MHz, CHLOROFORM-d) δ = -10.31 (s, 1P)

TLC: Petroleum ether: Ethyl acetate = 3: 1, Rf = 0.38

*3. **Preparation of compound 2 :***



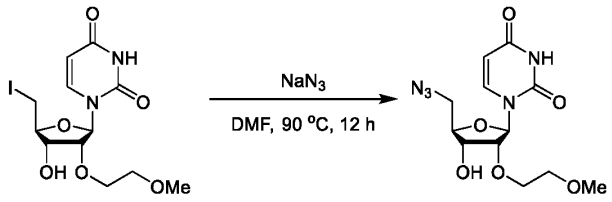
1 2

Two batches were carried out in parallel: To a solution of compound **2** (17.5 g, 57.89 mmol) in THF (400 mL) was added imidazole (10.25 g, 150.52 mmol), I_2 (23.51 g, 92.63 mmol, 18.66 mL) and PPh_3 (24.30 g, 92.63 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 h. LCMS showed compound **2** was consumed completely and one main peak with desired mass was detected. Two reactions were combined for work up. The reaction mixture was quenched by addition 10% $Na_2S_2O_3$ aq. 100 mL at 25 °C, and then concentrated under reduced pressure to remove THF, diluted with H_2O (700 mL) and extracted with EtOAc (500 mL * 2). The combined organic layers were washed with brine (600 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly

for the next step without purification. Compound **2** (48 g, crude) was obtained as a yellow oil.

LCMS: ($M+H^+$): 412.9.

4. Preparation of compound 3 :



2 **3**

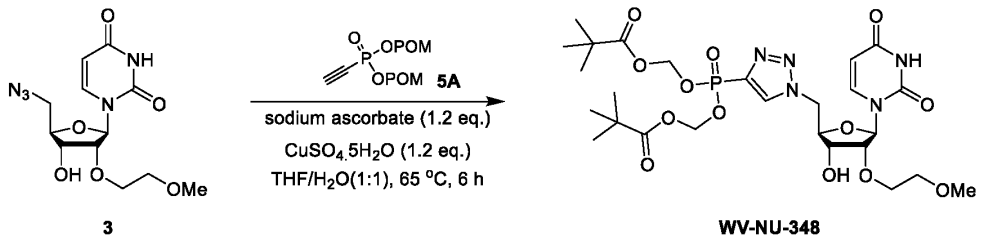
For two batches: To a solution of compound **2** (22 g, 53.38 mmol) in DMF (250 mL) was added NaN_3 (3.09 g, 47.53 mmol) at 0 °C under N_2. The mixture was stirred at 90 °C for 12 h. LCMS showed compound **2** was consumed completely and desired mass was detected. The reaction was quenched by H_2O (500 mL), and extracted with Ethyl acetate (500mL * 3). The combined organic dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **3** (34 g, crude) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.40 (s, 1H), 7.70(d, J = 8.2 Hz, 1H), 5.82 (d, J = 4.5 Hz, 1H), 5.68 (d, J = 7.8 Hz, 1H), 5.26 (d, J = 5.6 Hz, 1H), 4.10 - 4.02 (m, 2H), 3.92 (q, J = 4.8 Hz, 1H), 3.74 - 3.67 (m, 1H), 3.66 - 3.57 (m, 3H), 3.47 - 3.42 (m, 2H), 3.25 - 3.20 (m, 3H)

LCMS: ($M+H^+$): 328.2

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.34

5. Preparation of compound WV-NU-348 :



3 **WV-NU-348**

2'-OMOE-5'-PO(POM)$_2$-Triazolyl Phosphonate Uridine (**WV-NU-348**)

To a solution of compound **3** (11.5 g, 35.14 mmol) and compound **5A** (15.27 g, 45.68 mmol)

in THF (50 mL) and H_2O (50 mL) was added sodium ascorbate (8.35 g, 42.16 mmol) and $CuSO_4.5H_2O$ (10.53 g, 42.16 mmol). The mixture was stirred at 65 °C for 6 h. LCMS showed compound **3** was consumed completely and desired mass was detected. The mixture was concentrated, the reaction mixture was extracted with EtOAc (50 mL * 3) and H_2O 50 mL. Then the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **WV-NU-348** (10.7 g, 45.48% yield, 97.77% purity) was obtained as a yellow solid.

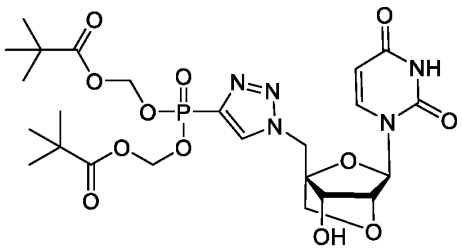
1HNMR (400 MHz, DMSO-d6) δ = 11.45 - 11.36 (m, 1H), 8.70 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 5.80 (d, J = 4.6 Hz, 1H), 5.70 (s, 2H), 5.68 - 5.64 (m, 3H), 5.40 (d, J = 5.6 Hz, 1H), 4.85 - 4.71 (m, 2H), 4.21 - 4.17 (m, 1H), 4.14 - 4.08 (m, 2H), 3.75 - 3.67 (m, 1H), 3.67 - 3.59 (m, 1H), 3.46 (t, J = 4.8 Hz, 2H), 3.22 - 3.22 (m, 1H), 3.22 (s, 2H), 1.08 (s, 18H)

31PNMR (162 MHz, DMSO-d6) δ = 7.08 (s, 1P)

LCMS: ($M+H^+$): 662.2, LCMS purity: 97.77%

TLC: Dichloromethane: Methanol = 10: 1, Rf = 0.32

EXAMPLE 24. Synthesis of WV-NU-349

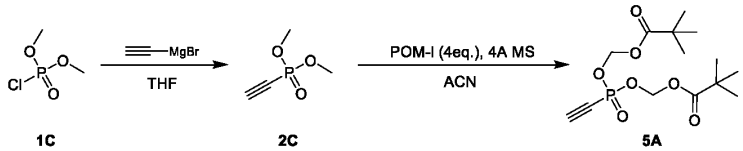


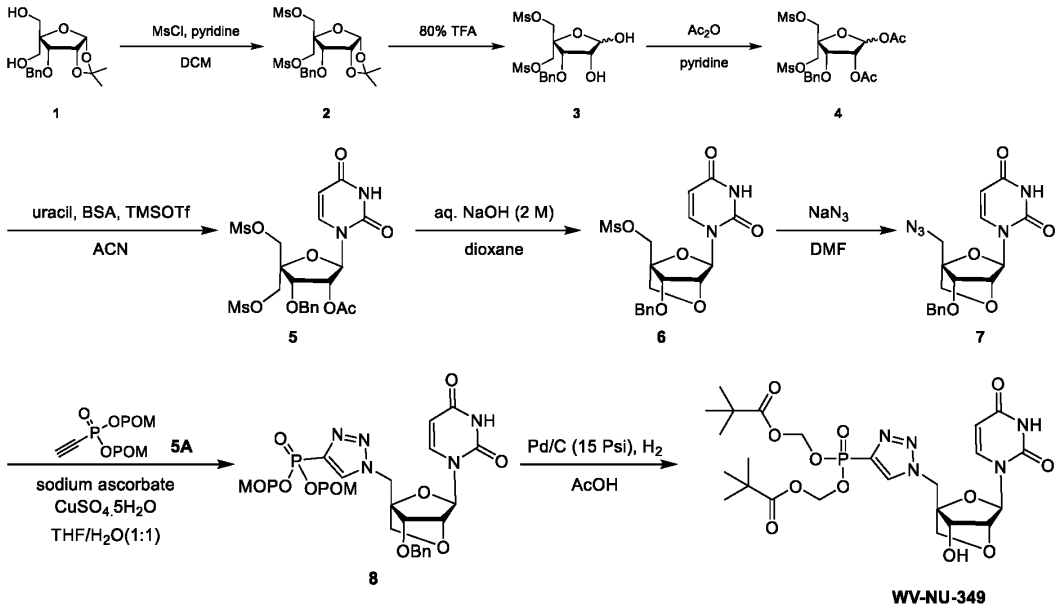
WV-NU-349

2'-LNA-5'-PO(POM)$_2$-Triazolyl Phosphonate Uridine (**WV-NU-349**)

(((1-(((1S,3R,4R,7S)-3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-7-hydroxy-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate) (**WV-NU-349**)

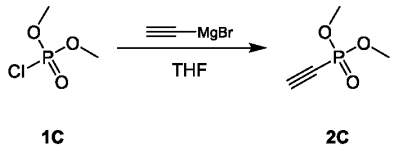
General Scheme:





Experimental Procedure:

1. Preparation of compound 2C:



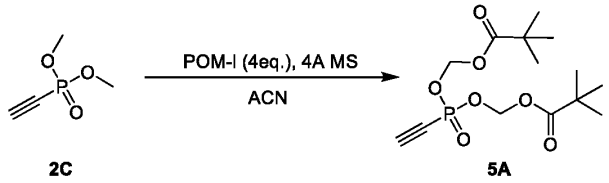
To a solution of compound **1C** (36 g, 249.15 mmol) in THF (400 mL) was added bromo (ethynyl) magnesium (0.5 M, 498.29 mL) under N_2. The mixture was stirred at 0 - 25 °C for 2 hr. TLC indicated compound **1C** was consumed completely and one new spot formed. The each reaction mixture was quenched by addition NH_4Cl 100mL at 0 °C. And then diluted with water 300 mL and extracted with EtOAc (100 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10:1 to 0:1). Compound **2C** (23 g, 17.21% yield) was obtained as a yellow oil

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 3.82 (s, 3H), 3.79 (s, 3H), 2.97 (d, J =13.4 Hz, 1H)

31P NMR (162 MHz, CHLOROFORM-d) δ = -5.07 - -5.22 (m, 1P)

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.31

2. Preparation of compound 5A:



2C 5A

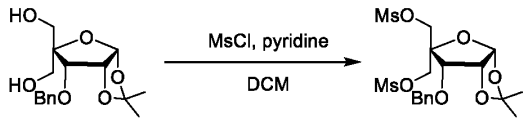
For two batches: To a solution of compound **2C** (11.5 g, 85.78 mmol) in ACN (500 mL) was added 4A MS (5 g, 85.78 mmol), iodomethyl 2,2-dimethylpropanoate (83.05 g, 343.10 mmol). The mixture was stirred at 82 °C for 15 hr. TLC indicated compound **2C** was consumed completely and two new spots formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 10:1 to 0:1). Compound **5A** (33 g, 57.89% yield) was obtained as a colorless.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.70 (d, J = 1.5 Hz, 2H), 5.66 (d, J = 0.8Hz, 2H), 3.06 (d, J = 14.3 Hz, 1H), 1.20 (s, 18H)

31P NMR (162 MHz, CHLOROFORM-d) δ = -10.31 (s, 1P)

TLC: Petroleum ether: Ethyl acetate = 3:1, Rf = 0.38

3. Preparation of compound 2:



1 2

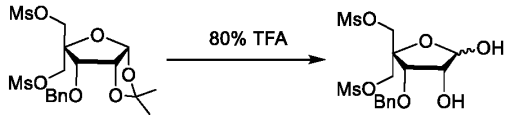
For two batches: to a solution of compound **1** (50 g, 161.11 mmol) in DCM (800 mL) was added pyridine (82.84 g, 1.05 mol) and the mixture was cooled to 0 °C, then MsCl (46.18 g, 403.14 mmol) was slowly added the mixture. The mixture was stirred at 0 - 20 °C for 12 hr. LCMS showed compound **1** was consumed completely and desired mass was detected. The mixture was cooled to 0 °C, the mixture of 100 mL ice water and aqueous $NaHCO_3$ 100 mL was dropped to the mixture under N_2, and stirred for 5 min. Then two batches with together, the organic layer was separated and washed with saturated aqueous $NaHCO_3$ (300 ml*2) and with water. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was used into the next step without further

purification. Compound **2** (150 g, crude) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.41 - 7.35 (m, 5H), 5.79 (d, J = 3.8 Hz, 1H), 4.88 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 11.6 Hz, 1H), 4.68 - 4.63 (m, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.22 - 4.12 (m, 2H), 3.08 (s, 3H), 2.98 (s, 3H), 1.68 (s, 3H), 1.34 (s, 3H)

LCMS (M+Na+): 489

4. Preparation of compound 3:



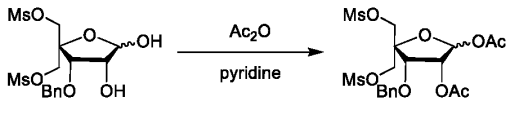
2 **3**

For three batches: to a solution of compound **2** (50 g, 107.18 mmol) was added TFA (250 mL) and H_2O (62.5 mL). The mixture was stirred at 20 °C for 12 hr. LCMS showed compound **2** was consumed completely and desired mass was detected. Three batches with together. The reaction mixture was concentrated under reduced pressure to remove TFA. The residue was diluted with $NaHCO_3$ (500 mL) and extracted with DCM (300 mL * 2). The combined organic layers were washed with brine 500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound **3** (137 g, crude) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.64 (br d, J = 4.6 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.41 - 7.30 (m, 5H), 5.39 - 5.34 (m, 1H), 4.66 - 4.59 (m, 2H), 4.35 -4.33 (m, 1H), 4.31 - 4.20 (m, 1H), 4.19 - 4.14 (m, 1H), 4.11 (d, J = 5.0 Hz, 1H), 3.05 - 2.97 (m, 6H)

LCMS (M+Na+): 449.1

5. Preparation of compound 4:



3 **4**

For two batches: to a solution of compound **3** (65 g, 152.42 mmol) in PYRIDINE (600 mL) was added Ac_2O (57.57 g, 563.95 mmol). The mixture was stirred at 20 °C for 12 hr. LCMS showed compound **3** was consumed completely and desired mass was detected. Two batches

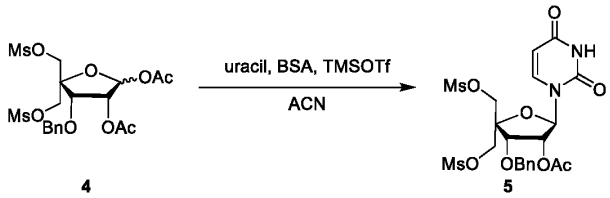
with together. The reaction mixture was diluted with $NaHCO_3$ (1000 mL) and extracted with EtOAc (500 mL *2). The combined organic layers were washed with brine 800 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 0:1 to 1:1). Compound **4** (155 g, crude) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.42 - 7.33 (m, 5H), 6.18 (s, 1H), 5.38 (d, J = 4.8 Hz, 1H), 4.65 - 4.60 (m, 1H), 4.55 - 4.48 (m, 2H), 4.43 (d, J = 4.8 Hz, 1H), 4.31 - 4.28 (m, 1H), 4.23 - 4.17 (m, 2H), 3.02 (d, J = 2.0 Hz, 6H), 2.16 (s, 3H), 2.11 (s, 3H)

LCMS (M+Na+):533.1

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.5

6. Preparation of compound 5:



4 5

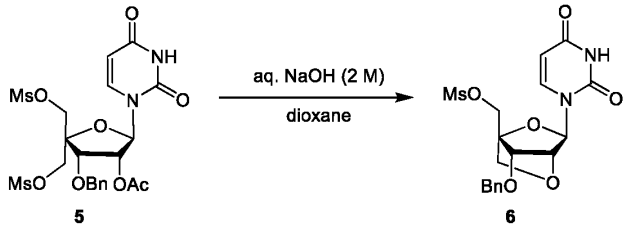
For three batches: to a solution of compound **4** (50 g, 97.94 mmol) and uracil (21.95 g, 195.87 mmol) in ACN (700 mL) was added BSA (69.73 g, 342.78 mmol) at 80 °C for 1 hr. Then TMSOTf (54.42 g, 244.84 mmol) was added to the mixture. The mixture was stirred at 60 °C for 12 hr. LCMS showed compound **4** was consumed completely and desired mass was detected. The reaction mixture was cooled to 0 °C, and added to $NaHCO_3$ (800 mL). Three batches with together. The residue was extracted with EtOAc (500 mL * 3). The combined organic layers were washed with brine 500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **5** (78 g, 47.27% yield) and 78 g (crude) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.46 (br s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.39 - 7.29 (m, 5H), 5.98 (d, J = 4.6 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.55 - 5.50 (m, 1H), 4.65 - 4.53 (m, 3H), 4.45 - 4.37 (m, 3H), 4.36 - 4.30 (m, 1H), 3.26 (s, 3H), 3.19 (s, 3H), 2.05 (s, 3H)

LCMS (M+Na+): 585.1, purity: 92.5%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.5

7. Preparation of compound 6:



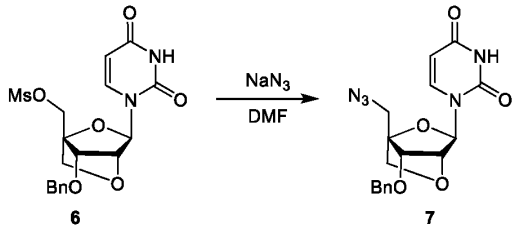
For two batches: To a solution of compound **5** (41.5 g, 73.77 mmol) in dioxane (100 mL) and H_2O (100 mL) was added NaOH (2 M, 221.31 mL). The mixture was stirred at 20 °C for 12 hr. LCMS showed compound **5** was consumed completely and one main peak with desired mass was detected. Two batches with together. The reaction mixture was washed with 10% AcOH (300 mL). The residue was diluted with H_2O (500 mL) and extracted with DCM (300 mL * 3). The combined organic layers were washed with $NaHCO_3$ (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOAc at 20 °C for 5 min. The mixture was filtered and the cake was concentrated under reduced pressure to give product. Compound **6** (50 g, 79.85% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.42 (br s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.37 - 7.25 (m, 5H), 5.60 (d, J = 8.0 Hz, 1H), 5.56 (s, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 3.0 Hz, 2H), 4.61 - 4.56 (m, 2H), 4.03 - 3.97 (m, 2H), 3.84 (d, J = 8.0 Hz, 1H), 3.27 (s, 3H)

LCMS (M+H+): 425.0, purity: 92.4%

TLC: Petroleum ether: Ethyl acetate = 0:1 Rf = 0.4

8. Preparation of compound 7:



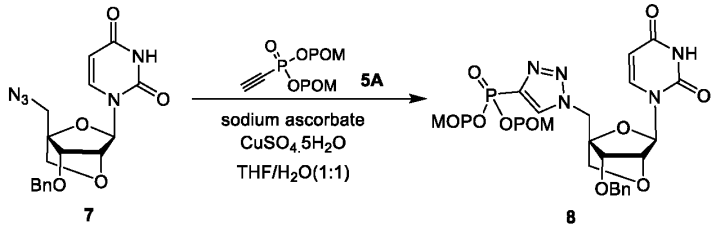
To a solution of compound **6** (20 g, 47.12 mmol) in DMF (200 mL) was added NaN_3 (3.17 g, 48.76 mmol). The mixture was stirred at 60 °C for 12 hr. LCMS showed compound **6** was consumed completely and desired mass was detected. The reaction was quenched by H_2O (100

mL), and extracted with Ethyl acetate (200 mL*3). The combined organic was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with Petroleum ether: Ethyl acetate = 10:1, at 20 °C for 5 min. Then the mixture was filtered, the cake was washed with Petroleum ether, concentrated under reduced pressure to give product. Compound **7** (15.5 g, 88.58% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.42 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.37 - 7.27 (m, 5H), 5.65 (d, J = 8.2 Hz, 1H), 5.54 (s, 1H), 4.66 - 4.57 (m, 2H), 4.54 (s, 1H), 4.01 (d, J = 14.0 Hz, 1H), 3.94 - 3.89 (m, 2H), 3.87 - 3.77 (m, 2H)

LCMS (M+H+): 372.0

9. Preparation of compound 8:



To a solution of compound **7** (10 g, 26.93 mmol) and compound **5A** (10.80 g, 32.31 mmol) in THF (100 mL) and H_2O (100 mL) was added copper; sulfate; pentahydrate (8.07 g, 32.31 mmol) and sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (6.40 g, 32.31 mmol). The mixture was stirred at 65 °C for 6 hr. TLC indicated compound **7** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (100 mL * 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **8** (18 g, 94.72% yield) was obtained as a white solid.

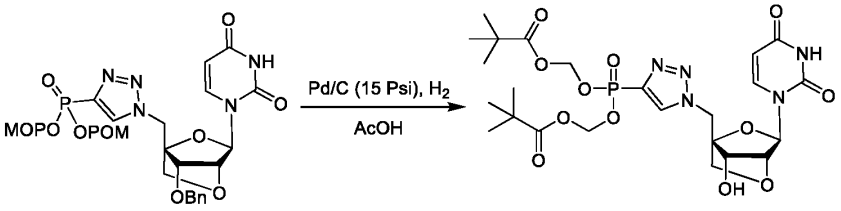
^{1}H NMR (400 MHz, DMSO-d6) δ =11.39 (s, 1H), 8.78 (s, 1H), 7.36 (d, J = 4.2 Hz, 4H), 7.33 - 7.26 (m, 2H), 5.73 (s, 2H), 5.69 (s, 2H), 5.52 (br d, J = 8.0 Hz, 1H), 5.47 (s, 1H), 5.28 (br d, J = 15.0 Hz, 1H), 5.02 (br d, J = 15.0 Hz, 1H), 4.66 (s, 2H), 4.57 (s, 1H), 4.11 (d, J = 8.0 Hz, 1H), 3.58 (br d, J = 8.2 Hz, 2H), 1.10 (s, 18H)

31P NMR (162 MHz, DMSO-d_6) δ = 6.73 (s, 1P)

LCMS (M+H+): 706.3, purity: 94.7%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.3

10. Preparation of WV-NU-349:



8 **WV-NU-349**

2'-LNA-5'-PO(POM)$_2$-Triazolyl Phosphonate Uridine (**WV-NU-349**)

For two batches: to a solution of compound **8** (9 g, 12.75 mmol) in AcOH (100 mL) was added Pd/C (1.36 g, 1.28 mmol, 10% purity). The mixture was stirred at 30 °C for 12 hr under H_2 (15 Psi). LCMS showed compound **8** was consumed completely and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether: Ethyl acetate = 1:0 to 0:1, Ethyl acetate: Methanol = 1:0 to 10:1). Compound **WV-NU-349** (7.49 g, 49.93% yield) was obtained as a white solid.

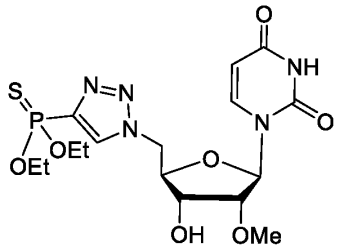
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.38 (s, 1H), 8.78 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.11 (br d, J = 4.0 Hz, 1H), 5.72 (br d, J = 13.8 Hz, 3H), 5.51 (d, J = 8.0 Hz, 1H), 5.39 (s, 1H), 5.22 (d, J = 15.0 Hz, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.25 (s, 1H), 4.07 (d, J = 8.0 Hz, 1H), 3.86 (d, J = 3.6 Hz, 1H), 3.50 (d, J = 8.0 Hz, 1H), 1.11 (s, 18H)

^{31}P NMR (162 MHz, DMSO-d$_6$) δ = 6.75 (s, 1P)

LCMS (M-H+): 616.2, purity: 98.88%

TLC: Ethyl acetate: Methanol = 10:1, Rf = 0.3

EXAMPLE 25. Synthesis of WV-NU-350

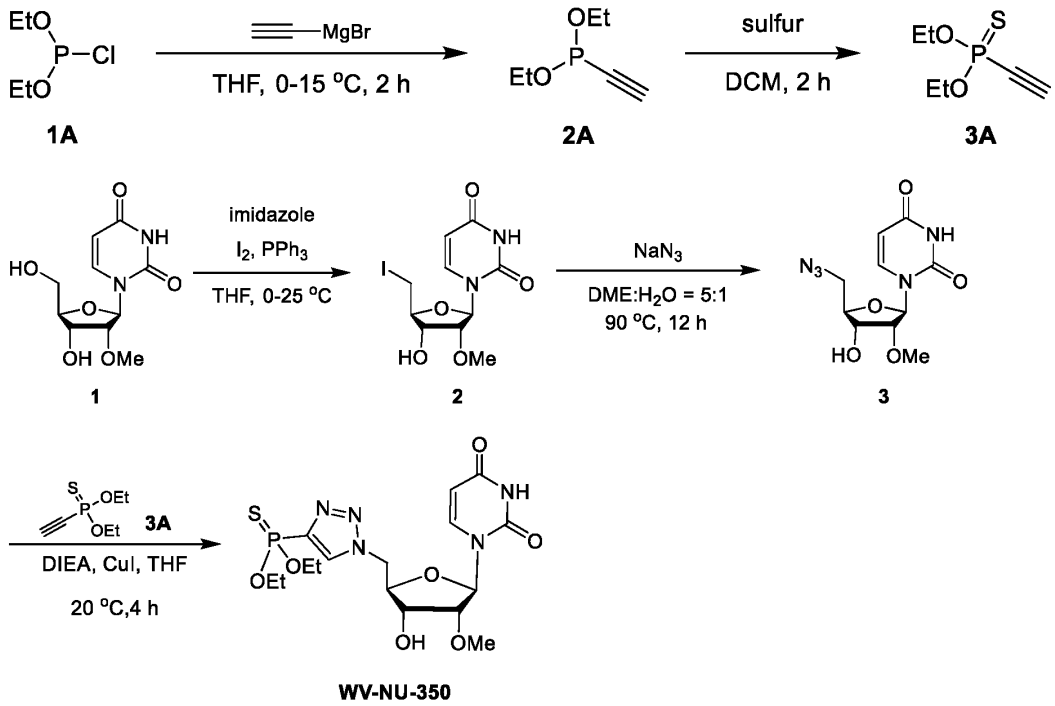


WV-NU-350

2'-OMe-5'-PS(OEt)$_2$-Triazolyl Thiophosphonate Uridine (**WV-NU-350**)

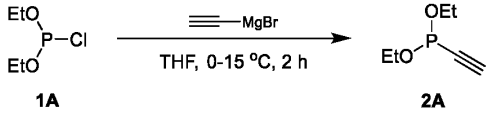
O,O-diethyl (1-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphonothioate **(WV-NU-350).**

General Scheme:



Experimental Procedure:

1. ***Preparation of compound 2A :***

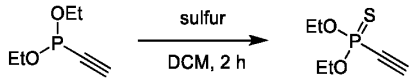


1A 2A

For three batches. To a solution of compound **1A** (9.3 g, 59.41 mmol) in THF (100 mL) was added bromo (ethynyl) magnesium (0.5 M, 120.00 mL) at 0 °C under N_2. The resulting mixture was stirred at 0-15 °C for 2 hr. TLC indicated compound **1A** was consumed completely and two new spots formed. The reaction was clean according to TLC. Three batches with together. The mixture was quenched by addition sat. NH_4Cl (aq. 150 mL) at 0 °C, then diluted with H_2O (100 mL) and extracted with DCM (200 mL*3). The combined organic layers were dried over Na_2SO_4, filtered to get the crude. Without purification. Compound **2A** (26 g, crude) was obtained as a brown oil.

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.95

2. Preparation of compound 3A :



2A 3A

For two batches. To a solution of compound **2A** (13 g, 88.97 mmol) in DCM (150 mL) was added S (5.40 g, 168.41 mmol). The mixture was stirred at 15 °C for 2 hr. TLC indicated compound **2A** was consumed completely and one new spot formed. The reaction was clean according to TLC. Two batches with together. The reaction mixture was cooled to 0 °C and quenched by addition H_2O 80 mL, and then diluted with H_2O 50 mL and extracted with DCM 150 mL (50 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **3A** (14 g, 44.16% yield) was obtained as a yellow oil.

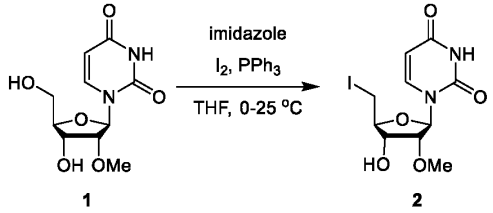
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.16 (qd, J = 7.2, 10.3 Hz, 4H), 3.12 (d, J = 12.4 Hz, 1H), 1.34 (t, J = 7.2 Hz, 6H)

^{31}P NMR (162 MHz, CHLOROFORM-d) δ = 51.30 (s, 1P)

LCMS (M+H+): 179.1

TLC: Petroleum ether: Ethyl acetate = 5:1, Rf = 0.7

3. Preparation of compound 2:



1 2

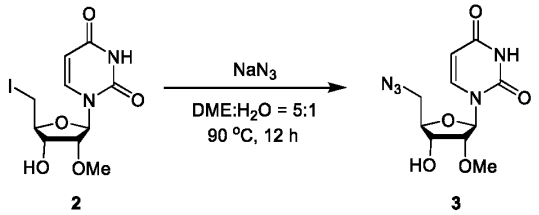
For five batches. To a solution of compound **1** (30 g, 116.18 mmol) in THF (420 mL) was added imidazole (20.56 g, 302.06 mmol), I_2 (47.18 g, 185.88 mmol) and PPh_3 (48.75 g, 185.88 mmol) at 0 °C. The mixture was stirred at 25 °C for 6 hr. TLC indicated compound **1** was consumed completely and two new spots formed. The reaction was clean according to TLC. Five batches with together. The reaction was quenched by 10% aqueous sodium thiosulfate solution (800 ml). After removing the solvent and volatiles under reduced pressure, the residue was extracted into Dichloromethane (200 mL * 3) and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1 to Dichloromethane: Methanol = 1: 0 to 3: 1). The crude product was purified by re-crystallization from Ethyl acetate (100 mL), Dichloromethane (300 mL) and Methanol (50 mL) at 15 °C. Compound **2** (200 g, 93.55% yield) was obtained as a purple solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.43 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 5.87 (d, J = 5.6 Hz, 1H), 5.70-5.68 (m, 1H), 5.46 (d, J = 6.0 Hz, 1H), 4.05-4.01 (m, 1H), 4.00-3.95 (m, 1H), 3.88-3.82 (m, 1H), 3.54-3.53 (m, 1H), 3.42-3.40 (m, 1H), 3.34 (s, 3H)

LCMS (M+H+): 369.0

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.45

4. Preparation of compound 3:



2 3

For five batches. To a solution of compound **2** (24 g, 65.20 mmol) in 1, 2-dimethoxyethane (300 mL) and H_2O (60 mL) was added NaN_3 (3.66 g, 56.30 mmol) at 0 °C under N_2. The

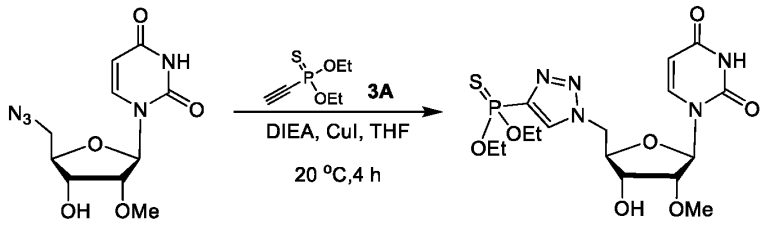
mixture was stirred at 90 °C for 12 hr. LCMS showed compound **2** was remained and the desired mass was detected. Five batches with together. The reaction was quenched by H_2O (500 mL), and extracted with Ethyl acetate (400 mL*3). The combined organic layers were washed with saturated aqueous NaCl 300 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). The crude product was triturated with Ethyl acetate (50 mL) at 15 °C for 10 min. Compound **3** (49 g, 85.51% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.48 - 10.91 (m, 1H), 7.70 (d, J = 8.2 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.36 (br d, J = 5.8 Hz, 1H), 4.07 (q, J = 5.2 Hz, 1H), 3.95 - 3.89 (m, 2H), 3.61 (d, J = 4.8 Hz, 2H), 3.36 (s, 3H)

LCMS: (M+H+): 284.0, purity: 90.16%

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.45

5. ***Preparation of WV-NU-350:***



3 **WV-NU-350**

2'-OMe-5'-PS(OEt)$_2$-Triazolyl Thiophosphonate Uridine (**WV-NU-350**)

To a solution of compound **3** (8 g, 28.24 mmol) and compound **3A** (5.54 g, 31.07 mmo) in THF (80 mL) was degassed and purged with N_2 for 3 times, then DIEA (7.30 g, 56.49 mmol), CuI (10.76 g, 56.49 mmol) was added. The mixture was stirred at 20 °C for 4 hr under N_2 atmosphere. LCMS showed compound **3** was remianed and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give product. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **WV-NU-350** (10 g, 76.92% yield) was obtained as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.41 (d, J = 1.6 Hz, 1H), 8.58 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 5.80 (d, J = 4.8 Hz, 1H), 5.64 - 5.62 (m, 1H), 5.49 (d, J = 6.2 Hz, 1H), 4.84 - 4.78 (m,

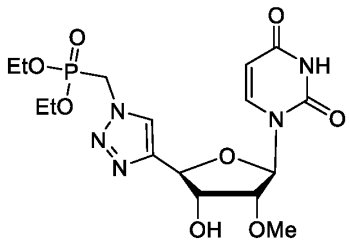
1H), 4.77 - 4.69 (m, 1H), 4.21 (td, J = 4.8, 7.8 Hz, 1H), 4.17 - 4.07 (m, 5H), 3.91 (t, J = 5.2 Hz, 1H), 3.36 (s, 3H), 1.24 (t, J = 7.0 Hz, 6H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 69.85 (s, 1P)

LCMS (M+H+): 462.1, purity: 98.75%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.25

EXAMPLE 26. Synthesis of WV-NU-352

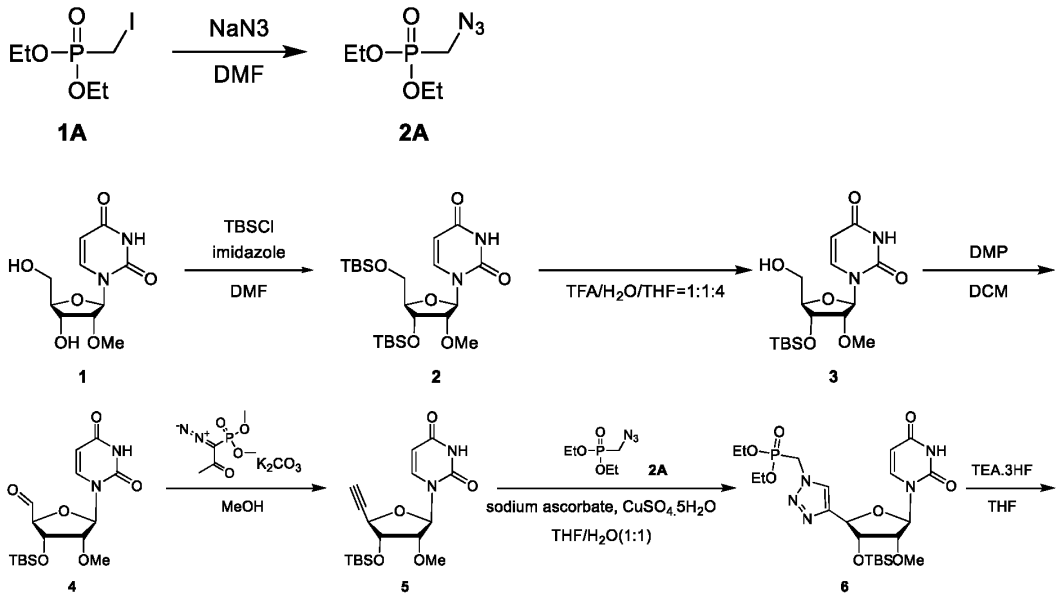


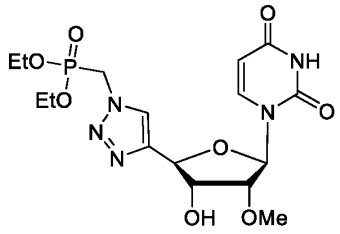
WV-NU-352

2'-OMe-5'-PO(OEt)$_2$-Triazolyl methyl phosphonate Uridine (**WV-NU-352**)

diethyl ((4-((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)-1H-1,2,3-triazol-1-yl)methyl)phosphonate (**WV-NU-352**)

General Scheme:

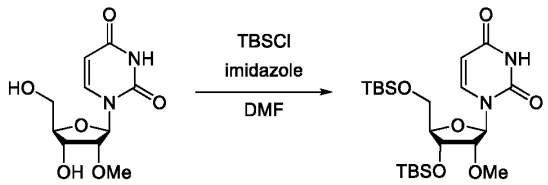




WV-NU-352

Experimental Procedure:

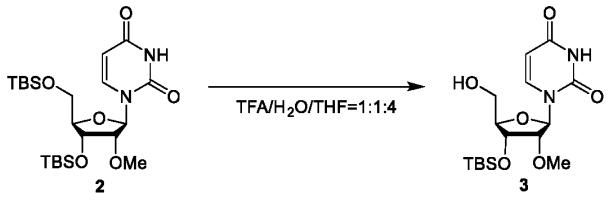
1. Preparation of compound 2:



For two batches: To a solution of compound **1** (50 g, 193.63 mmol) in DMF (1000 mL) was added imidazole (52.73 g, 774.51 mmol) and TBSCl (87.55 g, 580.88 mmol). The mixture was stirred at 20 °C for 12 hr. TLC indicated compound **1** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with H_2O 1500 mL and extracted with EtOAc 500 mL*3. The combined organic layers were washed with brine 1500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound **2** (188 g, crude) was obtained as a colorless oil.

