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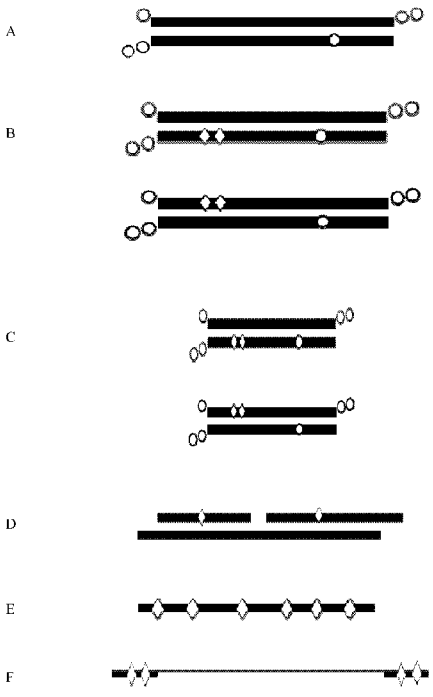

FIG. 1

(57) Abstract: This disclosure provides single-stranded and multi-stranded nucleic acid compounds having one or more double-stranded regions that regulate the function or expression of nucleic acid molecules expressed in a cell or a cell regulatory system dependent upon a nucleic acid. The disclosure provides a range of nucleic acid compounds having one or more conformationally restricted nucleomonomers (CRN). Certain nucleic acid compounds may have one or more conformationally restricted nucleomonomers and one or more hydroxymethyl substituted nucleomonomers (UNA). The nucleic acid compounds are useful in various therapeutic modalities.

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NUCLEIC ACID COMPOUNDS WITH CONFORMATIONALLY RESTRICTED MONOMERS AND USES THEREOF

TECHNICAL FIELD

This disclosure relates generally to nucleic acid compounds for use in treating disease by regulating the expression of genes and other cell regulatory systems dependent upon a nucleic acid in a cell. More specifically, this disclosure relates to single-stranded and multi-stranded nucleic acid compounds having one or more duplex regions that can regulate the function or expression of nucleic acid molecules expressed in a cell. This disclosure provides a range of nucleic acid compounds having one or more conformationally restricted nucleomonomers (CRN). This disclosure further provides nucleic acid compounds containing one or more CRNs and one or more hydroxymethyl substituted nucleomonomers (UNA).

SEQUENCE LISTING

This application includes a Sequence Listing submitted electronically herewith via EFS as an ASCII file created on April 23, 2011, named MAR230PCT_SeqList_ST25_fin.txt, which is 126,128 bytes in size, and is hereby incorporated by reference in its entirety.

BACKGROUND

RNA interference (RNAi) refers to the cellular process of sequence specific, post-transcriptional gene silencing in animals mediated by small inhibitory nucleic acid molecules, such as a double-stranded RNA (dsRNA) that is homologous to a portion of a targeted messenger RNA (Fire *et al.*, *Nature 391*:806, 1998; Hamilton *et al.*, *Science 286*:950-951, 1999). RNAi has been observed in a variety of organisms, including mammalians (Fire *et al.*, *Nature 391*:806, 1998; Bahramian and Zarbl, *Mol. Cell. Biol. 19*:274-283, 1999; Wianny and Goetz, *Nature Cell Biol. 2*:70, 1999). RNAi can be induced by introducing an exogenous synthetic 21-nucleotide RNA duplex into cultured mammalian cells (Elbashir *et al.*, *Nature 411*:494, 2001a).

The mechanism by which dsRNA mediates targeted gene-silencing can be described as involving two steps. The first step involves degradation of long dsRNAs by a ribonuclease III-like enzyme, referred to as Dicer, into short interfering RNAs (siRNAs) having from 21 to 23 nucleotides with double-stranded regions of about 19 base pairs and a two nucleotide, generally, overhang at each 3'-end (Berstein *et al.*, *Nature 409*:363, 2001; Elbashir *et al.*, *Genes Dev. 15*:188, 2001b; and Kim *et al.*, *Nature Biotech. 23*:222, 2005). The second step of RNAi gene-silencing involves activation of a multi-component nuclease having one strand (guide or

antisense strand) from the siRNA and an Argonaute protein to form an RNA-induced silencing complex ("RISC") (Elbashir *et al.*, *Genes Dev. 15*:188, 2001). Argonaute initially associates with a double-stranded siRNA and then endonucleolytically cleaves the non-incorporated strand (passenger or sense strand) to facilitate its release due to resulting thermodynamic instability of the cleaved duplex (Leuschner *et al.*, *EMBO 7*:314, 2006). The guide strand in the activated RISC binds to a complementary target mRNA, which is then cleaved by the RISC to promote gene silencing. Cleavage of the target RNA occurs in the middle of the target region that is complementary to the guide strand (Elbashir *et al.*, 2001b).

What is needed are alternative effective therapeutic modalities useful for treating or preventing diseases or disorders by regulating the expression of genes and other nucleic acid based regulatory systems in a cell.

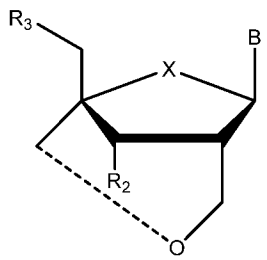
A need therefore exists for nucleic acid compounds having enhanced stability that are useful in various therapeutic modalities such as RNA interference.

BRIEF SUMMARY

This disclosure provides single-stranded and multi-stranded nucleic acid compounds having one or more double-stranded regions that can regulate the function or expression of nucleic acid molecules expressed in a cell and/or cell regulatory system dependent upon a nucleic acid in a cell. The disclosure provides a range of nucleic acid compounds having one or more conformationally restricted nucleomonomers (CRN). In some embodiments, a nucleic acid compound may have one or more conformationally restricted nucleomonomers and one or more hydroxymethyl substituted nucleomonomers (UNA).

In some embodiments, this disclosure provides a range of nucleic acid compound comprising a first strand having from 10 to 60 nucleomonomers, wherein from 1 to 45 of the nucleomonomers of the first strand are the same or different conformationally restricted nucleomonomers each independently selected from

Monomer R having the formula:

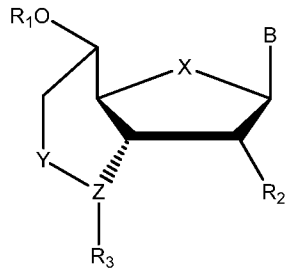


wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2;

R_2 and R_3 are phosphodiester linkages of the nucleic acid compound; and

B is a nucleobase or nucleobase analog; and

Monomer Q having the formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2 ;

Z is independently for each occurrence selected from N or CH;

R_2 is independently for each occurrence selected from hydrogen, -F, -OH, $-OCH_3$, $-OCH_3OCH_3$, $-OCH_2CH_3OCH_3$, $-CH_2CH_3OCH_3$, $-CH(OCH_3)CH_3$, and allyl;

R_1 and R_3 are phosphodiester linkages of the nucleic acid compound; and

B is a nucleobase or nucleobase analog;

wherein each nucleobase or nucleobase analog in the strand is independently selected from adenine, cytosine, guanine, uracil, hypoxanthine, thymine, 7-deazaadenine, inosine, C-phenyl, C-naphthyl, inosine, an azole carboxamide, nebularine, a nitropyrrole, a nitroindole, 2-aminopurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-methyluridine, 5-propynylcytidine, isocytidine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 2-thioribothymidine, 5,6-dihydrouracil, 4-methylindole, ethenoadenine, deoxyuridine, and any existing deoxy analogs of the foregoing.

A compound of this disclosure may contain two or more of the same or different Monomer R. In some embodiments, a compound may contain two or more of the same or different Monomer Q. In certain embodiments, the first strand may have from 19 to 27 nucleomonomers. In some aspects, the compounds of this disclosure RNA, or RNA and DNA.

In certain aspects, a compound of this disclosure may include one or more hydroxymethyl substituted nucleomonomers.

This disclosure further provides a range of compounds having one or two additional strands each having from 7 to 60 nucleomonomers, wherein at least a portion of each of the additional strands is complementary to a portion of the first strand, wherein the first strand and the one or two additional complementary strands can anneal to form one or more duplex

portions having a total of from 8 to 60 base pairs in the duplex portions, and wherein one or more of the nucleomonomers of the one or two additional strands is a conformationally restricted nucleomonomer.

A compound of this disclosure may have a sequence targeted for various genes. In some embodiments, a compound of this disclosure may have a sequence targeted for PLK1, a sequence targeted for Survivin BIRC5, a sequence targeted for Factor VII, or a sequence targeted for ApoB.

In certain embodiments, a compound of this disclosure may have conformationally restricted nucleomonomers only present in either of the one or more additional strands, and the first strand does not contain any conformationally restricted nucleomonomers.

In further embodiments, a compound may have a melting temperature increased by at least 1°C over the same compound that does not contain any conformationally restricted nucleomonomers.

Some compounds of this disclosure are siRNAs, or mdRNAs, or RNA and DNA. In certain embodiments, a compound may have one of the additional strands having one or more nicks. A compound may have one or more duplex gaps that are each independently from 1 to 10 unpaired nucleomonomers in length. A compound may have a blunt end. A compound may have a 3'-end overhang.

This disclosure further contemplates compounds for use in delivering an RNA agent into a cell or an organism. A compound may be used in mediating nucleic acid modification of a target nucleic acid in a cell or an organism. A compound may be used use in decreasing expression levels of a target mRNA in a cell or an organism.

In some embodiments, a compound may be used in inhibiting an endogenous nucleic acid-based regulatory system in a cell or an organism.

In further embodiments, a compound may be used in gene regulation, gene analysis, or RNA interference.

In some aspects, a compound may be used in the manufacture of a medicament for a therapeutic target, including targets for cancers, metabolic diseases, inflammatory diseases, and viral infections.

In certain aspects, a compound may be used in treating a disease, condition or disorder, including cancers, metabolic diseases, inflammatory diseases, and viral infections.

In further aspects, this disclosure contemplates methods for treating a disease, condition or disorder in a subject including cancers, metabolic diseases, inflammatory diseases, and viral infections, the method comprising administering to the subject a compound according to any one of claims 1-23.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Example nucleic compounds containing one or more hydroxymethyl substituted nucleomonomer (represented by an "O" in the nucleic acid compound) and/or a conformationally restricted nucleomonomer (represented by a "◊" in the nucleic acid compound). Fig. 1A is a double-stranded nucleic acid compound. The nucleic acid compounds of Fig. 1B have the same configuration as the nucleic acid compound of Fig. 1A, but each has two conformationally restricted nucleomonomers. Fig. 1C shows two nucleic acid compounds having equal length antisense and sense strands, each from 10 to 17 nucleomonomers in length. Fig. 1D is a nucleic acid compound complex having a nicked or gapped sense strand and a continuous antisense strand. Fig. 1E is a single-stranded nucleic acid compound having from 10 to 40 nucleomonomers. Fig. 1F is a single-stranded nucleic acid compound having from 10 to 40 nucleomonomers. The middle region noted as white represents from 4 to 8 deoxynucleotides, and the solid black regions at the 5'-end and 3'-end of the compound are ribonucleotides.

FIG. 2: Examples of conformationally restricted nucleoside analogs that may be incorporated or substituted into nucleic acid compounds.

FIG. 3: Dimers A and B represents possible backbone linkages between two Q Monomers.

FIG. 4: Monomers A, B, C and D are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds.

FIG. 5: Monomers E, F, G and H are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds.

FIG. 6: Monomers I, J, K and L are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds.

FIG. 7: Monomers M, N, O and P are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds.

DETAILED DESCRIPTION

This disclosure relates generally to nucleic acid compounds for use in treating disease by gene silencing or modulating the function of a cell regulatory system dependent upon a nucleic acid in a cell and, more specifically, to nucleic acid compounds comprising a single strand of nucleomonomers or double-stranded nucleic acid compound comprising an antisense strand and a continuous or a discontinuous passenger strand, i.e., "sense strand" containing a nick or gap, that decreases expression of a target gene, and to uses of such nucleic acid compound to treat, prevent or manage a disease or condition associated with inappropriate expression of a nucleic acid.

The nuclei acid compounds of this disclosure may further contain one or more conformationally restricted nucleomonomers (CRN) which advantageously enhance the stability of the compound in various therapeutic modalities.

In some embodiments, a nucleic acid compound may contain one or more CRNs and one or more hydroxymethyl substituted nucleomonomers (UNA).

The structures of a range of compounds of this invention are shown in Fig. 1. Example nucleic compounds containing one or more hydroxymethyl substituted nucleomonomers, represented by an "O" in the nucleic acid compound, and/or a conformationally restricted nucleomonomer, represented by a "◊" in the nucleic acid compound. Fig. 1A is a double-stranded nucleic acid compound (e.g., double-stranded RNA (dsRNA) complex) with an antisense strand (bottom strand) and sense strand (top strand) of equal length (e.g., from 18 to 40 nucleomonomers in length) having two hydroxymethyl substituted nucleomonomers at the 3'-end of the sense strand and one hydroxymethyl substituted nucleomonomer at the 5'-end of the sense strand, and two hydroxymethyl substituted nucleomonomers at the 3'-end of the antisense strand. A hydroxymethyl substituted nucleomonomer may also be in the antisense strand of the duplex region. The nucleic acid compounds of Fig. 1B have the same configuration as the nucleic acid compound of Fig. 1A, but each has two conformationally restricted nucleomonomers. In one example, the two conformationally restricted nucleomonomer are in the antisense strand of the duplex region, and in another example, the two conformationally restricted nucleomonomer are in the sense strand of the duplex region. Fig. 1C shows two nucleic acid compounds (double-stranded) having the same modifications as the two nucleic acid compounds of Fig. 1B, but for these two examples, the equal length antisense and sense strands of each are from 10 to 17 nucleomonomers in length. Fig. 1D is a nucleic acid compound complex having a nicked or gapped sense strand (top strand) having two conformationally restricted nucleomonomers that flank the nick or gap in the sense strand (each of the two double-stranded regions of the nucleic acid compound have a conformationally restricted nucleomonomer), and a continuous antisense strand. The two double-stranded regions of the nucleic acid compound are each from 7 to 20 base pairs. The nucleic acid compound has two 3'-end overhangs. Fig. 1E is a single-stranded nucleic acid compound having from 10 to 40 nucleomonomers and six conformationally restricted nucleomonomers. Fig. 1F is a single-stranded nucleic acid compound having from 10 to 40 nucleomonomers. The middle region (noted as white) represents from 4 to 8 deoxynucleotides, and the solid black regions at the 5'-end and 3'-end of the compound are ribonucleotides, each solid black region has two conformationally restricted nucleomonomers.

Some conformationally restricted nucleomonomers and nucleic acid compounds comprising conformationally restricted nucleomonomers may be found in U.S. Patent Nos. 6,833,361; 6,403,566 and 6,083,482, each of which is hereby incorporated by reference in its entirety.

In one aspect, this disclosure provides a nucleic acid compound comprising a first strand having from 10 to 60 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, or 60) nucleomonomers, wherein one or more of the nucleomonomers is a conformationally restricted nucleomonomer.

In some embodiments, this disclosure provides a nucleic acid compound comprising a first strand having from 10 to 40 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40) nucleomonomers, wherein one or more of the nucleomonomers is a conformationally restricted nucleomonomer.

In certain embodiments, the melting temperature of the nucleic acid compound is from 40°C to 100°C, or from 60°C to 90°C, or from 75°C to 80°C.

In certain embodiments, from 1% to 75% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 40% to 50% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, the nucleic acid compound comprises RNA. In certain embodiments, the nucleic acid compound comprises DNA. In certain embodiments, the nucleic acid compound comprises RNA and DNA.

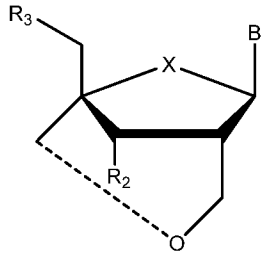
In other embodiments, the first strand is from 10 to 30 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30) nucleomonomers in length.

Examples of conformationally restricted nucleoside analogs that may be incorporated or substituted into nucleic acid compounds are shown in Fig. 2. Monomer Q contains a C3'-C5' bridge. Monomer R contains a C2'-C4' bridge. For Monomers Q and R, X may be an –O-, -S-, $-CH_2$, C=O, C=S, $C=CH_2$, CHF or CF_2; Z may be an N or CH; R_2 may be -H, -OH, -O-alkyl, -F, -SH, -S-alkyl, -S-F, -NH(CH=O), -NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

Dimers A and B shown in Fig. 3 represent possible backbone linkages between two Q Monomers. For Dimers A and B, Z_2 and Z_3 may be O, S, CO, P(O), P(O)R, P(O)O, CH_2 ; R_1 and R_3 may be OH, NH, NH2, DMTO, TBDMSO, $OP(OR)N(iPr)_2$, OP(OR)(O)H; and R may be methyl or 2-cyanoethyl.

Embodiments of this invention include a nucleic acid compound comprising a first strand having from 10 to 60 nucleomonomers, wherein from 1 to 45 of the nucleomonomers of the first strand are the same or different conformationally restricted nucleomonomers each independently selected from

Monomer R having the formula:

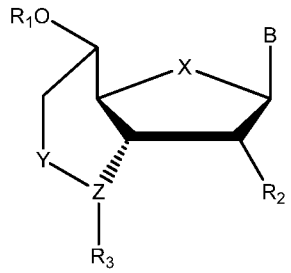


wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2;

R_2 and R_3 are phosphodiester linkages of the nucleic acid compound; and

B is a nucleobase or nucleobase analog; and

Monomer Q having the formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2 ;

Z is independently for each occurrence selected from N or CH;

R_2 is independently for each occurrence selected from hydrogen, -F, -OH, $-OCH_3$, $-OCH_3OCH_3$, $-OCH_2CH_3OCH_3$, $-CH_2CH_3OCH_3$, $-CH(OCH_3)CH_3$, allyl;

R_1 and R_3 are phosphodiester linkages of the nucleic acid compound; and

B is a nucleobase or nucleobase analog;

wherein each nucleobase or nucleobase analog in the strand is independently selected from adenine, cytosine, guanine, uracil, hypoxanthine, thymine, 7-deazaadenine, inosine, C-phenyl, C-naphthyl, inosine, an azole carboxamide, nebularine, a nitropyrrole, a nitroindole, 2-aminopurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-methyluridine, 5-propynylcytidine, isocytidine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-

dihydrothymine, 2-thioribothymidine, 5,6-dihydrouracil, 4-methylindole, ethenoadenine, deoxyuridine, and any existing deoxy analogs of the foregoing.

The compound above, wherein the compound contains two or more of the same or different Monomer R.

The compound above, wherein the compound contains two or more of the same or different Monomer Q.

The compound above, wherein the first strand has from 19 to 27 nucleomonomers.

The compound above, wherein the nucleic acid is RNA.

The compound above, wherein the nucleic acid is RNA and DNA.

The compound above, further comprising one or more hydroxymethyl substituted nucleomonomers.