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.7

2. Preparation of compound 3:



For four batches: To a solution of compound **2** (94 g, 193.12 mmol) in THF (1000 mL) at 0 °C under N_2, and then added mixture of TFA (383.75 g, 3.37 mol) and H_2O (250.00 g, 13.88 mol)

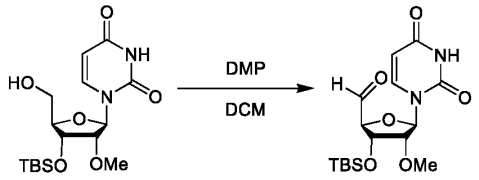
slowly. The mixture was stirred at 0 °C for 3 hr. TLC indicated compound **2** was consumed completely and one new spot formed. The reaction mixture was quenched with $NH_3.H_2O$ (230 mL *4) at 0 °C. Four batches with together. The residue was diluted with H_2O 500 mL and extracted with DCM (1000 mL * 3). The combined organic layers were washed with brine 1000 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **3** (230 g, 79.93% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.36 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 5.0 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.21 (t, J = 5.0 Hz, 1H), 4.30 (t, J = 4.8 Hz, 1H), 3.87 - 3.81 (m, 2H), 3.70 - 3.61 (m, 1H), 3.55 – 3.51 (m, 1H), 3.34 (s, 3H), 0.88 (s, 9H), 0.09 (s, 6H)

LCMS (M+H+): 373.1, purity: 100%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.6

3. Preparation of compound 4:



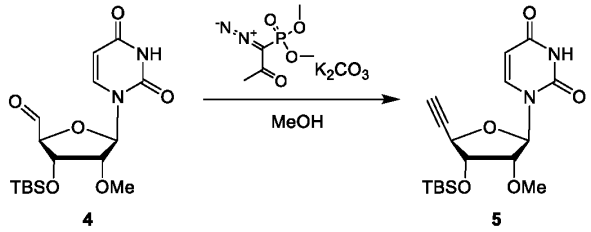
3 **4**

To a solution of compound **3** (25 g, 67.12 mmol) in DCM (500 mL) was added DMP (28.47 g, 67.12 mmol). The mixture was stirred at 0-25 °C for 3 hr. TLC indicated compound **3** was consumed completely and one new spot formed. The reaction mixture of three batches were diluted with $NaHCO_3$ 500 mL and extracted with DCM 500 mL*3. The combined organic layers were washed with Sat. NaCl 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude product. The crude product was used into the next step without further purification. Compound **4** (24 g, crude) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.59 - 11.25 (m, 1H), 7.92 - 7.89 (m, 1H), 5.94 (d, J = 7.7 Hz, 1H), 5.73 - 5.68 (m, 1H), 4.90 (d, J = 3.0 Hz, 1H), 4.46 (d, J = 4.6 Hz, 1H), 3.87 – 3.85 (m, 1H), 3.72 (d, J = 2.6 Hz, 1H), 3.61 - 3.58 (m, 3H), 0.90 - 0.88 (m, 9H), 0.10 (s, 6H)

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.45

4. Preparation of compound 5:



4 5

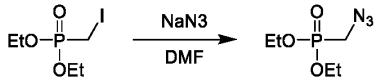
For two batches: to a solution of compound **4** (22 g, 59.38 mmol) and 1-diazo-1-dimethoxyphosphoryl-propan-2-one (11.41 g, 59.38 mmol) in MeOH (400 mL) was added K_2CO_3 (16.41 g, 118.77 mmol) at 0 °C under N_2. The mixture was stirred at 0-20 °C for 12 hr. LCMS showed compound **4** was consumed completely and one main peak with desired mass was detected. Two batches with together. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O 300 mL and extracted with DCM 200 mL * 3. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **5** (25 g, 57.44% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.43 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 5.82 (d, J = 4.4 Hz, 1H), 5.75 (d, J = 8.0 Hz, 1H), 4.49 - 4.46 (m, 1H), 4.44 (d, J = 4.6 Hz, 1H), 4.04 - 4.01 (m, 1H), 3.87 (d, J = 1.4 Hz, 1H), 3.36 (s, 3H), 0.89 (s, 9H), 0.13 (d, J = 3.2 Hz, 6H)

LCMS (M-H+):367.1; purity: 95.3%

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.4

5. Preparation of compound 2A:



1A **2A**

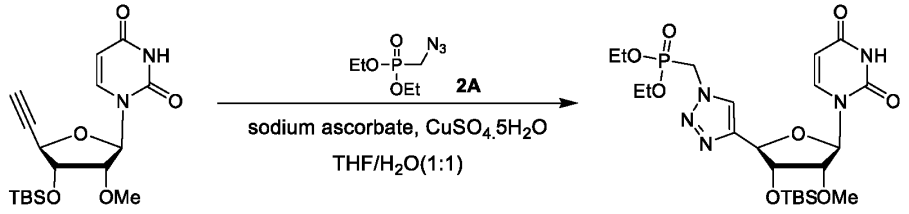
To a solution of compound **1A** (30 g, 107.90 mmol) in DMF (300 mL) was added NaN_3 (7.27 g, 111.83 mmol. The mixture was stirred at 90 °C for 12hr. TLC indicated compound **1A** was consumed completely and one new spot formed. The reaction was cooled to 0 °C, and quenched by H_2O (300 mL), and extracted with Ethyl acetate (200 mL*3). The combined organic dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **2A** (12 g, 57.58% yield) was obtained as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 4.25 - 4.14 (m, 4H), 3.46 (d, J = 11.8 Hz, 1H), 3.03 (d, J = 10.4 Hz, 1H), 1.39 - 1.32 (m, 6H)

LCMS (M-H+):194.1

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.25

6. Preparation of compound 6 :



To a solution of compound **5** (10 g, 27.29 mmol) and compound **2A** (6.85 g, 35.47 mmol) in THF (50 mL) and H_2O (50 mL) was added copper; sulfate; pentahydrate (8.18 g, 32.74 mmol) and sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (6.49 g, 32.74 mmol). The mixture was stirred at 65 °C for 6 hr. TLC indicated compound **5** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O 100 mL and extracted with EtOAc (100 mL * 2). The combined organic layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **6** (9.7 g, 63.52% yield) was obtained as a white solid.

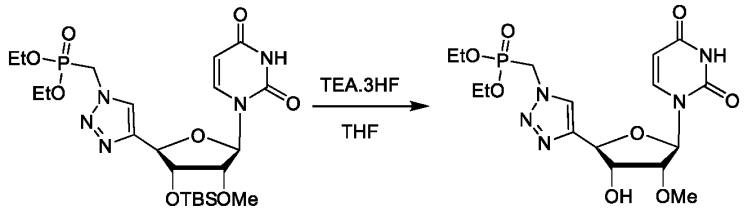
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.42 (s, 1H), 8.21 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 5.90 (d, J = 3.4 Hz, 1H), 5.72 – 5.69 (m, 1H), 5.12 (br d, J = 13.0 Hz, 2H), 5.01 (d, J = 6.0 Hz, 1H), 4.60 - 4.54 (m, 1H), 4.12 - 4.03 (m, 5H), 3.43 (s, 3H), 1.24 - 1.18 (m, 6H), 0.80 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 17.19 (s, 1P)

LCMS (M-H+):560.3; purity: 96.99%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.3

7. Preparation of compound WV-NU-352:



6 **WV-NU-352**

2'-OMe-5'-PO(OEt)$_2$-Triazolyl methyl phosphonate Uridine (**WV-NU-352**)

To a solution of compound **6** (9 g, 16.08 mmol) in THF (95 mL) was added N,N-diethylethanamine; trihydrofluoride (10.37 g, 64.33 mmol). The mixture was stirred at 40 °C for 12 hr. TLC indicated compound **6** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1, Ethyl acetate: Methanol = 1:0 to 5:1). Compound **WV-NU-352** (4.3 g, 60.04% yield) was obtained as a white solid.

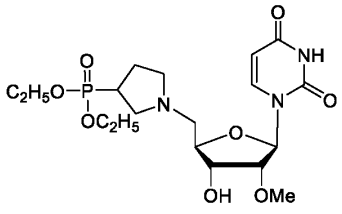
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.41 (br s, 1H), 8.18 (s, 1H), 7.89 – 7.87 (m, 1H), 5.96 (d, J = 3.8 Hz, 1H), 5.69 (d, J = 8.0 Hz, 1H), 5.54 -5.52 (m, 1H), 5.11 (br d, J = 13.0 Hz, 2H), 5.01 (d, J = 4.6 Hz, 1H), 4.40 (q, J = 5.0 Hz, 1H), 4.12 - 4.01 (m, 5H), 3.42 (d, J = 1.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 6H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 17.28 (s, 1P)

LCMS (M-H+): 446.1; purity: 96.79%

TLC: Ethyl acetate: Methanol = 8:1, Rf = 0.25

EXAMPLE 28. Synthesis of WV-NU-362

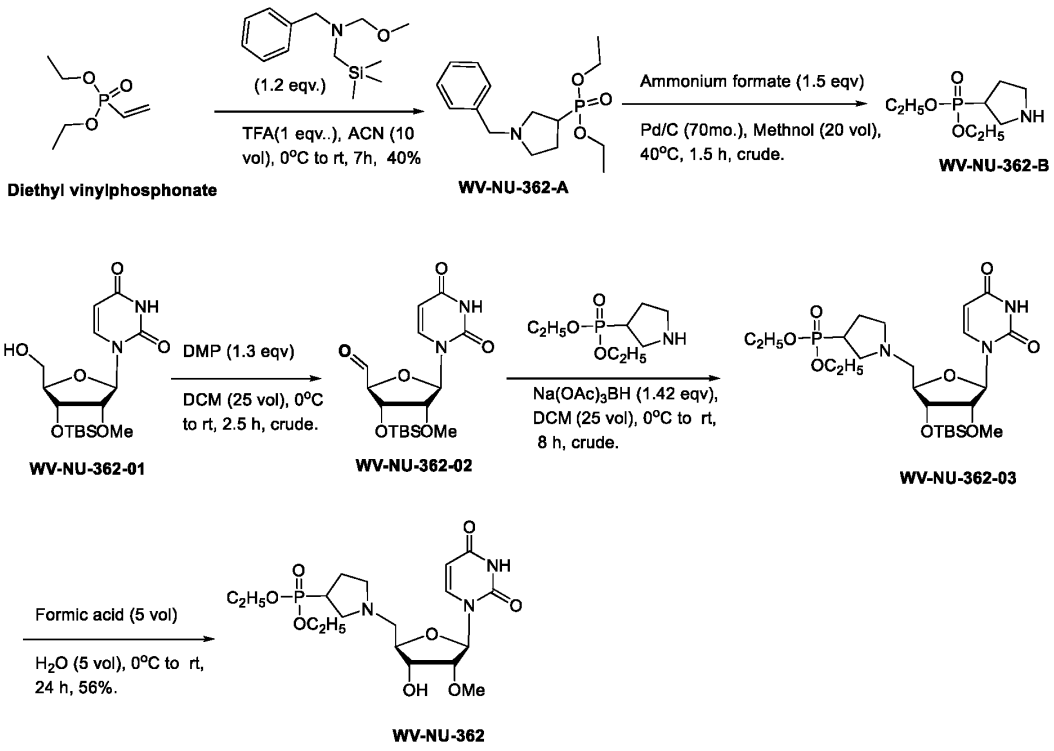


WV-NU-362

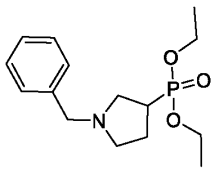
2'-OMe-5'-(3-PO(OEt)$_2$-pyrrolidinyl) phosphonate Uridine (**WV-NU-362**)

diethyl (1-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)pyrrolidin-3-yl)phosphonate (**WV-NU-362**)

General Scheme:



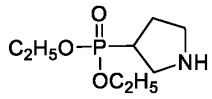
Preparation of diethyl (1-benzylpyrrolidin-3-yl)phosphonate (WV-NU-362-A) :



WV-NU-362-A

To a stirred solution of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl) methenamine (12 g, 0.05063 mol) and diethyl vinylphosphonate (8.3 g, 0.05063) in dry ACN (120 mL, 10 vol), was added TFA (3.9 mL, 0.0563 mol) dropwise over a period for 10 min at 0°C. The resulting mixture was stirred at rt for 6 h. Progress of the reaction was monitored by TLC. Then reaction mixture was concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 40% acetone in hexane to get a yellow oil **(WV-NU-362-A)** (6 g, 40%), TLC Mobile phase details: 50% Acetone in Hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ in ppm = 7.30 (m, 4H), 7.25 (m, 1H), 4.10 (m, 4H), 3.63 (s, 2H), 2.98 (m, 1H), 2.83 (m, 1H), 2.49 (m, 3H), 2.11 (m, 2H), 1.31 (t, 6H, *J1* = 7.1 Hz). MS: *m/z* calcd for $C_{15}H_{24}NO_3P$, 297.3; found 298.52, $[M+H]^+$.

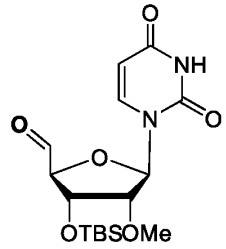
Preparation of diethyl pyrrolidin-3-ylphosphonate (WV-NU-362-B):



WV-NU-362-B

To a stirred solution of **(WV-NU-362-A)** (6 g, 0.02289 mol) in dry MeOH (120 mL, 20 vol) was added Ammonium formate (2.16 g, 0.03434 mol) and Pd/C (1.8 g, 30 mol %) portion wise at rt. The resulting mixture was stirred 40°C and kept for 1.5 h. Progress of the reaction was monitored by TLC. After completion as monitored by TLC, the reaction mixture was filtered through celite bed, washed with MeOH (2 x 50 mL) and concentrated under reduced pressure to afford light yellow oil **(WV-NU-362-B)** (3.2 g, crude), TLC Mobile phase details: 10% MeOH in DCM. ^{1}H NMR (400 MHz, $CDCl_3$): δ in ppm = 4.12 (m, 4H), 3.44 (s, 2H), 3.13 (m, 2H), 2.91 (m, 1H), 2.36 (m, 1H), 2.01 (m, 2H), 1.33 (t, 6H, *J1* = 7.1 Hz. MS: *m/z* calcd for $C_8H_{18}NO_3P$, 207.2; found 208.24 $[M-H]^+$.

Preparation of (2S,3S,4R,5R)-3-((tert-butyldimethylsilyl)oxy)-5-(2,4-dioxo-3,4-dihydro pyrimidin-1(2H)-yl)-4-methoxytetrahydrofuran-2-carbaldehyde **(WV-NU-362-02):**

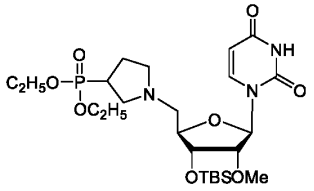


WV-NU-362-02

To a stirred solution of **(WV-NU-362-01)** (5 g, 0.0134 mol) in dry DCM (125 mL, 25 vol) was added Dess-Martin Periodinane (7.4 g, 0.0174 mol) portion wise over a period of 20 min at 0°C. The reaction mixture was allowed to stirr at rt for 2.5 h. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with a solution (1:1 ratio of $Na_2S_2O_3$: $NaHCO_3$ (80 mL), extracted with DCM (2 x 60 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford off white solid **(WV-NU-362-02)** (4.6 g, crude), TLC Mobile phase details: 70% EtOAc in Hexane. ^{1}H NMR (500 MHz, $CDCl_3$): δ in ppm = 9.78 (s, 1H), 8.58 (s, 1H), 7.63 (d, 1H, *J1* = 7.6 Hz), 5.80 (t, 2H, *J1* = 5.9 Hz), 4.54 (d, 1H, *J1* = 4.1 Hz), 4.43 (t, 1H, *J1* = 4.1 Hz), 3.93 (t, 1H, *J1* = 4.8 Hz), 3.46 (m, 4H), 0.92 (m, 9H),

0.12 (m, 8H). MS: *m/z* calcd for $C_{16}H_{26}N_2O_6Si$, 370.05; found 371.32. $[M-H]^+$.

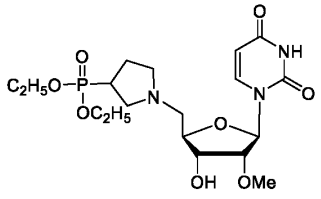
Preparation of diethyl (1-(((2R,3R,4R,5R)-3-((tert-butyldimethylsilyl)oxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-methoxytetrahydrofuran-2-yl)methyl)pyrrolidin3yl)phosphonate **(WV-NU-362-03):**



WV-NU-362-03

To a stirred solution of **(WV-NU-362-B)** (9 g, 0.0434 mol) in dry DCM (225 mL, 25 vol), **(WV-NU-362-02)** (15 g, 0.04086 mol) at rt. was added Na $(OAc)_3BH$ (8.9 g, 0.06173 mol) portion wise over a period of 10 min, at 0°C. Then reaction mixture was stirred to 20°C for 8 h. Progress of the reaction was monitored by TLC. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) at 0°C and extracted with DCM (2 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford light yellow semi syrup. **(WV-NU-362-03)** (14.6 g, crude), TLC Mobile phase details: 10% MeOH in DCM. ^1H NMR (500 MHz, $CDCl_3$): δ in ppm = 9.32 (s, 1H), 7.56 (dd, 1H, *J1* = 45.4 Hz, *J2* = 7.6 Hz), 5.81 (m, 1H), 5.72 (m, 1H), 4.11 (m, 6H), 3.96 (m, 1H), 3.64 (td, 1H, *J1* = 5.9 Hz, *J2* = 1.4 Hz), 3.51 (m, 3H), 3.38 (m, 1H), 3.00 (m, 2H), 2.79 (m, 2H), 2.55 (m, 3H), 2.05 (m, 2H), 1.31 (m, 7H), 0.91 (td, 11H, *J1* = 6.7 Hz, *J2* = 3.7 Hz), 0.79 (m, 6H). MS: *m/z* calcd for $C_{24}H_{44}N_3O_8PSi$, 561.7; found 362-59. $[M-H]^+$.

Preparation of diethyl (1-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)pyrrolidin-3-yl)phosphonate **(WV-NU-362):**

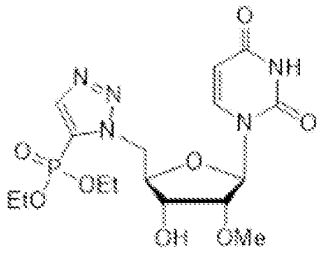


WV-NU-362

2'-OMe-5'-$PO(OEt)_2$-Pyrrolidinyl phosphonate Uridine (WV-NU-362)

To a stirred solution of **(WV-NU-362-03)** (14.6 g, 0.0260 mol) in H_2O (73 mL, 5 vol), was added formic acid (73 mL, 5 vol) at 0°C. Then the reaction mixture was allowed to stirr at rt for 24 h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under reduced pressure and the crude mass was codistilled with toluene (50 ml x3). The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 6% MeOH in DCM to afford brown solid **(WV-NU-362)** (6.6 g, 56%), TLC Mobile phase details: 10% MeOH in DCM. ^{1}H NMR (500 MHz, D_2O): δ in ppm = 7.65 (d, 1H, *J1* = 8.3 Hz), 5.87 (t, 2H, *J1* = 3.4 Hz), 4.16 (m, 6H), 4.07 (q, 1H, *J1* = 3.7 Hz), 3.49 (s, 3H), 3.32 (m, 1H), 3.06 (m, 3H), 2.76 (m, 3H), 2.18 (d, 1H, *J1* = 7.6 Hz), 2.06 (dt, 1H *J1* = 14.0 Hz, *J2* = 6.0 Hz), 1.31 (m, 6H). MS: *m/z* calcd for $C_{18}H_{30}N_3O_8P$, 447.4; found 449.7. $[M-H]^+$.

EXAMPLE 29. Synthesis of WV-NU-343

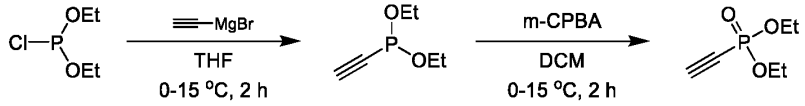


WV-NU-343

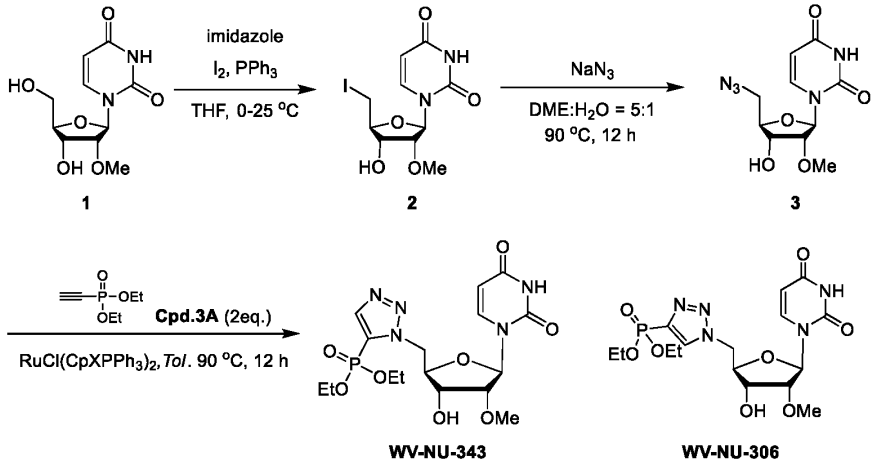
2'-OMe-5'-PO(OEt)$_2$-1,5-Triazolyl Phosphonate Uridine (**WV-NU-343**)

Diethyl (1-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-5-yl)phosphonate (WV-NU-343)

General Scheme:

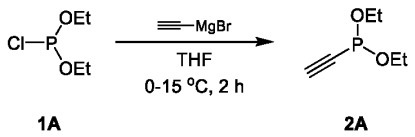


1A **2A** **3A**



Experimental Procedure:

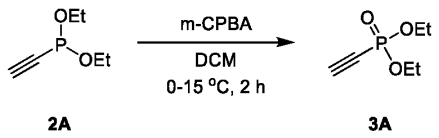
1. Preparation of compound 2A :



For three batches. To a solution of compound **1A** (11 g, 70.27 mmol) in THF (150 mL) was added bromo (ethynyl) magnesium (0.5 M, 140.53 mL) at 0 °C under N_2. The resulting mixture was stirred at 15 °C for 2 hr. TLC indicated compound **1A** was consumed completely and two new spots formed. The reaction was clean according to TLC. Three batches with together. The reaction mixture was quenched by sat. aq. NH_4Cl (150 mL) at 0 °C, then extracted with DCM (100 mL*3). The combined organic layers were dried over Na_2SO_4, filtered to get the crude. Without purification. Compound **2A** (1.87 g, crude) was obtained as a brown oil.

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.95

2. Preparation of compound 3A :



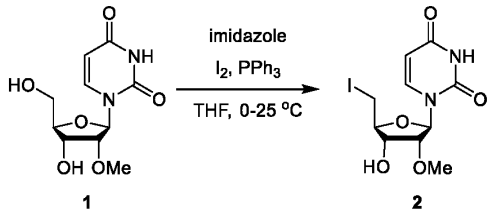
For two batches. To a solution of compound **2A** (16 g, 109.50 mmol) in DCM (400 mL) was added m-CPBA (44.46 g, 218.99 mmol) at 0 °C. The mixture was stirred at 0-15 °C for 2 hr. TLC indicated compound **2A** was consumed completely and two new spots formed. The reaction was clean according to TLC. Two batches with together. The reaction mixture was quenched by sat. aq. Na_2SO_3 (300 mL) and $NaHCO_3$ (300mL), then extracted with DCM (200 mL * 3). The combined organic layers were washed with brine (100 mL * 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **3A** (35 g, 50.72% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.17 (quin, J = 7.6 Hz, 4H), 2.92 (d, J = 13.4 Hz, 1H), 1.36 (t, J = 7.2 Hz, 6H)

^{31}P NMR (162 MHz, CHLOROFORM-d) δ = -8.41 (s, 1P), -8.41 (s, 1P)

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.4

*3. **Preparation of compound 2 :***



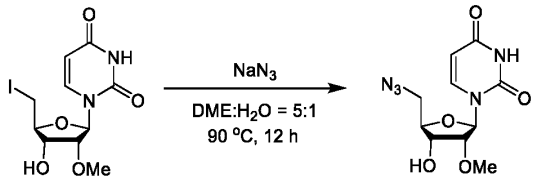
For five batches. To a solution of compound **1** (30 g, 116.18 mmol) in THF (420 mL) was added imidazole (20.56 g, 302.06 mmol), I_2 (47.18 g, 185.88 mmol) and PPh_3 (48.75 g, 185.88 mmol) at 0 °C. The mixture was stirred at 25 °C for 6 hr. TLC indicated compound **1** was consumed completely and two new spots formed. The reaction was clean according to TLC. Five batches with together. The reaction was quenched by 10% aqueous sodium thiosulfate solution (800 ml). After removing the solvent and volatiles under reduced pressure, the residue was extracted into Dichloromethane (200 mL * 3) and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1 to Dichloromethane: Methanol =1: 0 to 3: 1). The crude product was purified by re-crystallization from Ethyl acetate (100 mL), Dichloromethane (300 mL) and Methanol (50 mL) at 15 °C. Compound **2** (200 g, 93.55% yield) was obtained as a purple solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.43 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 5.87 (d, J = 5.6 Hz, 1H), 5.70-5.68 (m, 1H), 5.46 (d, J = 6.0 Hz, 1H), 4.05-4.01 (m, 1H), 4.00-3.95 (m, 1H), 3.88-3.82 (m, 1H), 3.54-3.53 (m, 1H), 3.42-3.40 (m, 1H), 3.34 (s, 3H)

LCMS (M+H+): 369.0

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.45

4. Preparation of compound 3 :



2 3

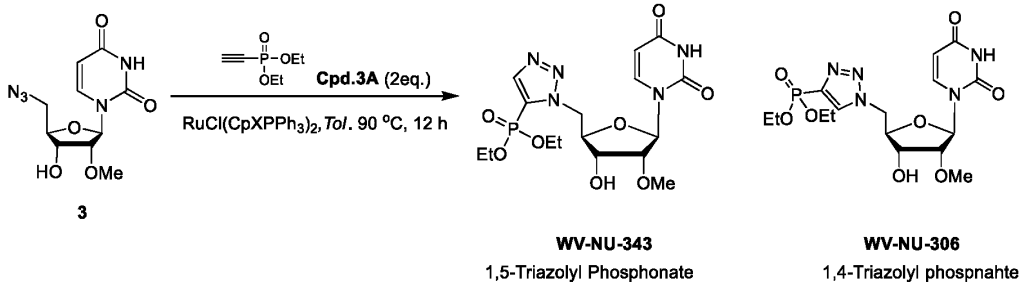
For five batches. To a solution of compound **2** (24 g, 65.20 mmol) in 1, 2-dimethoxyethane (300 mL) and H_2O (60 mL) was added NaN_3 (3.66 g, 56.30 mmol) at 0 °C under N_2. The mixture was stirred at 90 °C for 12 hr. LCMS showed compound **2** was remained and the desired mass was detected. Five batches with together. The reaction was quenched by H_2O (500 mL), and extracted with Ethyl acetate (400 mL*3). The combined organic layers were washed with saturated aqueous NaCl 300 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). The crude product was triturated with Ethyl acetate (50 mL) at 15 °C for 10 min. Compound **3** (49 g, 85.51% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.48 - 10.91 (m, 1H), 7.70 (d, J = 8.2 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.36 (br d, J = 5.8 Hz, 1H), 4.07 (q, J = 5.2 Hz, 1H), 3.95 - 3.89 (m, 2H), 3.61 (d, J = 4.8 Hz, 2H), 3.36 (s, 3H)

LCMS: (M+H+): 284.0, purity: 90.16%

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.45

5. Preparation of WV-NU-343:



For four batches. To a solution of compound **3** (10 g, 35.31 mmol) and compound **3A** (11.45 g, 70.61 mmol) in Tol. (100 mL) was added chlororuthenium; cyclopentane; triphenylphosphane (3.61 g, 4.94 mmol). The mixture was stirred at 90 °C for 12 hr. LCMS showed compound **3** was remained and the desired mass was detected. Four batches with together. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex luna c18 250mm*100mm*15um; mobile phase: [H_2O (0.02%FA)-ACN]; gradient: 5%-25% B over 25.0 min). Compound **WV-NU-343** (1.2 g, 1.91% yield) was obtained as a yellow solid. Compound **WV-NU-306** (22 g, 34.98% yield) was obtained as a pale yellow solid.