The compound above, further comprising one or two additional strands each having from 7 to 60 nucleomonomers, wherein at least a portion of each of the additional strands is complementary to a portion of the first strand, wherein the first strand and the one or two additional complementary strands can anneal to form one or more duplex portions having a total of from 8 to 60 base pairs in the duplex portions, and wherein one or more of the nucleomonomers of the one or two additional strands is a conformationally restricted nucleomonomer.

The compound above, wherein any one or more of the strands has a sequence for PLK1 selected from SEQ ID NOs:161-220.

The compound above, wherein any one or more of the strands has a sequence for Survivin BIRC5 selected from SEQ ID NOs:1-160.

The compound above, wherein any one or more of the strands has a sequence for Factor VII selected from SEQ ID NOs:474-495.

The compound above, wherein any one or more of the strands has a sequence for ApoB selected from SEQ ID NOs:496-507.

The compound above, wherein any one or more of the strands has a sequence selected from SEQ ID NOs:221-230, 231-245, 246-255, 256-265, 266-275, 276-285, 286-295, 296-305, 306-315, 316-325, 326-335, 336-345, 346-355, 356-365, 366-375, 376-385, 386-395, 396-405, 406-415, 416-425, 426-435, 436-445, 446-455, 456-465, 508-517, and 518-527.

The compound above, wherein the conformationally restricted nucleomonomers are only present in either of the one or more additional strands, and the first strand does not contain any conformationally restricted nucleomonomers.

The compound above, wherein the melting temperature of the compound is increased by at least 1°C over the same compound that does not contain any conformationally restricted nucleomonomers.

The compound above, wherein the compound is an siRNA.

The compound above, wherein the compound is an mdRNA.

The compound above, wherein the compound is RNA and DNA.

The compound above, wherein one of the additional strands has one or more nicks.

The compound above, wherein the compound has one or more duplex gaps that are each independently from 1 to 10 unpaired nucleomonomers in length.

The compound above, wherein the compound has a blunt end.

The compound above, wherein the compound has a 3'-end overhang.

The compound above, further comprising one or more hydroxymethyl substituted nucleomonomers.

The compound above for use in delivering an RNA agent into a cell or an organism.

The compound above for use in mediating nucleic acid modification of a target nucleic acid in a cell or an organism.

The compound above for use in decreasing expression levels of a target mRNA in a cell or an organism.

The compound above for use in inhibiting an endogenous nucleic acid-based regulatory system in a cell or an organism.

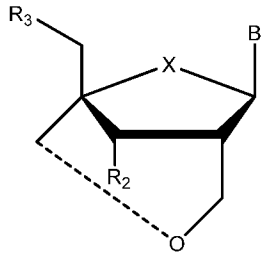
The compound above for use in gene regulation, gene analysis, or RNA interference.

The compound above for use in the manufacture of a medicament for a therapeutic target, including targets for cancers, metabolic diseases, inflammatory diseases, and viral infections.

The compound above for use in treating a disease, condition or disorder, including cancers, metabolic diseases, inflammatory diseases, and viral infections.

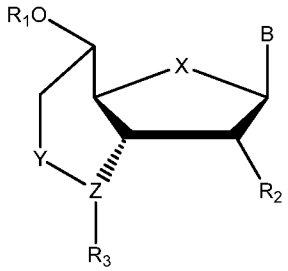
A method for treating a disease, condition or disorder in a subject including cancers, metabolic diseases, inflammatory diseases, and viral infections, the method comprising administering to the subject a compound above.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



where X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



where X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OCH_3; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more Monomer R and one or more Monomer Q.

In some embodiments, B represents a nucleobase or nucleobase analog independently selected from adenine, cytosine, guanine, uracil, hypoxanthine, thymine, 7-deazaadenine, inosine, C-phenyl, C-naphthyl, inosine, an azole carboxamide, nebularine, a nitropyrrole, a

nitroindole, 2-aminopurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-methyluridine, 5-propynylcytidine, isocytidine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 2-thioribothymidine, 5,6-dihydrouracil, 4-methylindole, ethenoadenine, deoxyuridine, and any existing deoxy analogs of the foregoing.

In some embodiments, B represents a nucleobase or nucleobase analog independently selected from adenine, cytosine, guanine, uracil, and any existing deoxy analogs of the foregoing.

In certain embodiments, the nucleic acid compound further comprises a second strand.

Monomers A, B, C and D shown in Fig. 4 are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds. Monomer B is an exemplary hydroxymethyl substituted nucleomonomer (the hydroxymethyl group is attached at the C1' atom of the acyclic ribose-based scaffold) of Monomer A, and Monomer D is an exemplary hydroxymethyl substituted nucleomonomer (the hydroxymethyl group is attached at the C1' atom of the acyclic-ribose-based scaffold) of Monomer C. Monomers A and B are the D-isoform of an acyclic-ribose-based scaffold, and Monomers C and D are the L-isoform of an acyclic-ribose-based scaffold. For Monomers A and C, X may be an –O-, -S-, or $-CH_2$; Z may be an -H, -OH, $-CH_2OH$, $-CH_3$ or saturated or unsaturated C(2-22) alkyl chain; J may be P or S; R_2 may be -H, -OH, -O-alkyl, -F, -SH, -S-alkyl, -S-F, -NH(CH=O), -NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

Monomers E, F, G and H shown in Fig. 5 are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds. Monomer F is an exemplary hydroxymethyl substituted nucleomonomer (the hydroxymethyl group is attached at the C4' atom of the acyclic ribose-based scaffold) of Monomer E, and Monomer H is an exemplary hydroxymethyl substituted nucleomonomer (the hydroxymethyl group is attached at the C4' atom of the acyclic ribose-based scaffold) of Monomer G. Monomers E and F are the D-isoform of an acyclic-ribose-based scaffold, and Monomers C and D are the L-isoform of an acyclic ribose-based scaffold. For Monomers E and G, X may be an –O-, -S-, or $-CH_2$; Z may be an -H, -OH, $-CH_2OH$, $-CH_3$ or saturated or unsaturated C(2-22) alkyl chain; J may be P or S; R_2 may be -H, -OH, -O-alkyl, -F, -SH, -S-alkyl, -S-F, -NH(CH=O), -NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

Monomers I, J, K and L shown in Fig. 6 are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds. Monomer J is an exemplary hydroxymethyl substituted nucleomonomer (the hydroxymethyl group is attached at the C1' atom of the acyclic ribose-based scaffold) of Monomer I, and Monomer L is an exemplary hydroxymethyl

substituted nucleomonomer (the hydroxymethyl group is attached at the C1' atom of the acyclic ribose-based scaffold) of Monomer K. Monomers I and J are the D-isoform of an acyclic-ribose-based scaffold, and Monomers K and L are the L-isoform of an acyclic ribose-based scaffold. For Monomers I and K, X may be an –O-, -S-, or -CH_2; Z may be an -H, -OH, -CH_2OH,

-CH_3 or saturated or unsaturated C(2-22) alkyl chain; J may be P or S; R_2 may be -H, -OH, -O-alkyl, -F, -SH, -S-alkyl, -S-F, -NH(CH=O), -NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

Monomers M, N, O and P shown in Fig. 7 are acyclic non-nucleotide monomers that may be incorporated into nucleic acid compounds. Monomer N is an exemplary hydroxymethyl substituted nucleomonomer (two hydroxymethyl groups are attached at the C4' atom of the acyclic ribose-based scaffold) of Monomer M, and Monomer P is an exemplary hydroxymethyl substituted nucleomonomer (two hydroxymethyl groups are attached at the C4' atom of the acyclic ribose-based scaffold) of Monomer O. Monomers M and N are the D-isoform of an acyclic-ribose-based scaffold, and Monomers O and P are the L-isoform of an acyclic ribose-based scaffold. For Monomers M and O, X may be an –O-, -S-, or -CH_2; Z may be an -H, -OH, -CH_2OH, -CH_3 or saturated or unsaturated C(2-22) alkyl chain; J may be P or S; R_2 may be -H, -OH, -O-alkyl, -F, -SH, -S-alkyl, -S-F, -NH(CH=O), -NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

Some hydroxymethyl substituted nucleomonomers and nucleic acid compounds comprising hydroxymethyl substituted nucleomonomers may be synthesised using phosphoramidite derivatives using the standard techniques for nucleic acid synthesis. Some methods for synthesis of hydroxymethyl substituted nucleomonomers and hydroxymethyl substituted nucleic acid compounds may be found in PCT International Application PCT/US2008/064417, which is hereby incorporated by reference in its entirety.

In certain embodiments, the nucleic acid compound comprises a hydroxymethyl substituted nucleomonomer. In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or -CH_2; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In another aspect, the instant disclosure provides a nucleic acid compound comprising a first strand having from 10 to 60 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, or 60) nucleomonomers, and a second strand complementary to the first strand, wherein the first strand and the second strand can anneal to form 8 to 60 (or 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, or 60) base pairs, and wherein one or more of the nucleomonomers of the first strand or the second strand is a conformationally restricted nucleomonomer.

In certain embodiments, the melting temperature of the nucleic acid compound is from 40°C to 100°C, or from 60°C to 90°C, or from 75°C to 80°C.

In certain embodiments, from 1% to 75% of the nucleomonomers of the first strand or second strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the first strand or second strand of the nucleic acid compound are conformationally restricted nucleomonomers, or wherein from 40% to 50% of the nucleomonomers of the first strand or second strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, the first strand is from 10 to 40 nucleomonomers in length. In other embodiments, the first strand is from 15 to 35 nucleomonomers in length. In yet other embodiments, the first strand is from 18 to 30 nucleomonomers in length. In yet other embodiments, the first strand is from 19 to 23 nucleomonomers in length. In yet another embodiment, the first strand is from 25 to 30 nucleomonomers in length.

In certain embodiments, the second strand is from 8 to 60 nucleomonomers in length. In other embodiments, the second strand is from 10 to 40 nucleomonomers in length. In yet other embodiments, the second strand is from 15 to 35 nucleomonomers in length. In yet other embodiments, the second strand is from 18 to 30 nucleomonomers in length. In yet other embodiments, the second strand is from 19 to 23 nucleomonomers in length. In yet another embodiment, the second strand is from 25 to 30 nucleomonomers in length.

In certain embodiments, any one or more of the last 15 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, any one or more of the last 10 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, two or more of the last 15 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, two or more of the last 10 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, three or more of the last 15 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, three or more of the last 10 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, four or more of the last 15 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, four or more of the last 10 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, five or more of the last 15 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, five or more of the last 10 positions at the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiment, any one or more of the last 15 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiment, any one or more of the last 10 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, two or more of the last 15 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, two or more of the last 10 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, three or more of the last 15 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, three or more of the last 10 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, four or more of the last 15 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, four or more of the last 10 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

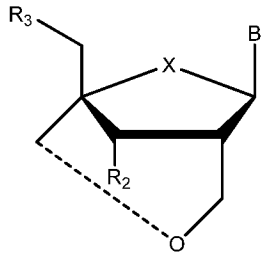
In certain embodiments, five or more of the last 15 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, five or more of the last 10 positions at the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, the nucleic acid compound comprises RNA. In certain embodiments, the nucleic acid compound comprises DNA. In certain embodiments, the nucleic acid compound comprises RNA and DNA.

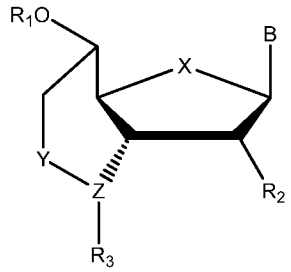
In certain embodiments, the nucleic acid compound is an siRNA.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



where X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



where X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH;

R_2 is independently for each occurrence selected from hydrogen, F, OH, or OCH_3; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$,

P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more Monomer R and one or more Monomer Q.

In certain embodiments, the first and second strands are a contiguous strand of nucleomonomers. In certain embodiments, the second strand has one or more nicks. In certain embodiments, the second strand has one or more gaps. In a related embodiment, the one or more gaps, independently for each occurrence, comprise from 1 to 10 (or 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) unpaired nucleomonomers.

In certain embodiments, the nucleic acid comprises two or more conformationally restricted nucleomonomers, wherein the two or more conformationally restricted nucleomonomers flank the one or more gaps of the second strand of the nucleic acid.

In certain embodiments, the nucleic acid comprises two or more conformationally restricted nucleomonomers, wherein the two or more conformationally restricted nucleomonomers flank the one or more nicks of the second strand of the nucleic acid.

In certain embodiments, the nucleic acid compound has a blunt end. In certain embodiments, the nucleic acid compound has a 3'-end overhang.

In certain embodiments, the nucleic acid compound comprises a hydroxymethyl substituted nucleomonomer. In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or $-CH_2$; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In another aspect, the instant disclosure provides a use of a nucleic acid compound as described herein for the manufacture of a medicament for use in the therapy of disease.

In another aspect, the instant disclosure provides a method for reducing the expression of a gene or reducing the function an endogenous nucleic acid based regulatory system of a cell, comprising administering a nucleic acid compound as described herein to a cell, wherein the nucleic acid compound reduces the expression of the gene in the cell.

In another aspect, the instant disclosure provides a method for reducing the function of an endogenous nucleic acid based regulatory system of a cell, comprising administering a nucleic acid compound described herein to a cell, wherein the nucleic acid compound reduces the function of the endogenous nucleic acid based regulatory system in the cell.

In certain embodiments, the cell is a human cell.

In another aspect, the instant disclosure provides a method for treating or managing a disease or condition in a subject associated, linked, and/or resulting from aberrant nucleic acid expression, comprising administering to the subject in need of treatment or management a nucleic acid compound as disclosed herein, wherein the nucleic acid compound reduces the expression or function of the nucleic acid thereby treating or managing the disease or condition.

In further embodiments, the nucleic acid compound is a single stranded nucleic acid comprising from 10 to 40 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40) nucleomonomers, wherein one or more of the from 10 to 40 nucleomonomers is a conformationally restricted nucleomonomer.

In certain embodiments, the minimum percent occurrence of conformationally restricted nucleomonomers of the nucleic acid compound is greater than 0% and less than 95%, or greater than 0% and less than 85%, or greater than 0% and less than 75%, or greater than 10% and less than 70%, or greater than 20% and less than 60%, or greater than 30% and less than 55%, or greater than 40% and less than 60%.

In certain embodiments, the percent of nucleomonomers of the from 10 to 40 nucleomonomers of nucleic acid compound that are conformationally restricted nucleomonomers is from 1% to 95%, or from 5% to 90%, or from 10% to 85%, or from 15% to 80%, or from 20% to 75%, or from 25% to 70%, or from 30% to 65%, or from 35% to 60%, or from 40% to 55% , or from 45% to 50%.

In certain embodiments, every other nucleomonomer of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every third nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every forth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every fifth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every sixth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

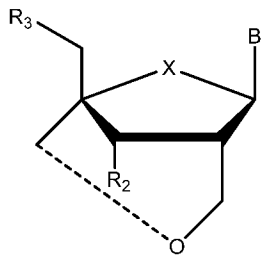
In certain embodiments, every seventh nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every eight nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every ninth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

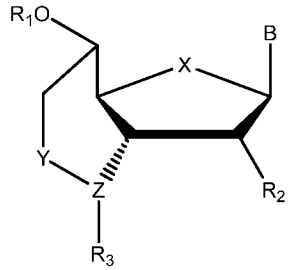
In certain embodiments, every tenth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OCH_3; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more of the same or different Monomer R and one or more of the same or different Monomer Q.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomer that are independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or -CH_2; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomers that are independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In certain embodiments, the nucleic acid compound comprises one or more RNA nucleomonomers.

In certain embodiments, the nucleic acid compound comprises one or more DNA nucleomonomers.

In certain embodiments, the nucleic acid compound comprises RNA and DNA nucleomonomers.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomers.

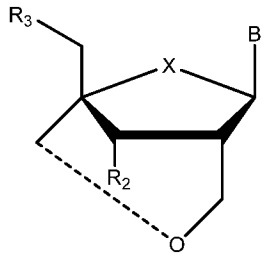
In certain embodiments, the nucleic acid compound has the following formula:

5' A-B-A 3'

wherein, A is independently, for each occurrence, a sequence of from 3 to 16 (or 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,14, 15, or 16) nucleomonomers, wherein the minimum percent occurrence of conformationally restricted nucleomonomers of the sequence is greater than 0% and less than 95%, or greater than 0% and less than 85%, or greater than 0% and less than 75%, or greater than 10% and less than 70%, or greater than 20% and less than 60%, or greater than 30% and less than 55%, or greater than 40% and less than 60%; and wherein B is independently, for each occurrence, is a sequence of from 4 to 8 (or 4, 5, 6, 7, or 8) nucleomonomers.

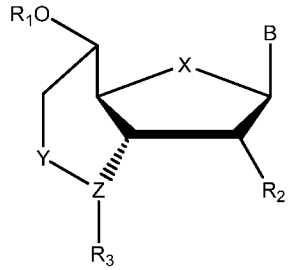
In certain embodiments, the nucleic acid compound is from 10 to 40 nucleomonomers in length, from 12 to 30 nucleomonomers in length or from 12 to 14 nucleomonomers in length.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OCH_3; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more of the same or different Monomer R and one or more of the same or different Monomer Q.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomers that are independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or -CH_2; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the one or more hydroxymethyl substituted nucleomonomers are independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In certain embodiments, B does not contain a conformationally restricted nucleomonomer.

In certain embodiments, the nucleomonomers of B are DNA, phosphorothioates or a combination thereof.

In certain embodiments, the nucleomonomers of A are RNA.

In certain embodiments, the nucleic acid compound functions as an antisense RNA, microRNA or antagomir.

In another embodiment, the nucleic acid compound is single stranded and has no double stranded region.

In another aspect, the instant disclosure provides a nucleic acid compound comprising a first strand having from 10 to 60 (or 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, or 60) nucleomonomers, and a second strand complementary to the first strand, wherein the first strand and the second strand can anneal to form 8 to 60 base pairs, and wherein one or more of the nucleomonomers of the first strand or the second strand is a conformationally restricted nucleomonomer.

In certain embodiments, the melting temperature of the nucleic acid compound is from 40°C to 100°C, or from 60°C to 90°C, or from 75°C to 80°C.

In certain embodiments, from 1% to 75% of the nucleomonomers of the first strand or second strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the first strand or second strand of the nucleic acid compound are conformationally restricted nucleomonomers, or wherein from 40% to 50% of the nucleomonomers of the first strand or second strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, the first strand is from 10 to 40 nucleomonomers in length. In other embodiments, the first strand is from 15 to 35 nucleomonomers in length. In yet other embodiments, the first strand is from 18 to 30 nucleomonomers in length. In yet other embodiments, the first strand is from 19 to 23 nucleomonomers in length. In yet another embodiment, the first strand is from 25 to 30 nucleomonomers in length.

In certain embodiments, the second strand is from 8 to 60 nucleomonomers in length. In other embodiments, the second strand is from 10 to 40 nucleomonomers in length. In yet other embodiments, the second strand is from 15 to 35 nucleomonomers in length. In yet other embodiments, the second strand is from 18 to 30 nucleomonomers in length. In yet other embodiments, the second strand is from 19 to 23 nucleomonomers in length. In yet another embodiment, the second strand is from 25 to 30 nucleomonomers in length.

In certain embodiments, any one or more of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 counting from the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, any one or more of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 counting from the 3'-end of the first strand is occupied by the same or different conformationally restricted nucleomonomer.

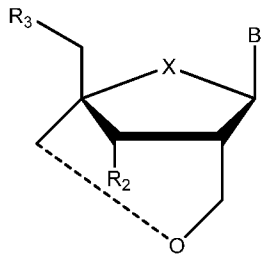
In certain embodiments, any one or more of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 counting from the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, any one or more of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 counting from the 5'-end of the second strand is occupied by the same or different conformationally restricted nucleomonomer.

In certain embodiments, the nucleic acid compound comprises RNA. In certain embodiments, the nucleic acid compound comprises DNA. In certain embodiments, the nucleic acid compound comprises RNA and DNA.

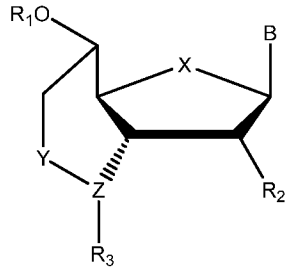
In certain embodiments, the nucleic acid compound is an siRNA.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



where X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



where X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OMe; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more Monomer R and one or more Monomer Q.

In certain embodiments, the first and second strands are a contiguous strand of nucleomonomers. In certain embodiments, the second strand has one or more nicks. In certain embodiments, the second strand has one or more gaps. In a related embodiment, the one or more gaps, independently for each occurrence, comprise from 1 to 10 (or 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) unpaired nucleomonomers.

In certain embodiments, the nucleic acid compound has a blunt end. In certain embodiments, the nucleic acid compound has a 3'-end overhang.

In certain embodiments, the nucleic acid compound comprises a hydroxymethyl substituted nucleomonomer. In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or $-CH_2$; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In one aspect, the disclosure provide for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 10 to 24 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24) base pairs, wherein any one or more of the last three positions at the 5'-end of the sense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer, and wherein any one or more of the last 10 positions at the 3'-end of the antisense strand is occupied by the same or different conformationally restricted nucleomonomer.

In one aspect, the disclosure provide for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 10 to 24 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24) base pairs, wherein any one or more of the last three positions at the 5'-end of the sense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer, and wherein any one or more of the last 10 positions at the 5'-end of the sense strand is occupied by the same or different conformationally restricted nucleomonomer.

In another aspect, the antisense strand is from 10 to 24 nucleomonomers in length.

In another aspect, the senses strand is from 10 to 24 nucleomonomers in length.

In another aspect, no more than two conformationally restricted nucleomonomers are adjacent to one another.

In another aspect, the nucleic acid compound further comprises that one or both of the last two positions of the 3'-end of the sense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer.

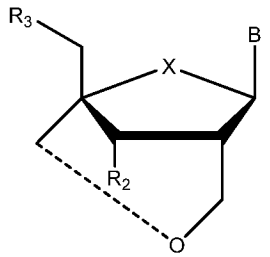
In yet another aspect, the nucleic acid compound further comprises that one or both of the last two positions of the 3'-end of the antisense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer.

In another aspect, the nucleic acid compound further comprises that one or more of positions 5, 6, 7 and 8 of the antisense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer, wherein the positions of the antisense strand are numbered beginning with position 1 at the 5'end of the antisense strand.

In another aspect, the nucleic acid compound further comprises that one or both of the last two positions of the 3'-end of the sense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer.

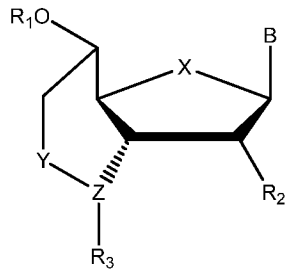
In yet another aspect, the nucleic acid compound further comprises that one or both of the last two positions of the 3'-end of the antisense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OMe; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more of the same or different Monomer R and one or more of the same or different Monomer Q.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomers that are independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or -CH_2; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the one or more hydroxymethyl substituted nucleomonomers are independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In another aspect, the nucleic acid compound has a double-stranded region of 10 to 23 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 12 to 21 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 14 to 21 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 15 to 21 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 16 to 21 base pairs.

In another aspect, the nucleic acid compound has a blunt end.

In another aspect, the nucleic acid compound further comprises a 3'-end overhang. In another aspect, the 3'-end overhang comprises nucleotides. In another aspect, the 3'-end overhang comprises non-nucleotide monomers. In another aspect, the 3'-end overhang comprise both nucleotides and non-nucleotide monomers.

In another aspect, the 3'-end overhang is from 1 to 20 (or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) nucleomonomers in length. In another aspect, the 3'-end overhang is from 3 to 18 (or 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20) nucleomonomers in length. In another aspect, the 3'-end overhang is from 5 to 16 (or 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16) nucleomonomers in length.

In any aspect disclosed herein, the 3'-end overhang is an overhang of the sense strand. In any aspect disclosed herein, the 3'-end overhang is an overhang of the antisense strand. In any aspect disclosed herein, the sense strand has a 3'-overhang and the antisense strand has a 3'-

end overhang, which may be the same or different. In another aspect, the 3'-end overhang is from 1 to 5 (or 1, 2, 3, 4 or 5) nucleomonomers in length.

In another aspect, the 3'-end overhang is selected from the group of overhangs with a length of 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides and 8 nucleotides, and/or 1 hydroxymethyl substituted nucleomonomer, 2 hydroxymethyl substituted nucleomonomers, 3 hydroxymethyl substituted nucleomonomers, 4 hydroxymethyl substituted nucleomonomers, 5 hydroxymethyl substituted nucleomonomers, 6 hydroxymethyl substituted nucleomonomers, 7 hydroxymethyl substituted nucleomonomers and 8 hydroxymethyl substituted nucleomonomers, and combinations thereof.

In one aspect, this disclosure provides for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) base pairs, wherein the last position of the 3'-end of the antisense strand and the last position of the 3'-end of the sense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer, and wherein any one or more of the last 15 positions at the 3'-end of the antisense strand is occupied by the same or different conformationally restricted nucleomonomer.

In one aspect, this disclosure provides for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) base pairs, wherein the last position of the 3'-end of the antisense strand and the last position of the 3'-end of the sense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer, and wherein any one or more of the last 15 positions at the 5'-end of the sense strand is occupied by the same or different conformationally restricted nucleomonomer.

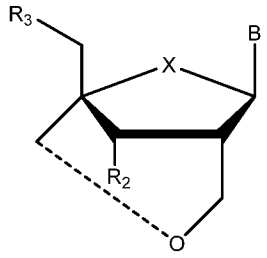
In another aspect, the antisense strand is from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) nucleomonomers in length.

In another aspect, the senses strand is from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) nucleomonomers in length.

In some embodiments, no more than two conformationally restricted nucleomonomers are adjacent to one another.

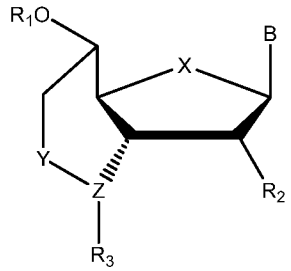
In another aspect, the last two positions of the 3'-end of the antisense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, C=CH_2, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, C=CH_2, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OMe; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more of the same or different Monomer R and one or more of the same or different Monomer Q.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomers that are independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or -CH_2; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the one or more hydroxymethyl substituted nucleomonomers are independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In another aspect, the nucleic acid compound has a double-stranded region of 25 to 40 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 25 to 35 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 25 to 30 base pairs. In another aspect, the nucleic acid compound has a double-stranded region of 25 to 27 base pairs.

In another aspect, the nucleic acid compound has a blunt end.

In another aspect, the nucleic acid compound further comprises a 3'-end overhang. In another aspect, the 3'-end overhang comprises nucleotides. In another aspect, the 3'-end overhang comprises non-nucleotide monomers. In another aspect, the 3'-end overhang comprise both nucleotides and non-nucleotide monomers.

In another aspect, the 3'-end overhang is from 1 to 20 (or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) nucleomonomers in length. In another aspect, the 3'-end overhang is from 3 to 18 (or 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20) nucleomonomers in length.

In another aspect, the 3'-end overhang is from 5 to 16 (or 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16) nucleomonomers in length. In any aspect disclosed herein, the 3'-end overhang is an overhang of the sense strand. In any aspect disclosed herein, the 3'-end overhang is an overhang of the antisense strand. In any aspect disclosed herein, the sense strand has a 3'-overhang and the antisense strand has a 3'-end overhang, which may be the same or different. In another aspect, the 3'-end overhang is from 1 to 5 (or 1, 2, 3, 4 or 5) nucleomonomers in length.

In another aspect, the 3'-end overhang is selected from the group of overhangs with a length of 1 nucleotide, 2 nucleotides, 3 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7

nucleotides and 8 nucleotides, and/or 1 hydroxymethyl substituted nucleomonomer, 2 hydroxymethyl substituted nucleomonomers, 3 hydroxymethyl substituted nucleomonomers, 4 hydroxymethyl substituted nucleomonomers, 5 hydroxymethyl substituted nucleomonomers, 6 hydroxymethyl substituted nucleomonomers, 7 hydroxymethyl substituted nucleomonomers and 8 hydroxymethyl substituted nucleomonomers, and combinations thereof.

In one aspect, this disclosure provide for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) base pairs, wherein one or more of positions 21, 22 and 23 of the sense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer, wherein the positions of the sense strand are numbered beginning with position 1 at the 5'-end of the sense strand, and wherein any one or more of the last 15 positions at the 3'-end of the antisense strand is occupied by the same or different conformationally restricted nucleomonomer.

In one aspect, this disclosure provide for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) base pairs, wherein one or more of positions 21, 22 and 23 of the sense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer, wherein the positions of the sense strand are numbered beginning with position 1 at the 5'-end of the sense strand, and wherein any one or more of the last 15 positions at the 5'-end of the sense strand is occupied by the same or different conformationally restricted nucleomonomer.

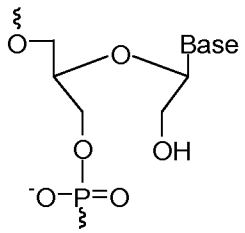
In one aspect, this disclosure provide for a nucleic acid compound comprising a sense strand and an antisense strand, and a double-stranded region having from 25 to 60 (or 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59 or 60) base pairs, wherein one or more of positions 18, 19, 20, 21, and 22 of the antisense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer, wherein the positions of the sense strand are numbered beginning with position 1 at the 3'-end of the antisense strand, and wherein any one or more of the last 15 positions at the 3'-end of the antisense strand is occupied by the same or different conformationally restricted nucleomonomer.

In another aspect, the nucleic acid compound further comprises that one or both of the last two positions of the 3'-end of the antisense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer.

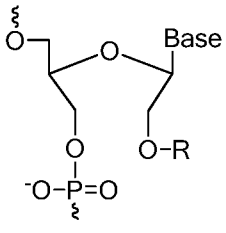
In another aspect, the nucleic acid compound further comprises that one or both of the last two positions of the 3'-end of the sense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer.

In another aspect, the hydroxymethyl substituted nucleomonomer is a 2'-3'-seco-nucleomonomer.

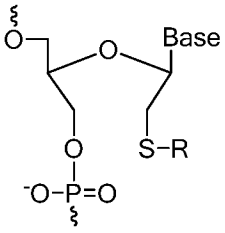
In another aspect, the hydroxymethyl substituted nucleomonomer is selected from:



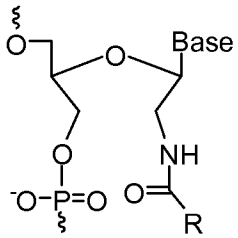
Monomer D



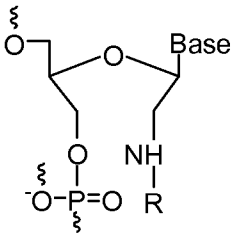
Monomer F



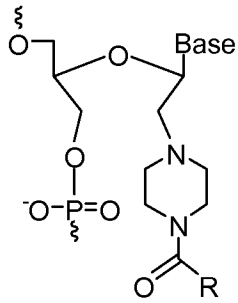
Monomer G



Monomer H



Monomer I

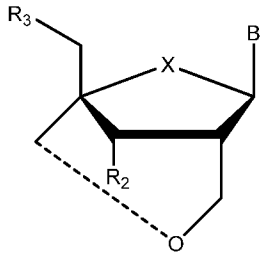


Monomer J

,

wherein R is selected from the group consisting of a hydrogen, an alkyl group, a cholesterol derivative, a fluorophore, a polyamine, a fatty acid, an amino acid, a saccharide, and a polypeptide, wherein Base is any purine, pyrimidine, or derivative or analogue thereof.

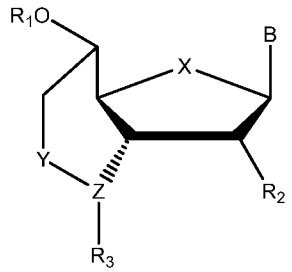
In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate,

monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OMe; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more of the same or different Monomer R and one or more of the same or different Monomer Q.

In certain embodiments, the one or more hydroxymethyl substituted nucleomonomer are independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or $-CH_2$; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the one or more hydroxymethyl substituted nucleomonomers are independently for each occurrence selected from Monomer B, Monomer D, Monomer F,

Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In another aspect, the nucleic acid compound further comprises a nucleotide analogue selected from the group consisting of 2'-O-alkyl-RNA monomers, 2'-amino-DNA monomers, 2'-fluoro-DNA monomers, LNA monomers, PNA monomers, HNA monomers, ANA monomers, FANA monomers, CeNA monomers, ENA monomers, DNA monomers, and INA monomers.

In another aspect, the instant disclosure provides for the use of a nucleic acid compound as disclosed herein for the manufacture of a medicament for use in the therapy of cancer.

In a related aspect, one or more hydroxymethyl substituted nucleomonomer(s) are at one or more of positions 5, 6, 7 or 8 counting from the 5'-end of the antisense strand.

In a related aspect, one or more hydroxymethyl substituted nucleomonomer(s) are at position 7 counting from the 5'-end of the antisense strand.

In a related aspect, the double-stranded region has 19 or 20 base pairs.

In a related aspect, the sense strand and the antisense strand each have 21 or 22 nucleomonomers.

In a related aspect, the dsRNA has a 3'-end overhang.

In a related aspect, the dsRNA has a blunt end.

In another aspect, the disclosure provides a nucleic acid compound (e.g., dsRNA) that downregulates the expression of a gene, the nucleic acid compound comprising a sense strand and an antisense strand, a double-stranded region having from 25 to 60 base pairs, and wherein the last two nucleomonomers of the 3'-end of the antisense strand and the last nucleomonomer of the 3'-end of the sense strand are hydroxymethyl substituted nucleomonomers, and and wherein any one or more of the last 15 positions at the 3'-end of the antisense strand is occupied by the same or different conformationally restricted nucleomonomer.

In another aspect, the disclosure provides a nucleic acid compound (e.g., dsRNA) that downregulates the expression of a gene, the nucleic acid compound comprising a sense strand and an antisense strand, a double-stranded region having from 25 to 60 base pairs, and wherein the last two nucleomonomers of the 3'-end of the antisense strand and the last nucleomonomer of the 3'-end of the sense strand are hydroxymethyl substituted nucleomonomers, and and wherein any one or more of the last 15 positions at the 5'-end of the sense strand is occupied by the same or different conformationally restricted nucleomonomer.

In another aspect, the disclosure provides a nucleic acid compound (e.g., dsRNA) that downregulates the expression of a gene, the nucleic acid compound comprising a sense strand and an antisense strand, a double-stranded region having from 25 to 60 base pairs, and wherein one or more hydroxymethyl substituted nucleomonomer(s) are at one or more of positions of the

sense strand that inhibit processing of the dsRNA by a Dicer enzyme, and wherein any one or more of the last 15 positions at the 3'-end of the antisense strand is occupied by the same or different conformationally restricted nucleomonomer.

In another aspect, the disclosure provides a nucleic acid compound (e.g., dsRNA) that downregulates the expression of a gene, the nucleic acid compound comprising a sense strand and an antisense strand, a double-stranded region having from 25 to 60 base pairs, and wherein one or more hydroxymethyl substituted nucleomonomer(s) are at one or more of positions of the sense strand that inhibit processing of the dsRNA by a Dicer enzyme, and wherein any one or more of the last 15 positions at the 5'-end of the sense strand is occupied by the same or different conformationally restricted nucleomonomer.

In a related aspect, one or more hydroxymethyl substituted nucleomonomer(s) are at one or more of positions 21, 22 or 23 of the sense strand counting from the 5'-end of the sense strand.

In a related aspect, one or more hydroxymethyl substituted nucleomonomer(s) are at one or more of positions 18, 19, 20 21 or 22 of the antisense strand counting from the 3'-end of the antisense strand.

In one aspect, the instant disclosure provides for a nucleic acid compound comprising at least three strands, designated herein as A, S1 and S2 (A:S1S2), wherein the S1 strand and the S2 strand are complementary to, and form base pairs (bp) with, non-overlapping regions of the A strand. Thus, for the nucleic acid compounds described herein; the double-stranded region (or a duplex) formed by the annealing of the S1 strand and the A strand is distinct from the double-stranded region formed by the annealing of the S2 strand and the A strand. An A:S1 duplex may be separated from an A:S2 duplex by a "gap" resulting from at least one unpaired nucleomonomer in the A strand that is positioned between the A:S1 duplex and the A:S2 duplex and that is distinct from any one or more unpaired nucleomonomer at the 3' end of either or both of the A, S1, and/or S2 strand. Alternatively, an A:S1 duplex may be separated from an A:S2 duplex by a "nick" (lack of a phosphodiester bond between adjacent nucleomonomers) such that there are no unpaired nucleotides in the A strand that are positioned between the A:S1 duplex and the A:S2 duplex such that the only unpaired nucleotide, if any, is at the 3' end of either or both of the A, S1, and/or S2 strand.

In one aspect, the nucleic acid compound comprises a first strand that is complementary to a target nucleic acid (e.g., mRNA or other nucleic acid molecule), and a second strand and a third strand that are each complementary to non-overlapping regions of the first strand, wherein the second strand and third strands can anneal with the first strand to form at least two double-stranded regions separated by a gap of from 1 to 10 (or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10)

nucleomonomers or nick, wherein the total number of base pairs of the double-stranded is from about 10 base pairs to about 60 base pairs, and wherein one or more of the nucleomonomers is a conformationally restricted nucleomonomer.

In certain embodiments, the minimum percent occurrence of conformationally restricted nucleomonomers of the nucleic acid compound is greater than 0% and less than 95%, or greater than 0% and less than 85%, or greater than 0% and less than 75%, or greater than 10% and less than 70%, or greater than 20% and less than 60%, or greater than 30% and less than 55%, or greater than 40% and less than 60%.

In certain embodiments, the percent of nucleomonomers that are conformationally restricted nucleomonomers is from 1% to 95%, or from 5% to 90% (or 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or 90%), or from 10% to 85% (or 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, or 85%), or from 15% to 80%, or from 20% to 75%, or from 25% to 70%, or from 30% to 65%, or from 35% to 60%, or from 40% to 55% , or from 45% to 50%.