WV-NU-343:

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.42 (d, J = 1.6 Hz, 1H), 8.21 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 5.79 (d, J = 5.0 Hz, 1H), 5.66-5.64 (m, 1H), 5.49 (d, J = 6.0 Hz, 1H), 4.89 (d, J = 6.0 Hz, 2H), 4.31 - 4.22 (m, 2H), 4.13 - 4.03 (m, 4H), 4.02 - 3.97 (m, 1H), 3.37 (s, 3H), 1.23 (q, J = 7.1 Hz, 6H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 3.10 (s, 1P)

LCMS (M+H+): 446.1, purity: 97.53%

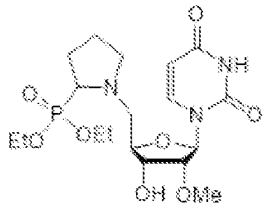
WV-NU-306:

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.41 (d, J = 1.6 Hz, 1H), 8.62 (s, 1H), 7.55 (d, J = 8.2 Hz, 1H), 5.80 (d, J = 4.8 Hz, 1H), 5.65-5.63 (m, 1H), 5.49 (d, J = 6.0 Hz, 1H), 4.87 - 4.69 (m, 2H), 4.21 (td, J = 4.6, 7.8 Hz, 1H), 4.15 (q, J = 5.6 Hz, 1H), 4.12 - 4.03 (m, 4H), 3.93 (t, J = 5.0 Hz, 1H), 3.37 (s, 3H), 1.24 (t, J = 7.0 Hz, 6H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 7.16 (s, 1P)

LCMS (M+H+): 446.1, purity: 94.23%

EXAMPLE 30. Synthesis of WV-NU-342

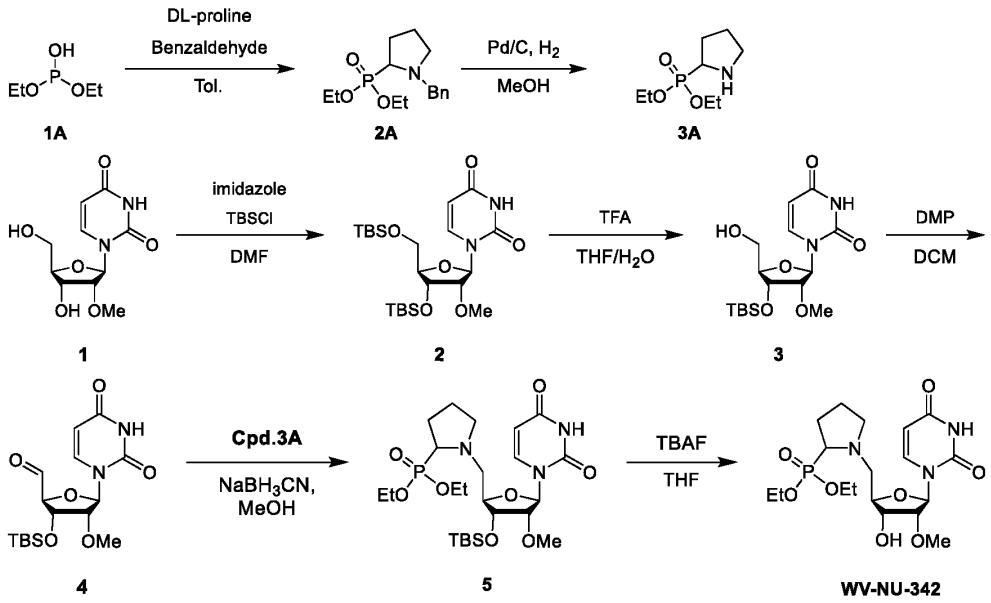


WV-NU-342

2'-OMe-5'-(2-PO(OEt)$_2$-pyrrolidinyl) phosphonate Uridine (**WV-NU-342**)

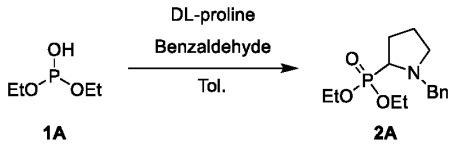
diethyl (1-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)pyrrolidin-2-yl)phosphonate (**WV-NU-342**)

General Scheme:



Experimental Procedures:

1. Preparation of compound 2A:



Compound **1A** (30 g, 217.23 mmol) was added to a stirred mixture of pyrrolidine-2-carboxylic acid (37.51 g, 325.85 mmol) in Tol. (150 mL) at 110°C. Benzaldehyde (34.58 g, 325.85 mmol) was then added to the reaction mixture in small portions over 3 h. TLC indicated compound

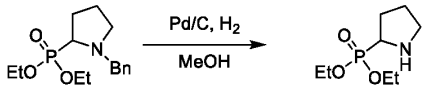
1A was consumed completely and three new spots formed. The reaction was clean according to TLC. The resultant solution was portioned to H_2O (500 mL), and extracted with EtOAc (2 X1000 mL). The organic layer was washed with brine (300 mL) and dried over Na_2SO_4. The filtrate was evaporated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100:1 to 1:1). Compound **2A** (55 g, 85.15% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 7.16-7.30 (m, 5H), 5.22 (s, 1H), 4.37 (d, J = 13.0 Hz, 1H), 4.02-4.23 (m, 4H), 3.34 (d, J = 13.0 Hz, 1H), 2.91 (dd, J = 9.8, 5.8 Hz, 1H), 2.86 (ddd, J = 9.0, 6.5, 2.8 Hz, 1H), 2.16 (td, J = 9.4, 6.7 Hz, 1H), 1.97-2.10 (m, 2H), 1.61-1.77 (m, 2H), 1.27 ppm (td, J = 7.0, 4.6 Hz, 6H)

^{31}P NMR (162 MHz, CHLOROFORM-d, 25°C): δ = 27.13 ppm (s, 1P)

TLC: Petroleum ether: Ethyl acetate = 1: 1; Rf = 0.5

2. Preparation of compound 3A:



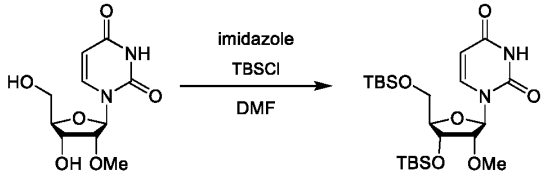
2A **3A**

For two batches: To a solution of compound **2A** (25 g, 84.08 mmol), AcOH (7.57 g, 126.12 mmol) in EtOH (250 mL) was added Pd $(OH)_2$ (2.5 g, 20% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 12 hr. TLC indicated compound **2A** was consumed completely and one new spot formed. The reaction was clean according to TLC. Filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 100:1 to 13:1). Compound **3A** (31 g, 88.97% yield) was obtained as a yellow oil.

1H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 4.04-4.16 (m, 4H), 3.33 (td, J = 8.0, 6.3 Hz, 1H), 2.96-3.05 (m, 1H), 2.85-2.96 (m, 1H), 1.97-2.06 (m, 1H), 1.77-1.94 (m, 2H), 1.66-1.76 (m, 1H), 1.27 ppm (t, J = 7.0 Hz, 6H)

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.15

3. Preparation of compound 2:



1 2

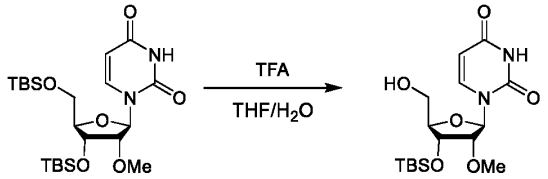
To a solution of compound **1** (50 g, 193.63 mmol) in DMF (500 mL) was added imidazole (65.91 g, 968.14 mmol) and TBSCl (116.73 g, 774.51 mmol). The mixture was stirred at 25 °C for 3hr. TLC indicated compound **1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was partitioned between Ethyl acetate (3L) and H_2O (1L). The organic phase was separated, washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100:1 to 0:1). Compound **2** (94 g, 99.74% yield) was obtained as a yellow oil.

1H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 8.63 (br s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 1.6 Hz, 1H), 5.57 (dd, J = 8.0, 2.0 Hz, 1H), 4.13 (dd, J = 7.0, 4.9 Hz, 1H), 3.91-3.97 (m, 2H), 3.63-3.70 (m, 1H), 3.50 (dd, J = 4.8, 1.7 Hz, 1H), 3.45 (s, 3H), 0.82 (d, J = 13.0 Hz, 18H), -0.04-0.03 ppm (m, 12H)

LCMS: (M+H+) = 487.4

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.48

4. Preparation of compound 3:



2 3

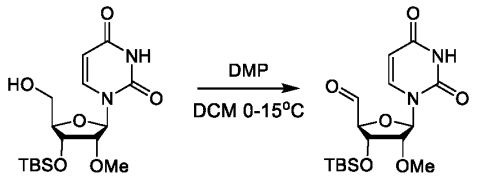
For 2 batches: To a solution of compound **2** (60 g, 123.27 mmol) in H_2O (300 mL)/TFA (300 mL) /THF (600 mL). The mixture was stirred at 0 °C for 3hr. TLC indicated compound **2** was consumed completely and one new spot formed. The reaction was clean according to TLC. 2 reactions were combined for workup. After completion of reaction, the resulting mixture was added con.NH_3*H_2O (1L) to pH = 7, and then extracted with ethyl acetate (2 L) washed with brine 500 mL dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a

residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100:1 to 0;1). Compound **3** (60 g, 65.34% yield) was obtained as a white solid.

1H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 9.38 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 5.67-5.76 (m, 2H), 4.36 (t, J = 5.4 Hz, 1H), 3.94-4.08 (m, 3H), 3.75 (br d, J = 12.2 Hz, 1H), 3.49 (s, 3H), 2.87 (br s, 1H), 0.92 (s, 9H), 0.11 ppm (d, J = 5.0 Hz, 6H)

TLC: Petroleum ether: Ethyl acetate = 1:2, Rf = 0.28

5. Preparation of compound 4:

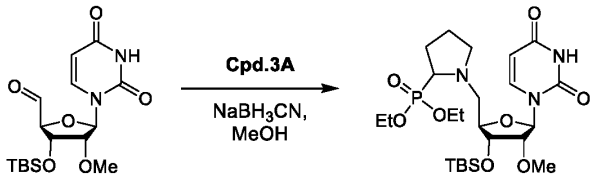


3 **4**

DMP (22.77 g, 53.69 mmol) was added to a stirred and cooled 0 °C solution of compound **3** (20 g, 53.69 mmol) in anhydrous DCM (300 mL) under argon atmosphere. The cooling bath was removed, and the mixture was stirred at 25°C for 3hr. TLC indicated compound **3** was consumed completely and one new spot formed. The reaction was clean according to TLC. The mixture was cooled to 0 °C and poured to a vigorously stirred mixture of 10% solution of sodium thiosulfate (100 mL) and saturated solution of sodium bicarbonate (100 mL). After stirring at room temperature for 45 minutes significant precipitation occurred. The precipitate was filtered off and the solids where washed with DCM (200 mL x 2). The filtrate was placed in a separator funnel, the organic phase was separated and dried over anhydrous sodium sulfate. Without further purification. Compound **4** (19 g, crude) was obtained as a white solid.

TLC: (Petroleum ether: Ethyl acetate = 0:1), Rf = 0.58

6. Preparation of compound 5:



4 **5**

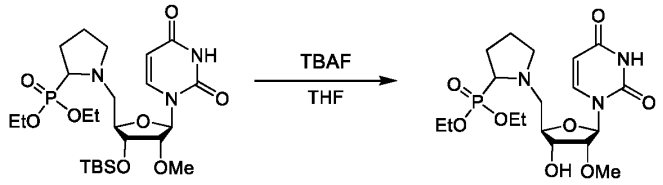
To a solution of compound **3A** (15.94 g, 76.93 mmol) compound **4** (19 g, 51.29 mmol) in

MeOH (200 mL) was added NaBH $(OAc)_3$ (43.48 g, 205.14 mmol). The mixture was stirred at 15 °C for 12 hr. TLC indicated compound **4** was consumed completely and two new spots formed. The reaction was clean according to TLC. Concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100:1 to 0;1). Compound **5** (13 g, 45.13% yield) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 28°C): δ = 11.36 (dd, J = 8.4, 1.7 Hz, 1H), 7.59-7.85 (m, 1H), 5.81 (dd, J = 17.6, 5.1 Hz, 1H), 5.57-5.72 (m, 1H), 4.31 (t, J = 4.2 Hz, 1H), 3.97-4.16 (m, 4H), 3.78-3.96 (m, 2H), 3.30-3.35 (m, 3H), 3.17-3.27 (m, 1H), 3.01-3.11 (m, 1H), 2.89 (ddd, J = 14.6, 9.8, 5.3 Hz, 1H), 2.53-2.70 (m, 1H), 2.20-2.38 (m, 1H), 1.92-2.08 (m, 1H), 1.79-1.84 (m 1H), 1.61-1.78 (m, 2H), 1.15-1.28 (m, 6H), 0.88 (d, J = 2.3 Hz, 9H), 0.09 ppm (s, 6H)

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf_1 = 0.18; Rf_2 = 0.10

7. Preparation of compound WV-NU-342:



2'-OMe-5'-(2-PO(OEt)$_2$-pyrrolidinyl) phosphonate Uridine (WV-NU-342)

To a solution of compound **5** (11.5 g, 20.47 mmol) in THF (130 mL) was added TBAF (1 M, 24.57 mL). The mixture was stirred at 25 °C for 0.5 hr. TLC indicated compound **5** was consumed completely and one new spot formed. The reaction was clean according to TLC. Concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 100/1 to 10/1). Compound **WV-NU-342** (7.5 g, 77.63% yield, 94.82% purity) was obtained as a yellow solid.

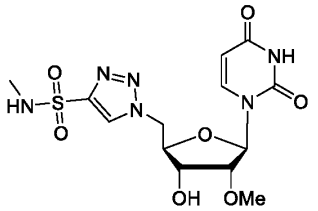
^{1}H NMR (400 MHz, DMSO-d6, 25°C): δ = 11.34 (br d, J = 3.9 Hz, 1H), 7.58-7.83 (m, 1H), 5.76-5.82 (m, 1H), 5.55-5.67 (m, 1H), 5.17 (dd, J = 10.8, 6.1 Hz, 1H), 3.94-4.08 (m, 5H), 3.85-3.92 (m, 1H), 3.74-3.82 (m, 1H), 3.34 (d, J = 10.7 Hz, 3H), 3.12-3.24 (m, 1H), 3.05 (br s, 1H), 2.90 (dd, J = 10.0, 5.1 Hz, 1H), 2.54-2.72 (m, 1H), 2.22-2.36 (m, 1H), 1.89-2.05 (m, 1H), 1.80 (ddt, J = 17.2, 8.6, 4.2 Hz, 1H), 1.61-1.74 (m, 2H), 1.15-1.26 ppm (m, 6H)

^{31}P NMR (162 MHz, DMSO-d$_6$, 26°C): δ = 26.47-26.81 ppm (m, 1P)

LCMS: (M+H+) = 448.1, purity: 94.82%

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.33

EXAMPLE 31. Synthesis of WV-NU-345

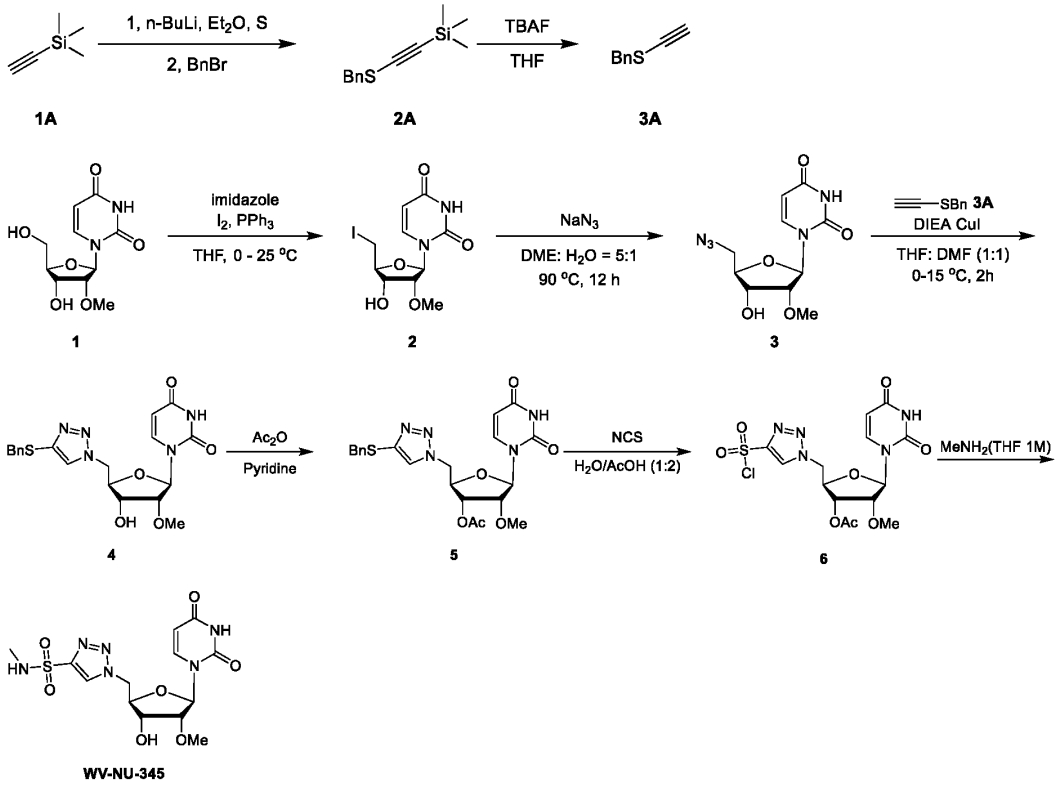


WV-NU-345

2'-OMe-5'-Sufonylamindo Triazolyl Uridine (**WV-NU-345**)

1-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)-*N*-methyl-1*H*-1,2,3-triazole-4-sulfonamide (**WV-NU-345**)

General Scheme:



Experimental Procedure:

1. Preparation of compound 2A:



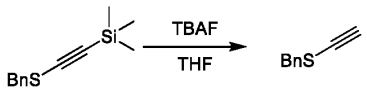
1A **2A**

For two batches: To a solution compound **1A** (20 g, 203.63 mmol) in THF (285 mL) was added n-BuLi (2.5 M, 81.45 mL) dropwise at -78 °C and the reaction was allowed to warm up to -20 °C during 2 h before it was re-cooled to -78°C. Then S (6.60 g, 205.71 mmol) was added in portions and the solution was warmed to 0°C and treated with BnBr (35.18 g, 205.66 mmol, 24.43 mL), which was stirred at 25 °C for 12 hr. TLC indicated compound **1A** was consumed completely and one new spot formed. The reaction was clean according to TLC. 2 reactions were combined for workup. The reaction was quenched with saturated aqueous NH_4Cl (1000 mL). The aqueous layer was extracted with Petroleum ether (2000 mL) and the combined organic layer was washed sequentially with water (500 mL) and brine (500 mL), dried over anhydrous Na_2SO_4. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 0 to 40:1). Compound **2A** (80 g, 89.12% yield) was obtained as a yellow oil.

1H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 7.12-7.25 (m, 5H), 3.80 (s, 2H), -0.02 (S, 9H)

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.67

2. Preparation of compound 3A:



2A **3A**

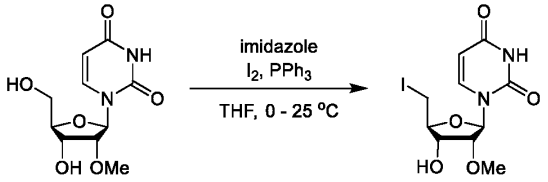
For two batches: To a solution of compound **2A** (40 g, 181.48 mmol) in THF (800 mL) was added TBAF (1 M, 217.72 mL). The mixture was stirred at 25 °C for 12 hr. TLC indicated compound **2A** was consumed completely and one new spot formed. The reaction was clean according to TLC. Two reactions were combined for workup. The reaction mixture was partitioned between H_2O (1000 mL) and Ethyl acetate (1000 mL). The organic phase was separated, washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2,

Petroleum ether: Ethyl acetate = 100:1 to 10:1). Compound **3A** (50 g, 92.94% yield) was obtained as a yellow oil.

1H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 7.21-7.31 (m, 5H), 3.89 (s, 2H), 2.74 ppm (s, 1H)

TLC: Petroleum ether: Ethyl acetate = 1:0, Rf = 0.52

3. Preparation of compound 2:



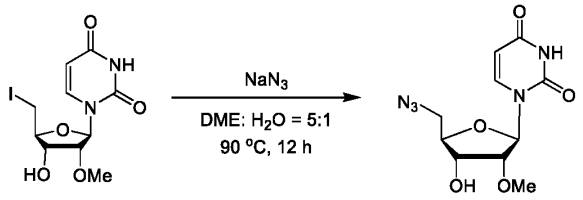
1 **2**

For two batches: To a solution of compound **1** (50 g, 193.63 mmol) in THF (700 mL) was added IMIDAZOLE (34.27 g, 503.43 mmol), I_2 (78.63 g, 309.80 mmol) and PPh_3 (81.26 g, 309.80 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr. TLC indicated compound **1** was consumed completely and one new spot formed. The reaction was clean according to TLC. Two reactions were combined for workup. The reaction was quenched by 10% aqueous sodium thiosulfate solution (500 mL). After removing the solvent and volatiles under reduced pressure, the residue was extracted into EtOAc (1000 mL*3) and washed with saturated aqueous $NaHCO_3$ solution (500 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 100:1 to 10:1). Compound **2**(140 g, 98.59% yield) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 25°C): δ = 11.42 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 5.86 (d, J = 5.4 Hz, 1H), 5.69 (d, J = 8.0 Hz, 1H), 5.45 (d, J = 6.0 Hz, 1H), 3.95-4.00 (m, 1H), 3.82-3.88 (m, 1H), 3.55 (dd, J = 10.6, 5.4 Hz, 1H), 3.40 (dd, J = 10.6, 6.9 Hz, 1H), 3.34 ppm (s, 3H)

TLC: (Dichloromethane: Methanol = 10:1), Rf = 0.48

4. Preparation of compound 3:



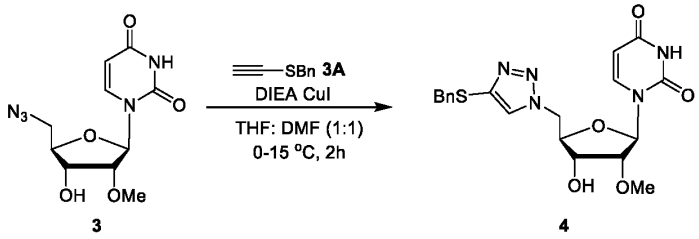
For 4 batches: To a solution of compound **2** (25 g, 67.91 mmol) in 1, 2-dimethoxyethane (500 mL) and H_2O (70 mL) was added NaN_3 (4.27 g, 65.64 mmol) at 0 °C under N_2. The mixture was stirred at 90 °C for 12hr. LCMS showed compound **2** was remained and the desired mass was detected. Four batches with together. The reaction was quenched by H_2O (1000 mL) and extracted with Ethyl acetate (1500 mL*3). The combined organic layers were washed with saturated aqueous NaCl (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol = 100:1 to 0:1). Compound **3** (65 g, 87.25% yield) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 25°C): δ = 11.40 (s, 1H), 7.63-7.77 (m, 1H), 5.83 (d, J = 4.9 Hz, 1H), 5.68 (d, J = 8.1 Hz, 1H), 5.35 (d, J = 6.3 Hz, 1H), 4.05-4.12 (m, 1H), 3.88-3.96 (m, 2H), 3.61 (d, J = 4.9 Hz, 2H), 3.36 ppm (s, 3H)

LCMS: (M+ H +) = 284

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.45

5. Preparation of compound 4:



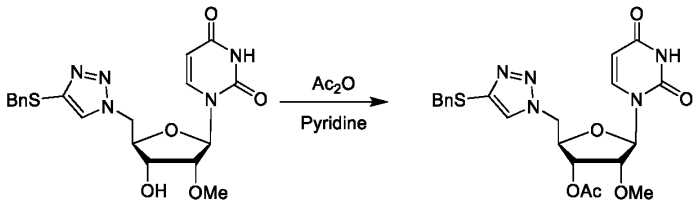
For 2 batches: To a solution of compound **3A** (15.39 g, 103.80 mmol) and compound **3** (24.5 g, 86.50 mmol) in DMF (115 mL) and THF (230 mL) was degassed and purged with N_2 for 3 times, then DIEA (22.36 g, 173.00 mmol), CuI (32.95 g, 173.00 mmol) was added. The mixture was stirred at 25 °C for 12 hr under N_2 atmosphere. LCMS showed compound **3** was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 0 to 0: 1). Compound **4** (74.64

g, crude) was obtained as a yellow solid.

LCMS: (M+H+) = 432.1

TLC: Petroleum ether: Ethyl acetate = 1:3, Rf = 0.42

6. ***Preparation of compound 5:***



4 **5**

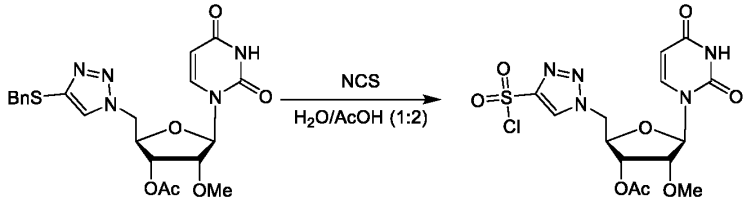
To a solution of compound **4** (74 g, 171.51 mmol) in Py (700 mL) was added Ac_2O (26.26 g, 257.26 mmol). The mixture was stirred at 15 °C for 12hr. TLC indicated compound **4** was consumed completely and one new spot formed. The reaction was clean according to TLC. Concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100:1 to 0:1). Compound **5** (50 g, 61.57% yield) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 25°C): δ = 11.44-11.61 (m, 1H), 8.04 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.13-7.32 (m, 5H), 5.81 (d, J = 5.7 Hz, 1H), 5.71 (dd, J = 8.0, 2.0 Hz, 1H), 5.23-5.31 (m, 1H), 4.65-4.79 (m, 2H), 4.34-4.44 (m, 1H), 4.28 (t, J = 5.7 Hz, 1H), 4.11 (s, 2H), 3.29 (s, 3H), 2.09 ppm (s, 3H)

LCMS: (M+H+) = 474.4

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.42

7. ***Preparation of compound 6:***



5 **6**

NCS (30.46 g, 228.09 mmol) was added to a solution of compound **5** (40 g, 84.48 mmol) in AcOH (400 mL) and Water (200 mL) and the mixture stirred at 15 °C for 1hr. TLC indicated compound **5** was consumed completely and one new spot formed. The reaction was clean according to TLC. Water (500 mL) was added and the mixture was extracted with ethyl acetate

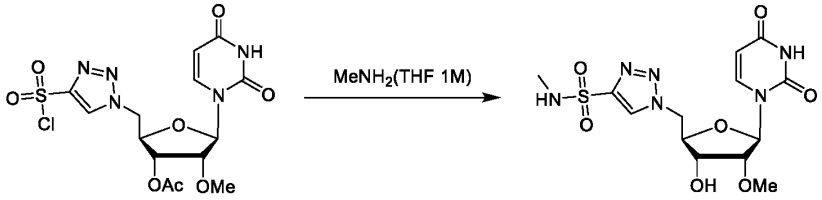
(1000 mL). The organic phase was washed sequentially with a saturated aqueous sodium hydrogen carbonate solution (3 × 300 mL) and brine (400 mL), then dried ($MgSO_4$), concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100:1 to 0:1). Compound **6** (30 g, 78.95% yield) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 27°C): δ = 11.50 (br s, 1H), 8.16 (d, J = 3.1 Hz, 1H), 7.65 (dd, J = 8.0, 4.5 Hz, 1H), 5.87 (d, J = 5.8 Hz, 1H), 5.77 (dd, J = 8.0, 2.0 Hz, 1H), 5.29-5.38 (m, 1H), 4.83 (br d, J = 6.0 Hz, 2H), 4.45-4.54 (m, 1H), 4.26 (td, J = 5.7, 2.5 Hz, 1H), 3.34 (d, J = 2.0 Hz, 3H), 2.14 ppm (d, J = 2.0 Hz, 3H)

LCMS: (M+H+) = 450.2

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.72

8. Preparation of compound WV-NU-345:



6 **WV-NU-345**

2'-OMe-5'-Sufonylamindo Triazolyl Uridine (WV-NU-345)

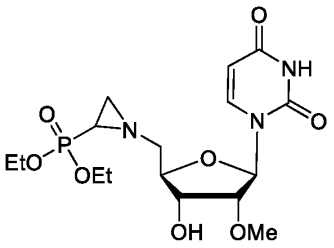
A mixture of compound **6** (10 g, 22.23 mmol) in $MeNH_2$ (2 M, THF 100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 15 °C for 12hr under N_2 atmosphere. LCMS showed compound **6** was consumed completely and one main peak with desired m/z. Concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol=100/1 to 0/1). Compound **WV-NU-345** (7 g, 16.60 mmol, 74.65% yield, 95.56% purity) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 27°C): δ = 8.69 (s, 1H), 7.66-7.91 (m, 1H), 7.58 (d, J = 8.0 Hz, 1H), 5.81 (d, J = 4.8 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.51 (br d, J = 5.8 Hz, 1H), 4.79-4.88 (m, 1H), 4.70-4.78 (m, 1H), 4.20-4.27 (m, 1H), 4.16 (q, J = 5.0 Hz, 1H), 3.95 (t, J = 5.0 Hz, 1H), 3.37-3.39 (m, 3H), 3.18 (d, J = 3.1 Hz, 1H), 2.54 ppm (s, 3H)

LCMS: (M+H+) = 403, purity: 95.56%

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.28

EXAMPLE 32. Synthesis of WV-NU-365

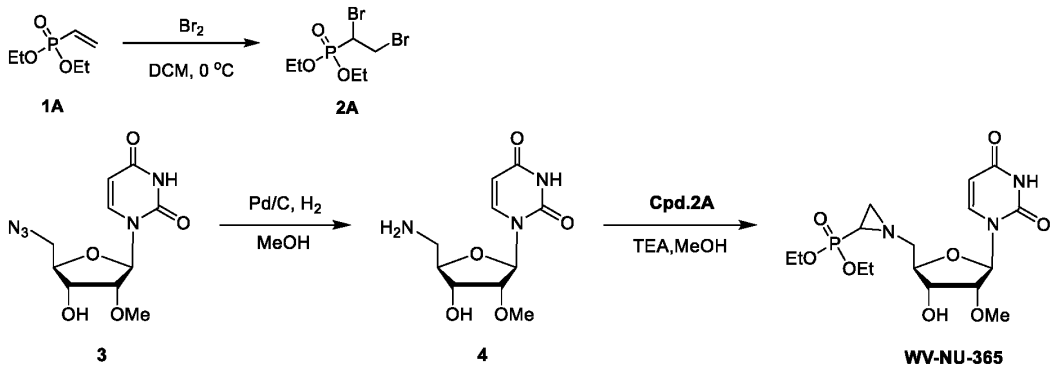


WV-NU-365

2'-OMe-5'-PO(OEt)$_2$-Aziridinyl Phosphonate Uridine (**WV-NU-365**)

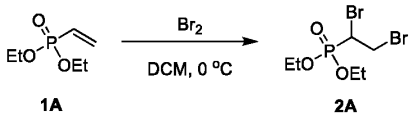
diethyl (1-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)aziridin-2-yl)phosphonate (WV-NU-365)

General Scheme:



Experimental Procedures:

1. ***Preparation of compound 2A:***

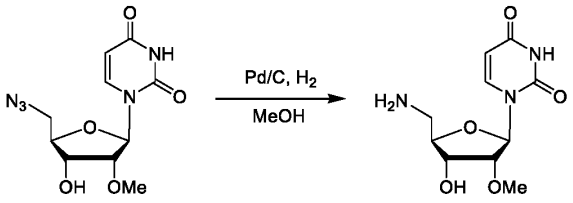


Compound **1A** (20 g, 121.85 mmol) was added into a pre-dried three necked flask and was dissolved in DCM (200 mL) and the reaction mixture cooled to 0°C, Br_2 (27.26 g, 170.59 mmol) was added to this solution, after 25 °C stirring at 0.5 hr. TLC indicated compound **1A** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100:1 to 1:1). Compound **2A** (30 g, 76.00% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 4.27 (quind, J = 7.3, 4.4 Hz, 4H), 4.00-4.11 (m, 2H), 3.60-3.72 (m, 1H), 1.39 ppm (t, J = 7.1 Hz, 6H)

TLC: Petroleum ether: Ethyl acetate = 1: 1, Rf = 0.5

2. ***Preparation of compound 4:***



3 **4**

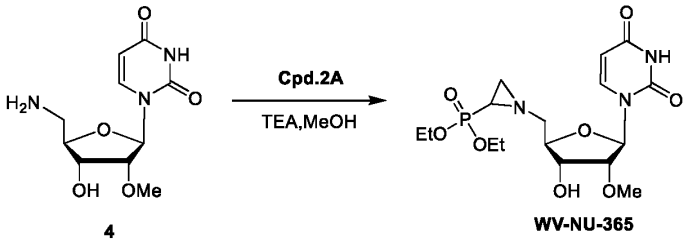
To a solution of compound **3** (15 g, 52.96 mmol) in MeOH (150 mL) was added Pd/C (1.5 g, 1.41 mmol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H2 for 3 times. The mixture was stirred under H_2 (5 Psi) at 25 °C for 12hr. TLC indicated compound **3** was consumed completely and one new spot formed. The reaction was clean according to TLC. Filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Dichloromethane: Methanol =100:1 to 20:1). Compound **4** (13 g, 95.43% yield) was obtained as a white solid.

1H NMR (400 MHz, DMSO-d6, 25°C): δ = 7.93 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 5.0 Hz, 1H), 5.61-5.69 (m, 1H), 4.09 (t, J = 4.8 Hz, 1H), 3.85 (br t, J = 5.2 Hz, 1H), 3.78 (q, J = 4.8 Hz, 1H), 3.34-3.37 (m, 3H), 2.75-2.87 ppm (m, 2H)

LCMS: (M+H+) = 258.0

TLC: Dichloromethane: Methanol = 10:1, Rf = 0.2

3. ***Preparation of compound WV-NU-365:***



4 **WV-NU-365**

2'-OMe-5'-PO(OEt)$_2$-Aziridinyl Phosphonate Uridine (WV-NU-365)

Compound **2A** (22.67 g, 69.97 mmol) was weighed into a pre-dried three necked flask and dissolved by adding MeOH (230 mL). After adding TEA (14.16 g, 139.95 mmol) at 25°C for

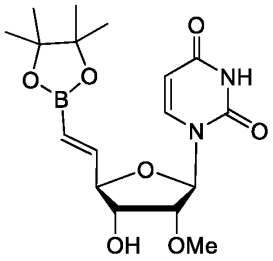
0.5 h. Then the compound **4** (12 g, 46.65 mmol) was added and the resulting mixture was refluxed at 70 °C for 12 hr. LCMS showed compound **4** was consumed completely and one main peak with desired m/z. Concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch X timate C18 250*100mm#10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 0%-30% B over 18.0 min). Compound **WV-NU-365** (14.5 g, 70.55% yield, 95.18 % purity) was obtained as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d6, 25°C): δ = 11.28-11.47 (m, 1H), 7.81-8.21 (m, 1H), 5.85 (t, J = 4.6 Hz, 1H), 5.60 (dd, J = 13.8, 8.0 Hz, 1H), 5.17-5.32 (m, 1H), 4.10-4.22 (m, 1H), 3.97-4.09 (m, 4H), 3.88-3.96 (m, 1H), 3.85 (td, J = 4.8, 1.8 Hz, 1H), 3.38 (d, J = 3.6 Hz, 3H), 2.74-2.97 (m, 1H), 2.19-2.43 (m, 1H), 1.92-2.00 (m, 1H), 1.82-1.91 (m, 1H), 1.67-1.82 (m, 1H), 1.19-1.32 ppm (m, 6H)

^{31}P NMR (162 MHz, DMSO-d_6, 25°C): δ = 22.94 ppm (d, *J* = 77.3 Hz, 1P)

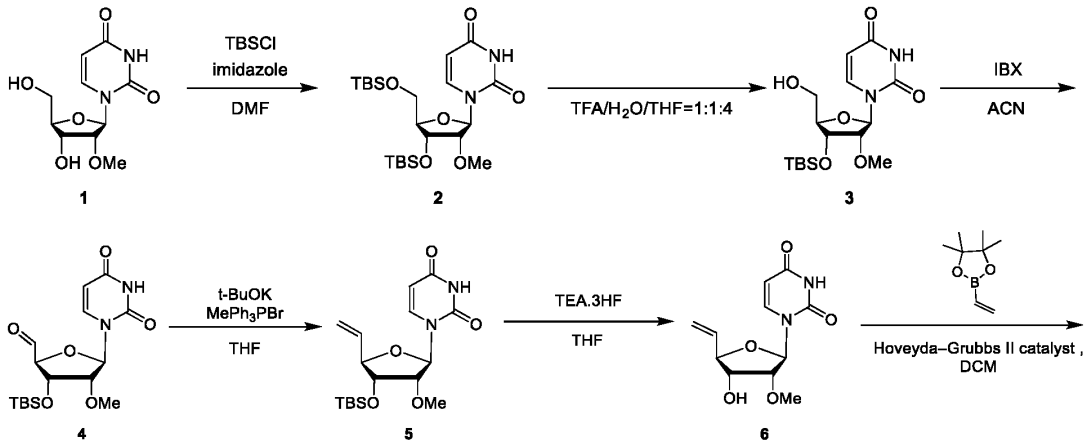
LCMS: (M+H+) = 420.1, purity: 95.18 %

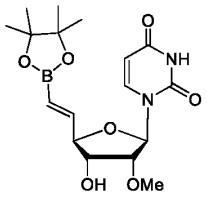
EXAMPLE 33. Synthesis of WV-NU-426



WV-NU-426

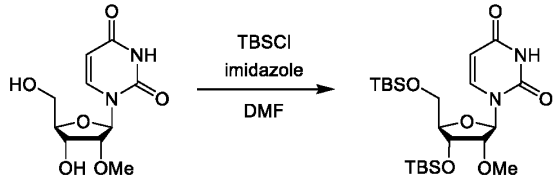
General Scheme:





WV-NU-426

1. Preparation of compound 2:

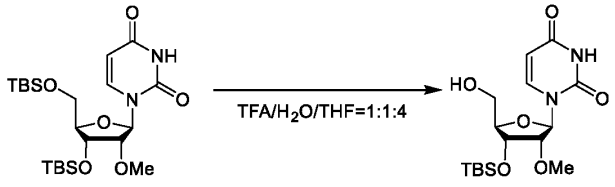


1 2

To a solution of compound **1** (50 g, 193.63 mmol) in DMF (1000 mL) was added imidazole (52.73 g, 774.51 mmol) and TBSCl (87.55 g, 580.88 mmol). The mixture was stirred at 20 °C for 12 hr. LCMS showed that compound **1** was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with H_2O 1500 mL and extracted with EtOAc 500 mL*3. The combined organic layers were washed with brine 1500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound **2** (188 g, crude) was obtained as a yellow oil.

LCMS (M+H+): 487.4, LCMS purity: 99%

2. Preparation of compound 3:



2 3

To a solution of compound **2** (94 g, 193.12 mmol) in THF (1000 mL) was added TFA (383.75 g, 3.37 mol) and H_2O (250.00 g, 13.88 mol). The mixture was stirred at 0 °C for 3 hr. TLC indicated compound **2** was consumed completely and one new spot formed. The reaction mixture was quenched with $NH_3.H_2O$ (230 mL *4) at 0 °C. The residue was diluted with H_2O 500 mL and extracted with DCM (1000 mL * 3). The combined organic layers were washed with brine 1000 mL, dried over Na_2SO_4, filtered and concentrated under

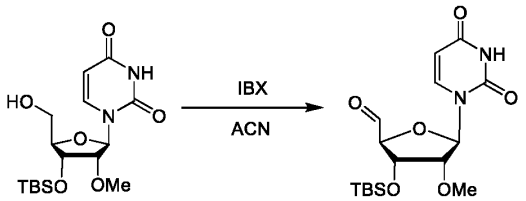
reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **3** (45 g, 62.56% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.36 (br s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 5.66 (d, J = 8.1 Hz, 1H), 5.20 (br t, J = 4.6 Hz, 1H), 4.29 (t, J = 4.6 Hz, 1H), 3.87 - 3.81 (m, 2H), 3.70 - 3.62 (m, 1H), 3.57 - 3.50 (m, 1H), 3.34 (s, 3H), 0.88 (s, 9H), 0.09 (s, 6H)

LCMS (M+H+): 373.2, LCMS purity: 97%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.6

3. Preparation of compound 4:



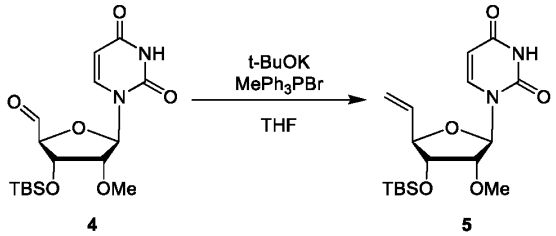
3 **4**

To a solution of compound **3** (25 g, 67.12 mmol) in ACN (300 mL) was added IBX (37.59 g, 134.23 mmol) at 0 °C. The mixture was stirred at 70 °C for 3 hr. TLC indicated compound **3** was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to get crude product. The crude product was used into the next step without further purification. Compound **4** (49 g, crude) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.44 - 11.24 (m, 2H), 7.82 - 7.78 (m, 1H), 5.85 - 5.81 (m, 1H), 5.67 - 5.61 (m, 1H), 4.36 - 4.31 (m, 1H), 3.89 - 3.85 (m, 1H), 3.77 - 3.73 (m, 1H), 3.21 - 3.17 (m, 3H), 0.82 - 0.79 (m, 9H), 0.00 - -0.02 (m, 6H)

TLC: Commercial hexanes: Ethyl acetate = 1:1, Rf = 0.18

4. Preparation of compound 5:



4 **5**

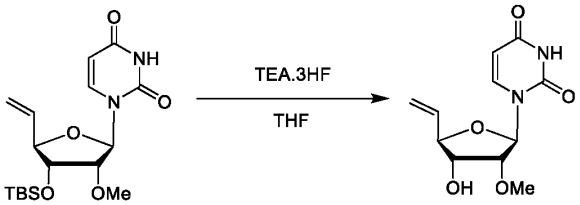
To a solution of methyl (triphenyl) phosphonium;bromide (141.74 g, 396.79 mmol) and potassium;2-methylpropan-2-olate (44.52 g, 396.79 mmol) in THF (500 mL) was added compound **4** (49 g, 132.26 mmol) in THF (500 mL). The mixture was stirred at 0 - 20 °C for 12 hr. LCMS showed compound **4** was consumed completely and desired mass was detected. The mixture was diluted with DCM (200 mL) and organic layer was washed with saturated NH_4Cl solution (200 mL). Organic layer then separated, dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated to dryness. The residue was purified by column chromatography (SiO_2, Commercial hexanes: Ethyl acetate = 1:0 to 1:1). Compound **5** (30 g, 61.55% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.40 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 5.98 (ddd, J = 7.0, 10.2, 17.2 Hz, 1H), 5.78 (d, J = 3.7 Hz, 1H), 5.66 (dd, J = 1.7, 8.0 Hz, 1H), 5.35 (d, J = 17.0 Hz, 1H), 5.27 (d, J = 10.3 Hz, 1H), 4.20 - 4.12 (m, 2H), 3.91 - 3.87 (m, 1H), 3.36 (s, 3H), 0.87 (s, 9H), 0.07 (d, J = 4.9 Hz, 6H)

LCMS (M+H+): 369.2

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.4

5. Preparation of compound 6:



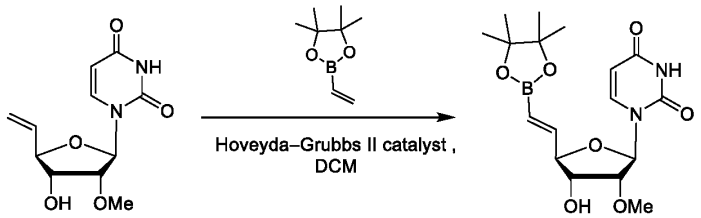
5 6

To a solution of compound **5** (8 g, 21.71 mmol) in THF (80 mL) was added N,N-diethylethanamine; trihydrofluoride (10.50 g, 65.13 mmol). The mixture was stirred at 40 °C for 6 hr. TLC indicated compound **5** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was purified by column chromatography (SiO_2, Commercial hexanes: Ethyl acetate = 1:0 to 0:1). Compound **6** (5 g, 90.59% yield) was obtained as a white solid.

LCMS (M+H+): 255.1, LCMS purity: 94%

TLC: Commercial hexanes: Ethyl acetate = 0:1, Rf = 0.2

6. Preparation of compound WV-NU-426:



6 WV-NU-426

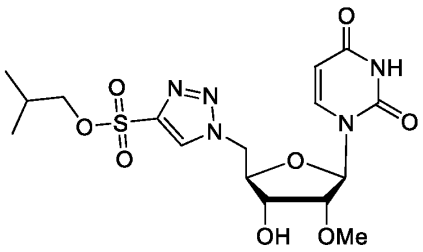
To a solution of compound **6** (5 g, 19.67 mmol,) and [1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene]-dichloro-[(2-isopropoxyphenyl)methylene]ruthenium (2.46 g, 3.93 mmol) in DCM (200 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (6.06 g, 39.33 mmol) under N_2. The mixture was stirred at 39 °C for 12 hr. LCMS showed 16% of Reactant 1 remained. Several new peaks were shown on LCMS and 17% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by column chromatography (SiO2, Commercial hexanes: Ethyl acetate = 1:0 to 0:1). The crude product was purified by normal-phase HPLC column: Welch Ultimate XB-CN 250*50*10um; mobile phase: [Heptane-DCM: CAN = 2:1]; gradient: 0%-46% B over 20.0 min. **WV-NU-426** (0.7 g, 58.33% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.37 (br s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 6.58 (dd, J = 6.3, 18.0 Hz, 1H), 5.81 (d, J = 4.0 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.61 (dd, J = 1.1, 18.0 Hz, 1H), 5.36 (d, J = 6.8 Hz, 1H), 4.23 (dt, J = 1.0, 6.2 Hz, 1H), 4.01 (q, J = 6.3 Hz, 1H), 3.89 - 3.83 (m, 1H), 3.38 (s, 3H), 1.21 (s, 12H)

LCMS (M+H+): 381.1, LCMS purity: 90%

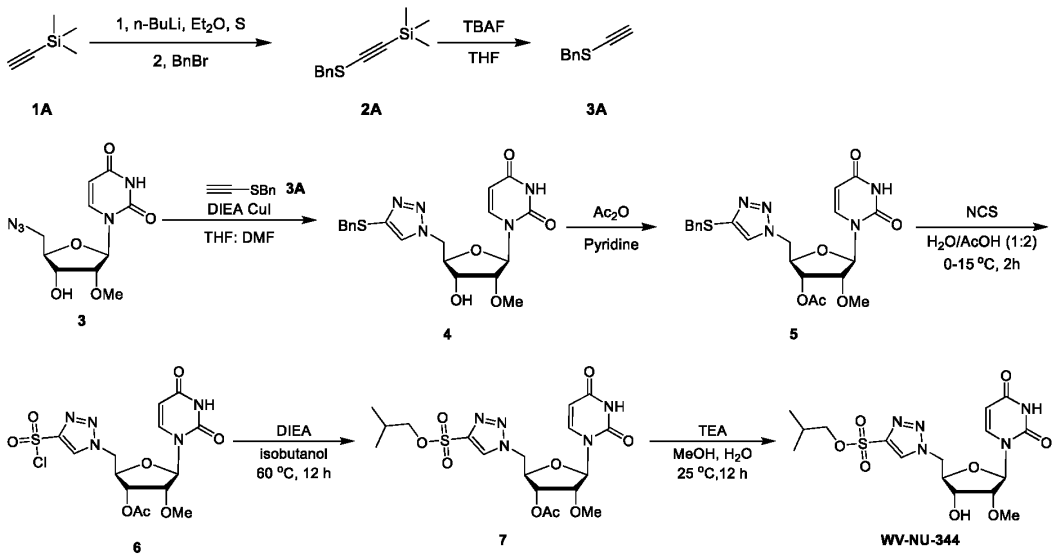
TLC: Commercial hexanes: Ethyl acetate = 0:1, Rf = 0.3

EXAMPLE 34. Synthesis of WV-NU-344



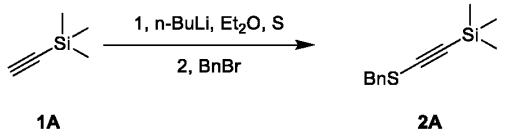
WV-NU-344

General Scheme:



Experimental Procedure:

1. Preparation of compound 2A:

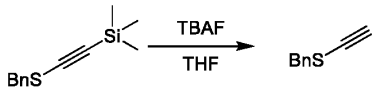


To a solution compound **1A** (20 g, 203.63 mmol) in THF (285 mL) was added n-BuLi (2.5 M, 81.45 mL) dropwise at -78 °C and the reaction was allowed to warm up to -20 °C during 2 h before it was re-cooled to -78 °C. Then S (6.60 g, 205.71 mmol) was added in portions and the solution was warmed to 0 °C and treated with BnBr (35.18 g, 205.66 mmol, 24.43 mL), which was stirred at 25 °C for 12 h. TLC indicated compound **1A** was consumed completely and one new spot formed. The reaction was clean according to TLC. Two reactions were combined for workup. The reaction was quenched with saturated aqueous NH_4Cl (1000 mL). The aqueous layer was extracted with Petroleum ether (2000 mL) and the combined organic layer was washed sequentially with water (500 mL) and brine (500 mL), dried over anhydrous Na_2SO_4. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 0 to 40: 1). Compound **2A** (40 g, 89.12% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d, 25°C): δ = 7.12-7.25 (m, 5H), 3.80 (s, 2H), -0.02 (S, 9H)

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.67

2. Preparation of compound 3A:



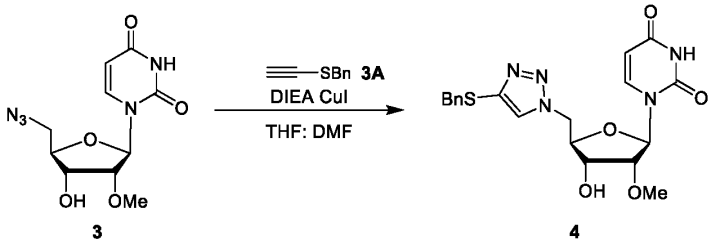
2A **3A**

To a solution of compound **2A** (40 g, 181.48 mmol) in THF (800 mL) was added TBAF (1 M, 217.72 mL). The mixture was stirred at 25 °C for 12 h. TLC indicated compound **2A** was consumed completely and one new spot formed. The reaction was clean according to TLC. Two reactions were combined for workup. The reaction mixture was partitioned between H_2O (1000 mL) and Ethyl acetate (1000 mL). The organic phase was separated, washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 1 to 10: 1). Compound **3A** (25 g, 92.94% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d, 25°C) δ = 7.21-7.31 (m, 5H), 3.89 (s, 2H), 2.74 ppm (s, 1H)

TLC: Petroleum ether: Ethyl acetate = 1: 0, Rf = 0.52

3. Preparation of compound 4:



3 **4**

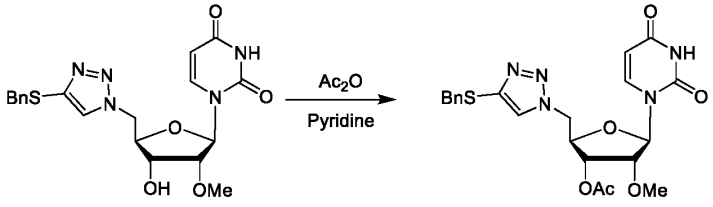
To a solution of compound **3A** (15.39 g, 103.80 mmol) and compound **3** (24.5 g, 86.50 mmol) in DMF (115 mL) and THF (230 mL) was degassed and purged with N_2 for 3 times, then DIEA (22.36 g, 173.00 mmol), CuI (32.95 g, 173.00 mmol) was added. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. LCMS showed compound **3** was consumed completely and the desired mass was detected. The reaction mixture was

concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 0 to 0: 1). Compound **4** (37.64 g, crude) was obtained as a yellow solid.

LCMS: ($M+H^+$) = 432.1

TLC: Petroleum ether: Ethyl acetate = 1: 3, Rf = 0.42

4. Preparation of compound 5:



4 **5**

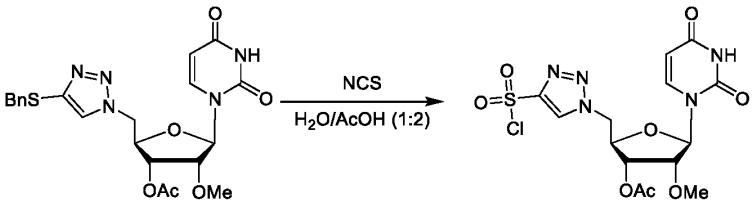
To a solution of compound **4** (74 g, 171.51 mmol) in Py (700 mL) was added Ac_2O (26.26 g, 257.26 mmol). The mixture was stirred at 15 °C for 12 h. TLC indicated compound **4** was consumed completely and one new spot formed. The reaction was clean according to TLC. Concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 1 to 0: 1). Compound **5** (50 g, 61.57% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6, 25°C) δ = 11.44-11.61 (m, 1H), 8.04 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.13-7.32 (m, 5H), 5.81 (d, J = 5.7 Hz, 1H), 5.71 (dd, J = 8.0, 2.0 Hz, 1H), 5.23-5.31 (m, 1H), 4.65-4.79 (m, 2H), 4.34-4.44 (m, 1H), 4.28 (t, J = 5.7 Hz, 1H), 4.11 (s, 2H), 3.29 (s, 3H), 2.09 ppm (s, 3H)

LCMS: ($M+H^+$) = 474.4

TLC: Petroleum ether: Ethyl acetate = 1: 1, Rf = 0.42

5. Preparation of compound 6:



5 **6**

NCS (30.46 g, 228.09 mmol) was added to a solution of compound **5** (40 g, 84.48 mmol) in

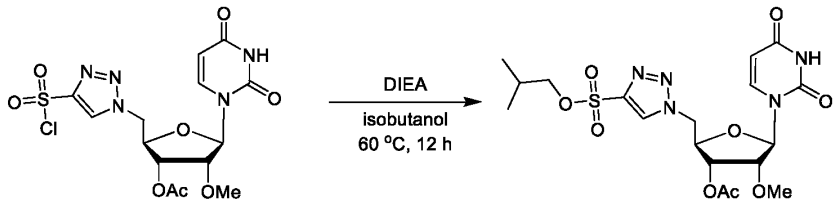
AcOH (400 mL) and Water (200 mL) and the mixture stirred at 15 °C for 1 h. TLC indicated compound **5** was consumed completely and one new spot formed. The reaction was clean according to TLC. Water (500 mL) was added and the mixture was extracted with ethyl acetate (1000 mL). The organic phase was washed sequentially with a saturated aqueous sodium hydrogen carbonate solution (300 mL * 3) and brine (400 mL), then dried ($MgSO_4$), concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 1 to 0: 1). Compound **6** (30 g, 78.95% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6, 27°C) δ = 11.50 (br s, 1H), 8.16 (d, J = 3.1 Hz, 1H), 7.65 (dd, J = 8.0, 4.5 Hz, 1H), 5.87 (d, J = 5.8 Hz, 1H), 5.77 (dd, J = 8.0, 2.0 Hz, 1H), 5.29-5.38 (m, 1H), 4.83 (br d, J = 6.0 Hz, 2H), 4.45-4.54 (m, 1H), 4.26 (td, J = 5.7, 2.5 Hz, 1H), 3.34 (d, J = 2.0 Hz, 3H), 2.14 ppm (d, J = 2.0 Hz, 3H)

LCMS: ($M+H^+$) = 450.2

TLC: (Petroleum ether: Ethyl acetate = 0: 1), Rf = 0.72

6.Preparation of compound 7:



6 **7**

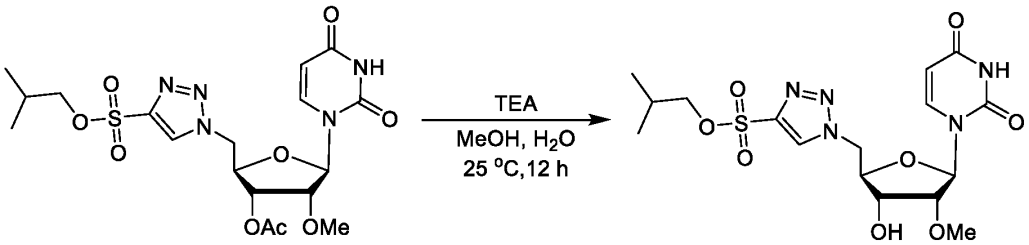
To a solution of compound **6** (17 g, 37.79 mmol) in isobutanol (70 mL) was added DIEA (9.77 g, 75.59 mmol, 13.17 mL) .The mixture was stirred at 60 °C for 12 h. LCMS showed compound **6** was consumed completely and desired mass was detected. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **7** (3 g, 16.28% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.48 (s, 1H), 9.04 (s, 1H), 7.80 - 7.71 (m, 1H), 5.80 (d, J = 5.8 Hz, 1H), 5.70 (dd, J = 1.8, 8.0 Hz, 1H), 5.28 (t, J = 4.9 Hz, 1H), 4.95 - 4.80 (m, 2H), 4.53 - 4.46 (m, 1H), 4.42 - 4.30 (m, 1H), 3.98 (d, J = 6.4 Hz, 2H), 3.28 (s, 3H), 2.08 (s, 3H), 1.88 (quind, J = 6.5, 13.1 Hz, 1H), 0.87 - 0.79 (m, 6H)

LCMS: ($M+H^+$) = 488.1

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.31

7.Preparation of compound WV-NU-344:



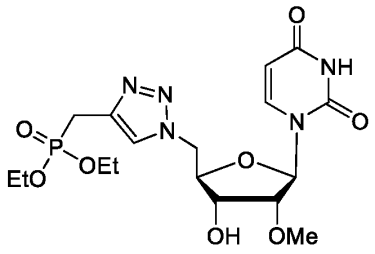
7 **WV-NU-344**

To a solution of compound **7** (3 g, 6.15 mmol) in MeOH (4 mL) H_2O (1 mL) was added TEA (9 mL). The mixture was stirred at 25 °C for 12 h. LCMS showed compound **7** was consumed completely and desired mass was detected. The mixture was concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250 * 50mm * 10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 10% - 50% B over 10.0 min). Compound **WV-NU-344** (0.37 g, 12.17% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.40 (s, 1H), 9.00 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 5.80 (d, J = 4.9 Hz, 1H), 5.70 - 5.61 (m, 1H), 5.50 (d, J = 6.1 Hz, 1H), 4.90 - 4.74 (m, 2H), 4.27 - 4.14 (m, 2H), 4.01 - 3.95 (m, 3H), 3.38 (s, 3H), 1.90 (quind, J = 6.6, 13.2 Hz, 1H), 0.84 (d, J = 6.6 Hz, 6H)

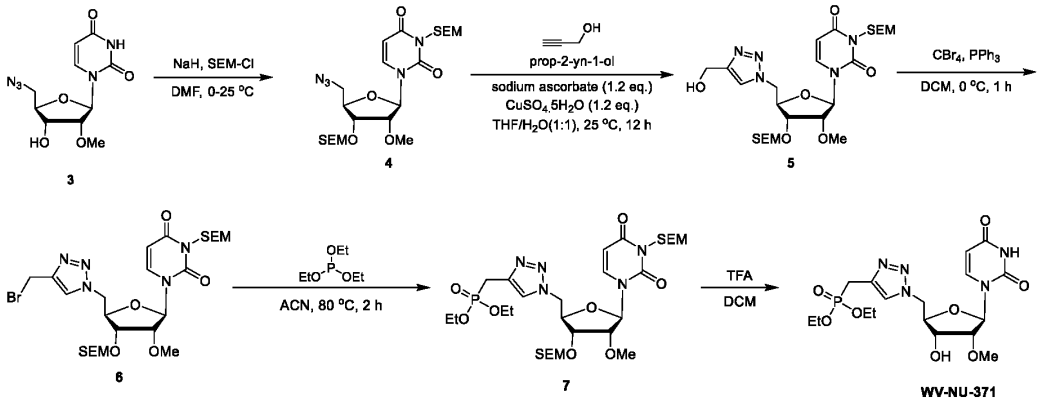
LCMS: ($M+H^+$) = 446.1, purity: 90.17%

EXAMPLE 35. Synthesis of WV-NU-371

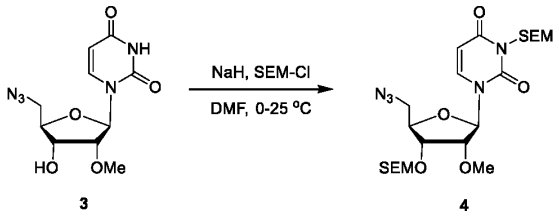


WV-NU-371

General Scheme:



1.Preparation of compound 4:

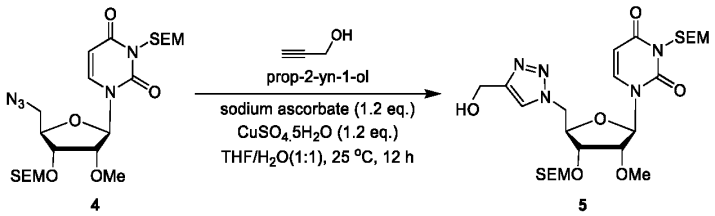


To a solution of compound **3** (20 g, 70.61 mmol) in DMF (200 mL) was added dropwise SEM-Cl (35.32 g, 211.83 mmol, 37.49 mL) at 0 °C for 1 h. Then NaH (7.06 g, 176.53 mmol, 60% purity) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 10 h. TLC indicated compound **3** was consumed completely and new spot formed. The reaction mixture was quenched by aq. NH_4Cl (50 ml) at 0 °C and then the mixture was extracted with EtOAc (50 mL * 3), the combined organic layers were washed with aq. NaCl 50 mL * 3, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 1: 1). Compound **4** (30 g, 78.13% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 7.83 (d, J = 8.1 Hz, 1H), 5.91 - 5.86 (m, 2H), 5.25 (s, 2H), 4.78 - 4.72 (m, 2H), 4.21 - 4.10 (m, 3H), 3.72 - 3.60 (m, 6H), 3.43 - 3.40 (m, 3H), 0.96 - 0.85 (m, 4H), 0.06 - 0.04 (m, 9H), 0.01 - -0.01 (m, 9H)

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.86

2. Preparation of compound 5:



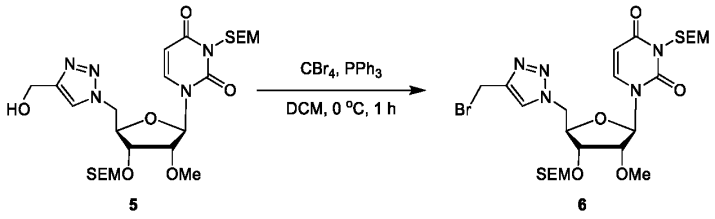
To a solution of compound **4** (30 g, 55.17 mmol) prop-2-yn-1-ol (6.45 g, 115.05 mmol, 6.80 mL) in t-BuOH (150 mL) and H_2O (150 mL) was added $CuSO_4.5H_2O$ (13.78 g, 55.17 mmol) and sodium ascorbate (10.93 g, 55.17 mmol). The mixture was stirred at 25 °C for 12 h. TLC indicated compound **4** was consumed completely and new spot formed. The reaction mixture was extracted with EtOAc (200 mL * 3) and H_2O 200 mL, then the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **5** (18 g, 54.39% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.02 (br s, 1H), 7.73 - 7.68 (m, 1H), 7.68 - 7.63 (m, 1H), 7.49 (br d, J = 7.4 Hz, 1H), 5.91 - 5.70 (m, 2H), 5.19 (br s, 3H), 4.71 (br s, 3H), 4.52 (br s, 2H), 4.32 (br s, 1H), 4.24 - 4.11 (m, 3H), 3.69 - 3.53 (m, 4H), 3.36 (s, 3H), 1.71 - 1.56 (m, 2H), 1.37 (qd, J = 7.4, 14.8 Hz, 2H), 0.90 (s, 4H), 0.86 - 0.81 (m, 2H), -0.02 (d, J = 18.8 Hz, 18H)

LCMS: ($M+H^+$): 328.2

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.17

3. Preparation of compound 6:



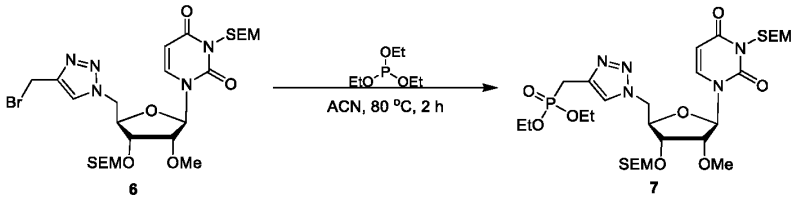
To a solution of compound **5** (18 g, 30.01 mmol) in DCM (400 mL) was added CBr_4 (11.94 g, 36.01 mmol) and PPh_3 (11.81 g, 45.01 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. LCMS showed compound **5** was consumed completely and desired mass was detected. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 3: 0 to 0: 1). Compound **6** (12 g, 60.34% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 7.73 - 7.70 (m, 1H), 7.68 - 7.65 (m, 1H), 7.59 (s, 1H), 5.86 - 5.77 (m, 2H), 5.19 (s, 1H), 4.83 - 4.67 (m, 4H), 4.22 (t, J = 6.5 Hz, 3H), 3.57 (br t, J = 7.9 Hz, 3H), 3.36 (br s, 4H), 1.68 - 1.60 (m, 2H), 1.41 - 1.33 (m, 2H), 0.85 - 0.81 (m, 2H), 0.00 (d, J = 1.5 Hz, 9H), -0.05 (s, 9H)

LCMS: ($M+H^+$): 662.2

TLC: Petroleum ether: Ethyl acetate = 0: 1, Rf = 0.75

4. Preparation of compound 7:



6 7

To a solution of compound **6** (12 g, 18.11 mmol) in ACN (120 mL) was added triethyl phosphite (15.82 g, 95.21 mmol, 16.33 mL). The mixture was stirred at 80°C for 2 h. LCMS showed compound **6** was consumed completely and desired mass was detected. The mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1). Compound **7** (6 g, 46.03% yield) was obtained as a yellow oil.