In certain embodiments, from 1% to 75% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers, or wherein from 40% to 50% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, from 1% to 75% of the nucleomonomers of the second strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the second strand of the nucleic acid compound are conformationally restricted nucleomonomers, or wherein from 40% to 50% of the nucleomonomers of the second strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, from 1% to 75% of the nucleomonomers of the second strand or the third strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the second strand or the third strand of the nucleic acid compound are conformationally restricted nucleomonomers, or wherein from 40% to 50% of the nucleomonomers of the second strand or the third strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, every other nucleomonomer of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every third nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every forth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every fifth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every sixth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every seventh nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every eight nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

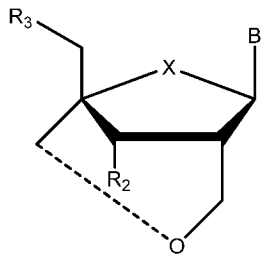
In certain embodiments, every ninth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, every tenth nucleomonomer counting from the 5'-end of the nucleic acid compound is a conformationally locked nucleomonomer.

In certain embodiments, each double-stranded region comprises an equal number of the same or different conformationally restricted nucleomonomers.

In certain embodiments, each double-stranded region comprises one or more conformationally restricted nucleomonomers, wherein the one or more conformationally restricted nucleomonomers may be the same or different.

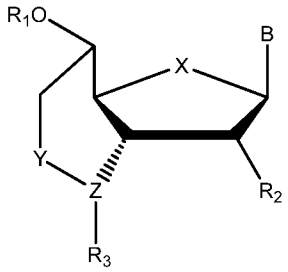
In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl

chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OMe; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more of the same or different Monomer R and one or more of the same or different Monomer Q.

In certain embodiments the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or $-CH_2$; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In certain embodiments, the nucleic acid compound comprises one or more RNA nucleomonomers.

In certain embodiments, the nucleic acid compound comprises one or more DNA nucleomonomers.

In certain embodiments, the nucleic acid compound comprises RNA and DNA nucleomonomers.

In certain embodiments, the nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomers.

In certain embodiments, at least one double-stranded region is from about 5 base pairs up to 13 base pairs.

In certain embodiments, the double-stranded regions combined total from about 15 base pairs to about 40 base pairs.

In certain embodiments, the first strand is from about 10 to about 40 nucleomonomers in length, and the second and third strands are each, individually, from about 5 to about 20 nucleomonomers, wherein the combined length of the second and third strands is about 10 nucleomonomers to about 40 nucleomonomers.

In other embodiments, the nucleic acid compound is a RISC activator (*e.g.*, the first strand has about 15 nucleotides to about 25 nucleotides) or a Dicer substrate (*e.g.*, the first strand has about 26 nucleotides to about 40 nucleotides).

In some embodiments, the gap comprises at least one to ten unpaired nucleomonomers in the first strand positioned between the double-stranded regions formed by the second and third strands when annealed to the first strand.

In some embodiments, the double-stranded regions are separated by a nick.

In certain embodiments, the nick or gap is located 10 nucleomonomers from the 5'-end of the first (antisense) strand or at the Argonaute cleavage site.

In another embodiment, the nick or gap is positioned such that the thermal stability is maximized for the first and second strand duplex and for the first and third strand duplex as compared to the thermal stability of such meroduplexes having a nick or gap in a different position.

In one aspect of the disclosure, the number of hydroxymethyl substituted nucleomonomers in the antisense strand is 10. In other embodiments of the disclosure, the number of hydroxymethyl substituted nucleomonomer(s) in the antisense strand is 9, 8, 7, 6, 5, 4, 3, 2 or 1, respectively.

In another aspect, all nucleomonomers of the antisense strand are hydroxymethyl substituted nucleomonomers.

In one aspect of the disclosure, all hydroxymethyl substituted nucleomonomers in the antisense strand are present in positions 1, 2, 3, 4, 5, 6, 7, and/or 8, wherein the positions are counted from the 5' end of the antisense strand. Even more preferably, the hydroxymethyl substituted nucleomonomers in the antisense strand are present in positions 2, 3, 4, 5, 6, and/or 7, counted from the 5' end of the antisense strand or in the corresponding to the so-called seed region of a microRNA. In another aspect, the hydroxymethyl substituted nucleomonomers in the antisense strand are present in positions 4, 5, 6, 7 and/or 8, counted from the 5' end of the antisense strand. In another aspect, the hydroxymethyl substituted nucleomonomers in the antisense strand are present in positions 6, 7 and/or 8, counted from the 5' end of the antisense strand. In another aspect, the hydroxymethyl substituted nucleomonomers in the antisense strand are present in positions in the antisense strand that reduce the microRNA activity of the nucleic acid compound compared to the same nucleic acid compound without hydroxymethyl substituted nucleomonomers. Thus, presence of hydroxymethyl substituted nucleomonomers in the aforementioned regions may prevent the antisense strand from acting as a microRNA, which reduces off target effects when the antisense strand is intended to function as siRNA.

In a preferred embodiment, at least one hydroxymethyl substituted nucleomonomer is present in any one of positions 9, 10, 11, 12, 13, 14, 15, and/or 16, wherein the positions are counted from the 5'-end of the antisense strand. Even more preferred is hydroxymethyl substituted nucleomonomers present in any one of positions 9, 10, 11, 12, 13, 14, 15, and/or 16, wherein the positions are counted from the 5'end of the antisense strand. In another embodiment, hydroxymethyl substituted nucleomonomers in the antisense strand is present in all of positions 9, 10, 11, 12, 13, 14, 15, and/or 16. In one embodiment, hydroxymethyl substituted nucleomonomer are only present in regions 9, 10, 11, 12, 13, 14, 15, and/or 16 and not in the rest of the antisense strand.

Even more preferably, the hydroxymethyl substituted nucleomonomers in the antisense strand is present in position 9, 10, and/or 11, counted from the 5' end of the antisense strand, and preferably, not in the rest of the oligonucleotide. In another aspect, the hydroxymethyl substituted nucleomonomers in the antisense strand are present in positions in the antisense strand that enhance the microRNA activity of the nucleic acid compound compared to the same nucleic acid compound without hydroxymethyl substituted nucleomonomers. The presence of hydroxymethyl substituted nucleomonomers in the aforementioned regions may induce the antisense strand to act as a microRNA, i.e. ensure that the siRNA effect will be minimal and the microRNA effect much higher.

In another embodiment of the disclosure, the number of hydroxymethyl substituted nucleomonomers in the passenger strand of a nucleic acid compound of the disclosure is 10. In

other embodiments of the disclosure, the number of hydroxymethyl substituted nucleomonomers in the passenger strand of a nucleic acid compound of the disclosure is 9, 8, 7, 6, 5, 4, 3, 2 or 1, respectively.

In another embodiment, all nucleomonomers of the passenger strand of a nucleic acid compound of the disclosure are hydroxymethyl substituted nucleomonomers.

In certain aspects, the sense (passenger strand) of a nucleic acid compound comprises one or more hydroxymethyl substituted nucleomonomer(s). In certain aspects, the sense (passenger strand) of a nucleic acid compound comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 hydroxymethyl substituted nucleomonomer(s). In certain aspects, the entire sense (passenger strand) of a nucleic acid compound comprises hydroxymethyl substituted nucleomonomer(s).

In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 1, 2, 3, 4, 5, 6, 7, and/or 8 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 1, 2, 3, and/or 4 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 1, 2 and/or 3 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 5, 6, 7, and/or 8 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 7 and/or 8 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, hydroxymethyl substituted nucleomonomers in the sense strand are present in positions in the sense strand of an nucleic acid compound that reduce the RNAi activity of the sense strand of the nucleic acid compound compared to the same nucleic acid compound without hydroxymethyl substituted nucleomonomers.

In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 9, 10, 11, 12, 13, 14, 15, and/or 16 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 9, 10, and/or 11, wherein the positions are counted from the 5'-end of the sense strand.

In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and/or 32 wherein the positions are counted from the 5'-end of the sense strand. In certain aspects, a hydroxymethyl substituted nucleomonomer in the sense strand is present in positions 1, 2, 3, 4, 5, 6, 7, 8, 9 and/or 10, wherein the positions are counted from the 3'-end of the sense strand.

In one embodiment, both the antisense strand and the passenger strand of a nucleic acid compound of the disclosure contain one or more hydroxymethyl substituted nucleomonomer(s).

In certain embodiments, one or both of the last two positions at the 3'-end of the sense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer. In certain embodiments, one or both of the last two positions at the 3'-end of the antisense strand are occupied by the same or different hydroxymethyl substituted nucleomonomer. In certain embodiments, any one or more of the last three positions at the 5'-end of the sense strand is occupied by the same or different hydroxymethyl substituted nucleomonomer. In certain embodiments, at least one hydroxymethyl substituted nucleomonomer is in a double-stranded region of the nucleic acid compound.

In yet another embodiment, the core double stranded region of a nucleic acid compound of the disclosure is shorter than 10 base pairs and thus comprises from one to nine base pairs.

In one aspect, the present disclosure provides a nucleic acid compound capable of mediating nucleic acid modifications of a target nucleic acid. Such nucleic acid compound may, for example, be an siRNA, microRNA or microRNA precursor (pre-microRNA).

In any of the aspects of this disclosure, some embodiments provide a nucleic acid comprising one or more 5-methyluridine (ribothymidine), a 2-thioribothymidine, or 2'-O-methyl-5-methyluridine, deoxyuridine, locked nucleic acid (LNA) molecule, or a universal-binding nucleotide, or a G clamp. Exemplary universal-binding nucleotides include C-phenyl, C-naphthyl, inosine, azole carboxamide, 1-β-D-ribofuranosyl-4-nitroindole, 1-β-D-ribofuranosyl-5-nitroindole, 1-β-D-ribofuranosyl-6-nitroindole, or 1-β-D-ribofuranosyl-3-nitropyrrole. In some embodiments, the nucleic acid further comprises a 2'-sugar substitution, such as a 2'-O-methyl, 2'-O-methoxyethyl, 2'-O-2-methoxyethyl, 2'-O-allyl, or halogen (*e.g.*, 2'-fluoro).

In certain embodiments, the nucleic acid further comprises a terminal cap substituent on one or both ends of one or more of the first strand, second strand, or third strand, such as independently an alkyl, abasic, deoxy abasic, glyceryl, dinucleotide, acyclic nucleotide, or inverted deoxynucleotide moiety. In other embodiments, the nucleic acid further comprises at least one modified internucleoside linkage, such as independently a phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate, 3'-alkylene phosphonate, 5'-alkylene phosphonate, chiral phosphonate, phosphonoacetate, thiophosphonoacetate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate, or boranophosphate linkage.

In any of the aspects disclosed herein, the nucleic acid compound comprises a 2'-O-methyl nucleomonomer. In a related aspect, the nucleic acid compound comprises from zero to twelve 2'-O-methyl nucleomonomer(s) (or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 2'-O-methyl nucleomonomer(s)). In a related aspect, the passenger strand of the nucleic acid compound comprises from zero to twelve 2'-O-methyl nucleomonomer(s) (or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 2'-O-methyl nucleomonomer(s)). In a related aspect, the guide strand of the nucleic acid compound comprises from zero to six 2'-O-methyl nucleomonomer(s) (or 0, 1, 2, 3, 4, 5 or 6 2'-O-methyl nucleomonomer(s)). In certain aspects, the hydroxymethyl substituted monomer is a 2'-O-methyl nucleomonomer.

In any of the aspects of this disclosure, some embodiments provide nucleic acid compound comprising an overhang of one to five (or 1, 2, 3, 4, 5) nucleomonomers on at least one 3'-end that is not part of the gap. In any of the aspects of this disclosure, some embodiments provide a nucleic acid compound has a blunt end at one or both ends. In other embodiments, the 5'-terminal of the sense strand, antisense strand or both strands is a hydroxyl or a phosphate.

In one embodiment, the nucleic acid compound may be a bifunctional nucleic acid compound having two blunt-ends and a hydroxymethyl substituted nucleomonomer at position(s) 5, 6, 7, and/or 8 from the 5'-end of each of the guide strand and passenger strand, and wherein nucleic acid compound comprises one or more conformationally restricted nucleomonomers.

In one embodiment, the bifunctional nucleic acid compound comprise two blunt-ends, a sense strand and a antisense strand, wherein the sense strand comprises an hydroxymethyl substituted nucleomonomer at position(s) 5, 6, 7, and/or 8 from the 5'-end of the sense strand, and the antisense strand comprises an hydroxymethyl substituted nucleomonomer at position(s) 5, 6, 7, and/or 8 from the 5'-end of antisense strand, and wherein the sense strand is complementary to a first region of a target nucleic acid and the antisense region is complementary to a second region of the target nucleic acid, wherein the first region and the second region are non-overlapping regions of the target nucleic acid. In a related embodiment, the first and second regions of the target nucleic acid partially overlap.

In one embodiment, the bifunctional nucleic acid compound comprise two blunt-ends, a sense strand and a antisense strand, wherein the sense strand comprises an hydroxymethyl substituted nucleomonomer at position(s) 5, 6, 7, and/or 8 from the 5'-end of the sense strand, and the antisense strand comprises an hydroxymethyl substituted nucleomonomer at position(s) 5, 6, 7, and/or 8 from the 5'-end of antisense strand, and wherein the sense strand is complementary to a first region of a first target nucleic acid and the antisense region is complementary to a second region of a second target nucleic acid, wherein the first target

nucleic acid and the second target nucleic acid are different target nucleic acid molecules, or have less than 95% homology, or 90% homology, or 85% homology, or 80% homology, or 75% homology, or 70% homology, or 65% homology, or 60% homology, or 55% homology or 50% homology. In a related embodiment, the first and second target nucleic acid molecules are in the same cellular pathway.

In one aspect, the present disclosure provides a nucleic acid compound comprising a first strand and a second strand complementary to the first strand, wherein the first strand and the second strand can anneal to form a double-stranded region, and wherein the double-stranded region comprises one or more mismatches, and wherein one or more of the nucleomonomers of the first strand or the second strand is a conformationally restricted nucleomonomer

In certain embodiments, the first strand has from 10 to 60 (or 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, or 60) nucleomonomers.

In certain embodiments, the double-stranded region comprises from 8 to 60 (or 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, or 60) base pairs.

In certain embodiments, the double-stranded region comprises two mismatches. In certain embodiments, the double-stranded region comprises three mismatches. In certain embodiments, the double-stranded region comprises four mismatches. In certain embodiments, the double-stranded region comprises five mismatches. In certain embodiments, the double-stranded region comprises six mismatches. In certain embodiments, the double-stranded region comprises seven mismatches. In certain embodiments, the double-stranded region comprises eight mismatches.

In certain embodiments, the first and second strands are joined by a non-pairing region of nucleomonomers.

In certain embodiments, the nucleic compound comprises a short hairpin structure.

In certain embodiments, the nucleic compound is a short hairpin RNA (shRNA).

In certain embodiments, the conformationally restricted nucleomonomer reduces or eliminates the microRNA acivity of the nucleic acid compound.

In one aspect, the instant disclosure provides a nucleic acid compound comprising a strand having from 10 to 100 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100)

nucleomonomers, two or more double-strand regions, wherein the double-stranded regions are separated by mismatches, wherein the nucleic acid compound comprises a hairpin turn, and wherein one or more of the nucleomonomers is a conformationally restricted nucleomonomer.

In one aspect, the instant disclosure provides a nucleic acid compound comprising a strand having from 10 to 100 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 ,41, 42, 43, 44 ,45, 46, 47, 48, 49, 50, 51, 52, 53 ,54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100) nucleomonomers, a double-strand region, a hairpin turn, and wherein one or more of the nucleomonomers is a conformationally restricted nucleomonomer.

In certain embodiments, the double-stranded region comprises one mismatch. In certain embodiments, the double-stranded region comprises two mismatches. In certain embodiments, the double-stranded region comprises three mismatches. In certain embodiments, the double-stranded region comprises four mismatches. In certain embodiments, the double-stranded region comprises five mismatches. In certain embodiments, the double-stranded region comprises six mismatches. In certain embodiments, the double-stranded region comprises seven mismatches. In certain embodiments, the double-stranded region comprises eight mismatches.

In certain embodiments, the conformationally restricted nucleomonomer reduces or eliminates the microRNA acivity of the nucleic acid compound.

In certain embodiments, the conformationally restricted nucleomonomer is located in the seed region of the nucleic acid compound.

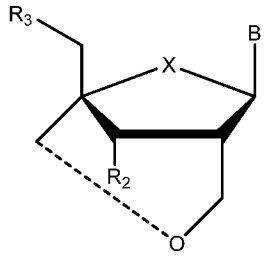
In certain embodiments, the melting temperature of the nucleic acid compound is from 40°C to 100°C, or from 60°C to 90°C, or from 75°C to 80°C.

In certain embodiments, from 1% to 75% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 20% to 60% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers, or from 40% to 50% of the nucleomonomers of the first strand of the nucleic acid compound are conformationally restricted nucleomonomers.

In certain embodiments, the nucleic acid compound comprises RNA. In certain embodiments, the nucleic acid compound comprises DNA. In certain embodiments, the nucleic acid compound comprises RNA and DNA.

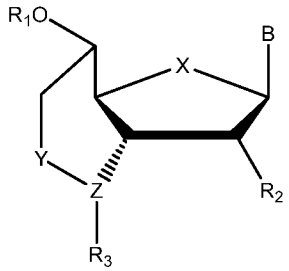
In other embodiments, the first strand is from 10 to 40 (or 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40) nucleomonomers in length. In other embodiments, the first strand is from 10 to 30 nucleomonomers in length.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer R and has the following formula:



where X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2; R_2 and R_3 are independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, S-F, CN, N_3, OCH_3, monosphosphate, diphosphate, triphosphate, monophosphate, diphosphonate, triphosphonate, an amino acid ester with an OH group the sugar portion, or a prodrug of the monophosphate, diphosphate, triphosphate, monophosphonate, diphosphonate, or triphosphonate, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is independently for each occurrence a nucleobase or nucleobase analog.

In certain embodiments, the conformationally restricted nucleomonomer is Monomer Q and has the following formula:



where X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2; Z is independently for each occurrence selected from N or CH; R_2 is independently for each occurrence selected from hydrogen, F, OH, or OMe; R_1 and R_3 are independently for each occurrence selected from hydrogen, OH, $P(OR)_2$, $P(O)(OR)_2$, $P(S)(OR)_2$, P(O)(SR)OR, acyl, carbobenzoxy, trifluoroacetyl, p-nitrophenyloxycarbonyl, or any suitable protecting group or an activating group for building oligomers; and R is independently for each occurrence selected from H, 2-cyanoethyl, diisopropylamino, alkyl, alkenyl, alkynyl, or a hydrophobic masking group, where R can be same or different from each other in case of $(OR)_2$, or (SR)OR.

In certain embodiments, the nucleic acid compound comprises one or more Monomer R and one or more Monomer Q.

In certain embodiments, the nucleic acid compound further comprises a second strand.

In certain embodiments, the second strand comprises one or more conformationally restricted nucleomonomers.

In certain embodiments, the nucleic acid compound further comprises a hydroxymethyl substituted nucleomonomer. In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer A, Monomer C, Monomer E, Monomer G, Monomer I, Monomer K, Monomer M, and Monomer O; wherein, X is independently for each occurrence selected from O, S, or $-CH_2$; Z is independently for each occurrence selected from hydrogen, OH, CH_2OH, CH_3 or saturated or unsaturated C(2-22) alkyl chain; J is independently for each occurrence selected from P or S; R_2 is independently for each occurrence selected from hydrogen, OH, O-alkyl, F, SH, S-alkyl, SF, NH(CH=O), NH(C=O)-C(1-22) saturated or unsaturated alkyl chain, cycloalkyl, aryl or heterocyclic; and B is a nucleobase or nucleobase analog.

In certain embodiments, the hydroxymethyl substituted nucleomonomer is independently for each occurrence selected from Monomer B, Monomer D, Monomer F, Monomer H, Monomer J, Monomer L, Monomer N and Monomer P; wherein, B is a nucleobase or nucleobase analog.

In certain embodiments, the first strand is from 10 to 40 nucleomonomers in length or from 10 to 30 nucleomonomers in length

Synthesis of Nucleic Acid Molecules

Exemplary molecules of the instant disclosure are recombinantly produced, chemically synthesized, or a combination thereof. Oligonucleotides (*e.g.*, certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, *Methods in Enzymol. 211*:3-19, 1992; Thompson *et al.*, PCT Publication No. WO 99/54459, Wincott *et al.*, *Nucleic Acids Res. 23*:2677-2684, 1995; Wincott *et al.*, *Methods Mol. Bio. 74*:59, 1997; Brennan *et al.*, *Biotechnol Bioeng. 61*:33-45, 1998; and Brennan, U.S. Patent No. 6,001,311. Synthesis of RNA, including certain dsRNA molecules and analogs thereof of this disclosure, can be made using the procedure as described in Usman *et al.*, *J. Am. Chem. Soc. 109*:7845, 1987; Scaringe *et al.*, *Nucleic Acids Res. 18*:5433, 1990; and Wincott *et al.*, *Nucleic Acids Res. 23*:2677-2684, 1995; Wincott *et al.*, *Methods Mol. Bio. 74*:59, 1997.

In certain embodiments, the nucleic acid molecules of the present disclosure can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, *Science 256*:9923, 1992; Draper *et al.*, PCT Publication No. WO 93/23569; Shabarova *et al.*, *Nucleic Acids Res. 19*:4247, 1991; Bellon *et al.*, *Nucleosides & Nucleotides 16*:951, 1997;

Bellon *et al.*, *Bioconjugate Chem. 8*:204, 1997), or by hybridization following synthesis or deprotection.

In certain embodiments, double-stranded portions of dsRNAs, in which two or more strands pair up, are not limited to completely paired nucleotide segments, and may contain non-pairing portions due to a mismatch (the corresponding nucleotides are not complementary), bulge (lacking in the corresponding complementary nucleotide on one strand), overhang, or the like. Non-pairing portions can be contained to the extent that they do not interfere with dsRNA formation and function. In certain embodiments, a "bulge" may comprise 1 to 2 non-pairing nucleotides, and the double-stranded region of dsRNAs in which two strands pair up may contain from about 1 to 7, or about 1 to 5 bulges. In addition, "mismatch" portions contained in the double-stranded region of dsRNAs may include from about 1 to 7, or about 1 to 5 mismatches. In other embodiments, the double-stranded region of dsRNAs of this disclosure may contain both bulge and mismatched portions in the approximate numerical ranges specified herein.

A dsRNA or analog thereof of this disclosure may be further comprised of a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the dsRNA to the antisense region of the dsRNA. In one embodiment, a nucleotide linker can be a linker of more than about 2 nucleotides length up to about 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer.

A non-nucleotide linker may be comprised of an abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (*e.g.*, polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res. 18*:6353, 1990, and *Nucleic Acids Res. 15*:3113, 1987; Cload and Schepartz, *J. Am. Chem. Soc. 113*:6324, 1991; Richardson and Schepartz, *J. Am. Chem. Soc. 113*:5109, 1991; Ma *et al.*, *Nucleic Acids Res. 21*:2585, 1993, and *Biochemistry 32*:1751, 1993; Durand *et al.*, *Nucleic Acids Res. 18*:6353, 1990; McCurdy *et al.*, *Nucleosides & Nucleotides 10*:287, 1991; Jaschke *et al.*, *Tetrahedron Lett. 34*:301, 1993; Ono *et al.*, *Biochemistry 30*:9914, 1991; Arnold *et al.*, PCT Publication No. WO 89/02439; Usman *et al.*, PCT Publication No. WO 95/06731; Dudycz *et al.*, PCT Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc. 113*:4000, 1991. The synthesis of a dsRNA molecule of this disclosure, which can be further modified, comprises: (a) synthesis of a first (antisense) strand and synthesis of a second (sense) strand and a third (sense) strand that are each complementary to non-overlapping regions of the first strand; and (b) annealing the first, second and third strands together under conditions suitable to obtain a dsRNA molecule. In another embodiment, synthesis of the first, second and third strands of a

dsRNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the first, second, and third strands of a dsRNA molecule is by solid phase tandem oligonucleotide synthesis.

Chemically synthesizing nucleic acid molecules with substitutions or modifications (base, sugar, phosphate, or any combination thereof) can prevent their degradation by serum ribonucleases, which may lead to increased potency. *See, e.g.*, Eckstein *et al.*, PCT Publication No. WO 92/07065; Perrault *et al.*, *Nature 344*:565, 1990; Pieken *et al.*, *Science 253*:314, 1991; Usman and Cedergren, *Trends in Biochem. Sci. 17*:334, 1992; Usman *et al.*, *Nucleic Acids Symp. Ser. 31*:163, 1994; Beigelman *et al.*, *J. Biol. Chem. 270*:25702, 1995; Burgin *et al.*, *Biochemistry 35*:14090, 1996; Burlina *et al.*, *Bioorg. Med. Chem. 5*:1999, 1997; Thompson *et al.*, Karpeisky *et al.*, *Tetrahedron Lett. 39*:1131, 1998; Earnshaw and Gait, *Biopolymers (Nucleic Acid Sciences) 48*:39-55, 1998; Verma and Eckstein, *Annu. Rev. Biochem. 67*:99-134, 1998; Herdewijn, *Antisense Nucleic Acid Drug Dev. 10*:297, 2000; Kurreck, *Eur. J. Biochem. 270*:1628, 2003; Dorsett and Tuschl, *Nature Rev. Drug Discov. 3*:318, 2004; PCT Publication Nos. WO 91/03162; WO 93/15187; WO 97/26270; WO 98/13526; U.S. Patent Nos. 5,334,711; 5,627,053; 5,716,824; 5,767, 264; 6,300,074. Each of the above references discloses various substitutions and chemical modifications to the base, phosphate, or sugar moieties of nucleic acid molecules, which can be used in the dsRNAs described herein. For example, oligonucleotides can be modified at the sugar moiety to enhance stability or prolong biological activity by increasing nuclease resistance. Representative sugar modifications include 2′-amino, 2′-C-allyl, 2′-fluoro, 2′-O-methyl, 2′-O-allyl, or 2′-H. Other modifications to enhance stability or prolong biological activity can be internucleoside linkages, such as phosphorothioate, or base-modifications, such as locked nucleic acids (*see, e.g.*, U.S. Patent Nos. 6,670,461; 6,794,499; 6,268,490), or 5-methyluridine or 2'-O-methyl-5-methyluridine in place of uridine (*see, e.g.*, U.S. Patent Application Publication No. 2006/0142230). Hence, dsRNA molecules of the instant disclosure can be modified to increase nuclease resistance or duplex stability while substantially retaining or having enhanced RNAi activity as compared to unmodified dsRNA.

In one embodiment, this disclosure features substituted or modified dsRNA molecules, such as phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, or alkylsilyl substitutions. For a review of oligonucleotide backbone modifications, *see* Hunziker and Leumann, *Nucleic Acid Analogues: Synthesis and Properties, in Modern Synthetic Methods, VCH*, 331-417, 1995; and Mesmaeker *et al.*, *ACS*, 24-39, 1994.

In another embodiment, a conjugate molecule can be optionally attached to a dsRNA or analog thereof that decreases expression of a target gene by RNAi. For example, such conjugate molecules may be polyethylene glycol, human serum albumin, polyarginine, Gln-Asn polymer, or a ligand for a cellular receptor that can, for example, mediate cellular uptake (*e.g.*, HIV TAT, *see* Vocero-Akbani *et al.*, *Nature Med.* 5:23, 1999; *see also* U.S. Patent Application Publication No. 2004/0132161).. Examples of specific conjugate molecules contemplated by the instant disclosure that can be attached to a dsRNA or analog thereof of this disclosure are described in Vargeese *et al.*, U.S. Patent Application Publication No. 2003/0130186, and U.S. Patent Application Publication No. 2004/0110296.

In another embodiment, a conjugate molecule is covalently attached to a nucleic acid compound (e.g., dsRNA) or analog thereof that decreases expression of a target gene by RNAi via a biodegradable linker. In certain embodiments, a conjugate molecule can be attached at the 3′-end of either the sense strand, the antisense strand, or both strands of a dsRNA molecule provided herein. In another embodiment, a conjugate molecule can be attached at the 5′-end of either the sense strand, the antisense strand, or both strands of the dsRNA or analog thereof. In yet another embodiment, a conjugate molecule is attached at both the 3′-end and 5′-end of either the sense strand, the antisense strand, or both strands of a dsRNA molecule, or any combination thereof. In further embodiments, a conjugate molecule of this disclosure comprises a molecule that facilitates delivery of a dsRNA or analog thereof into a biological system, such as a cell. A person of skill in the art can screen dsRNA of this disclosure having various conjugates to determine whether the dsRNA-conjugate possesses improved properties (*e.g.*, pharmacokinetic profiles, bioavailability, stability) while maintaining the ability to mediate RNAi in, for example, an animal model as described herein or generally known in the art.

In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated.

As used herein, "about" or "consisting essentially of" mean ± 20% of the indicated range, value, or structure, unless otherwise indicated.

As used herein, the terms "include" and "comprise" are open ended and are used synonymously.

It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components.

The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives.

As used herein, the term "linked" encompasses a covalent linkage either directly between two chemical entities (e.g., RNA and a hydroxymethyl substituted nucleomonomer), or indirectly between two chemical entities, for example via a linker.

As used herein, the term "overhang" (e.g., 3'-end overhang or 3' overhang) means an unpaired region of a nucleic acid compound which may contain all nucleotides, non-nucleotides (e.g., hydroxymethyl substituted nucleomonomers), or a combination of nucleotides and non-nucleotides.

As used herein, the term "nucleobase analog" refers to a substituted or unsubstituted nitrogen-containing parent heteroaromatic ring that is capable of forming Watson-Crick hydrogen bonds with a complementary nucleobase or nucleobase analog. Exemplary nucleobase analogs include, but are not limited to, 7-deazaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-propynylcytidine, isocytidine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methyl guanine, N^6-methyl adenine, O^4-methyl thymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, ethenoadenine. Additional exemplary nucleobase analogs can be found in Fasman, 1989, Practical Handbook of Biochemistry and Molecular Biology, pp. 385-394, CRC Press, Boca Raton, Fla., and the references cited therein, incorporated herein by reference.

As used herein, the term "nucleomonomer" means a moiety comprising (1) a base covalently linked to (2) a second moiety. Nucleomonomers can be linked to form oligomers that bind to target or complementary base sequences in nucleic acids in a sequence specific manner. Nucleomonomers may be nucleosides, nucleotides, non-nucleotides or non-nucleosides (e.g. hydroxymethyl substituted nucleomonomer).

As used herein, the terms "hydroxymethyl substituted nucleomonomer", "hydroxymethyl nucleomonomer", "hydroxymethyl monomer", "acyclic nucleomonomer", "acyclic monomer", "acyclic hydroxymethyl substituted nucleomonomer" may be used interchangeably throughout.

As used herein, the terms "conformationally restricted nucleomonomer", "conformationally restricted nucleotide" may be used interchangeably and refer to a nucleomonomer that has a bicyclic sugar moiety (e.g. bicyclic ribose) wherein the C2' and C4' of the sugar moiety are bridged (e.g., Monomer R) or the C3' and C5' are bridged (e.g., Monomer Q). Additional examples may be found in Patent Nos. U.S. 6,833,361; U.S. 6,403,566 and U.S. 6,083,482, which are hereby incorporated by reference in their entirety.

As used herein, the terms "RISC length" or "RISC length RNA complex" means a nucleic acid molecule having less than 25 base pairs.

As used herein the terms "Dicer length" or "Dicer length RNA complex" means a nucleic acid molecule have 25 or more base pairs, generally, from 25 to 40 base pairs.

As used herein the term "bifunctional nucleic acid compound" or "bifunctional RNA complex" or "bifunctional dsRNA" means a nucleic acid compound having a sense strand and antisense strand, wherein the sense strand and the antisense strand are each complementary to different regions of the same target RNA (i.e., a first region and a second region), or are each complementary to a region of at least two different target RNAs.

As used herein, the terms "seed region" or "seed sequence" refer to the region of a microRNA that is implicated in gene regulation by inhibition of translation and/or mRNA degradation, or the portion of the guide strand in a siRNA that is analogous to the ***seed region*** of a microRNA

As used herein, the term "isolated" means that the referenced material (*e.g.*, nucleic acid molecules of the instant disclosure), is removed from its original environment, such as being separated from some or all of the co-existing materials in a natural environment (*e.g.*, a natural environment may be a cell).

As used herein, "complementary" refers to a nucleic acid molecule that can form hydrogen bond(s) with another nucleic acid molecule or itself by either traditional Watson-Crick base pairing or other non-traditional types of pairing (*e.g.*, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary nucleosides or nucleotides. In reference to the nucleic molecules of the present disclosure, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid molecule to proceed, for example, RNAi activity, and there is a sufficient degree of complementarity to avoid non-specific binding of the nucleic acid molecule (*e.g.*, dsRNA) to non-target sequences under conditions in which specific binding is desired, *i.e.*, under physiological conditions in the case of *in vivo* assays or therapeutic treatment, or under conditions in which the assays are performed in the case of *in vitro* assays (*e.g.*, hybridization assays). Determination of binding free energies for nucleic acid molecules is well known in the art (*see, e.g.*, Turner *et al.*, *CSH Symp. Quant. Biol. LII*:123, 1987; Frier *et al.*, *Proc. Nat'l. Acad. Sci. USA 83*:9373, 1986; Turner *et al.*, *J. Am. Chem. Soc. 109*:3783, 1987). Thus, "complementary" or "specifically hybridizable" or "specifically binds" are terms that indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between a nucleic acid molecule (*e.g.*, dsRNA) and a DNA or RNA target. It is understood in the art that a nucleic acid molecule need not be 100% complementary to a target

nucleic acid sequence to be specifically hybridizable or to specifically bind. That is, two or more nucleic acid molecules may be less than fully complementary and is indicated by a percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds with a second nucleic acid molecule.

For example, a first nucleic acid molecule may have 10 nucleotides and a second nucleic acid molecule may have 10 nucleotides, then base pairing of 5, 6, 7, 8, 9, or 10 nucleotides between the first and second nucleic acid molecules, which may or may not form a contiguous double-stranded region, represents 50%, 60%, 70%, 80%, 90%, and 100% complementarity, respectively. In certain embodiments, complementary nucleic acid molecules may have wrongly paired bases – that is, bases that cannot form a traditional Watson-Crick base pair or other non-traditional types of pair (*i.e.*, "mismatched" bases). For instance, complementary nucleic acid molecules may be identified as having a certain number of "mismatches," such as zero or about 1, about 2, about 3, about 4 or about 5.

"Perfectly" or "fully" complementary nucleic acid molecules means those in which a certain number of nucleotides of a first nucleic acid molecule hydrogen bond (anneal) with the same number of residues in a second nucleic acid molecule to form a contiguous double-stranded region. For example, two or more fully complementary nucleic acid molecule strands can have the same number of nucleotides (*i.e.*, have the same length and form one double-stranded region, with or without an overhang) or have a different number of nucleotides (*e.g.*, one strand may be shorter than but fully contained within another strand or one strand may overhang the other strand).

By "ribonucleic acid" or "RNA" is meant a nucleic acid molecule comprising at least one ribonucleotide molecule. As used herein, "ribonucleotide" refers to a nucleotide with a hydroxyl group at the 2′-position of a β-*D*-ribofuranose moiety. The term RNA includes double-stranded (ds) RNA, single-stranded (ss) RNA, isolated RNA (such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA), altered RNA (which differs from naturally occurring RNA by the addition, deletion, substitution or alteration of one or more nucleotides), or any combination thereof. For example, such altered RNA can include addition of non-nucleotide material, such as at one or both ends of an RNA molecule, internally at one or more nucleotides of the RNA, or any combination thereof. Nucleotides in RNA molecules of the instant disclosure can also comprise non-standard nucleotides, such as naturally occurring nucleotides, non-naturally occurring nucleotides, chemically-modified nucleotides, deoxynucleotides, or any combination thereof. These altered RNAs may be referred to as analogs or analogs of RNA containing standard nucleotides (*i.e.*, standard nucleotides, as used herein, are considered to be adenine, cytidine, guanidine, thymidine, and uridine).

The term "dsRNA" and "RNA complex" as used herein, refers to any nucleic acid molecule comprising at least one ribonucleotide molecule and capable of inhibiting or down regulating gene expression, for example, by promoting RNA interference ("RNAi") or gene silencing in a sequence-specific manner. The dsRNAs (mdRNAs) of the instant disclosure may be suitable substrates for Dicer or for association with RISC to mediate gene silencing by RNAi. Examples of dsRNA molecules of this disclosure are provided in the Sequence Listing identified herein. One or both strands of the dsRNA can further comprise a terminal phosphate group, such as a 5'-phosphate or 5', 3'-diphosphate. As used herein, dsRNA molecules, in addition to at least one ribonucleotide, can further include substitutions, chemically-modified nucleotides, and non-nucleotides. In certain embodiments, dsRNA molecules comprise ribonucleotides up to about 100% of the nucleotide positions.

The nucleic acid compounds disclosed herein may comprise two strands that together constitute an RNA duplex composed of an antisense strand (the antisense strand is also herein referred to as the guide strand or first strand) and a passenger strand (the passenger strand is also herein referred to as the sense strand or second strand), a single stranded RNA molecule (e.g. antisense RNA), a functional RNA (fRNA), or non-coding RNA (ncRNA), such as small temporal RNA (stRNA), microRNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof, an RNAa molecule, a microRNA mimicking molecule is also considered herein as an RNA complex of the disclosure, as is a single stranded antisense molecule that for example is useful for targeting microRNAs.