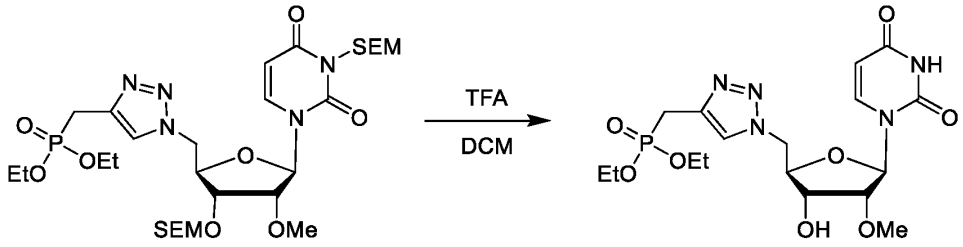
^{1}H NMR (400 MHz, DMSO-d6) δ = 7.92 (d, J = 2.3 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 5.87 - 5.78 (m, 2H), 5.18 (s, 2H), 4.78 - 4.67 (m, 4H), 4.35 - 4.26 (m, 1H), 4.16 (t, J = 5.5 Hz, 1H), 4.00 - 3.93 (m, 4H), 3.68 - 3.54 (m, 4H), 3.36 (s, 4H), 3.32 (s, 1H), 3.28 (s, 1H), 1.19 - 1.15 (m, 6H), 0.90 - 0.88 (m, 2H), 0.86 - 0.80 (m, 2H), 0.00 (s, 9H), -0.03 - -0.07 (m, 9H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 25.03 (s, 1P)

LCMS: ($M+H^+$): 720.4

TLC: Petroleum ether: Ethyl acetate = 1: 1, Rf = 0.16

5. Preparation of compound WV-NU-371:



7 WV-NU-371

To a solution of compound **7** (6 g, 8.33 mmol) in DCM (60 mL) was added TFA (9.50 g, 83.34 mmol, 6.19 mL). The mixture was stirred at 25 °C for 2 h. LCMS showed compound **7** was consumed completely and desired mass was detected. The mixture was concentrated. The residue was purified by column chromatography (SiO2, Petroleum ether : Ethyl acetate = 1: 0 to 1: 1). Compound **WV-NU-371** (2.9 g, 71.93% yield, 94.96% purity) was obtained as a yellow oil.

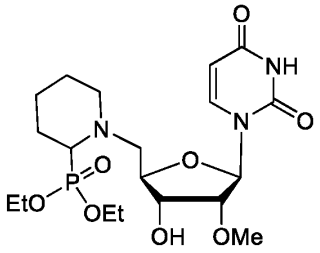
1H NMR (400 MHz, DMSO-d6) δ = 11.46 - 11.38 (m, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 5.80 (d, J = 5.3 Hz, 1H), 5.68 - 5.65 (m, 1H), 5.50 (d, J = 5.8 Hz, 1H), 4.78 - 4.60 (m, 2H), 4.16 - 4.09 (m, 2H), 4.03 - 3.92 (m, 4H), 3.82 (t, J = 5.0 Hz, 1H), 3.34 (s, 3H), 3.33 - 3.27 (m, 2H), 1.19 - 1.15 (m, 6H)

^{31}P NMR (162 MHz, DMSO-d6) δ = 25.08 (s, 1P)

LCMS: (M+H+): 460.1, purity: 94.97%

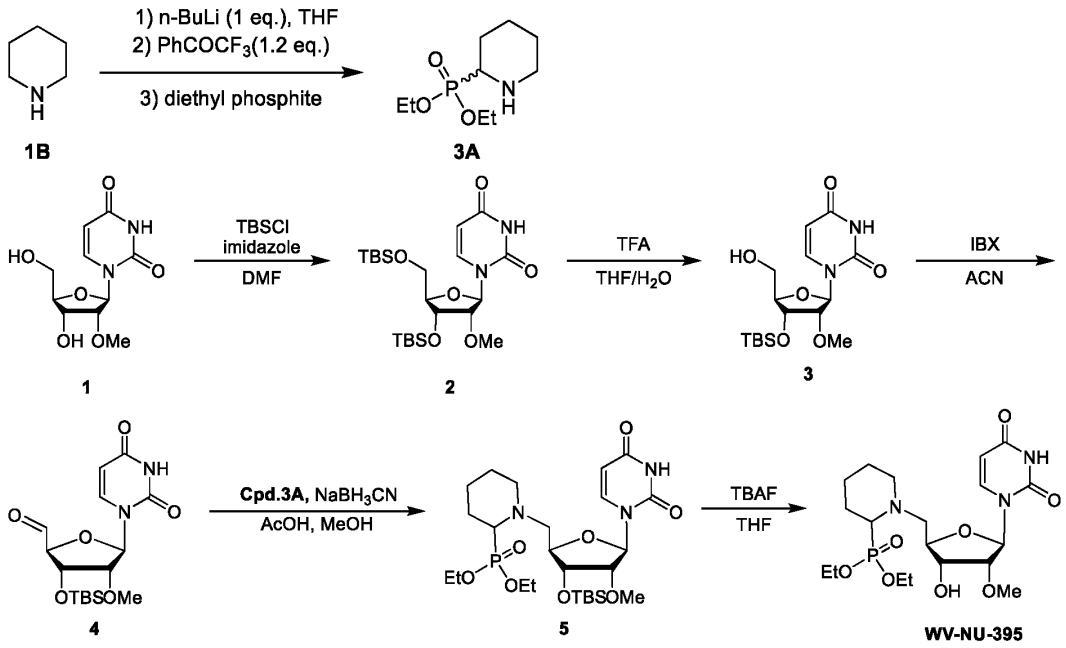
TLC: Dichloromethane: Methanol = 10: 1, Rf = 0.26

EXAMPLE 36. Synthesis of WV-NU-395



WV-NU-395

General Scheme:



1.Preparation of compound 3A:

To a solution of compound **1B** (30 g, 352.33 mmol) in THF (500 mL) was added dropwise n-BuLi (2.5 M, 140.93 mL) at -78 °C under N_2. After addition, the mixture was stirred at this temperature for 10 min, and then 2,2,2-trifluoro-1-phenyl-ethanone (73.62 g, 422.80 mmol) was added dropwise at -78 °C, the mixture was stirred at this temperature for 10 min, 1-ethoxyphosphonoyloxyethane (72.99 g, 528.50 mmol) was added dropwise at -78 °C. The resulting mixture was stirred at 25°C for 12h. TLC indicated no of compound **1B** was remained, and one major new spot with larger polarity was detected. The each reaction mixture was added dropwise NH_4Cl 250 mL at 0 °C, and then diluted with water 1500 mL and extracted with EtOAc (400 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~10% Dichloromethane: Methanol @ 150 mL/min).(Plate 1, Dichloromethane : Methanol = 10: 1, Rf = 0.23). Compound **3A** (7.3 g, 9.34% yield, 95% purity) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.12 - 4.05 (m, 5H), 3.13 - 2.99 (m, 1H), 2.93 (br s, 1H), 2.59 - 2.45 (m, 1H), 1.96 - 1.96 (m, 1H), 1.98 (s, 1H), 2.01 - 1.94 (m, 1H), 1.87 - 1.70 (m, 4H), 1.58 - 1.37 (m, 3H), 1.29 - 1.25 (m, 6H)

TLC: Dichloromethane : Methanol = 10: 1, Rf = 0.23

2.Preparation of compound 2:

To a solution of compound **1** (100 g, 387.26 mmol) in DMF (1000 mL) was added IMIDAZOLE (131.82 g, 1.94 mol) then added TBSCl (233.47 g, 1.55 mol) the reaction mixture was stirred at 25 °C for 2h. LCMS showed that compound **2** was consumed completely and the desired mass was detected. The reaction mixture was partitioned between Ethyl acetate (3L) and H_2O (1L). The organic phase was separated, washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound **2** (188 g, crude) was obtained as a white solid.

LCMS(M+H+): 487.2

3.Preparation of compound 3:

To a solution of compound **2** (188 g, 386.24 mmol) in THF (1200 mL) was added H_2O (399 mL) and TFA (399 mL), the mixture was stirred at 0 °C for 4 h. TLC showed the product was detected. The reaction mixture was added $NaHCO_3$ 1L then extracted with EtOAc 3000 mL (1000mL * 3), the combined organic layers were washed with H_2O 3000 mL (1000 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether: Ethyl acetate = 10: 1 to 0:1). Compound **3** (79 g, 54.91% yield) was obtained as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.56 (br s, 1H), 7.74 (d, J = 8.1 Hz, 1H), 5.79 - 5.68 (m, 2H), 4.35 (t, J = 5.3 Hz, 1H), 4.09 - 4.03 (m, 1H), 4.02 - 3.92 (m, 2H), 3.75 (dd, J = 2.0, 12.3 Hz, 1H), 3.49 (s, 3H), 0.91 (s, 9H), 0.11 (d, J = 5.0 Hz, 6H)

TLC: Petroleum ether : Ethyl acetate = 1:1, Rf = 0.38

4.Preparation of compound 4:

A mixture of compound **3** (12.5 g, 33.56 mmol), IBX (18.79 g, 67.12 mmol) in ACN (100 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 50 °C for 6 h under N_2 atmosphere. LCMS showed compound **3** was consumed completely desired mass was detected. The mixture was filtered to remove the insoluble. The filter liquor was concentrated in vacuum. Compound **4** (13 g, crude) was obtained as a yellow solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.70 - 9.62 (m, 1H), 7.96 - 7.88 (m, 1H), 7.57 (br d, J = 8.1 Hz, 1H), 5.71 - 5.62 (m, 2H), 4.45 - 4.39 (m, 1H), 4.32 - 4.26 (m, 1H), 3.86 - 3.79 (m, 1H), 3.78 - 3.74 (m, 1H), 3.35 - 3.30 (m, 3H), 0.82 - 0.79 (m, 10H), 0.03 - -0.01 (m,

6H)

LCMS(M+H+): 371.2

5. Preparation of compound 5:

To a solution of compound **4** (10 g, 45.20 mmol) in MeOH (400 mL) was added dropwise AcOH (2.71 g, 45.20 mmol) and **Cpd.3A** (16.75 g, 45.20) at 20 °C, then $NaBH_3CN$ (4.26 g, 67.80 mmol) was added at 20 °C. The resulting mixture was stirred at 20 °C for 2 hr. LCMS showed compound **4** was consumed completely desired mass was detected. The reaction mixture was added dropwise H_2O 200 mL at 0 °C, and then diluted with water 200 mL and extracted with EtOAc (200 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 50-100% Ethyl acetate: Petroleum ether gradient @ 150 mL/min) (Petroleum ether: Ethyl acetate = 0:1, Rf = 0.2). Compound **5** (5.5 g, 20.75% yield, 90% purity) was obtained as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.53 - 11.28 (m, 1H), 7.79 - 7.58 (m, 1H), 5.82 - 5.76 (m, 1H), 5.70 - 5.64 (m, 1H), 4.24 - 4.14 (m, 1H), 4.06 - 3.98 (m, 6H), 3.93 - 3.87 (m, 1H), 3.86 - 3.79 (m, 1H), 3.31 - 3.29 (m, 1H), 3.34 - 3.29 (m, 4H), 3.17 - 2.98 (m, 2H), 2.95 - 2.91 (m, 1H), 1.87 - 1.59 (m, 3H), 1.57 - 1.36 (m, 3H), 1.33 - 1.19 (m, 7H), 0.88 (d, J = 1.5 Hz, 9H), 0.11 - 0.07 (m, 6H), -1.56 - -1.83 (m, 1H)

LCMS (M+H+): 576.4

6. Preparation of WV-NU-395:

A mixture of compound **5** (10 g, 17.37 mmol), TBAF (1 M, 34.74 mL), and in THF (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 2h under N_2 atmosphere. LCMS showed compound **5** was consumed completely desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; WePure Biotech XP tC18 150*40*7um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient:15%-55% B over 8.0 min). **WV-NU-395** (2.7 g, 32% yield, 95% purity) was obtained as a yellow solid.

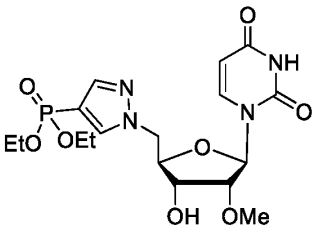
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.45 - 11.31 (m, 1H), 7.88 - 7.59 (m, 1H), 5.88 - 5.72 (m, 1H), 5.69 - 5.60 (m, 1H), 5.20 - 5.12 (m, 1H), 4.06 - 3.97 (m, 5H), 3.87 - 3.77 (m, 2H), 3.39 - 3.35 (m, 3H), 3.13 - 2.89 (m, 3H), 3.00 - 2.87 (m, 1H), 1.84 - 1.63 (m, 3H), 1.63 - 1.46

(m, 3H), 1.27 - 1.19 (m, 7H)

^{31}P NMR (400 MHz, DMSO-d6) δ = 27.24 - 27.18 (m, 1P), 27.13 - 27.05 (m, 1P)

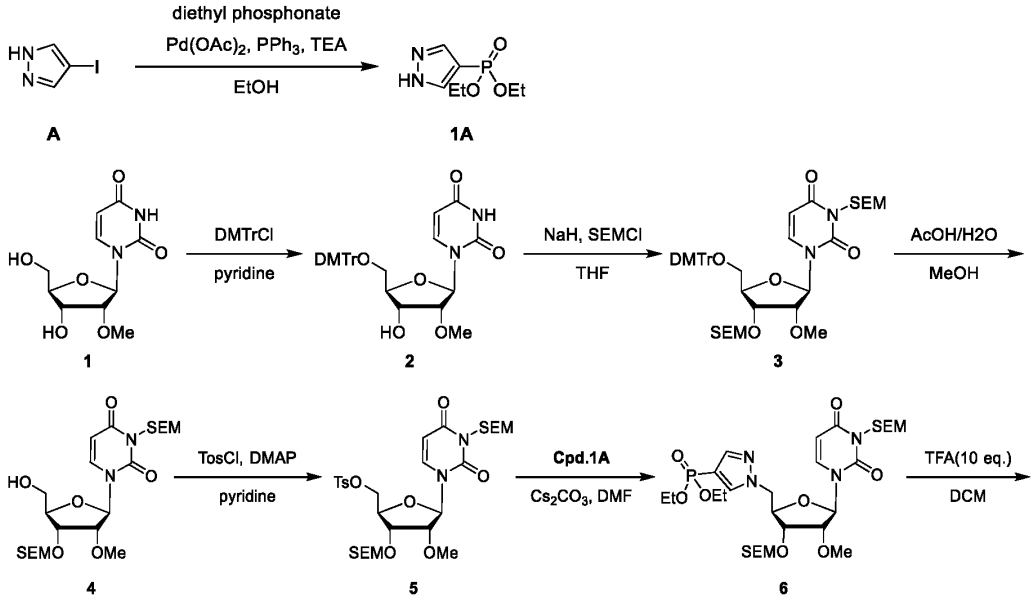
LCMS (M+H+): 462.2, purity: 91.97%

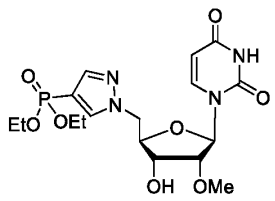
EXAMPLE 37. Synthesis of WV-NU-418



WV-NU-418

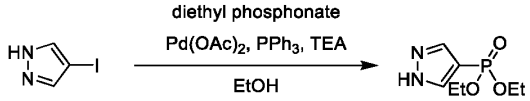
General Scheme:





WV-NU-418

1.Preparation of compound 1A:



A 1A

A mixture of compound **A** (20 g, 103.11 mmol), PPh_3 (8.11 g, 30.93 mmol) and Pd $(OAc)_2$ (2.31 g, 10.31 mmol) in EtOH (200 mL) was degassed and purged with N_2 for 3 times, then 1-ethoxyphosphonoyloxyethane (31.33 g, 226.84 mmol) and TEA (20.87 g, 206.21 mmol) was added to the mixture. The mixture was stirred at 78 °C for 12 hr under N_2 atmosphere. LCMS showed compound **A** was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched with Sat.NH_4Cl (200 mL), and extracted with EtOAc 300 mL * 4. The combined organic layers were washed with brine 300 mL * 3, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1, Ethyl acetate: Methanol = 1:0 to 10:1). Compound **1A** (9.17 g, 43.56% yield) was obtained as a white solid.

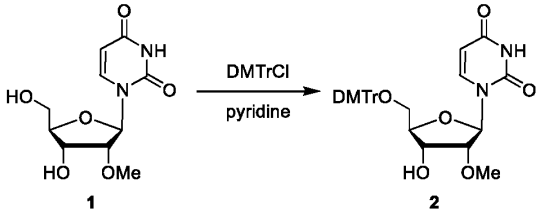
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 11.22 (br d, J = 2.0 Hz, 1H), 7.90 (d, J = 1.2 Hz, 2H), 4.18 - 4.00 (m, 4H), 1.32 (t, J = 7.0 Hz, 6H)

^{31}P NMR (162 MHz, CHLOROFORM-d) δ = 15.00 (s, 1P)

LCMS (M+H+): 205.0

TLC: Ethyl acetate: Methanol = 10:1, Rf = 0.5

2. Preparation of compound 2:



1 2

To a solution of compound **1** (40 g, 154.90 mmol) in Pyridine (1000 mL) was added DMTCl (57.73 g, 170.39 mmol). The mixture was stirred at 20 °C for 2 hr. TLC indicated compound **1** was consumed completely and one new spot formed. The reaction mixture was diluted with H_2O 1500 mL and extracted with EtOAc 800 mL * 2. The combined organic layers were washed with brine 500 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **2** (58 g, 66.79% yield) was obtained

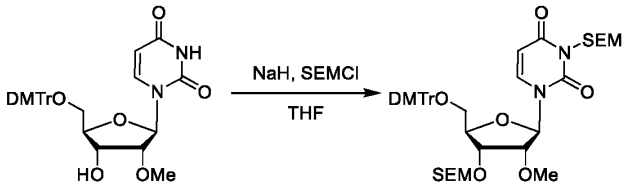
as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d6) δ = 11.39 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.40 - 7.36 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.26 – 7.24 (m, 5H), 6.91 (d, J = 8.4 Hz, 4H), 5.82 (d, J = 3.4 Hz, 1H), 5.30 (d, J = 8.0 Hz, 1H), 5.23 (d, J = 7.0 Hz, 1H), 4.25 - 4.18 (m, 1H), 3.99 - 3.93 (m, 1H), 3.83 – 3.81 (m, 1H), 3.74 (s, 6H), 3.41 (s, 3H), 3.32 - 3.28 (m, 1H), 3.26 - 3.21 (m, 1H)

LCMS (M-H+): 559.2, LCMS purity: 97%

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.6

3.Preparation of compound 3:



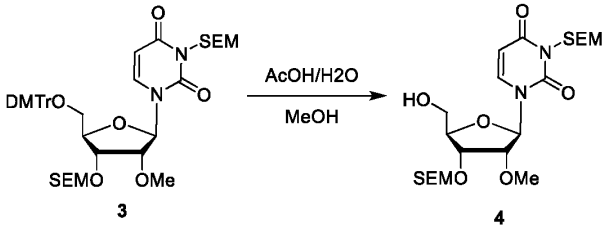
2 **3**

To a solution of compound **2** (56 g, 99.89 mmol) in DMF (800 mL) was added NaH (9.19 g, 229.76 mmol, 60% purity) at 0 °C under N_2 for 1 h, and SEM-Cl (38.31 g, 229.76 mmol) was added to the mixture at 0 °C under N_2. The mixture was stirred at 0-25 °C for 11 h. LCMS showed compound **2** was consumed completely. The reaction mixture was diluted with NH_4Cl 500 mL. The residue was diluted with H_2O 1000 mL extracted with EtOAc 500 mL *3. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **3** (60 g, 73.15% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 7.88 (d, J = 8.2 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.25 – 7.23 (m, 5H), 6.90 (d, J = 8.6 Hz, 4H), 5.84 (d, J = 2.6 Hz, 1H), 5.37 (d, J = 8.0 Hz, 1H), 5.19 (s, 2H), 4.69 - 4.66 (m, 2H), 4.30 - 4.25 (m, 1H), 4.12 – 4.09 (m, 1H), 4.00 – 3.98 (m, 1H), 3.74 (s, 6H), 3.61 - 3.58 (m, 2H), 3.57 - 3.48 (m, 3H), 3.41 (s, 3H), 0.87 - 0.80 (m, 5H), -0.04 (d, J = 2.0 Hz, 18H)

TLC: Petroleum ether: Ethyl acetate = 3:1, Rf = 0.5

3.Preparation of compound 4:



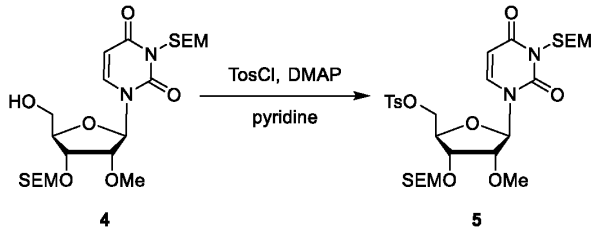
3 4

To a solution of compound **3** (60 g, 73.07 mmol) in MeOH (600 mL) was added AcOH (413.79 g, 6.89 mol) and H_2O (103.45 g, 5.74 mol). The mixture was stirred at 20 °C for 2 hr. TLC indicated compound **3** was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with H_2O 200 mL and extracted with EtOAc 100 mL * 3. The combined organic layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **4** (26 g, 68.59% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.09 (d, J = 8.2 Hz, 1H), 5.85 (d, J = 3.8 Hz, 1H), 5.80 (d, J = 8.0 Hz, 1H), 5.28 (t, J = 4.8 Hz, 1H), 5.20 (s, 2H), 4.70 (d, J = 1.0 Hz, 2H), 4.17 - 4.12 (m, 1H), 4.02 - 3.99 (m, 1H), 3.92 (t, J = 4.2 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.68 - 3.62 (m, 1H), 3.61 - 3.54 (m, 4H), 3.39 (s, 3H), 0.91 - 0.81 (m, 4H), 0.00 (s, 9H), -0.04 (s, 9H)

TLC: Petroleum ether: Ethyl acetate = 1:1, Rf = 0.4

4.Preparation of compound 5:



4 5

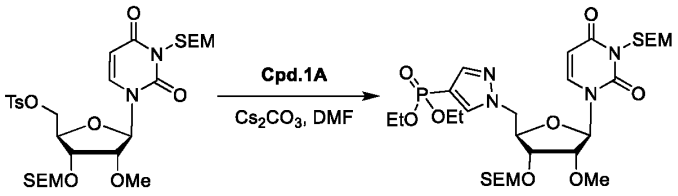
To a solution of compound **4** (29 g, 55.90 mmol) in Pyridine (300 mL) was added DMAP (682.96 mg, 5.59 mmol) and TosCl (15.99 g, 83.86 mmol). The mixture was stirred at 30 °C for 12 hr. LCMS showed compound **4** was consumed completely. The reaction mixture was concentrated under reduced pressure to remove pyridine. The residue was diluted with H_2O 500 mL and extracted with EtOAc 300 mL * 3. The combined organic layers were washed with brine 300 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:

Ethyl acetate = 1:0 to 0:1). Compound **5** (26 g, 69.11% yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.82 - 7.78 (m, 2H), 7.54 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 5.87 (s, 1H), 5.62 (d, J = 8.1 Hz, 1H), 5.40 - 5.37 (m, 1H), 5.36 - 5.32 (m, 1H), 4.71 (s, 2H), 4.46 - 4.41 (m, 1H), 4.36 - 4.32 (m, 1H), 4.30 - 4.26 (m, 1H), 4.00 (dd, J = 4.9, 8.7 Hz, 1H), 3.86 (d, J = 4.5 Hz, 1H), 3.75 - 3.71 (m, 1H), 3.71 - 3.67 (m, 2H), 3.66 (s, 1H), 3.60 (s, 3H), 2.47 (s, 3H), 1.00 - 0.96 (m, 2H), 0.96 - 0.91 (m, 2H), 0.03 - 0.01 (m, 9H), 0.00 (s, 9H)

TLC: Petroleum ether: Ethyl acetate = 3:1, Rf =0.55

5.Preparation of compound 6:



5 **6**

To a solution of compound **5** (26 g, 38.64 mmol) and 4-diethoxyphosphoryl-1H-pyrazole (9.15 g, 44.82 mmol) in DMF (200 mL) was added Cs_2CO_3 (25.18 g, 77.27 mmol). The mixture was stirred at 80 °C for 12 hr. LCMS showed compound **5** was consumed completely and desired mass was detected. The reaction mixture was diluted with H_2O 800 mL and extracted with EtOAc 300 mL * 3. The combined organic layers were washed with brine 500 mL *2, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1). Compound **6** (20 g, 73.44% yield) was obtained as a colorless oil.

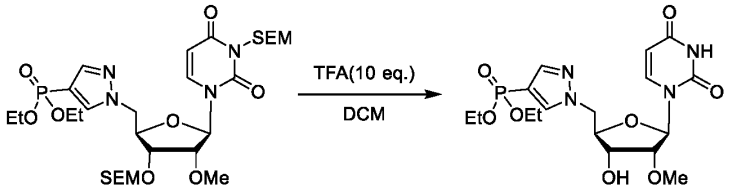
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.84 (d, J = 2.0 Hz, 1H), 7.75 (s, 1H), 6.31 (d, J = 8.4 Hz, 1H), 5.83 (d, J = 1.2 Hz, 1H), 5.65 (d, J = 8.0 Hz, 1H), 5.33 (q, J = 9.6 Hz, 2H), 4.89 - 4.85 (m, 1H), 4.82 - 4.78 (m, 1H), 4.61 - 4.55 (m, 1H), 4.54 - 4.48 (m, 1H), 4.41 - 4.35 (m, 1H), 4.15 - 4.09 (m, 4H), 4.00 (dd, J = 5.3, 8.6 Hz, 1H), 3.78 - 3.72 (m, 2H), 3.69 - 3.62 (m, 3H), 3.55 (s, 3H), 1.37 - 1.30 (m, 6H), 1.00 - 0.91 (m, 4H), 0.03 - 0.00 (m, 9H), -0.01 - -0.04 (m, 9H)

^{31}P NMR (162 MHz, CHLOROFORM-d) δ = 13.01 (s, 1P)

LCMS (M+H+): 705.2, LCMS purity: 97%

TLC: Petroleum ether: Ethyl acetate = 0:1, Rf = 0.25

6.Preparation of WV-NU-418:



6 **WV-NU-418**

To a solution of compound **6** (20 g, 28.37 mmol) in DCM (300 mL) was added TFA (32.35 g, 283.73 mmol, 21.08 mL). The mixture was stirred at 20 °C for 12 hr. LCMS showed compound **6** was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1:0 to 0:1, Ethyl acetate: Methanol = 1:0 to 8:1). **WV-NU-418** (10.74 g, 85.18% yield) was obtained as a white solid.

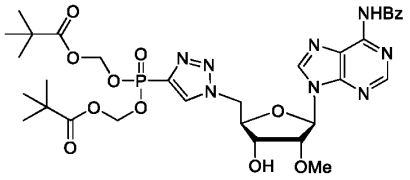
^{1}H NMR (400 MHz, DMSO-d6) δ = 11.40 (s, 1H), 8.15 (d, J = 1.9 Hz, 1H), 7.75 (s, 1H), 7.43 (d, J = 8.1 Hz, 1H), 5.80 (d, J = 5.0 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 5.44 (d, J = 5.8 Hz, 1H), 4.54 - 4.42 (m, 2H), 4.14 (qd, J = 5.0, 9.8 Hz, 2H), 4.00 - 3.92 (m, 4H), 3.80 (t, J = 4.9 Hz, 1H), 3.35 (s, 3H), 1.21 (dt, J = 1.7, 7.0 Hz, 6H)

^{31}P NMR (162 MHz, CHLOROFORM-d) δ = 13.34 (s, 1P)

LCMS (M+H+): 445.1, LCMS purity: 96.64%

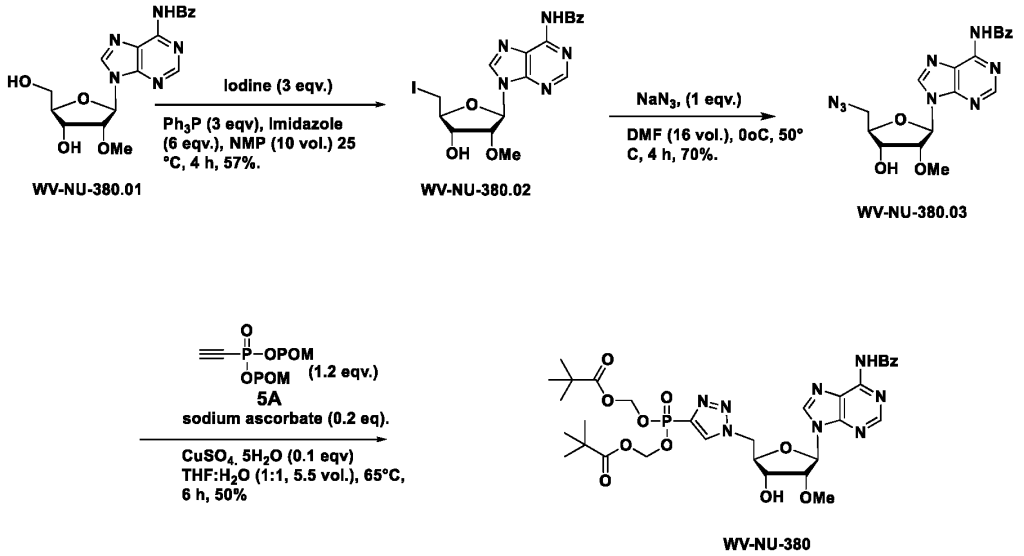
TLC: Ethyl acetate: Methanol = 10:1, Rf = 0.3

EXAMPLE 38. Synthesis of WV-NU-380



WV-NU-380

Synthetic Scheme for (WV-NU-380)



Preparation of N-(9-((2R,3R,4S,5S)-4-hydroxy-5-(iodomethyl)-3-methoxytetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (WV-NU-380.02) :

To a stirred solution of **WV-NU-380.01** (10 g, 0.0259 mol) in N- Methyl -2- pyrrolidone (100 mL, 10 vol.), was added iodine (19.7 g, 0.07793 mol), PPh_3 (20 g, 0.07792 mol.) and imidazole (10.5 g 0.1558 mol.) at 25°C. Then resulting mixture was stirred at rt for 4 h. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with saturated sodium thiosulfate (100 mL), extracted with EtOAc (2 x 100 mL), washed with cold brine (2 X 80 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH in DCM to get an off white solid **(WV-NU-380.02)** (7.3 g, 57%), TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (400 MHz, DMSO-d_6): δ in ppm = 11.26 (s, 1H), 8.79 (s, 1H), 8.75 (s, 1H), 8.05 (m, 2H), 7.66 (t, 1H, *J1* = 7.4 Hz), 7.56 (m, 2H), 6.19 (d, 1H, *J1* = 5.8 Hz), 5.64 (d, 1H, *J1* = 5.6 Hz), 4.68 (t, 1H, *J1* = 5.4 Hz), 4.43 (dd, 1H, *J1* = 8.9 Hz, *J2* = 5.2 Hz), 4.07 (m, 1H), 3.65 (dd, 1H, *J1* = 10.5 Hz, *J2* = 6.0 Hz), 3.52 (dd, 1H, *J1* = 10.5 Hz, *J2* =6.9 Hz), 3.36 (s, 3H). MS: *m/z* calcd for $C_{18}H_{18}IN_5O_4$, 495.3; found 496.5, $[M+H]^+$.

Preparation of N-(9-((2R,3R,4R,5R)-5-(azidomethyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (WV-NU-362-B):

To a stirred solution of **(WV-NU-380.02)** (18 g, 0.0363 mol) in dry DMF (288 mL, 16 vol.) was added sodium azide (2.36 g, 0.03634 mol) at 0°C. The resulting mixture was stirred at

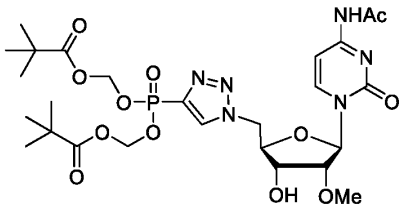
40°C and kept for 4 h. Progress of the reaction was monitored by TLC. After that reaction was quenched with ice water (100 mL), extracted with EtOAc (3 x 80 mL), washed with cold brine (2 X 70 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography over silica-gel (230-400 mesh) eluted in 2% MeOH in DCM to get off white solid **(WV-NU-380.03)** (10.5 g, 70%) TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 11.24 (s, 1H), 8.79 (s, 1H), 8.74 (s, 1H), 8.05 (m, 2H, *J1* = 7.6 Hz), 7.65 (t, 1H, *J1* = 7.6 Hz), 7.56 (t, 2H, *J1* = 7.6 Hz), 6.19 (d, 1H, *J1* = 5.5 Hz), 5.53 (d, 1H, *J1* = 5.5 Hz), 4.60 (t, 1H, *J1* = 5.2 Hz), 4.44 (q, 1H, *J1* = 5.0 Hz), 4.12 (m, 1H), 3.72 (q, 1H, *J1* = 6.7 Hz), 3.61 (dd, 1H, *J1* = 13.4 Hz, *J2* =3.8 Hz), 3.38 (s, 3H). MS: *m/z* calcd for $C_{18}H_{18}N_8O_4$, 410.4; found 411.6 $[M+H]^+$.

Preparation of (((1-(((2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-3-hydroxy-4-methoxy tetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphoryl)bis(oxy))bis(methylene) bis(2,2dimethylpropanoate) **(WV-NU-380):**

The compound **(WV-NU-380.03)** (10 g, 0.0243 mol) and **5A** (12.2 g, 0.0243 mol) was dissolved in a mixture of solvent (THF: Water) (1:1) (50 mL, 5 vol.) and water (50 mL, 5 vol.). Then the solution was degassed with nitrogen for 30 minutes at rt. After that sodium ascorbate (0.965 g, 0.00487 mol), $CuSO_4.5H_2O$ (0.64 g, 0.00256 mol) was added to the solution. Then reaction mixture was allowed to 65°C for 6 h. Progress of the reaction was monitored by TLC. The reaction mass was diluted with EtOAc (80 mL), washed with water (2 x 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by column chromatography over silica-gel (230-400 mesh) eluted in 2% MeOH in EtOAC to get light green solid **(WV-NU-380)** (9.2 g, 50%) TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 11.24 (s, 1H), 8.76 (d, 2H, *J1* = 19.3 Hz), 8.67 (s, 1H), 8.05 (d, 2H, *J1* = 7.6 Hz), 7.66 (t, 1H, *J1* = 7.2 Hz), 7.56 (t, 2H, *J1* = 7.6 Hz), 6.18 (d, 1H, *J1* = 4.8 Hz), 5.66 (m, 5H), 4.92 (m, 2H), 4.55 (td, 2H, *J1* = 9.6 Hz, *J1* = 4.6 Hz), 4.39 (m, 1H), 3.39 (s, 3H), 1.02 (s, 18H). MS: *m/z* calcd for $C_{32}H_{41}N_8O_{11}P$, 744.7; found 745.9 $[M+H]^+$

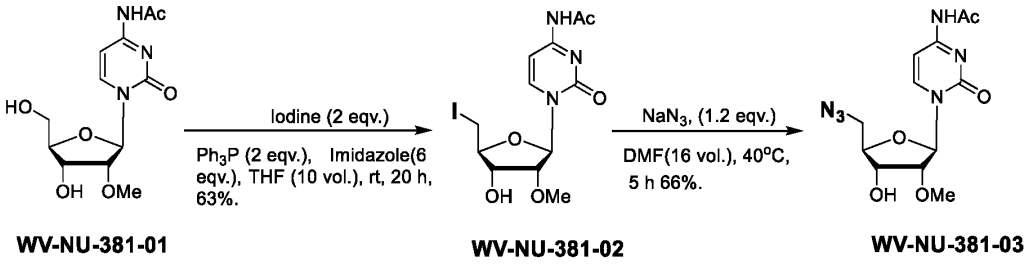
calcd for $C_{14}H_{23}O_7P$, 334.3; found 335.1 $[M+H]^+$.

EXAMPLE 39. Synthesis of WV-NU-381

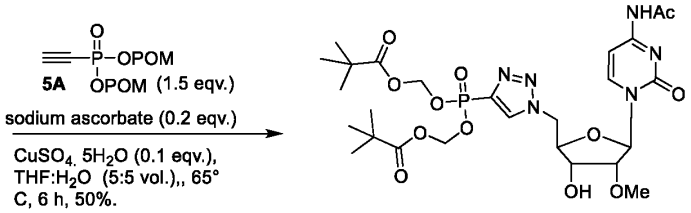


WV-NU-381

Synthetic Scheme for (WV-NU-381)



WV-NU-381-01 WV-NU-381-02 WV-NU-381-03



WV-NU-381

Preparation of N-(1-((2R,3R,4S,5S)-4-hydroxy-5-(iodomethyl)-3-methoxytetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (WV-NU-381-02) :

To a stirred solution of **WV-NU-380-01** (20 g, 0.0668 mol) in dry THF (300 mL, 15 vol.), was added iodine (33.8 g, 0.1337 mol), PPh_3 (35 g, 0.1337 mol.) and imidazole (27.2 g 0.4016 mol.) at 20°C. Then resulting mixture was stirred at rt for 20 h. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with saturated sodium thiosulfate (200 mL), extracted with EtOAc (2 x 150 mL), washed with brine (1 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 3% MeOH in DCM to get an off white solid **(WV-NU-381-02)** (17 g, 63%), TLC Mobile phase details: 5% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 10.96 (s, 1H), 8.11 (d, 1H, *J1* = 7.6 Hz), 7.25 (s, 1H), 5.90 (d, 1H, *J1* = 2.8 Hz), 3.91 (t, 3H, *J1* = 3.1 Hz), 3.59 (dd, 1H, *J1* = 10.3 Hz, *J2* = 3.4 Hz), 3.49 (m, 1H), 3.11 (s, 3H), 2.11 (s, 3H). MS: *m/z* calcd for $C_{12}H_{16}IN_3O_5$, 409.18; found 410.1, $[M+H]^+$.

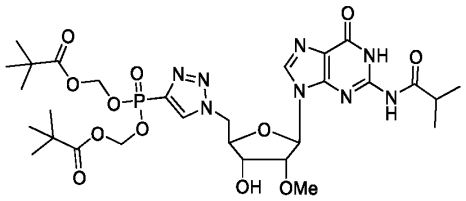
Preparation of N-(1-((2R,3R,4R,5R)-5-(azidomethyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl) acetamide (WV-NU-381-03):

To a stirred solution of **(WV-NU-381-02)** (17 g, 0.0415 mol) in dry DMF (272 mL, 16 vol.) was added sodium azide (3.2 g, 0.0498 mol) at 0°C. Then resulting mixture was stirred at 40°C for 5 h. Progress of the reaction was monitored by TLC. Then reaction was quenched with ice water (150 mL), extracted with EtOAc (2 x 150 mL), washed with cold brine (2 X 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by column chromatography over silica-gel (230-400 mesh) eluted in 3% MeOH in DCM to get off white solid **(WV-NU-381-03)** (9 g, 66%) TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 11.94 (s, 1H), 8.11 (t, 1H, *J1* = 7.2 Hz), 7.25 (q, 1H, *J1* = 4.1 Hz), 5.88 (dd, 1H, *J1* = 15.1 Hz, *J2* = 2.8 Hz), 5.39 (dd, 1H, *J1* = 41.0 Hz, *J2* = 5.9 Hz), 3.98 (d, 2H, *J1* = 2.8 Hz), 3.91 (t, 1H, *J1* = 2.8 Hz), 3.83 (q, 1H, *J1* = 2.5 Hz), 3.66 (m, 2H), 3.43 (d, 3H, *J1* = 13.1 Hz), 2.11 (s, 3H). MS: *m/z* calcd for $C_{12}H_{16}N_6O_5$, 324.3; found 325.36 $[M+H]^+$.

***Preparation of (((1-(((2R,3R,4R,5R)-5-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-3-hydroxy-4-methoxytetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphoryl)bis(oxy))bis-(methylene) bis(2,2-dimethylpropanoate)* (WV-NU-381):**

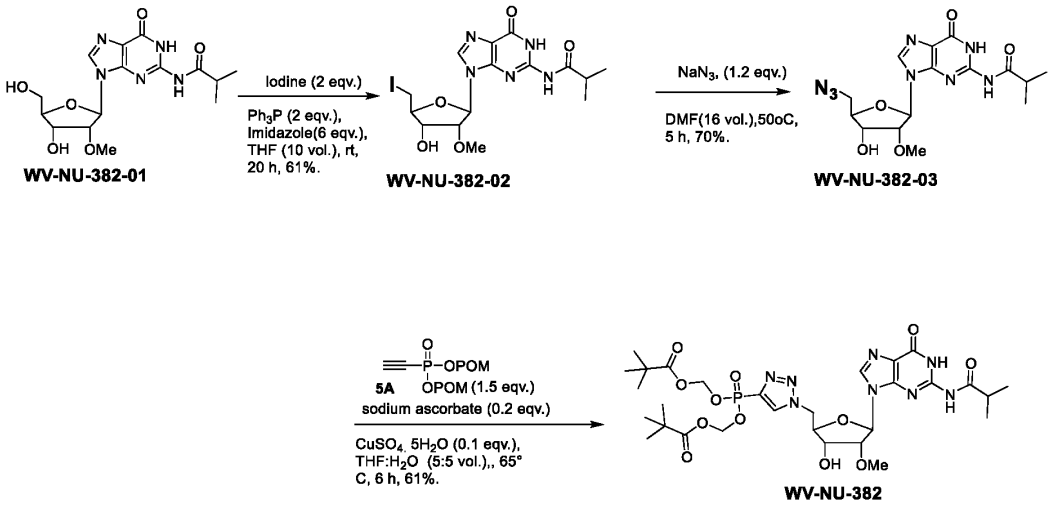
To a stirred solution of **(WV-NU-381-03)** (9 g, 0.0227 mol) and **(WV-NU-380-B)** (13.9 g 0.0416 mol**)** in mixture of solvent (1:1) THF (45 mL, 5 vol.), water (45 mL, 5 vol.) was degassed with nitrogen atmosphere for 25 minutes. Then added sodium ascorbate (0.1.09 g, 0.0055 mol), $CuSO_4.5H_2O$ (0.69 g, 0.00277 mol) at rt. The reaction mixture was stirred at 65°C for 6 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt and concentrated under reduced pressure The crude mass was purified by column chromatography over silica-gel (230-400 mesh) eluted in 3% MeOH in EtOAC to get light green solid **(WV-NU-381)** (9.2 g, 50%) TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (400 MHz, DMSO-d_6): δ in ppm = 10.95 (s, 1H), 8.74 (s, 1H), 8.04 (d, 1H, *J1* = 7.6 Hz), 7.26 (d, 1H, *J1* = 6.9 Hz), 5.80 (d, 1H, *J1* = 2.8 Hz), 5.70 (s, 2H), 5.67 (s, 2H), 5.51 (d, 1H, *J1* = 6.9 Hz), 4.85 (m, 2H), 4.24 (m, 1H), 4.07 (d, 1H, *J1* = 6.2 Hz), 3.88 (m, 1H, *J1* = 3.4 Hz), 3.44 (s, 3H), 2.11 (s, 3H), 1.06 (s, 18H). MS: *m/z* calcd for $C_{26}H_{39}N_6O_{12}P$, 658.6; found 660.0 $[M+H]^+$.

EXAMPLE 40. Synthesis of WV-NU-382



WV-NU-382

Synthetic Scheme for (WV-NU-382)



Preparation of N-(9-((2R,3R,4S,5S)-4-hydroxy-5-(iodomethyl)-3-methoxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (WV-NU-382-02) :

To a stirred solution of **WV-NU-380-01** (25 g, 0.0681 mol) in dry THF (375 mL, 15 vol.), was added iodine (34.4 g, 0.1362 mol), PPh_3 (35.6 g, 0.1362 mol.) and imidazole (27.8 g 0.4087 mol.) at 25°C. Then resulting mixture was stirred at rt for 20 h. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with saturated sodium thiosulfate (150 mL), extracted with EtOAc (2 x 150 mL), washed with brine (1 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 5% MeOH in DCM to get off white solid **(WV-NU-382-02)** (20 g, 61%), TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 12.08 (s, 1H), 11.64 (s, 1H), 8.29 (s, 1H), 5.93 (d, 1H, *J1* = 6.2 Hz), 5.57 (d, 1H, *J1* = 5.5 Hz), 4.47 (t, 1H, *J1* = 5.9 Hz), 4.32 (q, 1H, *J1* = 3.9 Hz), 4.02 (td, 1H, *J1* = 6.7 Hz, *J2* = 3.0 Hz), 3.58 (dd, 1H, *J1* = 10.3 Hz, *J2* = 6.9 Hz), 3.44 (dd, 1H, *J1* = 10.3 Hz, *J2* = 6.9 Hz), 3.34 (s, 3H), 2.76 (m, 1H), 1.13

(d, 6H, *J1* = 6.2 Hz), MS: *m/z* calcd for $C_{15}H_{20}IN_5O_5$, 477.26; found 478.48, $[M+H]^+$.

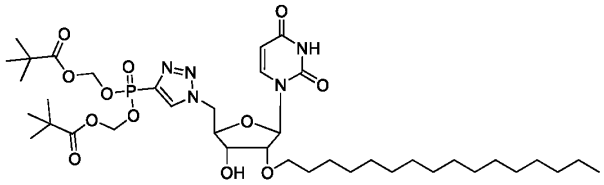
Preparation of N-(9-((2R,3R,4R,5R)-5-(azidomethyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (WV-NU-382-03):

To a stirred solution of **(WV-NU-380-02)** (20 g, 0.0417 mol) in dry DMF (320 mL, 16 vol.) was added sodium azide (3.28 g, 0.0503 mol) at 0°C. The resulting mixture was stirred 50°C and kept for 5 h. Progress of the reaction was monitored by TLC. Then reaction was quenched with ice water (200 mL), extracted with EtOAc (2 x 100 mL), washed with cold brine (2 X 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by column chromatography over silica-gel (230-400 mesh) eluted in 3% MeOH in DCM to get off white solid **(WV-NU-382-03)** (11.5 g, 70%) TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (00 MHz, DMSO-d_6): δ in ppm = 12.10 (s, 1H), 11.63 (s, 1H), 8.30 (s, 1H), 5.93 (d, 1H, *J1* = 6.2 Hz), 5.47 (d, 1H, *J1* = 5.1 Hz), 4.39 (dd, 1H, *J1* = 6.0 Hz, *J2* = 5.2 Hz), 4.30 (dd, 1H, *J1* = 8.6 Hz, *J2* = 4.9 Hz), 4.05 (m, 1H), 3.67 (q, 1H, *J1* = 6.6 Hz), 3.58 (dd, 1H, *J1* = 13.2 Hz, *J2* = 4.1 Hz), 3.35 (s, 3H), 2.77 (m, 1H), 1.13 (dd, 6H, *J1* = 6.9 Hz, *J1* = 0.8 Hz), MS: *m/z* calcd for $C_{15}H_{20}N_8O_5$, 392.38; found 393.5, $[M+H]^+$.

***Preparation of (((1-(((2R,3R,4R,5R)-3-hydroxy-5-(2-isobutyramido-6-oxo-1,6-dihydro-9H-purin-9-yl)-4-methoxytetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphoryl) bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)* (WV-NU-382):**

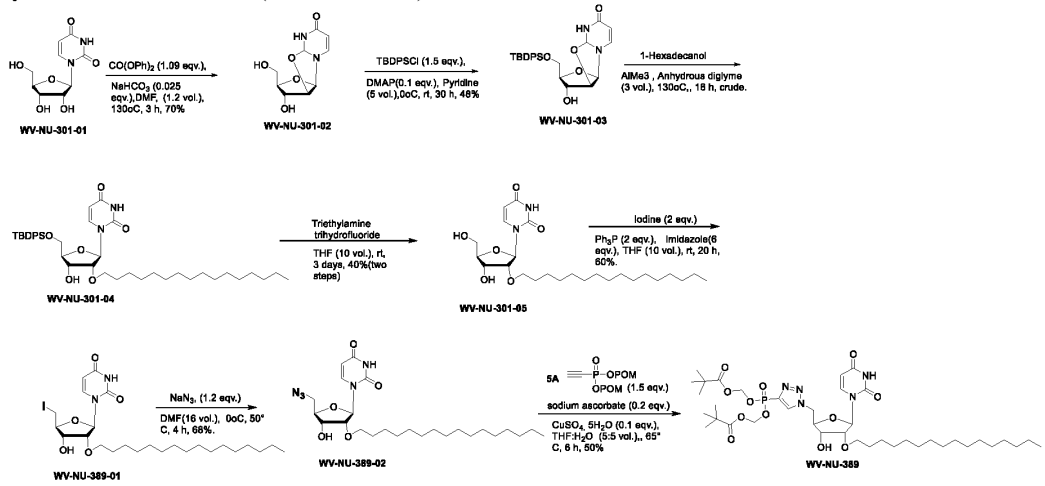
To a stirred solution of **(WV-NU-380-03)** (11.5 g, 0.0293 mol) and **(WV-NU-380-B) (14.6 g, 0.044 mol.)** in mixture of solvent (1:1) THF (57.5 mL, 5 vol.),water (57.5 mL, 5 vol.) was degassed with nitrogen atmosphere for 35 minutes. Then added sodium ascorbate (1.11 g, 0.0.00561 mol), $CuSO_4.5H_2O$ (0.73 g, 0.00293 mol) at rt. The reaction mixture was stirred at 65°C for 6 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to rt and concentrated under reduced pressure The crude mass was purified by column chromatography over silica-gel (230-400 mesh) eluted in 3% MeOH in EtOAC to get light green solid **(WV-NU-382)** (13.1 g, 61%) TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 12.10 (s, 1H), 11.60 (s, 1H), 8.66 (s, 1H), 8.29 (s, 1H), 5.93 (d, 1H, *J1* = 5.5 Hz), 5.65 (m, 5H), 4.84 (m, 2H), 4.46 (q, 1H, *J1* = 4.1 Hz), 4.36 (t, 1H, *J1* = 5.5 Hz), 4.32 (m, 1H), 3.36 (s, 3H), 2.75 (m, 1H), 1.11(d, 6H, *J1* = 6.9 Hz), 1.02 (s, 18H). MS: *m/z* calcd for $C_{29}H_{43}N_8O_{12}P$, 726.68; found 725.8 $[M-H]^+$.

EXAMPLE 41. Synthesis of WV-NU-389



WV-NU-389

Synthetic Scheme for (WV-NU-389)



Preparation of (2R,3R,3aS,9aR)-3-hydroxy-2-(hydroxymethyl)-2,3,3a,9a-tetrahydro-6H-furo[2',3':4,5] oxazolo[3,2-c]pyrimidine-6,8(7H)-dione (WV-NU-302-02) :

To a stirred solution of Uridine (30 g, 0.122 mol) and diphenyl carbonate (26 g, 0.1229 mol.) in dry DMF (36 mL, 1.2 vol.) was added sodium bicarbonate (258 mg, 0.00307 mol) stirred at 130°C for 3 h. Progress of the reaction was monitored by TLC. Then reaction mixture was cooled to rt, precipitated product was observed, filtered and washed with cold methanol (2 x 15 mL), dried under vacuum to get as off white solid **(WV-NU-301-02)** (21 g, 70%). TLC Mobile phase details: 15% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm =7.83 (d, 1H, J1 = 6.9 Hz), 6.30 (d, 1H, J1 = 6.2 Hz), 5.88(s, 1H), 5.84 (d, 1H, J1 = 6.9 Hz), 5.19 (d, 1H, J1 = 5.5 Hz), 4.98 (t, 1H, J1 = 5.2 Hz), 4.38 (s, 1H), 4.07 (t, 1H, *J1* = 4.5 Hz), 3.28 (m, 1H) 3.18 (m, 1H).

Preparation of (2R,3R,3aS,9aR)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-2,3,3a, 9a- tetrahydro-6H-furo[2',3':4,5]oxazolo[3,2-c]pyrimidine-6,8(7H)-dione(WV-NU-301-03):

To a stirred solution of **(WV-NU-301-02)** (40 g, 0.165 mol) and DMAP (2 g, 0.0165 mol.) in anhydrous pyridine (200 mL, 5 vol.) was added TBDPSCl (63 mL, 0.247 mol.) dropwise over a period of 30 mins, at 0°C. Above reaction mixture was stirred at rt for 30 h. Progress of the reaction was monitored by TLC. The reaction was diluted with cold sat.NaHCO3 (150 mL) and extracted with DCM (2 x 200 mL), washed with brine (1 x 150 mL) solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH in DCM to afford an off-white solid. **(WV-NU-301-03)** (38 g, 48%). TLC Mobile phase details: 10% MeOH in DCM. ^{1}H NMR (400 MHz, DMSO-d_6): δ in ppm =7.92 (d, 1H, J1 = 7.6 Hz), 7.53 (m, 4H), 7.43 (m, 7H), 6.32 (d, 1H, J1 = 5.5 Hz), 6.02 (d, 1H, J1 = 4.8 Hz), 5.87 (d, 1H, J1 = 7.6 Hz), 5.26 (m, 1H), 4.45 (q, 1H, *J1* = 2.8Hz), 4.17 (m, 1H, Hz), 3.59 (q, 1H, *J1* = 5.3Hz), 3.47 (q, 1H, *J1* = 6.0Hz) 3.08 (d, 1H, *J1* = 6.9Hz) ,0.92 (s, 9H)

Preparation of 1-((2R,3R,4R,5R)-3-(hexadecyloxy)-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-301-05):

To a stirred solution of 1-Hexadecanol (130.6 g, 0.541 mol)) in anhydrous diglyme (100 mL, 2.8 vol.) was added Trimethylaluminum (112.4 mL, 0.225 mol, 2M) dropwise over a period of 40 min. The resulting mixture was heated to 120°C and stirred for 2 h. Then the mass was allowed to rt and **(WV-NU-301-03)** (36 g, 0.075 mol) was added, stirred at 130°C for 16 h. Progress of the reaction was monitored by TLC. The reaction mixture was diluted 10% H_3Po_4 (500 mL) and EtOAc (300 mL), organic layer was separated washed with 5% NaCl (100 mL), dried over Na_2SO_4 and concentrated under vacuum to afford as a gummy syrup (64 g, crude). The syrup was dissolved in THF (360 mL, 10 vol.), was added triethylamine hydrofluride (48 mL, 0.30 mol.), stirred rt for 3 days. Progress of the reaction was monitored by TLC. The reaction was diluted 5% NaCl (250 mL) and EtOAc (300 mL), organic layer was separated washed with sat. NaCl solution (1 x 150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 3% MeOH in DCM to afford an off-white solid. **(WV-NU-301-05)** (14.3 g, 40%). TLC Mobile phase details: 10% MeOH in DCM. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm =11.33 (d, 1H, J1 = 1.4 Hz), 7.94 (d, 1H, J1 = 7.6 Hz), 5.84 (d, 1H, J1 = 4.8 Hz), 5.64 (dd, 1H, J1 = 7.9 Hz, J2 = 1.7 Hz), 5.13 (t, 1H, J1 = 5.2 Hz), 5.04 (d, 1H, J1 = 6.2 Hz), 4.09 (dt, 2H, J1 = 10.0 Hz, J1 = 4.8 Hz), 3.85 (t, 2H, J1 = 4.8 Hz), 3.63 (dq, 1H, J1 = 12.2 Hz, J2 = 2.8 Hz), 3.56 (m, 2H), 3.44 (m, 1H), 3.17 (d, 1H, *J1* = 5.5 Hz), 1.47 (q, 2H, *J1* = 6.7 Hz), 1.23 (s, 34H), 0.85 (t, 3H, J1 = 6.5 Hz), MS: *m/*

*cz*alcd for $C_{25}H_{44}N_2O_6$, 468.6; found 467.3 ($M\text{-}H^+$).

Preparation of 1-((2R,3R,4S,5S)-3-(hexadecyloxy)-4-hydroxy-5-(iodomethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-389-01):

To a stirred solution of **WV-NU-301.05** (14 g, 0.0299 mol) in dry THF (140 mL, 10 vol.), was added iodine (15 g, 0.0598 mol), PPh_3 (15.6 g, 0.0598 mol.) and imidazole (12.2 g 0.178 mol.) at rt. Then resulting mixture was stirred at rt for 20 h. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with saturated sodium thiosulfate (120 mL), extracted with EtOAc (2 x 100 mL), washed with cold brine (1 x 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 4% MeOH in DCM to get off white solid **(WV-NU-389-01)** (10.5 g, 61%), TLC Mobile phase details: 7% MeOH in DCM. ^{1}H NMR (400 MHz, DMSO-d_6): δ in ppm = 11.39 (s, 1H), 7.69 (d, 1H, *J1* = 8.3 Hz), 5.86 (d, 1H, *J1* = 5.5 Hz), 5.68 (dd, 1H, *J1* = 5.3 Hz, *J1* = 2.1 Hz), 5.34 (d, 1H, *J1* = 6.2 Hz), 4.07 (m, 1H), 4.05 (t, 1H, *J1* = 5.5 Hz), 3.99 (q, 1H, *J1* = 5.5 Hz), 3.86 (q, 1H, *J1* = 5.5 Hz), 3.56 (m, 2H), 1.46 (q, 1H, *J1* = 6.4 Hz), 1.26 (s, 28H), 0.85 (t, 3H, *J1* = 6.9 Hz), . MS: *m/z* calcd for $C_{25}H_{43}IN_2O_5$, 578.53; found 577.53, $[M\text{-}H]^+$.

Preparation of 1-((2R,3R,4R,5R)-5-(azidomethyl)-3-(hexadecyloxy)-4-hydroxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-389-02):

To a stirred solution of **(WV-NU-389-01)** (13 g, 0.0224 mol) in dry DMF (208 mL, 16 vol.) was added sodium azide (1.75 g, 0.0269 mol) at 0°C. The resulting mixture was stirred 50°C and kept for 4 h. Progress of the reaction was monitored by TLC. Then reaction was quenched with ice water (150 mL), extracted with EtOAc (2 x 150 mL), washed with cold brine (2 X 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by column chromatography over silica-gel (230-400 mesh) eluted in 40% EtOAc in Hexane to get off white solid **(WV-NU-389-02)** (7.5 g, 68%) TLC Mobile phase details: 60% EtOAc in Hexane. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 11.39 (s, 1H), 7.70 (d, 1H, *J1* = 8.3 Hz), 5.82 (d, 1H, *J1* = 4.8 Hz), 5.67 (d, 1H, *J1* = 8.3 Hz), 5.25 (d, 1H, *J1* = 6.2 Hz), 4.02 (q, 1H, *J1* = 5.3 Hz), 3.98 (t, 1H, *J1* = 5.2 Hz), 3.93 (q, 1H, *J1* = 5.0 Hz), 3.58 (m, 1H), 3.44 (m, 1H), 1.48 (t, 2H, *J1* = 6.5 Hz) 1.23 (s, 28H), 0.85 (t, 3H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{25}H_{43}N_5O_5$, 493.65; found 494.56 $[M+H]^+$.

Preparation of (((1-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-(hexadecyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phosphoryl)bis(oxy))bis(methylene) bis(2,2-dimethylpropanoate)) **(WV-NU-389):**

To a stirred solution of **(WV-NU-389-02)** (11 g, 0.0223 mol) and (WV-NU-380-B) (11.17, 0.033 mol) in mixture of solvent (1:1) THF (55 mL, 5 vol.), water (55 mL, 5 vol.) was degassed with nitrogen atmosphere for 30 minutes. Then added sodium ascorbate (0.88 g, 0.00446 mol), $CuSO_4.5H_2O$ (0.55 g, 0.00223 mol) at rt. The reaction mixture was stirred at 65°C for 6 h. Progress of the reaction was monitored by TLC. The reaction mass was diluted EtOAc (100 mL), washed with water (2 x 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure The crude compound was purified by column chromatography over silica-gel (230-400 mesh) eluted in 60% EtOAC in Hexane to get gummy syrup **(WV-NU-389)** (10.5 g, 56%) TLC Mobile phase details: 70% EtOAC in Hexane. ^{1}H NMR (500 MHz, DMSO-d_6): δ in ppm = 11.40 (d, 1H, *J1* = 2.1 Hz), 8.69 (s, 1H), 7.64 (d, 1H, *J1* = 8.3 Hz), 5.79 (d, 1H, *J1* = 4.8 Hz), 5.67 (m, 4H), 5.40 (d, 1H, *J1* = 5.5 Hz), 4.79 (m, 2H), 4.19 (m, 1H), 4.00 (t, 1H, *J1* = 5.2 Hz), 3.58 (m, 1H), 3.45 (m, 1H), 1.48 (t, 2H, *J1* = 6.5 Hz), 1.23 (s, 28H), 1.07 (s, 18H), 0.85 (t, 3H, *J1* = 6.9 Hz). MS: *m/z* calcd for $C_{39}H_{66}N_5O_{12}P$, 827.95; found 829.00 $[M+H]^+$.

All publications, patents, and patent applications herein are incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. In the event of a conflict between a term herein and a term in an incorporated reference, the term herein controls.

CLAIMS

1. A double-stranded RNAi (dsRNAi) agent capable of directing target-specific RNA interference, the dsRNAi agent comprising a guide strand and a passenger strand, wherein:

the guide strand is complementary or substantially complementary to a target RNA sequence;

the guide strand comprises a seed region at its 5'-end region that is capable of mediating the initial recognition of the target RNA sequence;

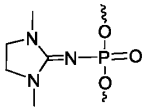
the guide strand comprises a backbone phosphoryl guanidine (PN) chiral center in the seed region; and

one or both of the guide strand and the passenger strand comprise a lipid ligand and/or a non-lipid ligand.

2. The dsRNAi agent of claim 1, wherein the seed region comprises nucleotides at positions 2-6, at positions 2-7, or at positions 2-8, relative to the 5'-end of the guide strand.

3. The dsRNAi agent of claim 1 or 2, wherein the backbone phosphoryl guanidine (PN) chiral center in the seed region of the guide strand is between the third (+3) nucleotide and the immediately downstream (+4) nucleotide, relative to the 5' terminal nucleotide of the guide strand.

4. The dsRNAi agent of any of claims 1-3, wherein the backbone phosphoryl guanidine (PN) chiral center in the seed region of the guide strand is in the *S*p configuration.

5. The dsRNAi agent of any of claims 1-4, wherein the backbone phosphoryl guanidine (PN) chiral center in the seed region of the guide strand comprises the structure of  (n001).

6. The dsRNAi agent of any of claims 1-5, wherein the passenger strand comprises a lipid ligand.

7. The dsRNAi agent of claim 6, wherein the passenger strand comprises one or more backbone phosphoryl guanidine (PN) chiral centers.

8. The dsRNAi agent of claim 7, wherein the passenger strand comprises a backbone

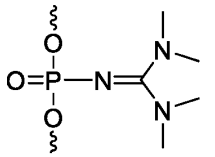
phosphoryl guanidine (PN) chiral center between the +7 nucleotide and the immediately downstream (+8) nucleotide, and/or a backbone phosphoryl guanidine (PN) chiral center between the +15 nucleotide and the immediately downstream (+16) nucleotide.

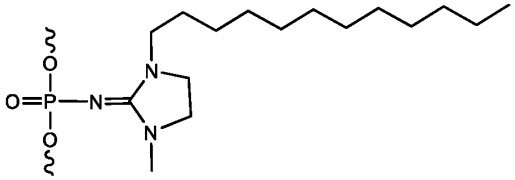
9. The dsRNAi agent of claim 8, wherein the backbone phosphoryl guanidine (PN) chiral center between the +7 nucleotide and the +8 nucleotide, and/or the backbone phosphoryl guanidine (PN) chiral center between the +15 nucleotide and the +16 nucleotide, of the passenger strand, is/are in the *R*p configuration.

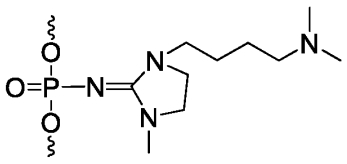
10. The dsRNAi agent of any of claims 7-9, wherein said one or more backbone phosphoryl guanidine (PN) chiral centers is/are modified with one or two of the lipid ligand (backbone PN-lipid ligand).

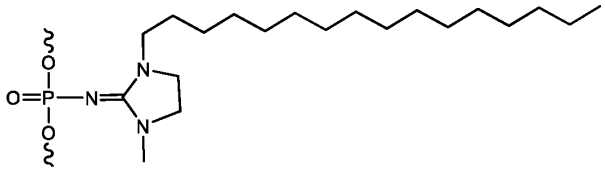
11. The dsRNAi agent of any of claims 6-10, wherein the lipid ligand comprises a saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain.