In addition, as used herein, the term dsRNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example, meroduplex RNA (mdRNA), nicked dsRNA (ndsRNA), gapped dsRNA (gdsRNA), short interfering nucleic acid (siNA), siRNA, micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering substituted oligonucleotide, short interfering modified oligonucleotide, chemically-modified dsRNA, post-transcriptional gene silencing RNA (ptgsRNA), or the like.

In some respects, dsRNA molecules described herein form a meroduplex RNA (mdRNA) having three or more strands, for example, an 'A' (first or antisense) strand, 'S1' (second) strand, and 'S2' (third) strand in which the 'S1' and 'S2' strands are complementary to and form base pairs (bp) with non-overlapping regions of the 'A' strand (*e.g.*, an mdRNA can have the form of A:S1S2). The S1, S2, or more strands together essentially comprise a sense strand to the 'A' strand. The double-stranded region formed by the annealing of the 'S1' and 'A' strands is distinct from and non-overlapping with the double-stranded region formed by the

annealing of the 'S2' and 'A' strands. An mdRNA molecule is a "gapped" molecule, meaning a "gap" ranging from 0 nucleotides up to about 10 nucleotides. In some embodiments, the A:S1 duplex is separated from the A:S2 duplex by a gap resulting from at least one unpaired nucleotide (up to about 10 unpaired nucleotides) in the 'A' strand that is positioned between the A:S1 duplex and the A:S2 duplex and that is distinct from any one or more unpaired nucleotide at the 3'-end of one or more of the 'A', 'S1', or 'S2' strands. In some embodiments, the A:S1 duplex is separated from the A:B2 duplex by a gap of zero nucleotides (*i.e.*, a nick in which only a phosphodiester bond between two nucleotides is broken or missing in the polynucleotide molecule) between the A:S1 duplex and the A:S2 duplex – which can also be referred to as nicked dsRNA (ndsRNA). For example, A:S1S2 may be comprised of a dsRNA having at least two double-stranded regions that combined total about 14 base pairs to about 40 base pairs and the double-stranded regions are separated by a gap of about 0 to about 10 nucleotides, optionally having blunt ends, or A:S1S2 may comprise a dsRNA having at least two double-stranded regions separated by a gap of up to 10 nucleotides wherein at least one of the double-stranded regions comprises between about 5 base pairs and 13 base pairs.

The term "large double-stranded RNA" ("large dsRNA") refers to any double-stranded RNA longer than about 40 base pairs (bp) to about 100 bp or more, particularly up to about 300 bp to about 500 bp. The sequence of a large dsRNA may represent a segment of an mRNA or an entire mRNA. A double-stranded structure may be formed by a self-complementary nucleic acid molecule or by annealing of two or more distinct complementary nucleic acid molecule strands.

In addition, as used herein, the term "RNAi" is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, dsRNA molecules of this disclosure can be used to epigenetically silence genes at the post-transcriptional level or the pre-transcriptional level or any combination thereof.

As used herein, the term “nucleic acid based regulatory system” or “cell regulatory system dependent upon a nucleic acid” refers to any cell regulatory system that is regulated, modified, controlled, or modulated, in full or part, by the presence and/or function of a nucleomonomer, nucleotide, nucleoside, and/or oligonucleotide.

As used herein, "target nucleic acid" refers to any nucleic acid sequence whose expression or activity is to be altered. The target nucleic acid can be DNA, RNA, or analogs thereof, and includes single, double, and multi-stranded forms.

By "target site" or "target sequence" is meant a sequence within a target nucleic acid (*e.g.*, mRNA) that, when present in an RNA molecule, is "targeted" for cleavage by RNAi and

mediated by a dsRNA construct of this disclosure containing a sequence within the antisense strand that is complementary to the target site or sequence.

As used herein, "off-target effect" or "off-target profile" refers to the observed altered expression pattern of one or more genes in a cell or other biological sample not targeted, directly or indirectly, for gene silencing by an mdRNA or dsRNA. For example, an off-target effect can be quantified by using a DNA microarray to determine how many non-target genes have an expression level altered by about two-fold or more in the presence of a candidate mdRNA or dsRNA, or analog thereof specific for a target sequence.

A "minimal off-target effect" means that an mdRNA or dsRNA affects expression by about two-fold or more of about 25% to about 1% of the non-target genes examined or it means that the off-target effect of substituted or modified mdRNA or dsRNA (*e.g.*, having at least one uridine substituted with a 5-methyluridine or 2-thioribothymidine and optionally having at least one nucleotide modified at the 2'-position), is reduced by at least about 1% to about 80% or more as compared to the effect on non-target genes of an unsubstituted or unmodified mdRNA or dsRNA.

By "sense region" or "sense strand" or “second strand” is meant one or more nucleotide sequences of a nucleic acid compound having complementarity to one or more antisense regions of the nucleic acid compound. In addition, the sense region of a nucleic acid compound comprises a nucleic acid sequence having homology or identity to a target sequence.

By "antisense region" or "antisense strand" or “first strand” is meant a nucleotide sequence of a dsRNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a dsRNA molecule can comprise nucleic acid sequence region having complementarity to one or more sense strands of the dsRNA molecule.

"Analog" as used herein refers to a compound that is structurally similar to a parent compound (*e.g.*, a nucleic acid molecule), but differs slightly in composition (*e.g.*, one atom or functional group is different, added, or removed). The analog may or may not have different chemical or physical properties than the original compound and may or may not have improved biological or chemical activity. For example, the analog may be more hydrophilic or it may have altered activity as compared to a parent compound. The analog may mimic the chemical or biological activity of the parent compound (*i.e.*, it may have similar or identical activity), or, in some cases, may have increased or decreased activity. The analog may be a naturally or non-naturally occurring (*e.g.*, chemically-modified or recombinant) variant of the original compound. An example of an RNA analog is an RNA molecule having a non-standard nucleotide, such as 5-methyuridine or 5-methylcytidine or 2-thioribothymidine, which may

impart certain desirable properties (*e.g.*, improve stability, bioavailability, minimize off-target effects or interferon response).

As used herein, the term "universal base" refers to nucleotide base analogs that form base pairs with each of the standard DNA/RNA bases with little discrimination between them. A universal base is thus interchangeable with all of the standard bases when substituted into a nucleotide duplex (*see, e.g.*, Loakes *et al.*, *J. Mol. Bio. 270*:426, 1997). Exemplary universal bases include C-phenyl, C-naphthyl and other aromatic derivatives, inosine, azole carboxamides, or nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole (*see, e.g.*, Loakes, *Nucleic Acids Res. 29*:2437, 2001).

The term "gene" as used herein, especially in the context of "target gene" or "gene target" for RNAi, means a nucleic acid molecule that encodes an RNA or a transcription product of such gene, including a messenger RNA (mRNA, also referred to as structural genes that encode for a polypeptide), an mRNA splice variant of such gene, a functional RNA (fRNA), or non-coding RNA (ncRNA), such as small temporal RNA (stRNA), microRNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for dsRNA mediated RNAi to alter the activity of the target RNA involved in functional or regulatory cellular processes.

As used herein, "gene silencing" refers to a partial or complete loss-of-function through targeted inhibition of gene expression in a cell, which may also be referred to as RNAi "knockdown," "inhibition," "down-regulation," or "reduction" of expression of a target gene. Depending on the circumstances and the biological problem to be addressed, it may be preferable to partially reduce gene expression. Alternatively, it might be desirable to reduce gene expression as much as possible. The extent of silencing may be determined by methods described herein and known in the art (*see, e.g.*, PCT Publication No. WO 99/32619; Elbashir *et al.*, *EMBO J. 20*:6877, 2001). Depending on the assay, quantification of gene expression permits detection of various amounts of inhibition that may be desired in certain embodiments of this disclosure, including prophylactic and therapeutic methods, which will be capable of knocking down target gene expression, in terms of mRNA level or protein level or activity, for example, by equal to or greater than 10%, 30%, 50%, 75% 90%, 95% or 99% of baseline (*i.e.*, normal) or other control levels, including elevated expression levels as may be associated with particular disease states or other conditions targeted for therapy.

As used herein, the term "therapeutically effective amount" means an amount of dsRNA that is sufficient to result in a decrease in severity of disease symptoms, an increase in frequency or duration of disease symptom-free periods, or a prevention of impairment or disability due to

the disease, in the subject (*e.g.*, human) to which it is administered. For example, a therapeutically effective amount of dsRNA directed against an mRNA of a target gene can inhibit the deposition of lipoproteins in the walls of arteries by at least about 20%, at least about 40%, at least about 60%, or at least about 80% relative to untreated subjects. A therapeutically effective amount of a therapeutic compound can decrease, for example, atheromatous plaque size or otherwise ameliorate symptoms in a subject. One of ordinary skill in the art would be able to determine such therapeutically effective amounts based on such factors as the subject's size, the severity of symptoms, and the particular composition or route of administration selected. The nucleic acid molecules of the instant disclosure, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein. For example, to treat a particular disease, disorder, or condition, the dsRNA molecules can be administered to a patient or can be administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs, under conditions suitable for treatment.

In addition, it should be understood that the individual compounds, or groups of compounds, derived from the various combinations of the structures and substituents described herein, are disclosed by the present application to the same extent as if each compound or group of compounds was set forth individually. Thus, selection of particular structures or particular substituents is within the scope of the present disclosure. As described herein, all value ranges are inclusive over the indicated range. Thus, a range of C_1-C_4 will be understood to include the values of 1, 2, 3, and 4, such that C_1, C_2, C_3 and C_4 are included.

The term "alkyl" as used herein refers to a saturated, branched or unbranched, substituted or unsubstituted aliphatic group containing from 1-22 carbon atoms (1, 2, 3, 4, 5 ,6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 carbon atoms). This definition applies to the alkyl portion of other groups such as, for example, alkoxy, alkanoyl, aralkyl, and other groups defined below. The term "cycloalkyl" as used herein refers to a saturated, substituted or unsubstituted cyclic alkyl ring containing from 3 to 12 carbon atoms.

The term "alkenyl" as used herein refers to an unsaturated, branched or unbranched, substituted or unsubstituted alkyl or cycloalkyl having 2 to 22 carbon atoms and at least one carbon-carbon double bond. The term "alkynyl" as used herein refers to an unsaturated, branched or unbranched, substituted or unsubstituted alkyl or cycloalkyl having 2 to 22 carbon atoms and at least one carbon-carbon triple bond.

The term "alkoxy" as used herein refers to an alkyl, cycloalkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom. The term "alkanoyl" as used herein refers to -C(=O)-alkyl, which may alternatively be referred to as "acyl." The term "alkanoyloxy" as used herein refers to –

O-C(=O)-alkyl groups. The term "alkylamino" as used herein refers to the group –NRR', where R and R' are each either hydrogen or alkyl, and at least one of R and R' is alkyl. Alkylamino includes groups such as piperidino wherein R and R' form a ring. The term "alkylaminoalkyl" refers to –alkyl-NRR'.

The term "aryl" as used herein refers to any stable monocyclic, bicyclic, or polycyclic carbon ring system of from 4 to 12 atoms in each ring, wherein at least one ring is aromatic. Some examples of an aryl include phenyl, naphthyl, tetrahydro-naphthyl, indanyl, and biphenyl. Where an aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is to the aromatic ring. An aryl may be substituted or unsubstituted.

The term "heteroaryl" as used herein refers to any stable monocyclic, bicyclic, or polycyclic carbon ring system of from 4 to 12 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur. Some examples of a heteroaryl include acridinyl, quinoxalinyl, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, and tetrahydroquinolinyl. A heteroaryl includes the N-oxide derivative of a nitrogen-containing heteroaryl.

The term "heterocycle" or "heterocyclyl" as used herein refers to an aromatic or nonaromatic ring system of from five to twenty-two atoms, wherein from 1 to 4 of the ring atoms are heteroatoms selected from oxygen, nitrogen, and sulfur. Thus, a heterocycle may be a heteroaryl or a dihydro or tetrathydro version thereof.

The term "aroyl" as used herein refers to an aryl radical derived from an aromatic carboxylic acid, such as a substituted benzoic acid. The term "aralkyl" as used herein refers to an aryl group bonded to an alkyl group, for example, a benzyl group.

The term "carboxyl" as used herein represents a group of the formula –C(=O)OH or $-C(=O)O^-$. The terms "carbonyl" and “acyl” as used herein refer to a group in which an oxygen atom is double-bonded to a carbon atom >C=O. The term "hydroxyl" as used herein refers to -OH or $-O^-$. The term "nitrile" or "cyano" as used herein refers to –CN. The term "halogen" or "halo" refers to fluoro (-F), chloro (–Cl), bromo (-Br), and iodo (-I).

The term "cycloalkyl" as used herein refers to a saturated cyclic hydrocarbon ring system containing from 3 to 12 carbon atoms that may be optionally substituted. Exemplary embodiments include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In certain embodiments, the cycloalkyl group is cyclopropyl. In another embodiment, the (cycloalkyl)alkyl groups contain from 3 to 12 carbon atoms in the cyclic portion and 1 to 6 carbon atoms in the alkyl portion. In certain embodiments, the (cycloalkyl)alkyl group is

cyclopropylmethyl. The alkyl groups are optionally substituted with from one to three substituents selected from the group consisting of halogen, hydroxy and amino.

The terms "alkanoyl" and "alkanoyloxy" as used herein refer, respectively, to -C(O)-alkyl groups and –O-C(=O)- alkyl groups, each optionally containing 2 to 10 carbon atoms. Specific embodiments of alkanoyl and alkanoyloxy groups are acetyl and acetoxy, respectively.

The term "alkynyl" as used herein refers to an unsaturated branched, straight-chain, or cyclic alkyl group having 2 to 10 carbon atoms and having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Exemplary alkynyls include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 4-pentynyl, 1-octynyl, 6-methyl-1-heptynyl, 2-decynyl, or the like. The alkynyl group may be substituted or unsubstituted.

The term "hydroxyalkyl" alone or in combination, refers to an alkyl group as previously defined, wherein one or several hydrogen atoms, preferably one hydrogen atom has been replaced by a hydroxyl group. Examples include hydroxymethyl, hydroxyethyl and 2-hydroxyethyl.

The term "aminoalkyl" as used herein refers to the group –NRR', where R and R' may independently be hydrogen or (C_1-C_4) alkyl.

The term "alkylaminoalkyl" refers to an alkylamino group linked via an alkyl group (*i.e.*, a group having the general structure -alkyl-NH-alkyl or -alkyl-N(alkyl)(alkyl)). Such groups include, but are not limited to, mono- and di-(C_1-C_8 alkyl)aminoC_1-C_8 alkyl, in which each alkyl may be the same or different.

The term "dialkylaminoalkyl" refers to alkylamino groups attached to an alkyl group. Examples include, but are not limited to, N,N-dimethylaminomethyl, N,N-dimethylaminoethyl N,N-dimethylaminopropyl, and the like. The term dialkylaminoalkyl also includes groups where the bridging alkyl moiety is optionally substituted.

The term "haloalkyl" refers to an alkyl group substituted with one or more halo groups, for example chloromethyl, 2-bromoethyl, 3-iodopropyl, trifluoromethyl, perfluoropropyl, 8-chlorononyl, or the like.

The term "carboxyalkyl" as used herein refers to the substituent -R^{10}-COOH, wherein R^{10} is alkylene; and “carbalkoxyalkyl” refers to –R^{10}-C(=O)OR^{11}, wherein R^{10} and R^{11} are alkylene and alkyl respectively. In certain embodiments, alkyl refers to a saturated straight- or branched-chain hydrocarbyl radical of 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, 2-methylpentyl, n-hexyl, and so forth. Alkylene is the same as alkyl except that the group is divalent.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. In one embodiment, the alkoxy group contains 1 to about 10 carbon atoms. Embodiments of alkoxy groups include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Embodiments of substituted alkoxy groups include halogenated alkoxy groups. In a further embodiment, the alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Exemplary halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, and trichloromethoxy.

The term "alkoxyalkyl" refers to an alkylene group substituted with an alkoxy group. For example, methoxyethyl ($CH_3OCH_2CH_2$-) and ethoxymethyl ($CH_3CH_2OCH_2$-) are both C_3 alkoxyalkyl groups.

The term "aroyl," as used alone or in combination herein, refers to an aryl radical derived from an aromatic carboxylic acid, such as optionally substituted benzoic or naphthoic acids.

The term "aralkyl" as used herein refers to an aryl group bonded to the 2-pyridinyl ring or the 4-pyridinyl ring through an alkyl group, preferably one containing 1 to 10 carbon atoms. A preferred aralkyl group is benzyl.

The term "carboxy," as used herein, represents a group of the formula –C(=O)OH or –$C(=O)O^-$.

The term "carbonyl" as used herein refers to a group in which an oxygen atom is double-bonded to a carbon atom -C=O.

The term "trifluoromethyl" as used herein refers to -CF_3.

The term "trifluoromethoxy" as used herein refers to -OCF_3.

The term "hydroxyl" as used herein refers to –OH or –O^-.

The term "nitrile" or "cyano" as used herein refers to the group –CN.

The term "nitro," as used herein alone or in combination refers to a -NO_2 group.

The term "amino" as used herein refers to the group –NR^9R^9, wherein R^9 may independently be hydrogen, alkyl, aryl, alkoxy, or heteroaryl. The term "aminoalkyl" as used

herein represents a more detailed selection as compared to "amino" and refers to the group -NR′R′, wherein R′ may independently be hydrogen or (C_1-C_4) alkyl. The term "dialkylamino" refers to an amino group having two attached alkyl groups that can be the same or different.

The term "alkanoylamino" refers to alkyl, alkenyl or alkynyl groups containing the group -C(=O)- followed by -N(H)-, for example acetylamino, propanoylamino and butanoylamino and the like.

The term "carbonylamino" refers to the group -NR′-CO-CH_2-R′, wherein R′ may be independently selected from hydrogen or (C_1-C_4) alkyl.

The term "carbamoyl" as used herein refers to -O-C(O)NH_2.

The term "carbamyl" as used herein refers to a functional group in which a nitrogen atom is directly bonded to a carbonyl, *i.e.*, as in -NR″C(=O)R″ or -C(=O)NR″R″, wherein R″ can be independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, cycloalkyl, aryl, heterocyclo, or heteroaryl.

The term "alkylsulfonylamino" refers to the group -NHS(O)$_2$$R^{12}$, wherein R^{12} is alkyl.

The term "halogen" as used herein refers to bromine, chlorine, fluorine or iodine. In one embodiment, the halogen is fluorine. In another embodiment, the halogen is chlorine.

The term "heterocyclo" refers to an optionally substituted, unsaturated, partially saturated, or fully saturated, aromatic or nonaromatic cyclic group that is a 4 to 7 membered monocyclic, or 7 to 11 membered bicyclic ring system that has at least one heteroatom in at least one carbon atom-containing ring. The substituents on the heterocyclo rings may be selected from those given above for the aryl groups. Each ring of the heterocyclo group containing a heteroatom may have 1, 2, or 3 heteroatoms selected from nitrogen, oxygen or sulfur. Plural heteroatoms in a given heterocyclo ring may be the same or different.