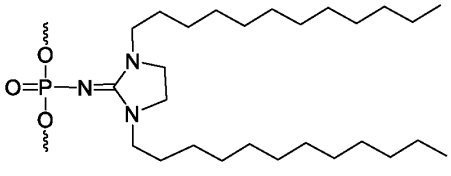
12. The dsRNAi agent of claim 10 or 11, wherein the backbone PN-lipid ligand is selected from the group consisting of: a mono PN-lipid, a bis PN-lipid, a mono PN-PEG lipid, a bis PN-PEG lipid,

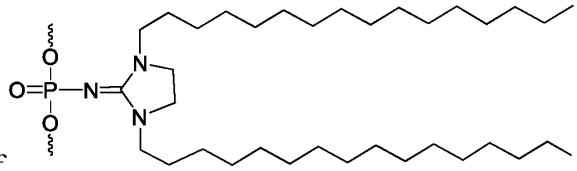
n003 comprising the structure of ,

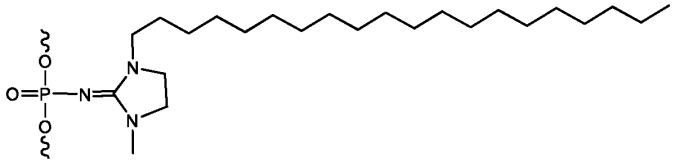
n009 comprising the structure of ,

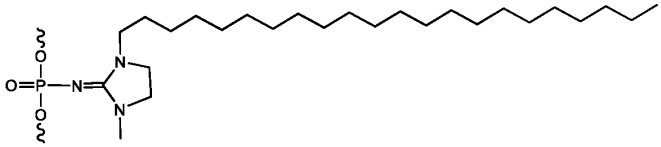
n029 comprising the structure of ,

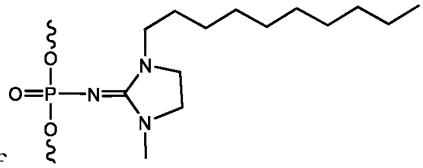
n033 comprising the structure of ,

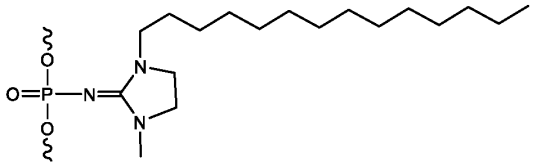
n039 comprising the structure of ,

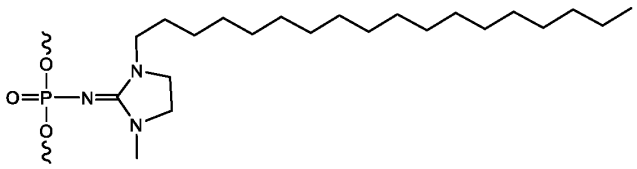
n040 comprising the structure of ,

n076 comprising the structure of ,

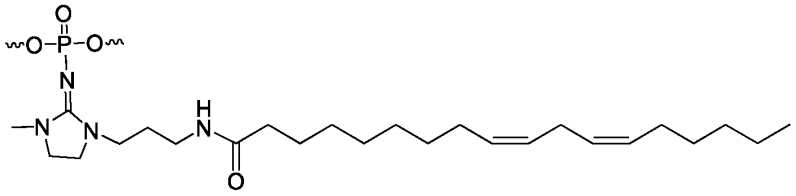
n077 comprising the structure of ,

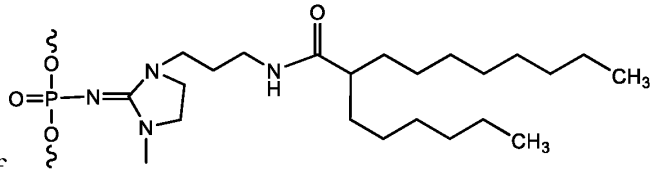
n082 comprising the structure of ,

n083 comprising the structure of ,

n084 comprising the structure of ,

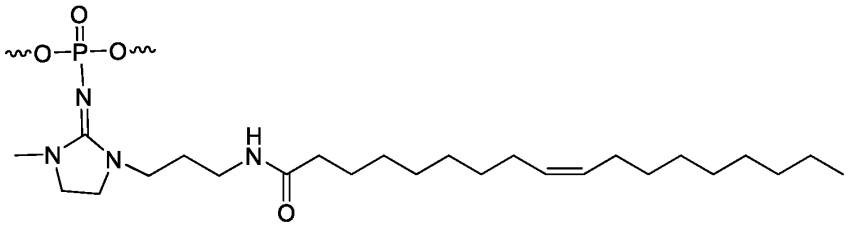
n086 comprising the structure of

,

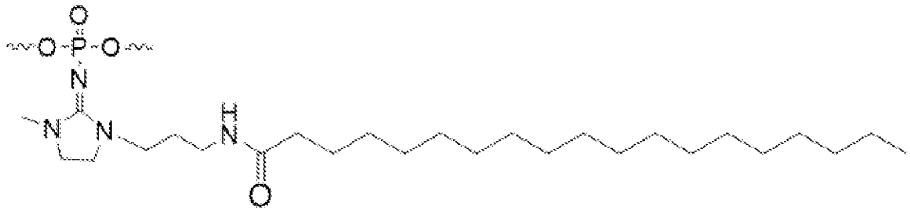


n087 comprising the structure of ,

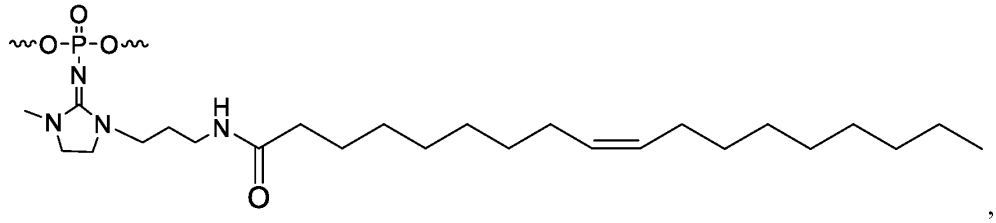
n088 comprising the structure of

,

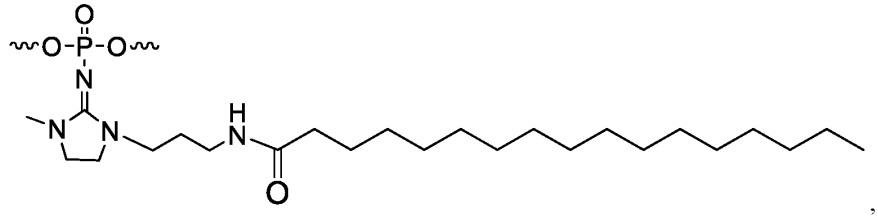
n089 comprising the structure of

,

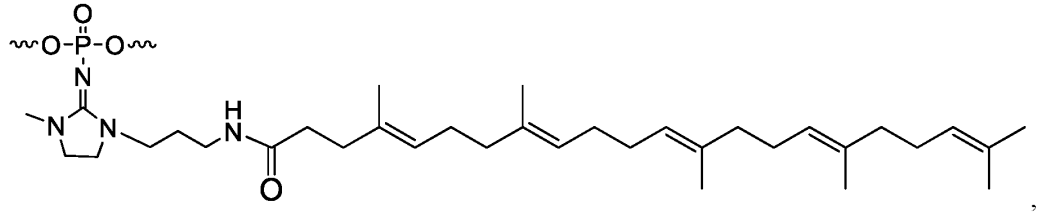
n090 comprising the structure of

,

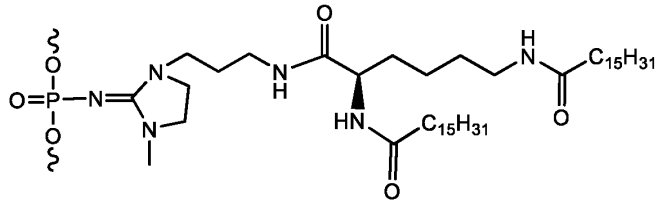
n091 comprising the structure of



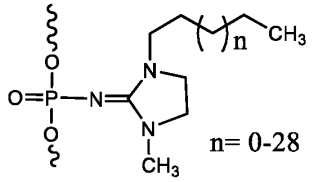
n092 comprising the structure of



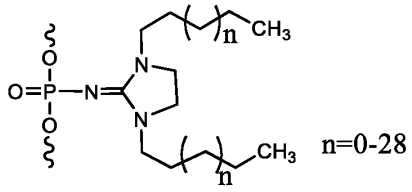
and a PN-lipid comprising the structure of



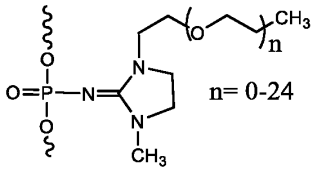
13. The dsRNAi agent of claim 12, wherein the mono PN-lipid comprises the structure of



14. The dsRNAi agent of claim 12, wherein the bis PN-lipid comprises the structure of

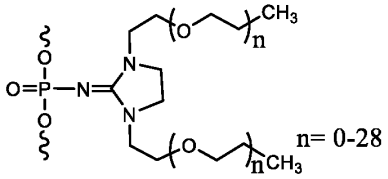


15. The dsRNAi agent of claim 12, wherein the mono PN-PEG lipid comprises the structure



of .

16. The dsRNAi agent of claim 12, wherein the bis PN-PEG lipid comprises the structure



of .

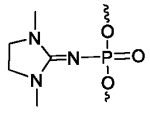
17. The dsRNAi agent of any of claims 1-16, wherein the passenger strand further comprises a backbone phosphorothioate (PS) chiral center between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide, and/or a backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide.

18. The dsRNAi agent of claim 17, wherein the backbone phosphorothioate (PS) chiral center between the 5' terminal (+1) nucleotide and the immediately downstream (+2) nucleotide, and/or the backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, of the passenger strand, is/are in the *S*p configuration.

19. The dsRNAi agent of any of claims 1-18, wherein the guide strand further comprises a backbone phosphoryl guanidine (PN) chiral center between the +7 nucleotide and the +8 nucleotide, and/or a backbone phosphoryl guanidine (PN) chiral center between the +18 nucleotide and the +19 nucleotide.

20. The dsRNAi agent of claim 19, wherein the backbone phosphoryl guanidine (PN) chiral center between the +7 nucleotide and the +8 nucleotide, and/or the backbone phosphoryl guanidine (PN) chiral center between the +18 nucleotide and the +19 nucleotide, of the guide strand, is/are in the *S*p configuration.

21. The dsRNAi agent of claim 19 or 20, wherein the backbone phosphoryl guanidine (PN) chiral center between the +7 nucleotide and the +8 nucleotide, and/or the backbone phosphoryl

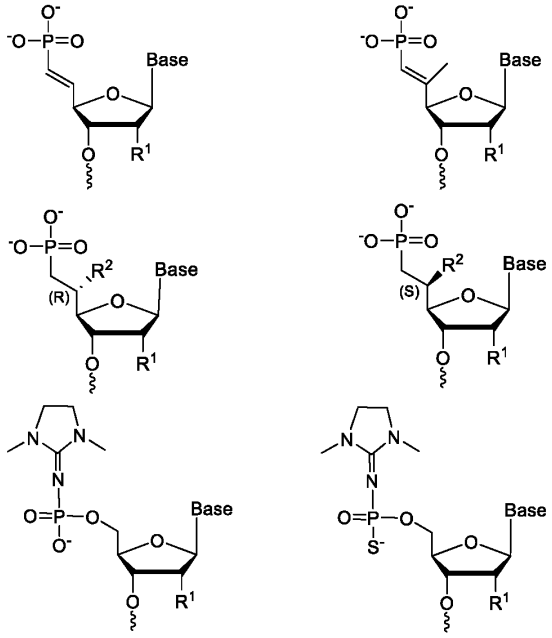
guanidine (PN) chiral center between the +18 nucleotide and the +19 nucleotide, of the guide strand, comprises the structure of  (n001).

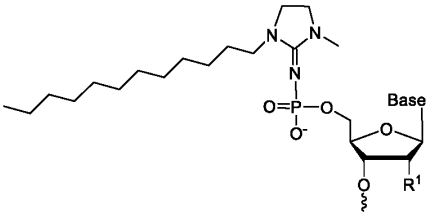
22. The dsRNAi agent of any of claims 1-21, wherein the guide strand further comprises a backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, between the +21 nucleotide and the +22 nucleotide, between the +20 nucleotide and the +21 nucleotide, and/or between the +19 nucleotide and the +20 nucleotide.

23. The dsRNAi agent of claim 22, wherein the backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, between the +21 nucleotide and the +22 nucleotide, between the +20 nucleotide and +21 nucleotide, and/or between the +19 nucleotide and the +20 nucleotide, of the guide strand, is/are in the *S*p configuration.

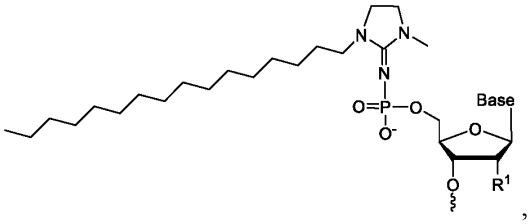
24. The dsRNAi agent of any of claims 1-23, wherein the guide strand further comprises a 5' terminal modification.

25. The dsRNAi agent of claim 24, wherein the 5' terminal modification is selected from the group consisting of:

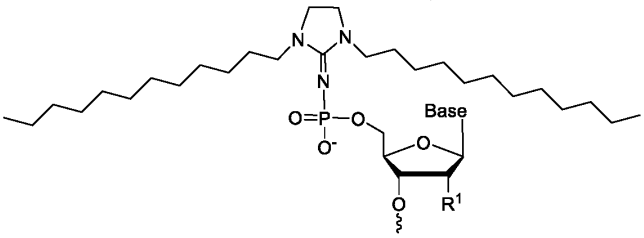




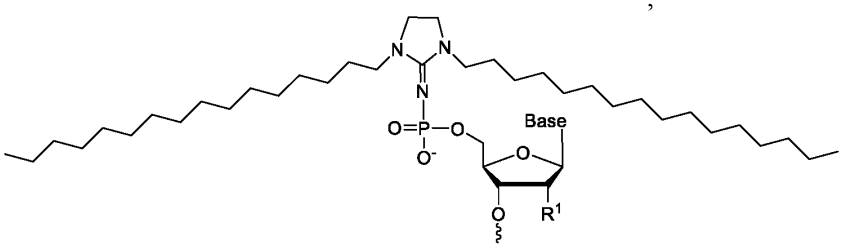
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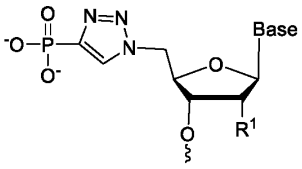
,



,



, and



, wherein

the base is A, C, G, T, U, abasic, or a modified nucleobase;

R^1 is selected from H, OH, *O*-alkyl, *O*-methyl (O-Me), F, *O*-methoxyethyl (MOE), and 2'-*O*,4'*C*-methylene-bridged or locked nucleic acid (2',4'-BNA or LNA); and

R^2 is selected from alkyl, methyl, ethyl, isopropyl, propyl, cyclohexyl, benzyl, phenyl, tolyl, xylyl, aryl, and arene group.

26. The dsRNAi agent of claim 25, wherein the 5' terminal modification is triazolyl phosphonate or methyl phosphonate.

27. The dsRNAi agent of any of claims 1-26, wherein one or both of the guide strand and the passenger strand comprise a non-lipid ligand.

28. The dsRNAi agent of claim 27, wherein the non-lipid ligand is conjugated to the 5'-end and/or the 3'-end of one or both of the guide strand and the passenger strand.

29. The dsRNAi agent of claim 28, wherein the non-lipid ligand is conjugated to the 5'-end and/or the 3'-end of one or both of the guide strand and the passenger strand via a linker.

30. The dsRNAi agent of claim 28 or 29, wherein the non-lipid ligand is conjugated to the 5'-end of the passenger strand.

31. The dsRNAi agent of claim 29 or 30, wherein the linker comprises 6-aminohexanoyl (nC6o) moiety.

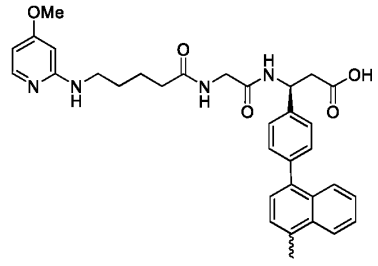
32. The dsRNAi agent of any of claims 29-31, wherein the linker further comprises a C_5 chain.

33. The dsRNAi agent of any of claims 27-32, wherein the non-lipid ligand is a carbohydrate, a protein, a peptide, a polyamine, a peptide mimic, a receptor ligand, or a combination thereof.

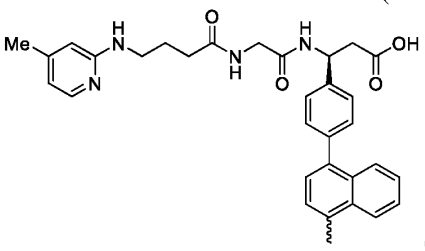
34. The dsRNAi agent of claim 33, wherein the non-lipid ligand is a receptor ligand.

35. The dsRNAi agent of claim 34, wherein the receptor ligand is an integrin receptor ligand.

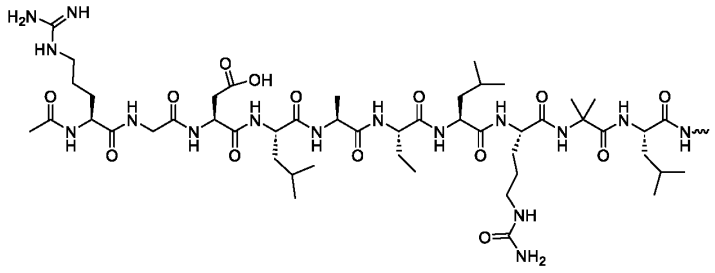
36. The dsRNAi agent of claim 35, wherein the integrin receptor ligand comprises the structure of



(OMe-integrin receptor ligand),

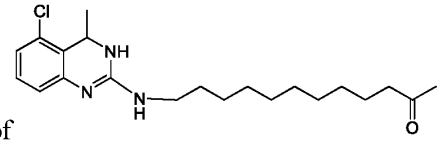


(Me-integrin receptor ligand), or



(peptide-integrin receptor ligand).

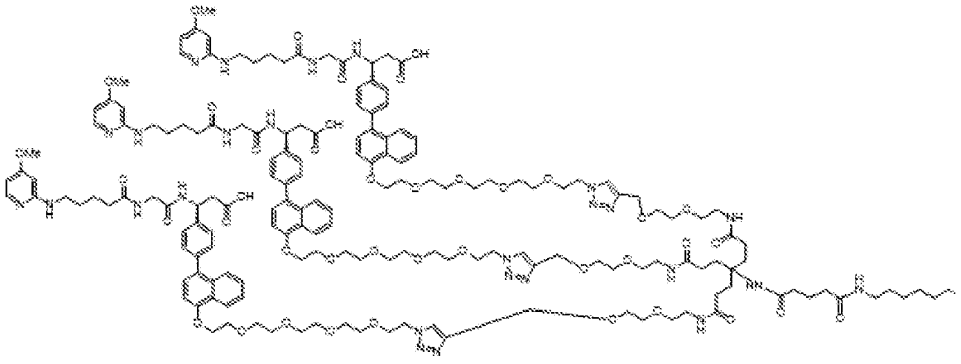
37. The dsRNAi agent of claim 34, wherein the receptor ligand is a serotonin receptor ligand.

38. The dsRNAi agent of claim 37, wherein the serotonin receptor ligand comprises the structure of .

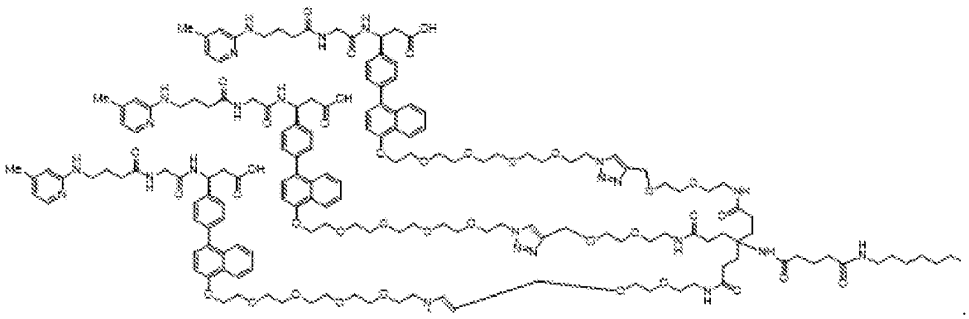
39. The dsRNAi agent of claim 36, wherein the OMe-integrin receptor ligand is a mono-OMe-integrin receptor ligand, a bis-OMe-integrin receptor ligand, or a tri-OMe-integrin receptor ligand.

40. The dsRNAi agent of claim 36, wherein the Me-integrin receptor ligand is a mono-Me-integrin receptor ligand, a bis-Me-integrin receptor ligand, or a tri-Me-integrin receptor ligand.

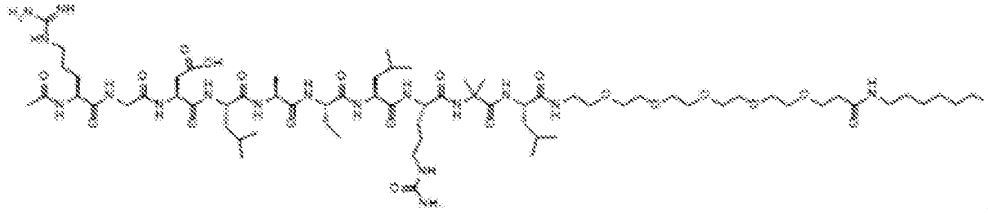
41. The dsRNAi agent of claim 39, wherein the tri-OMe-integrin receptor ligand conjugated to the guide strand or the passenger strand comprises the structure of

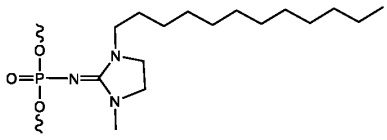


42. The dsRNAi agent of claim 40, wherein the tri-Me-integrin receptor ligand conjugated to the guide strand or the passenger strand comprises the structure of



43. The dsRNAi agent of claim 36, wherein the peptide-integrin receptor ligand conjugated to the guide strand or the passenger strand comprises the structure of



44. The dsRNAi agent of any of claims 27-43, wherein the backbone PN-lipid ligand between the +7 nucleotide and the +8 nucleotide, and/or the backbone phosphoryl guanidine (PN) chiral center between the +15 nucleotide and the +16 nucleotide, of the passenger strand, comprises the structure of  (n009), which is optionally in the *R*p configuration..

45. The dsRNAi agent of claim 33, wherein the non-lipid ligand is a carbohydrate.

46. The dsRNAi agent of claim 44, wherein the carbohydrate is a mono-GalNAc, a bis-GalNAc, a tri-GalNAc, a mannose derivative, a galactose derivative, a glucose sugar derivative, other saccharide derivatives or combinations thereof.

47. The dsRNAi agent of claim 46, wherein the carbohydrate is a tri-GalNAc.

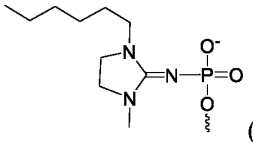
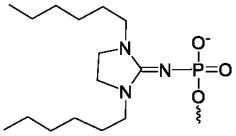
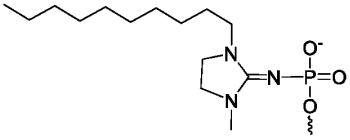
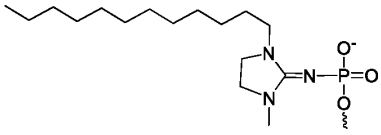
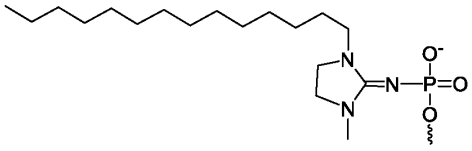
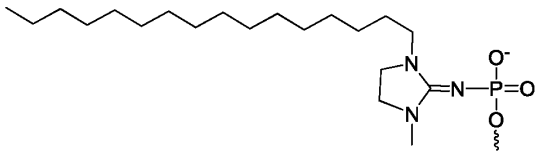
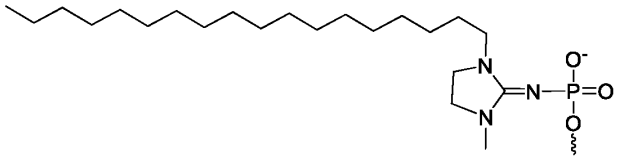
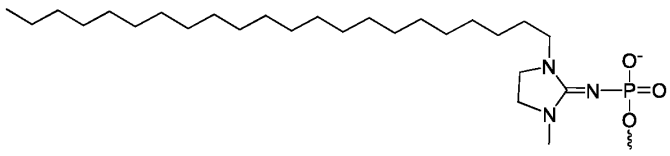
48. The dsRNAi agent of any of claims 1-47, wherein the guide strand comprises a lipid ligand.

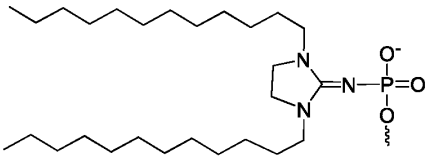
49. The dsRNAi agent of claim 48, wherein the lipid ligand is a phosphoryl guanidine-lipid

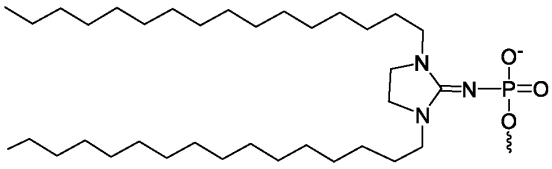
ligand (PN-lipid ligand).

50. The dsRNAi agent of claim 49, wherein the PN-lipid ligand is conjugated to the 5'-end of the guide strand (5'-end PN-lipid ligand) and/or the 3'-end of the guide strand (3'-end PN-lipid ligand).

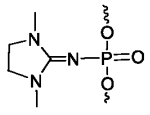
51. The dsRNAi agent of claim 50, wherein the 5'-end PN-lipid ligand or the 3'-end PN-lipid ligand comprises one or two saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain.

52. The dsRNAi agent of claim 51, wherein the 5'-end PN-lipid ligand or the 3'-end PN-lipid ligand comprises the structure of  (n031),  (n037),  (n082),  (n009),  (n083),  (n033),  (n084),  (n077),


(n039), or


(n040).

53. The dsRNAi agent of any of claims 45-50, wherein the guide strand comprises a backbone phosphoryl guanidine (PN) chiral center between the +10 nucleotide and the +11 nucleotide thereof, and wherein the backbone guanidine (PN) chiral center between the +10 nucleotide and the +11 nucleotide of the guide strand optionally comprises the structure of


(n001).

54. The dsRNAi agent of claim 53, wherein the backbone phosphoryl guanidine (PN) chiral center between the +10 nucleotide and the +11 nucleotide of the guide strand is in the *R*p configuration.

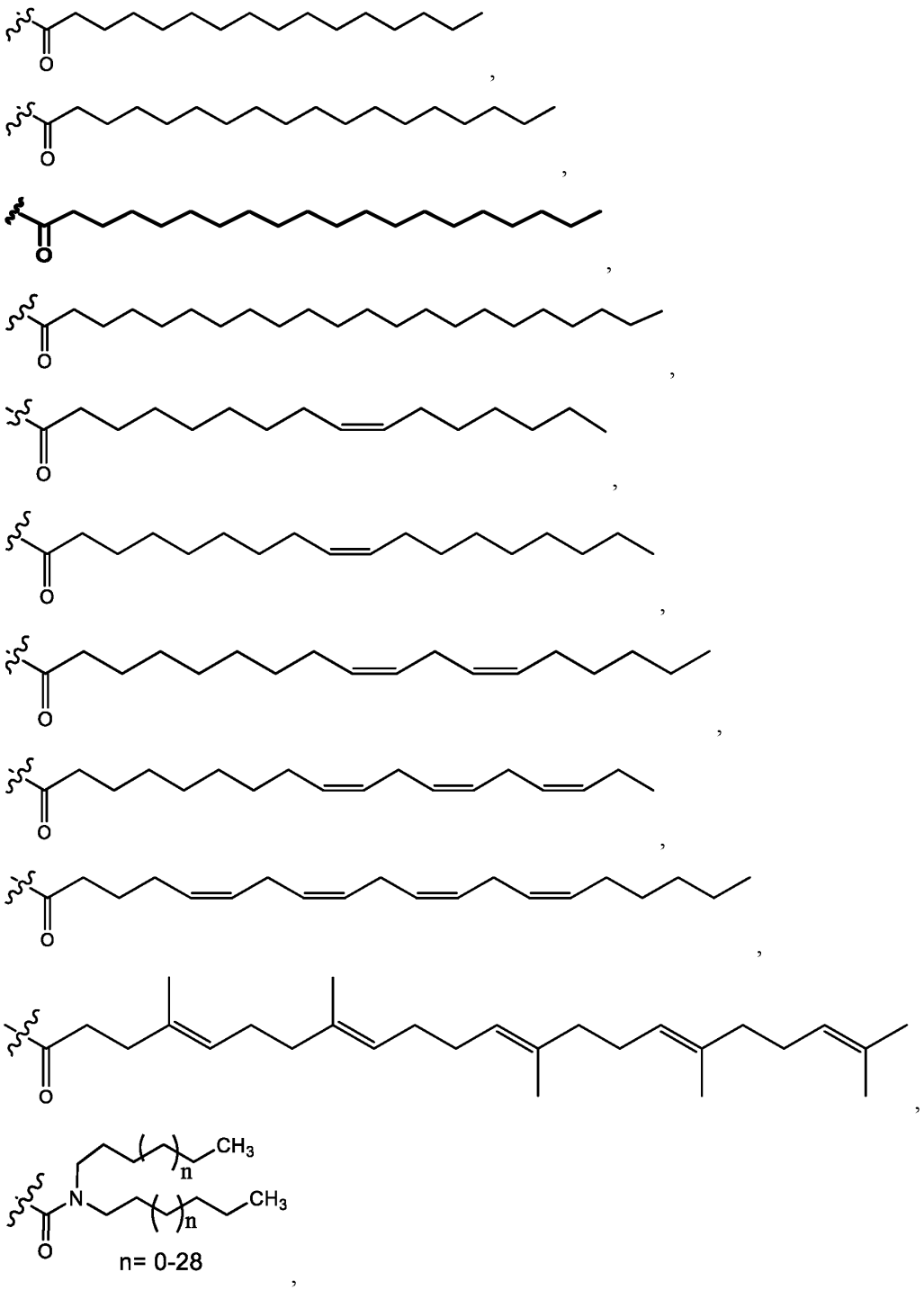
55. The dsRNAi agent of any of claims 6-26, wherein the passenger strand comprises a lipid ligand conjugated to its 5'-end and/or its 3'-end, and/or one or more internucleotidic linkages thereof.

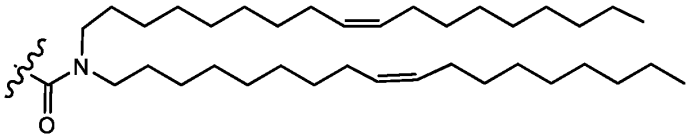
56. The dsRNAi agent of claim 55, wherein the lipid ligand is conjugated to the 5'-end and/or the 3'-end of the passenger strand via a linker.

57. The dsRNAi agent of claim 56, wherein the lipid ligand is conjugated to the 5'-end of the passenger strand, and wherein the linker comprises 6-aminohexanol (nC6o).

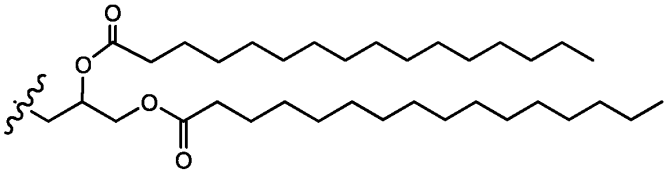
58. The dsRNAi agent of any of claims 55-57, wherein the lipid ligand comprises a saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain, cholesterol or a lipophilic cholesterol derivative, palmitoyl moiety, octadecanoyl moiety, linoleoyl moiety, turbinaric acid moiety, 2-hexyldecanoyl moiety, 20-oxoicosanoyl moiety, or a combination thereof.

59. The dsRNAi agent of claim 58, wherein the lipid comprises the structure of

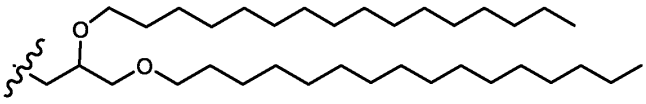




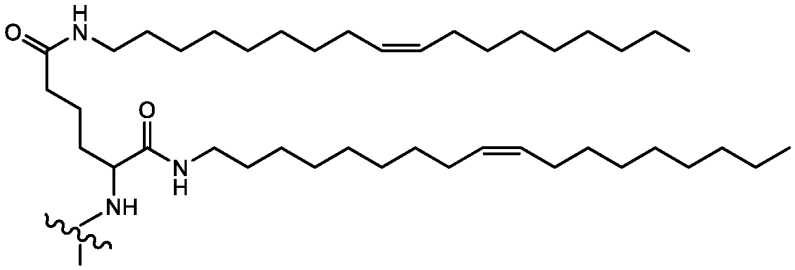
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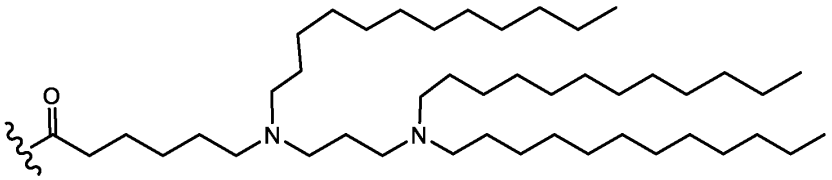
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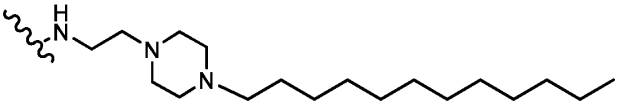
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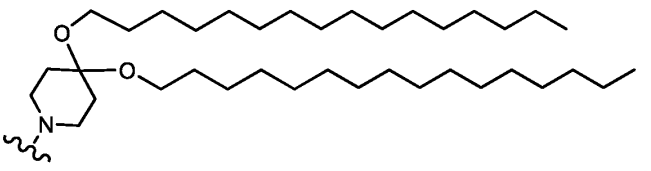
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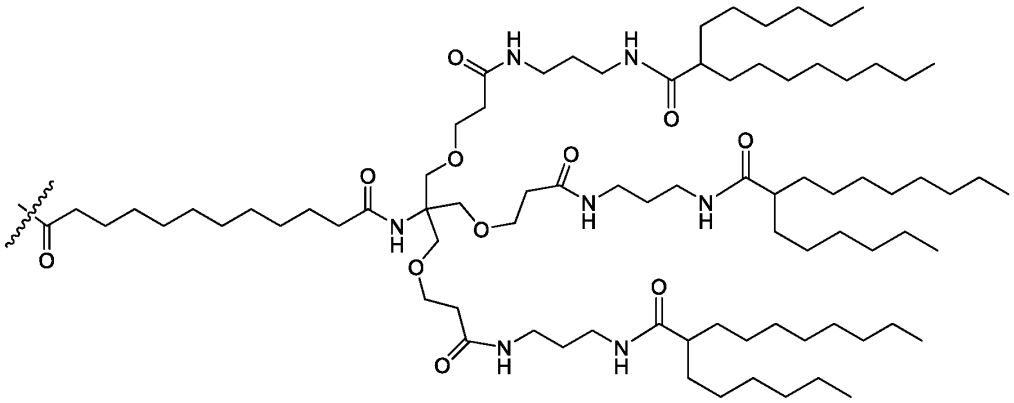
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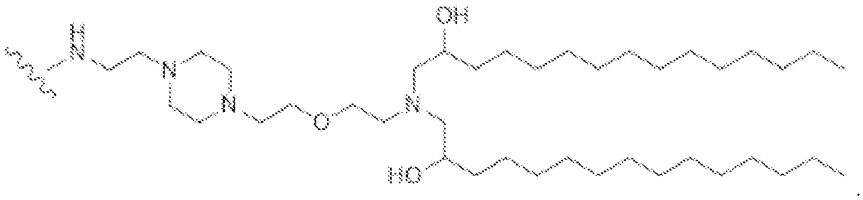
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, or



.

60. The dsRNAi agent of claim 59, wherein the lipid ligand comprises an octadecanoyl (C18) moiety.

61. The dsRNAi agent of any of claims 1-26, wherein one or both of the guide strand and the passenger strand comprise a modified sugar moiety.

62. The dsRNAi agent of claim 61, wherein the modified sugar moiety comprises a 2'-lipid modification, 2'-F modification, 2'-OH modification, 2'-OMe modification, 2'-*O*-alkyl modification, 2'-MOE modification, DNA, LNA, UNA, GNA, or a homo-DNA.

63. The dsRNAi agent of claim 61 or 62, wherein the modified sugar moiety is at one or more positions.

64. The dsRNAi agent of any of claims 61-63, wherein the modified sugar is at one or more of: position +1, position +2, position + 3, position + 4, position +5, position +6, and position +7, relative to the 5'-end of the passenger strand.

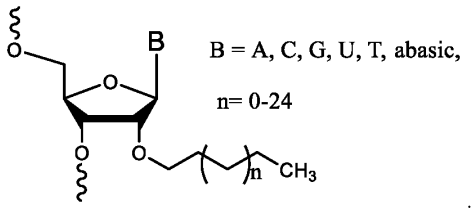
65. The dsRNAi agent of any of claims 62-64, wherein the 2'-modification is −L−, wherein L connects C2 and C4 of the sugar moiety.

66. The dsRNAi agent of any of claims 61-64, wherein the modified sugar moiety comprises a 2'-lipid modification.

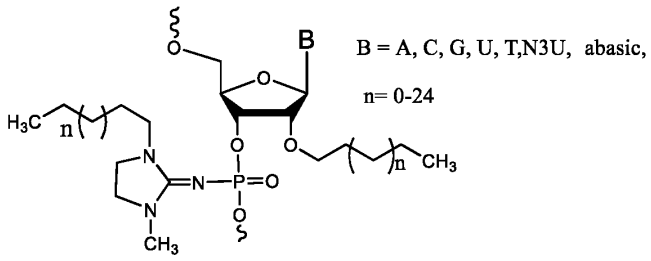
67. The dsRNAi agent of claim 66, wherein the passenger strand comprises a modified sugar moiety comprising a 2'-lipid modification.

68. The dsRNAi agent of claim 66 or 67, wherein the modified sugar moiety comprising a 2'-lipid modification is a 2'-lipid modified ribose moiety.

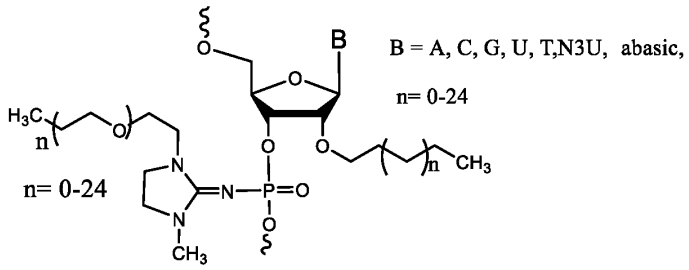
69. The dsRNAi agent of any of claims 66-68, wherein the 2'-lipid modification comprises a saturated or unsaturated, linear or branched C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chain.

70. The dsRNAi agent of claim 69, wherein the 2'-lipid modified ribose moiety comprises the structure of 

.

71. The dsRNAi agent of claim 70, wherein the 2'-lipid modified ribose moiety comprises the structure of 

.

72. The dsRNAi agent of claim 70, wherein the 2'-lipid modified ribose moiety comprises the structure of 

.

73. The dsRNAi agent of any of claims 66-72, wherein the 2'-lipid modification comprises 2'-*O*-hexadecyl moiety.

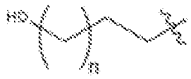
74. The dsRNAi agent of any of claims 66-73, wherein the +7 nucleotide of the passenger strand comprises the 2'-lipid modification.

75. The dsRNAi agent of claim 74, wherein the passenger strand comprises n001, n009 or n033 between the +7 nucleotide and the +8 nucleotide thereof.

76. The dsRNAi agent of any of claims 1-26, wherein one or both of the guide strand and the passenger strand comprise a phosphoryl guanidine-lipid (PN-lipid) ligand at the 5'-end or the 3'-end thereof, wherein the PN-lipid ligand further comprises a non-cleavable linker.

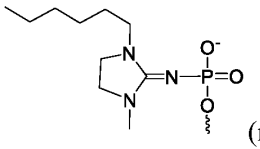
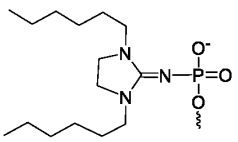
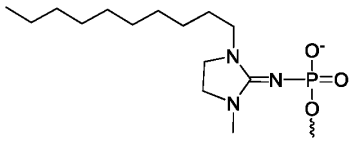
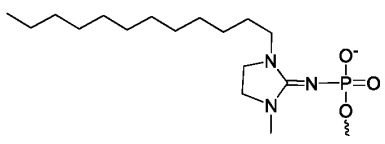
77. The dsRNAi agent of claim 76, wherein the PN-lipid ligand comprising the non-cleavable linker is conjugated to the 5'-end of the passenger strand.

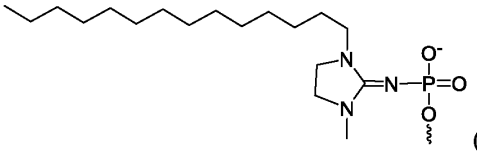
78. The dsRNAi agent of claim 76 or 77, wherein the PN-lipid ligand comprises one or two saturated or unsaturated C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}, C_{22}, C_{24}, C_{26}, or C_{28} chains.

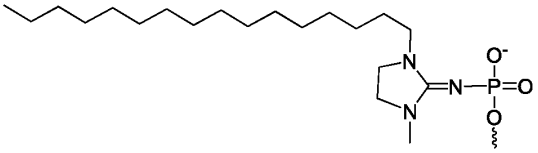
79. The dsRNAi agent of any of claims 76-77, wherein the non-cleavable linker is , wherein n = 0-24.

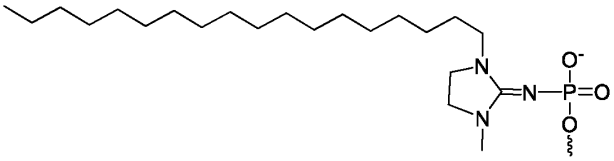
80. The dsRNAi agent of claim 80, wherein the non-cleavable linker is  (oC6o).

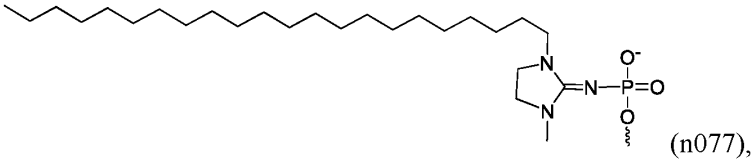
81. The dsRNAi agent of any of claims 76-80, wherein the non-cleavable linker is conjugated to the PN-lipid ligand via a phosphoester bond.

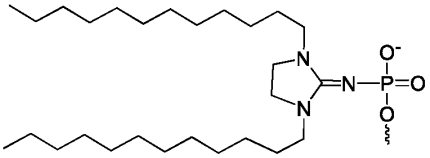
82. The dsRNAi agent of claim 81, wherein the PN-lipid ligand comprising the non-cleavable linker comprises the structure of  (n031),  (n037),  (n082),  (n009),

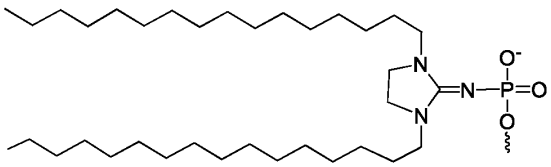

(n083),


(n033),

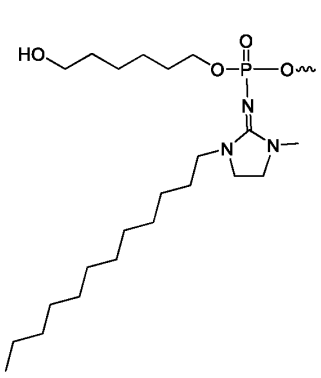

(n084),

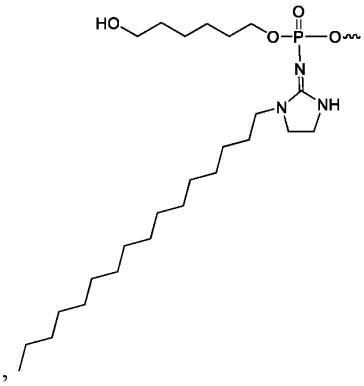

(n077),

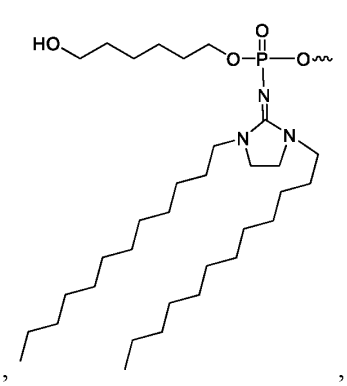

(n039), or

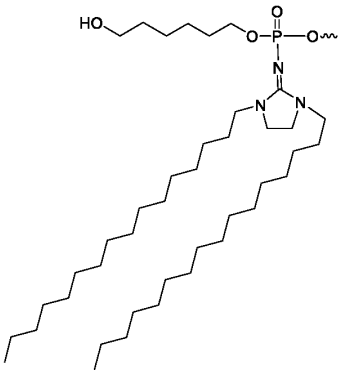

(n040).

83. The dsRNAi agent of claim 82, wherein the PN-lipid ligand comprising the non-cleavable linker comprises the structure of


,


,

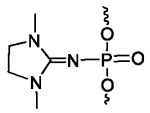

, or



84. A double-stranded RNAi (dsRNAi) agent capable of directing target-specific RNA interference, the dsRNAi agent comprising a guide strand and a passenger strand, wherein:

the guide strand is complementary or substantially complementary to a target RNA sequence; and

one or both of the guide strand and the passenger strand comprise one or more backbone phosphoryl guanidine (PN) chiral centers each independently comprising the structure of

 (n001) or a non-lipid variation (non-lipid PN variation) of.

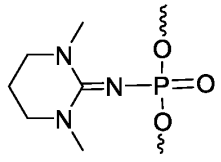
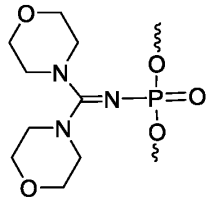
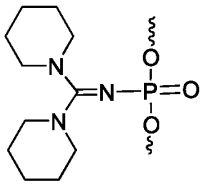
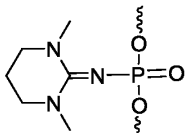
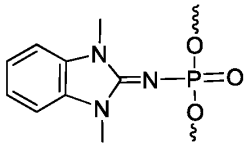
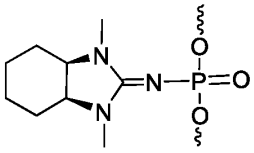
85. The dsRNAi agent of claim 84, wherein one or both of the guide strand and the passenger strand comprise at least one non-lipid PN variation of n001.

86. The dsRNAi agent of claim 85, wherein the guide strand comprises at least one non-lipid PN variation of n001.

87. The dsRNAi agent of any of claims 84-86, wherein the guide strand further comprises a backbone phosphoryl guanidine (PN) chiral center between the +10 nucleotide and the +11 nucleotide thereof.

88. The dsRNAi agent of claim 87, wherein the backbone phosphoryl guanidine (PN) chiral center between the +10 nucleotide and the +11 nucleotide in the guide strand is in the *R*p configuration.

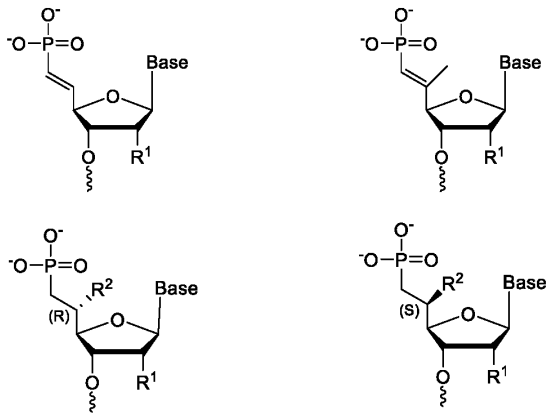
89. The dsRNAi agent of claim 87 or 88, wherein the guide strand comprises at least one non-lipid PN variation of n001 between the +3 nucleotide and the +4 nucleotide, and between the +10 nucleotide and the +11 nucleotide thereof.

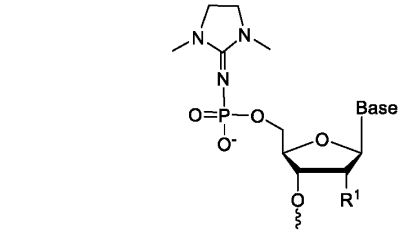
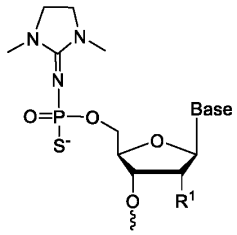
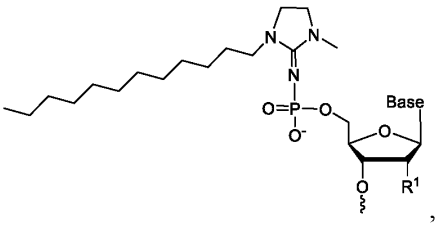
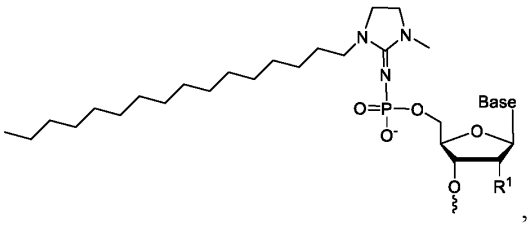
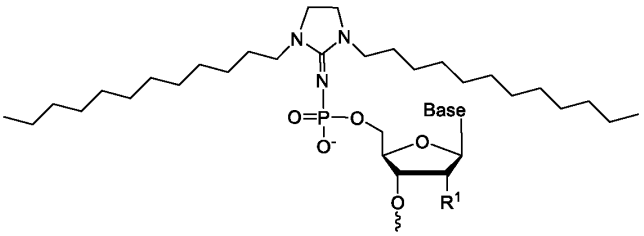
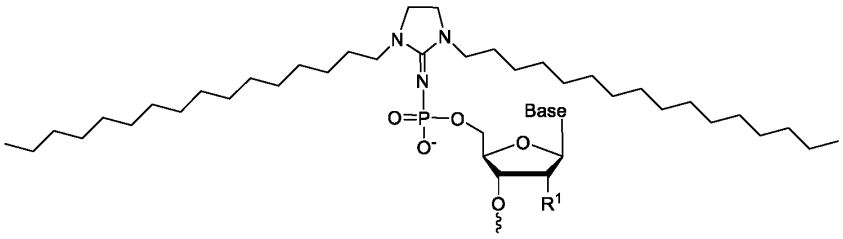
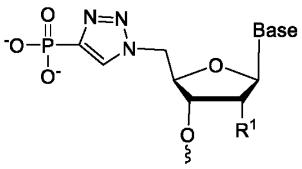
90. The dsRNAi agent of any of claims 84-89, wherein the non-lipid PN-variation of n001 comprises the structure of  (n003),  (n008),  (n078),  (n025),  (n065), or  (n070).

91. The dsRNAi agent of any of claims 84-80-, wherein the passenger strand comprises a backbone phosphorothioate (PS) chiral center between the 5' terminal (+1) nucleotide and the +2 nucleotide, and/or a backbone phosphorothioate (PS) chiral center between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide.

92. The dsRNAi agent of claim 91, wherein the PS chiral center between the 5' terminal (+1) nucleotide and the +2 nucleotide, and/or between the 3' terminal (N) nucleotide and the penultimate (N-1) nucleotide, of the passenger strand, is/are in the *S*p configuration.

93. The dsRNAi agent of any of claims 84-92, wherein the guide strand further comprises a 5' terminal modification selected from the group consisting of






,

,

,

, and

, wherein

the base is A, C, G, T, U, abasic, or a modified nucleobase;

R^1 is selected from H, OH, *O*-alkyl, *O*-methyl (O-Me), F, *O*-methoxyethyl (MOE), and 2'-*O*,4'*C*-methylene-bridged or locked nucleic acid (2',4'-BNA or LNA); and

R^2 is selected from alkyl, methyl, ethyl, isopropyl, propyl, cyclohexyl, benzyl, phenyl, tolyl, xylyl, aryl, and arene group.

94. The dsRNAi agent of claim 93, wherein the 5' terminal modification is triazolyl phosphonate or methyl phosphonate.

95. The dsRNAi agent of any of claims 1-26, wherein one or both of the guide strand and the

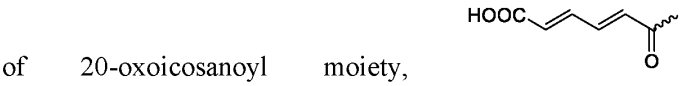
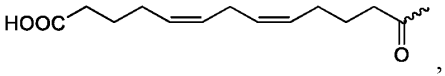
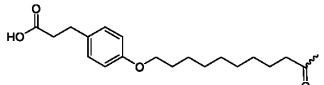
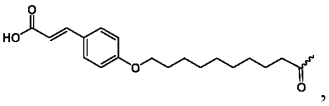
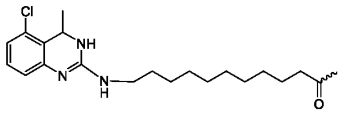
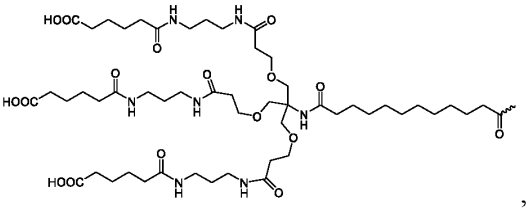
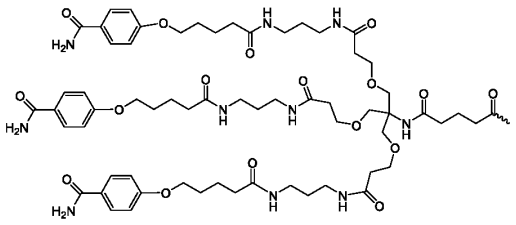
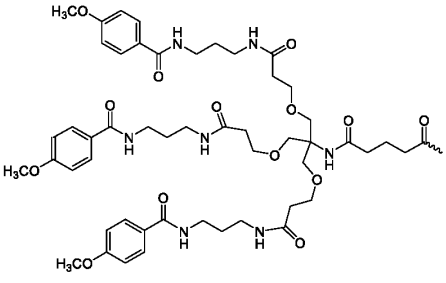
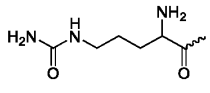
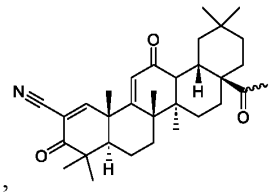
passenger strand comprise a hydrophilic or amphiphilic ligand.

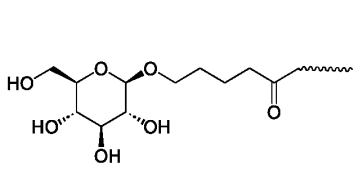
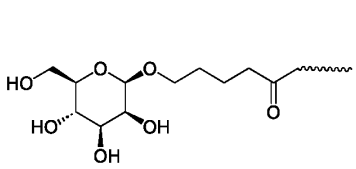
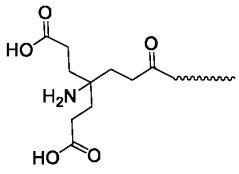
96. The dsRNAi agent of claim 95, wherein one or both of the guide strand and the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to the 5'-end and/or the 3'-end thereof, and/or one or more internucleotidic linkages.

97. The dsRNAi agent of claim 95 or 96, wherein one or both of the guide strand and the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to the 5'-end thereof via a linker.

98. The dsRNAi agent of claim 97, wherein the linker comprises 6-aminohexanol (nC6o).

99. The dsRNAi agent of any of claims 95-98, wherein the hydrophilic or amphiphilic ligand is conjugated to the 5'-end of the passenger strand.

100. The dsRNAi agent of any of claims 95-98, wherein the hydrophilic or amphiphilic ligand comprises the structure of 20-oxoicosanoyl moiety, , , , , , , , , , ,


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, or

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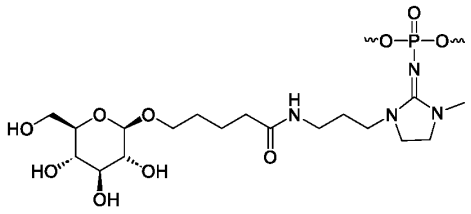
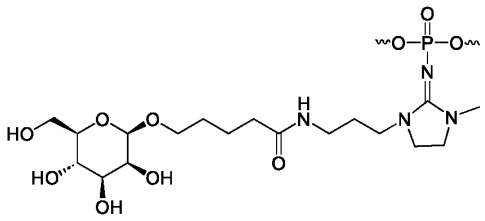
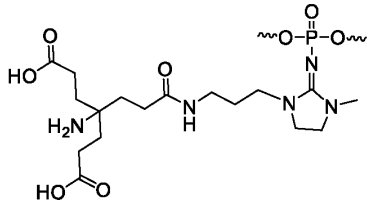
101. The dsRNAi agent of any of claims 95-100, wherein one or both of the guide strand and the passenger strand comprise a hydrophilic or amphiphilic ligand conjugated to a backbone phosphoryl guanidine (PN) chiral center.

102. The dsRNAi agent of claim 101, wherein the passenger strand comprises a hydrophilic or amphiphilic ligand conjugated to a backbone PN chiral center.

103. The dsRNAi agent of claim 101 or 102 wherein the backbone PN chiral center is between the +7 nucleotide and the +8 nucleotide of the passenger strand.

104. The dsRNAi agent of claim 103, wherein the backbone PN chiral center between the +7 nucleotide and the +8 nucleotide of the passenger strand is in the *R*p configuration.

105. The dsRNAi agent of any of claims 101-104, wherein the backbone PN chiral center comprising a hydrophilic or amphiphilic ligand conjugated thereto comprises the structure of


(n079),


(n085), or
(n081).

106. The dsRNAi agent of any of the preceding claims, wherein the guide strand further comprises backbone PS chiral centers in *S*p configuration between the 3' terminal nucleotide and the penultimate (N-1) nucleotide and between the penultimate (N-1) nucleotide and the immediately upstream (N-2) nucleotide.

107. The dsRNAi agent of any of the preceding claims, wherein the guide strand further comprises a backbone PN chiral center in the Rp configuration between the +10 nucleotide and the +11 nucleotide.

108. The dsRNAi agent of any of the preceding claims, wherein the guide strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs between any two adjacent nucleotides between the second (+2) nucleotide relative to the 5' terminal nucleotide of the guide strand and the penultimate 3' (N-1) nucleotide of the guide strand, where N is the 3' terminal nucleotide.

109. The dsRNAi agent of any of the preceding claims, wherein the guide strand comprises a 2' modification, of the 3' nucleotide of a nucleotide pair linked by an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage.

110. The dsRNAi agent of any of the preceding claims, wherein the guide strand comprises an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage between the tenth (+10) and eleventh (+11) nucleotides, relative to the 5' terminal nucleotide.

111. The dsRNAi agent of any of the preceding claims, wherein the guide strand comprises an Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage between the seventh (+7) and eighth (+8) nucleotides, relative to the 5' terminal nucleotide.

112. The dsRNAi agent of any of the preceding claims, wherein the guide strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration where linkage occurs between any two adjacent nucleotides between the penultimate 3' nucleotide of the guide strand, where N is the 3' terminal nucleotide, and the upstream N-10 nucleotide.

113. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand.

114. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises one or more Rp, Sp, or stereorandom non-negatively charged internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand.

115. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration internucleotidic linkage occurs upstream, i.e., in the 5' direction, relative to the central nucleotide of the passenger strand.

116. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises one or more backbone phosphorothioate chiral centers in Rp or Sp configuration internucleotidic linkage internucleotidic linkage occurs downstream, i.e., in the 3' direction, relative to the central nucleotide of the passenger strand.

117. The dsRNAi agent of any of the preceding claims, wherein the passenger strand in combination with one or more of the aforementioned guide strands, comprises one or more modified sugars between the 5' terminal (+1) nucleotide and the penultimate (N-1) nucleotide.

118. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises one or more of:

0-n Rp, Sp, or stereorandom non-negatively charged internucleotidic linkages, where n is about 1 to 49;

one or more backbone chiral centers in Rp or Sp configuration;

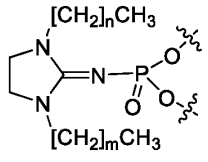
one or more backbone phosphoryl guanidine chiral centers in the Rp configuration between the +7 nucleotide and the immediately downstream (+8) nucleotide, i.e., in the 3' direction;

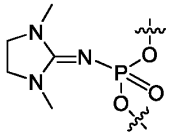
one or more backbone phosphoryl guanidine chiral centers in the Rp configuration between the +15 nucleotide and the immediately downstream (+16) nucleotide, i.e., in the 3' direction; and/or

backbone phosphorothioate chiral centers in the Sp configuration between the 5' terminal (+1) nucleotide and the immediately downstream, i.e., in the 3' direction, (+2) nucleotide and between the 3' terminal nucleotide and the penultimate (N-1) nucleotide.

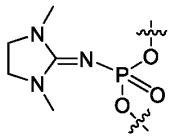
119. The dsRNAi agent of any of the preceding claims, wherein each strand of the dsRNAi agent independently has a length of about 15 to about 49 nucleotides.

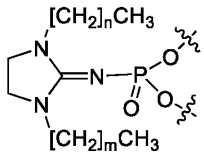
120. The dsRNAi agent of any of the preceding claims, wherein the Rp, Sp, or stereorandom non-negatively charged backbone internucleotidic linkages have neutral charge.

121. The dsRNAi agent of claim 120, wherein the neutral backbone internucleotidic linkage is , wherein n is about 0 to 49 and m is about 0 to 49.

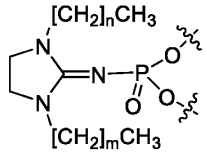
122. The dsRNAi agent of claim 121, wherein the guide strand comprises a linkage having the following structure  between the third (+3) and fourth (+4) nucleotides of the guide strand, between the tenth (+10) and eleventh (+11) nucleotides of the guide strand, or both.

123. The dsRNAi agent of claim 121, wherein the guide strand comprises a linkage having the following structure

 between the third (+3) and fourth (+4) nucleotides of the guide strand, between the seventh (+7) and eighth (+8) nucleotides of the guide strand, between the tenth (+10) and eleventh (+11) nucleotides of the guide strand, between the eighteenth (+18) and nineteenth (+19) nucleotides of the guide strand, or combinations thereof.

124. The dsRNAi agent of claim 121, wherein the passenger strand comprises a linkage having the following structure , where n is about 0 to 49 and m is about 0 to 49, at 5' to the central nucleotide of the passenger strand, 3' to the central nucleotide of the passenger strand, or both.

125. The dsRNAi agent of claim 121, wherein the passenger strand comprises a linkage

having the following structure , wherein n is about 11 to 49 and m is 0.

126. The dsRNAi agent of claim 125, wherein n is 11 or 15.

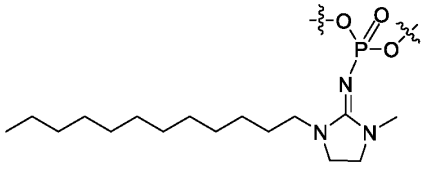
127. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises:

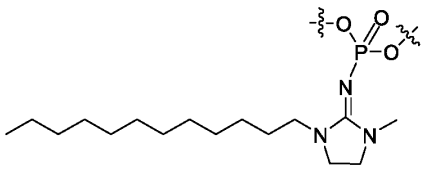
i. a non-negatively charged backbone internucleotidic linkage in the Rp configuration between the +7 nucleotide and the +8 nucleotide;

ii. a non-negatively charged backbone internucleotidic linkage in the Rp configuration between the +15 nucleotide and the +16 nucleotide; and/or

iii. backbone phosphorothioate chiral centers in the Sp configuration between the 5' terminal (+1) nucleotide and the +2 nucleotide and between the 3' terminal nucleotide and the penultimate (N-1) nucleotide.

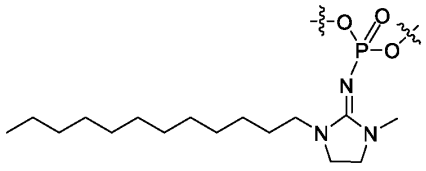
128. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises:

i.  in the Rp configuration between the +7 nucleotide and the +8 nucleotide;

ii.  in the Rp configuration between the +15 nucleotide and the +16 nucleotide; and

iii. backbone phosphorothioate chiral centers in the Sp configuration between the +1 nucleotide and the +2 nucleotide and between the 3' terminal nucleotide and the penultimate (N-1) nucleotide.

129. The dsRNAi agent of any of the preceding claims, wherein the passenger strand comprises:

i.  in the Rp configuration between the +7 nucleotide and the +8 nucleotide; and

ii. backbone phosphorothioate chiral centers in the Sp configuration between the +1 nucleotide and the +2 nucleotide and between the 3' terminal nucleotide and the penultimate (N-1) nucleotide.

130. A method for reducing level and/or activity of a transcript or a protein encoded thereby in a cell of a first tissue and a cell of a second tissue, comprising administering to the cells expressing the transcript a dsRNAi agent of any of the preceding claims, wherein the guide strand of the dsRNAi agent comprises a targeting-binding sequence that is completely complementary to a target sequence in the transcript.

131. The method of claim 131 wherein the cell is a liver cell, kidney cell, heart cell, white adipose cell, brown adipose cell, muscle cell, diaphragm cell, lung cell, sciatic nerve cell, pancreas cell, central nervous system cell, or spleen cell.

132. A method for allele-specific suppression of a transcript from a nucleic acid sequence for which a plurality of alleles exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the allele relative to other alleles of the same target nucleic acid sequence, the method comprising steps of:

contacting a sample comprising transcripts of the target nucleic acid sequence with a dsRNAi agent of any of the preceding claims,

wherein the guide strand of the dsRNAi agent comprises a targeting-binding sequence that is identical or completely complementary to a target sequence in the nucleic acid sequence, which target sequence comprises a characteristic sequence element that defines a particular allele, and

wherein when the guide strand of the dsRNAi agent is contacted with a cell comprising transcripts of both the target allele and another allele of the same nucleic acid sequence, transcripts of the particular allele are suppressed at a greater level than a level of suppression observed for another allele of the same nucleic acid sequence.

133. A method for allele-specific suppression of a transcript from a nucleic acid sequence for which a plurality of alleles exist within a population, each of which contains a specific nucleotide characteristic sequence element that defines the allele relative to other alleles of the same target nucleic acid sequence, the method comprising steps of:

administering to a subject comprising transcripts of the target nucleic acid sequence with a dsRNAi agent of any of the preceding claims,

wherein the guide strand of the dsRNAi agent comprises a targeting-binding sequence that is identical or completely complementary to a target sequence in the nucleic acid sequence, which target sequence comprises a characteristic sequence element that defines a particular allele, and

wherein when the guide strand of the dsRNAi agent is contacted with a cell comprising transcripts of both the target allele and another allele of the same nucleic acid sequence, transcripts of the particular allele are suppressed at a greater level than a level of suppression observed for another allele of the same nucleic acid sequence.

134. The method of any of claims 130-133, wherein when the dsRNAi agent is contacted with a cell comprising transcripts of both the target allele and another allele of the same nucleic acid sequence, it shows suppression of transcripts of the particular allele at a level that is:

greater than when the dsRNAi agent is absent;

greater than a level of suppression observed for another allele of the same nucleic acid sequence; or

both greater than when the dsRNAi agent is absent, and greater than a level of suppression observed for another allele of the same nucleic acid sequence.

135. The method of claim 133, wherein the cell is a liver cell, kidney cell, heart cell, white adipose cell, brown adipose cell, muscle cell, diaphragm cell, lung cell, sciatic nerve cell, pancreas cell, central nervous system cell, or spleen cell.

136. The method of any of claims 131-135, wherein suppression of transcripts of the particular allele is at a level that is both greater than when the dsRNAi agent is absent, and greater than a level of suppression observed for another allele of the same nucleic acid sequence.

137. The method of claim 130 further comprising reducing level and/or activity of a transcript or a protein encoded thereby in a cell of a third tissue and a fourth tissue, comprising administering to the cells of the first, second, third, and fourth tissues expressing the transcript a dsRNAi agent of any of the preceding claims, wherein the guide strand of the dsRNAi agent comprises a targeting-binding sequence that is completely complementary to a target sequence in the transcript.

138. The method of claim 137, wherein the cell of a third and a fourth tissue is a liver cell, kidney cell, heart cell, white adipose cell, brown adipose cell, muscle cell, diaphragm cell, lung cell, sciatic nerve cell, pancreas cell, central nervous system cell, or spleen cell.