Exemplary monocyclic heterocyclo groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, tetrahydrofuryl, thienyl, piperidinyl, piperazinyl, azepinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, dioxanyl, triazinyl and triazolyl. Preferred bicyclic heterocyclo groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, benzimidazolyl, benzofuryl, indazolyl, benzisothiazolyl, isoindolinyl and tetrahydroquinolinyl. In more detailed embodiments heterocyclo groups may include indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl and pyrimidyl.

The "percent identity" between two or more nucleic acid sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical positions / total number of positions x 100), taking into account the number of gaps, and the length of each gap that needs to be introduced to optimize alignment of two or more sequences.

The comparison of sequences and determination of percent identity between two or more sequences can be accomplished using a mathematical algorithm, such as BLAST and Gapped BLAST programs at their default parameters (*e.g.*, BLASTN, *see* Altschul *et al.*, *J. Mol. Biol. 215*:403-410, 1990).

"Aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule wherein the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art (*see, e.g.*, Gold *et al.*, *Annu. Rev. Biochem. 64*:763, 1995; Brody and Gold, *J. Biotechnol. 74*:5, 2000; Sun, *Curr. Opin. Mol. Ther. 2*:100, 2000; Kusser, *J. Biotechnol. 74*:27, 2000; Hermann and Patel, *Science 287*:820, 2000; and Jayasena, *Clinical Chem. 45*:1628, 1999).

The term "substituted" as used herein refers to an atom having one or more substitutions or substituents which can be the same or different and may include a hydrogen substituent. Thus, the terms alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkanoyloxy, alkylamino, alkylaminoalkyl, aryl, heteroaryl, heterocycle, aroyl, and aralkyl as used herein refer to groups which include substituted variations. Substituted variations include linear, branched, and cyclic variations, and groups having a substituent or substituents replacing one or more hydrogens attached to any carbon atom of the group. Substituents that may be attached to a carbon atom of the group include alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkanoyloxy, alkylamino, alkylaminoalkyl, aryl, heteroaryl, heterocycle, aroyl, aralkyl, acyl, hydroxyl, cyano, halo, haloalkyl, amino, aminoacyl, alkylaminoacyl, acyloxy, aryloxy, aryloxyalkyl, mercapto, nitro, carbamyl, carbamoyl, and heterocycle. For example, the term ethyl includes without limitation $-CH_2CH_3$, $-CHFCH_3$, $-CF_2CH_3$, $-CHFCH_2F$, $-CHFCHF_2$, $-CHFCF_3$, $-CF_2CH_2F$, $-CF_2CHF_2$, $-CF_2CF_3$, and other variations as described above. Representative substituents include -X, $-R^6$, -O-, =O, -OR, $-SR^6$, -S-, =S, $-NR^6R^6$, $=NR^6$, $-CX_3$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(=O)_2O-$, $-S(=O)_2OH$, $-S(=O)_2R^6$, $-OS(=O)_2O-$, $-OS(=O)_2OH$, $-OS(=O)_2R^6$, $-P(=O)(O^-)_2$, $-P(=O)(OH)(O^-)$, $-OP(=O)_2(O^-)$, $-C(-O)R^6$, $-C(=S)R^6$, $-C(=O)OR^6$, $-C(=O)O^-$, $-C(=S)OR^6$, $-NR^6-C(=O)-N(R^6)_2$, $-NR^6-C(=S)-N(R^6)_2$, and $-C(=NR^6)NR^6R^6$, wherein each X is independently a halogen; and each R^6 is independently hydrogen, halogen, alkyl, aryl, arylalkyl, arylaryl, arylheteroalkyl, heteroaryl, heteroarylalkyl, NR^7R^7, $-C(=O)R^7$, and $-S(=O)_2R^7$; and

each R^7 is independently hydrogen, alkyl, alkanyl, alkynyl, aryl, arylalkyl, arylheteralkyl, arylaryl, heteroaryl or heteroarylalkyl. Aryl containing substituents, whether or not having one or more substitutions, may be attached in a para (*p*-), meta (*m*-) or ortho (*o*-) conformation, or any combination thereof. In general, substituents may be further substituted with any atom or group of atoms.

For example purposes only, the position of a nucleomonomer in a strand may be described as follows where X represents any type of nucleomonomer (e.g., nucleoside, modified nucleotide, RNA, DNA, hydroxymethyl substituted nucleomonomer or conformationally restricted nucleomonomer) and the number represents the position of that nucleomonomer in the strand. For example, X1 represents position one of the strand below counting from the 5'-end of the strand; X7 represents position seven of the strand below counting from the 5'-end of the strand. Alternatively, X1, X2, and X3 represent the last three positions at the 5'-end of the strand below, and X1 to X10 represent the last ten positions at the 5'-end of the strand. The X_n may represent positions 11 to 60 (or n = 1 to 60), thus when n is 20 (or X20), this indicates position 20 of the strand counting from the 5'-end of the strand.

5' X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X_n 3'

The same approach may be taken by counting from the 3'-end of a strand in order to identify the position of a nucleomonomer in the strand (example strand shown below). For the strand below, the position of a nucleomonomer in the strand may be described as follows where X represents any type of nucleomonomer (e.g., nucleoside, modified nucleotide, RNA, DNA, hydroxymethyl substituted nucleomonomer or conformationally restricted nucleomonomer) and the number represents the position of that nucleomonomer in the strand. For example, X1 represents position one of the strand below counting from the 3'-end of the strand; X7 represents position seven of the strand below counting from the 3'-end of the strand. Alternatively, X1, X2, and X3 represent the last three positions at the 3'-end of the strand below, and X1 to X10 represent the last ten positions at the 3'-end of the strand. The X_n may represent positions 11 to 60 (or n = 1 to 60), thus when n is 20 (or X20), this indicates position 20 of the strand counting from the 3'-end of the strand.

5' X_n-X10-X9-X8-X7-X6-X5-X4-X3-X2-X1 3'

All publications, non-patent publications, references, patents, patent publications, patent applications and other literature cited herein are each hereby specifically incorporated by reference in entirety.

While this disclosure has been described in relation to certain embodiments, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that this disclosure includes additional embodiments, and that some of the details described herein may be varied considerably without departing from this disclosure. This disclosure includes such additional embodiments, modifications and equivalents. In particular, this disclosure includes any combination of the features, terms, or elements of the various illustrative components and examples.

The use herein of the terms "a," "an," "the" and similar terms in describing the disclosure, and in the claims, are to be construed to include both the singular and the plural.

The terms "comprising," "having," "including" and "containing" are to be construed as open-ended terms which mean, for example, "including, but not limited to." Thus, terms such as "comprising," "having," "including" and "containing" are to be construed as being inclusive, not exclusive.

Recitation of a range of values herein refers individually to each and any separate value falling within the range as if it were individually recited herein, whether or not some of the values within the range are expressly recited. For example, the range "4 to 12" includes without limitation the values 5, 5.1, 5.35 and any other whole, integer, fractional, or rational value greater than or equal to 4 and less than or equal to 12. Specific values employed herein will be understood as exemplary and not to limit the scope of the disclosure.

Recitation of a range of number of carbon atoms herein refers individually to each and any separate value falling within the range as if it were individually recited herein, whether or not some of the values within the range are expressly recited. For example, the term "C1-24" includes without limitation the species C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, and C24.

Definitions of technical terms provided herein should be construed to include without recitation those meanings associated with these terms known to those skilled in the art, and are not intended to limit the scope of the disclosure. Definitions of technical terms provided herein shall be construed to dominate over alternative definitions in the art or definitions which become incorporated herein by reference to the extent that the alternative definitions conflict with the definition provided herein.

The examples given herein, and the exemplary language used herein are solely for the purpose of illustration, and are not intended to limit the scope of the disclosure.

When a list of examples is given, such as a list of compounds or molecules suitable for this disclosure, it will be apparent to those skilled in the art that mixtures of the listed compounds or molecules are also suitable.

EXAMPLES

EXAMPLE 1

RNA Targeting Survivin (BIRC5)

Sequence specific RNAs targeting Survivin (BIRC5) are shown in Tables 1 and 2. CRN monomers in the sequences of Tables 1 and 2 are identified as "crnX" where X is the one letter code for the nucleotide: A, U, C or G. For example, "crnC" indicates a cytidine CRN. The CRN in Tables 1 and 2 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:1-80 will complex with one of the antisense sequences SEQ ID NOs:81-160, respectively, in other words, SEQ ID NO:1 will complex with SEQ ID NO:81, SEQ ID NO:2 will complex with SEQ ID NO:82, and so forth.

Table 1. RNA Targeting Survivin

SEQ ID NO:	Sense Sequence (5' to 3' left to right)
1	CUGCCUGGCAGCCCUUUCcrnU
2	CcrnUGCCUGGCAGCCCUUUCUUcrnU
3	crnUcrnCUGCCUGGCAGCCCUUUCUUcrnU
4	CcrnUcrnGCCUGGCAGCCCUUUCUUcrnU
5	CUGCCUGGCAGCCCUUUCcrnUUU
6	CcrnUGCCUGGCAGCCCUUUCcrnUUU
7	crnCcrnUGCCUGGCAGCCCUUUCcrnUUU
8	UcrnCcrnUGCCUGGCAGCCCUUUCcrnUUU
9	GACCACCGCAUCUCUAcrnCAcrnU
10	GcrnACCACCGCAUCUCUACAcrnUUcrnU
11	crnUcrnGACCACCGCAUCUCUACAcrnUUcrnU
12	GcrnAcrnCCACCGCAUCUCUACAcrnUUcrnU
13	GACCACCGCAUCUCUACAcrnUcrnUcrnU
14	GcrnACCACCGCAUCUCUACAcrnUcrnUcrnU
15	crnGcrnACCACCGCAUCUCUACAcrnUcrnUcrnU
16	UcrnGcrnACCACCGCAUCUCUACAcrnUcrnUcrnU
17	CGCAUCUCUACAUUCAAGA
18	CGCAUCUCUACAUUCAAGAUU
19	UCGCAUCUCUACAUUCAAGAUU
20	CGCAUCUCUACAUUCAAGAUU
21	CGCAUCUCUACAUUCAAGAUU
22	CGCAUCUCUACAUUCAAGAUU
23	CGCAUCUCUACAUUCAAGAUU
24	UCGCAUCUCUACAUUCAAGAUU
25	GCCCAGUGUUUCUUCUGCU
26	GCCCAGUGUUUCUUCUGCUUU
27	UGCCCAGUGUUUCUUCUGCUUU
28	GCCCAGUGUUUCUUCUGCUUU
29	GCCCAGUGUUUCUUCUGCUUU
30	GCCCAGUGUUUCUUCUGCUUU
31	GCCCAGUGUUUCUUCUGCUUU
32	UGCCCAGUGUUUCUUCUGCUUU
33	CcrnCCcrnAGcrnUGcrnUUcrnUCcrnUUcrnCUcrnGCcrnUU
34	CCcrnCAGcrnUGUcrnUUCcrnUUCcrnUGCcrnUUUcrnU
35	UCCcrnCAGUcrnGUUUcrnCUUCcrnUGCUcrnUUU

36	CCCAcrnGUGUUcrnUCUUCcrnUGCUUcrnUU
37	CCCAGcrnUGUUUCcrnUUCUGCcrnUUUU
38	CCCAGUcrnGUUUCUUcrnCUGCUUUcrnU
39	CCCAGUGcrnUUUCUUCUcrnGCUUUU
40	UCCCAGUGcrnUUUCUUCUGcrnCUUUU
41	CCAGUGUUUcrnCUUCUGCUUC
42	CCAGUGUUUcrnCcrnUUCUGCUUCUU
43	UCCAGUGUUcrnUCUcrnUCUGCUUCUU
44	CCAGUGcrnUcrnUcrnUCUUCUGCUUCUU
45	CCAGUGUcrnUcrnUCUUCUGCUUCUU
46	CCAGUGUUcrnUcrnCUUCUGCUUCUU
47	CCAGUGUcrnUUcrnCUUCUGCUUCUU
48	UCCAGUGUcrnUUCcrnUUCUGCUUCUU
49	CAGUGUUUCUUCUGCUcrnUCA
50	CcrnAGUGUUUCUUCUGCUUCAUcrnU
51	crnUcrnCAGUGUUUCUUCUGCUUCcrnAUcrnU
52	CcrnAcrnGUGUUUCUUCUGCUUCcrnAcrnUcrnU
53	crnCAGUGUUUCUUCUGCUUCAUU
54	CAcrnGUGUUUCUUCUGCUUCAcrnUU
55	crnCAcrnGUGUUUCUUCUGCUUCcrnAcrnUU
56	crnUcrnCcrnAGUGUUUCUUCUGCUUCAcrnUcrnU
57	AGUGUUUCcrnUcrnUCUGCUUCAA
58	AGUGUUUCcrnUcrnUCUGCUUCAAUU
59	UAGUGUUUCcrnUcrnUCUGCUUCAAUU
60	AGUGUUUcrnCUcrnUCcrnUGCUUCAAUU
61	AGUGUUUCcrnUUCcrnUGCUUCAAUU
62	AGUGUUUCUcrnUCUGcrnCUUCAAUU
63	AGUGUUUCUUcrnCUGcrnCUUcrnCAAUU
64	UAGUGUUUcrnCUUcrnCUGcrnCUUCAAUU
65	GAAGAcrnAAGAAUUUcrnGAGGAA
66	GAAGAAAGAAUUUGAGGAAUU
67	UGcrnAAGAAAGAAUUUGAGGcrnAAUU
68	GAcrnAGAAcrnAGAAUUUGAGGAAUcrnU
69	GAAGcrnAAAGAAUUcrnUGAGGAAUcrnU
70	GAAGAAAGAAUUUGAGGAAcrnUcrnU
71	crnGcrnAcrnAcrnGcrnAAAGAAUUUGAGGAAUU
72	UGAAcrnGAAAcrnGAAUUUGAGGAAUU
73	AGUGGCcrnACCAGcrnAGGUGCUcrnU
74	crnAGUGGCACCAGAGGUGCUUUcrnU
75	crnUAGUGGCACCAGAGGUGCUcrnUUcrnU
76	AGUGGCACCAGAGGUGCUUcrnUcrnU
77	crnAGUGGcrnCACCAGAGGUGCUUUU
78	AGUGGCACCAGAGGUGCcrnUUUU
79	AGUGGCACCAGAGGUGCUUcrnUU
80	UAGUGGCACCAGAGGUGCUUUcrnU

Table 2. RNA Targeting Survivin

SEQ ID NO:	Antisense Sequence (5' to 3')
81	AGAAAGGGCUGCCAGGCAG
82	AGAAAGGGCUGCCAGGCAGUU
83	AGAAAGGGCUGCCAGGCAGUU
84	AGAAAGGGCUGCCAGGCAGUU
85	AGAAAGGGCUGCCAGGCAGUU
86	AGAAAGGGCUGCCAGGCAGUU

87	AGAAAGGGCUGCCAGGCAGUU
88	AGAAAGGGCUGCCAGGCAGUU
89	AUGUAGAGAUGCGGUGGUC
90	AUGUAGAGAUGCGGUGGUCUU
91	AUGUAGAGAUGCGGUGGUCUU
92	AUGUAGAGAUGCGGUGGUCUU
93	AUGUAGAGAUGCGGUGGUCUU
94	AUGUAGAGAUGCGGUGGUCUU
95	AUGUAGAGAUGCGGUGGUCUU
96	AUGUAGAGAUGCGGUGGUCUU
97	crnUCUUGAAUGUAGAGAUGCG
98	UCcrnUUGAAUGUAGAGAUGCGUU
99	crnUCcrnUUGAAUGUAGAGAUGCGUU
100	crnUcrnCcrnUUGAAUGUAGAGAUGCGUU
101	crnUCUUGAAUGUAGAGAUGCGcrnUU
102	UCcrnUUGAAUGUAGAGAUGCGcrnUU
103	crnUCcrnUUGAAUGUAGAGAUGCGcrnUU
104	crnUcrnCcrnUUGAAUGUAGAGAUGCGcrnUU
105	crnAGCAGAAGAAACACUGcrnGcrnGC
106	AGcrnCAGAAGAAACACUGGGcrnCcrnUU
107	crnAGcrnCAGAAGAAACACUGGGcrnCcrnUU
108	crnAcrnGcrnCAGAAGAAACACUGGGcrnCcrnUU
109	crnAGCAGAAGAAACACUGGGCcrnUcrnU
110	AGcrnCAGAAGAAACACUGGGCcrnUcrnU
111	crnAGcrnCAGAAGAAACACUGGGCcrnUcrnU
112	crnAcrnGcrnCAGAAGAAACACUGGGCcrnUcrnU
113	AAGCAGAAGAAACACUGGG
114	AAGCAGAAGAAACACUGGGUU
115	AAGCAGAAGAAACACUGGGUU
116	AAGCAGAAGAAACACUGGGUU
117	AAGCAGAAGAAACACUGGGUU
118	AAGCAGAAGAAACACUGGGUU
119	AAGCAGAAGAAACACUGGGUU
120	AAGCAGAAGAAACACUGGGUU
121	GAAGCAGAAGAAACACUGG
122	GAAGCAGAAGAAACACUGGUU
123	GAAGCAGAAGAAACACUGGUU
124	GAAGCAGAAGAAACACUGGUU
125	GAAGCAGAAGAAACACUGGUU
126	GAAGCAGAAGAAACACUGGUU
127	GAAGCAGAAGAAACACUGGUU
128	GAAGCAGAAGAAACACUGGUU
129	UGAAGCAGAAGAAACAcrnCUG
130	UcrnGAAGCAGAAGAAACACUGUcrnU
131	crnUcrnGAAGCAGAAGAAACACUcrnGUcrnU
132	UcrnGcrnAAGCAGAAGAAACACUcrnGcrnUcrnU
133	crnUGAAGCAGAAGAAACACUGUU
134	UGcrnAAGCAGAAGAAACACUGcrnUU
135	crnUGcrnAAGCAGAAGAAACACUcrnGcrnUU
136	crnUcrnGcrnAAGCAGAAGAAACACUGcrnUcrnU
137	UUGAAGCcrnAcrnGcrnAAGAAACACU
138	UUGAAGCAcrnGcrnAcrnAGAAACACUUU
139	UUGAAGCAcrnGcrnAAGAAACACUUU
140	UUGAAGCcrnAGcrnAAcrnGAAACACUUU
141	UUGAAGCAcrnGAAcrnGAAcrnACACUUU

142	UUGAAGCcrnAGAAcrnGAAACACUUU
143	UUGAAGCAcrnGAAcrnGAAcrnACACUUU
144	UUGAAGCAGcrnAAGAAACACUUU
145	UUCCUCAAAUUCUUUCUUC
146	UUCCUCAAAUUCUUUCUUCUU
147	UUCCUCAAAUUCUUUCUUCUU
148	UUCCUCAAAUUCUUUCUUCUU
149	UUCCUCAAAUUCUUUCUUCUU
150	UUCCUCAAAUUCUUUCUUCUU
151	UUCCUCAAAUUCUUUCUUCUU
152	UUCCUCAAAUUCUUUCUUCUU
153	AAGCACCUCUGGUGCCACU
154	AAGCACCUCUGGUGCCACUUU
155	AAGCACCUCUGGUGCCACUUU
156	AAGCACCUCUGGUGCCACUUU
157	AAGCACCUCUGGUGCCACUUU
158	AAGCACCUCUGGUGCCACUUU
159	AAGCACCUCUGGUGCCACUUU
160	AAGCACCUCUGGUGCCACUUU

EXAMPLE 2

RNA Targeting PLK

Sequence specific RNAs targeting PLK1 are shown in Tables 3 and 4. CRN monomers in the sequences of Tables 3 and 4 are identified as "crnX" where X is the one letter code for the nucleobase: A, U, C or G. For example, "crnC" indicates a cytosine CRN. The CRN in Tables 3 and 4 is based on Monomer Q, Monomer R, or a combination of Monomers R and Q. In some embodiments, The CRN in Tables 3 and 4 is based on Monomer R. Each one of sense sequences SEQ ID NOs:161-190 will complex with one of the antisense sequences SEQ ID NOs:191-220, respectively, in other words, SEQ ID NO:161 will complex with SEQ ID NO:191, SEQ ID NO:162 will complex with SEQ ID NO:192, and so forth. "d" refers to "deoxy."

Table 3: RNA Targeting PLK1

SEQ ID NO:	Sense Sequence (5' to 3')
161	GAGGUCCUAGUGGACCCACGCAcrnGCC
162	AcrnGGUCCUAGUGGACCCACGCAGCCcrnG
163	crnCcrnCUAGUGGACCCACGCAGCCGGcrnCGcrnG
164	GcrnUcrnGGACCCACGCAGCCGGCGGCGcrnCcrnU
165	CUCCUGGAGCUGCACAAGAGGAGcrnGcrnA
166	CCcrnUGGAGCUGCACAAGAGGAGGAcrnAA
167	crnGGCUGCCAGUACCUGCACCGAAcrnAcrnCC
168	GACCUCAAGCUGGGCAACCUUUUcrnCcrnC
169	GCCUAAAAGAGACCUACCUCCGGAU
170	ACCUACCUCCGGAUCAAGAAGAAUG
171	AUACAGUAUUCCCAAGCACAUCAAC
172	GCCUCCCUCAUCCAGAAGAUGCUUC
173	AGAAGAUGCUUCAGACAGAUCCCAC

174	UCUUCUGGGUCAGCAAGUGGGUGGA
175	CAGCCUGCAGUACAUAGAGCGUGAC
176	CUGCAGUACAUAGAGCGUGACGGCA
177	CCcrnUUcrnGAcrnUGcrnAAcrnGAcrnAGcrnAUcrnCAcrnCCcrnCUcrnCCU
178	UAUcrnUUCcrnCGCcrnAAUcrnUACcrnAUGcrnAGCcrnGAGcrnC
179	GCCCcrnGGCUcrnGCCCcrnUACCcrnUACGcrnGACCcrnU
180	GCCAUcrnCAUCCcrnUGCACcrnCUCAGcrnCAACG
181	crnCcrnCUUGAUGAAGAAGAUCACdTdT
182	UUACAGUcrnAcrnUcrnUCCCAAGCACAUU
183	UACAGUAUcrnUCcrnCCAAGCACAUUU
184	UACCUCAAGcrnCcrnUGcrnGGCAACCUUU
185	UCCcrnUCAAcrnGCUcrnGGGCAACCUUUU
186	UAAUACAGUAUUCCCAAGcrnCAcrnUcrnU
187	UAGcrnAcrnAGAUGCUUCAGACAGAUU
188	crnUcrnUcrnCCUUGAUGAAGAAGAUCAUU
189	crnUcrnCCUUGAUGAAGAAGAUCACcrnUcrnU
190	crnUAUUUCCGCAAUUACAUGAGUcrnU

Table 4: RNA Targeting PLK1

SEQ ID NO:	Antisense Sequence (5' to 3')
191	GGCUGCGUGGGUCCACUAGGACCUCCG
192	CGGCUGCGUGGGUCCACUAGGACCUCC
193	CCGCCGGCUGCGUGGGUCCACUAGGAC
194	AGCGCCGCCGGCUGCGUGGGUCCACUA
195	UCCUCCUCUUGUGCAGCUCCAGGAGAG
196	UUUCCUCCUCUUGUGCAGCUCCAGGAG
197	GGUUUCGGUGCAGGUACUGGCAGCCAA
198	GGAAAAGGUUGCCCAGCUUGAGGUCUC
199	AUCCGGAGGUAGGUCUCUUUUAGGcrnCAA
200	CcrnAUUCUUCUUGAUCCGGAGGUAGGUCcrnU
201	crnGcrnUUGAUGUGCUUGGGAAUACUGUAcrnUUcrnC
202	GcrnAcrnAGCAUCUUCUGGAUGAGGGAGGcrnCcrnGcrnG
203	crnGUGGGAUCUGUCUGAAGCAUCUUCUGG
204	UCcrnCACCCACUUGCUGACCCAGAAGAcrnUG
205	crnGUcrnCACGCUCUAUGUACUGCAGGCUcrnGcrnUC
206	crnUcrnGcrnCCGUCACGCUCUAUGUACUGCAGcrnGcrnC
207	AGGAGGGUGAUCUUCUUCAUCAAGGAG
208	GCUCGCUCAUGUAAUUGCGGAAAUAUU
209	AGGUCCGUAGGUAGGGCAGCCGGGCGA
210	CGUUGCUGAGGUGCAGGAUGAUGGCGC
211	GUGAUCUUCUUCAUCAAGGdTdT
212	UGUGCUUGGGAAUACUGUAUU
213	AUGUGCUUGGGAAUACUGUUU
214	AGGUUGCCCAGCUUGAGGUUU
215	AAGGUUGCCCAGCUUGAGGUU
216	UGCUUGGGAAUACUGUAUUUU
217	UCUGUCUGAAGCAUCUUCUUU
218	UGAUCUUCUUCAUCAAGGAUU
219	crnGcrnUcrnGAUCUUCUUCAUCAAGGUU
220	CUCAUGUAAUUGCGGAAAcrnUcrnUcrnU

EXAMPLE 3

RNA Targeting AKT1-1

Sequence specific RNAs targeting AKT1-1 are shown in Tables 5 and 6. The CRN in Tables 5 and 6 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. In some embodiments, the CRN in Tables 5 and 6 is based on Monomer Q. Each one of sense sequences SEQ ID NOs:221-225 will complex with one of the antisense sequences SEQ ID NOs:226-230, respectively, in other words, SEQ ID NO:221 will complex with SEQ ID NO:226, SEQ ID NO:222 will complex with SEQ ID NO:227, and so forth.

Table 5: RNA Targeting AKT1-1

SEQ ID NO:	Sense Sequence (5' to 3')
221	GUAUUUUGAUGAGGAGUUCACGGcrnCC
222	GGCCCAGAUGAUCACCAUCACACcrnCA
223	GGGAAGAAAACUAUCCUGCGGGUcrnUU
224	GUUUUAAUUUAUUUCAUCCAGUUcrnUcrnG
225	ACGUAGGGAAAUGUUAAGGACUUcrnCcrnU

Table 6: RNA Targeting AKT1-1

SEQ ID NO:	Antisense Sequence (5' to 3')
226	GGCCGUGAACUCCUCAUCAAAAUACCU
227	UGGUGUGAUGGUGAUCAUCUGGGCCGU
228	AAACCCGCAGGAUAGUUUUCUUCCCUA
229	CAAACUGGAUGAAAUAAAUUAAAACCC
230	AGAAGUCCUUAACAUUUCCCUACGUGA

Sequence specific sense strands for an mdRNAs targeting AKT1-1 are shown in Tables 7, 8 and 9. The CRN in Tables 7, 8 and 9 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q.

In a nicked mdRNA, each one of sequences SEQ ID NOs:231-235 is attached with a nicked bond to one of the nick sequences SEQ ID NOs:236-240, respectively, in other words, SEQ ID NO:231 is attached to SEQ ID NO:236, SEQ ID NO:232 is attached to SEQ ID NO:237, and so forth, to form a nicked sense strand. The corresponding antisense strand is shown in Table 6.

In a gapped mdRNA, each one of sequences SEQ ID NOs:231-235 is strand S1 while one of the gap sequences SEQ ID NOs:236-240 is strand S2, respectively, in other words, SEQ ID NO:231 is strand S1 and SEQ ID NO:236 is strand S2, SEQ ID NO:232 is strand S1 and SEQ ID NO:237 is strand S2, and so forth. Strands S1 and S2 complex with the corresponding antisense strand of Table 6 to form a gapped structure.

Table 7: RNA Targeting AKT1-1

SEQ ID NO:	Nick position	Sequence (5' to 3')
231	14	crnGUAUUUUGAUGAGG
232	12	GGCCCAGAUGAcrnU
233	14	GGGAAGAAAACUAU
234	15	crnGUUUUAAUUUAUUUcrnC
235	12	crnAcrnCGUAGGGAAAU

Table 8: RNA Targeting AKT1-1

SEQ ID NO:	Nick Sequence 1 (5' to 3')
236	AGUUCACGGCcrnC
237	CACCAUCACACCcrnA
238	CCUGCGGGUcrnUcrnU
239	AUCCAGUUUG
240	GUUAAGGACUUcrnCcrnU

Table 9: RNA Targeting AKT1-1

SEQ ID NO:	Gap Sequence 2 (5' to 3')
241	GUUCACGGCcrnC
242	ACCAUCACACCcrnA
243	CUGCGGGUcrnUcrnU
244	UCCAGUUUcrnG
245	UUAAGGACUUCcrnU

EXAMPLE 4

RNA Targeting b2a2

Sequence specific RNAs targeting b2a2 are shown in Tables 10 and 11. The CRN in Tables 10 and 11 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:246-250 will complex with one of the antisense sequences SEQ ID NOs:251-255, respectively, in other words, SEQ ID NO:246 will complex with SEQ ID NO:251, SEQ ID NO:247 will complex with SEQ ID NO:252, and so forth.

Table 10: RNA Targeting b2a2

SEQ ID NO:	Sense Sequence (5' to 3')
246	crnGCUGCUUAUGUCUCCCAGCAUGGcrnCcrnC
247	AAGUGUUUCAGAAGCUUCUCCCUcrnGcrnA
248	GACCAUCAAUAAGGAAGAAGCCCcrnUcrnU
249	crnCcrnCAUCAAUAAGGAAGAAGCCCUUCA
250	crnUcrnCAAUAAGGAAGAAGCCCUUCAGCG

Table 11: RNA Targeting b2a2

SEQ ID NO:	Antisense Sequence (5' to 3')
251	GGCCAUGCUGGGAGACAUAAGCAGCAG
252	UCAGGGAGAAGCUUCUGAAACACUUCU
253	AAGGGCUUCUUCCUUAUUGAUGGUCAG
254	UGAAGGGCUUCUUCCUUAUUGAUGGUC
255	CGCUGAAGGGCUUCUUCCUUAUUGAUG

EXAMPLE 5

RNA Targeting b3a2

Sequence specific RNAs targeting b3a2 are shown in Tables 12 and 13. The CRN in Tables 12 and 13 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:256-260 will complex with one of the antisense sequences SEQ ID NOs:261-265, respectively, in other words, SEQ ID NO:256 will complex with SEQ ID NO:261, SEQ ID NO:257 will complex with SEQ ID NO:262, and so forth.

Table 12: RNA Targeting b3a2

SEQ ID NO:	Sense Sequence (5' to 3')
256	ACUGGAUUUAAGCAGAGUUCAAAAcrnG
257	CUGGAUUUAAGCAGAGUUCAAAAGcrnC
258	GAUUUAAGCAGAGUUCAAAAGCCCcrnU
259	AUUUAAGCAGAGUUCAAAAGCCCUcrnU
260	UUAAGCAGAGUUCAAAAGCCCUUCcrnA

Table 13: RNA Targeting b3a2

SEQ ID NO:	Antisense Sequence (5' to 3')
261	CUUUUGAACUCUGCUUAAAUCCAGUGG
262	GCUUUUGAACUCUGCUUAAAUCCAGUG
263	AGGGCUUUUGAACUCUGCUUAAAUCCA
264	AAGGGCUUUUGAACUCUGCUUAAAUCC
265	UGAAGGGCUUUUGAACUCUGCUUAAAU

EXAMPLE 6

RNA Targeting EGFR-1

Sequence specific RNAs targeting EGFR-1 are shown in Tables 14 and 15. The CRN in Tables 14 and 15 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:266-270 will complex with one of the antisense

sequences SEQ ID NOs:271-275, respectively, in other words, SEQ ID NO:266 will complex with SEQ ID NO:271, SEQ ID NO:267 will complex with SEQ ID NO:272, and so forth.

Table 14: RNA Targeting EGFR-1

SEQ ID NO:	Sense Sequence (5' to 3')
266	UUCCAGCCCACAUUGGAUUCAUcrnCAG
267	CAGCUGAGAAUGUGGAAUACCUcrnAAG
268	AACGUAUCUCCUAAUUUGAGGCcrnUCA
269	CCUAAAAUAAUUUCUCUACAAUcrnUGG
270	UGGAAGAUUCAGCUAGUUAGGAcrnGCC

Table 15: RNA Targeting EGFR-1

SEQ ID NO:	Antisense Sequence (5' to 3')
271	CUGAUGAAUCCAAUGUGGGCUGGAAUC
272	CUUAGGUAUUCCACAUUCUCAGCUGUG
273	UGAGCCUCAAAUUAGGAGAUACGUUUU
274	CCAAUUGUAGAGAAAUUAUUUUAGGAA
275	GGCUCCUAACUAGCUGAAUCUUCCAAU

EXAMPLE 7

RNA Targeting FLT-1

Sequence specific RNAs targeting FLT-1 are shown in Tables 16 and 17. The CRN in Tables 16 and 17 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:276-280 will complex with one of the antisense sequences SEQ ID NOs:281-285, respectively, in other words, SEQ ID NO:276 will complex with SEQ ID NO:281, SEQ ID NO:277 will complex with SEQ ID NO:282, and so forth.

Table 16: RNA Targeting FLT-1

SEQ ID NO:	Sense Sequence (5' to 3')
276	crnUGACCUGUGAAGCAACAGUCAAUGcrnG
277	crnCUAUCUCACACAUCGACAAACCAcrnAU
278	crnUGUCCUCAAUUGUACUGCUACCACcrnU
279	AcrnAACCGUAGCUGGCAAGCGGUCUcrnUA
280	UAcrnGCUGGCAAGCGGUCUUACCGGcrnCU

Table 17: RNA Targeting FLT-1

SEQ ID NO:	Antisense Sequence (5' to 3')
281	CCAUUGACUGUUGCUUCACAGGUCAGA
282	AUUGGUUUGUCGAUGUGUGAGAUAGUU
283	AGUGGUAGCAGUACAAUUGAGGACAAG
284	UAAGACCGCUUGCCAGCUACGGUUUCA
285	AGCCGGUAAGACCGCUUGCCAGCUACG

EXAMPLE 8

RNA Targeting FRAP1

Sequence specific RNAs targeting FRAP1 are shown in Tables 18 and 19. The CRN in Tables 18 and 19 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:286-290 will complex with one of the antisense sequences SEQ ID NOs:291-295, respectively, in other words, SEQ ID NO:286 will complex with SEQ ID NO:291, SEQ ID NO:287 will complex with SEQ ID NO:292, and so forth.

Table 18: RNA Targeting FRAP1

SEQ ID NO:	Sense Sequence (5' to 3')
286	ACUUUGGAUGUUCCAACGCAAGUcrnUcrnG
287	AAUGCUUCCACUAAACUGAAACCcrnAcrnU
288	GAGAAAGUUUGACUUUGUUAAAUAcrnU
289	AAAGAACUACUGUAUAUUAAAAGUcrnU
290	UUAGAAAUACGGGUUUUGACUUAAcrnC

Table 19: RNA Targeting FRAP1

SEQ ID NO:	Antisense Sequence (5' to 3')
291	CAACUUGCGUUGGAACAUCCAAAGUGU
292	AUGGUUUCAGUUUAGUGGAAGCAUUUA
293	AUAUUUAACAAAGUCAAACUUUCUCAC
294	AACUUUUAAUAUACAGUAGUUCUUUUC
295	GUUAAGUCAAAACCCGUAUUUCUAAAG

EXAMPLE 9

RNA Targeting HIF1A-1

Sequence specific RNAs targeting HIF1A-1 are shown in Tables 20 and 21. The CRN in Tables 20 and 21 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:296-300 will complex with one of the antisense sequences SEQ ID NOs:301-305, respectively, in other words, SEQ ID NO:296 will complex with SEQ ID NO:301, SEQ ID NO:297 will complex with SEQ ID NO:302, and so forth.

Table 20: RNA Targeting HIF1A-1

SEQ ID NO:	Sense Sequence (5' to 3')
296	CUAGUCCUUCCGAUGGAAcrnGCACUAG
297	CCAGUGAAUAUUGUUUUcrnUAUGUGGA
298	AUGAAUUCAAGUUGGAcrnAUUGGUAGA
299	CAGGACACAGAUUUAcrnGACUUGGAGA
300	CUCAAAGCACAGUUcrnACAGUAUUCCA

Table 21: RNA Targeting HIF1A-1

SEQ ID NO:	Antisense Sequence (5' to 3')
301	CUAGUGCUUCCAUCGGAAGGACUAGGU
302	UCCACAUAAAAACAAUAUUCACUGGGA
303	UCUACCAAUUCCAACUUGAAUUCAUUG
304	UCUCCAAGUCUAAAUCUGUGUCCUGAG
305	UGGAAUACUGUAACUGUGCUUUGAGGA

EXAMPLE 10

RNA Targeting IL17A

Sequence specific RNAs targeting IL17A are shown in Tables 22 and 23. The CRN in Tables 22 and 23 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:306-310 will complex with one of the antisense sequences SEQ ID NOs:311-315, respectively, in other words, SEQ ID NO:306 will complex with SEQ ID NO:311, SEQ ID NO:307 will complex with SEQ ID NO:312, and so forth.

Table 22: RNA Targeting IL17A

SEQ ID NO:	Sense Sequence (5' to 3')
306	UGAGCUAUUUAAGGAUCUAUUUAUG
307	AAAAGGUGAAAAAGCACUAUUAUCA
308	GAAAAAGCACUAUUAUCAGUUCUGC
309	GGCUGAAAAGAAAGAUUAAACCUAC
310	UAAACCCUUAUAAUAAAAUCCUUCU

Table 23: RNA Targeting IL17A

SEQ ID NO:	Antisense Sequence (5' to 3')
311	CAUAAAUAGAUCCUUAAAUAGCUCAAcrnA
312	UGAUAAUAGUGCUUUUUCACCUUUUUcrnC
313	GCAGAACUGAUAAUAGUGCUUUUUCAcrnC
314	GUAGGUUUAAUCUUUCUUUUCAGCCAcrnU
315	AGAAGGAUUUUAUUAUAAGGGUUUAAcrnU

EXAMPLE 11

RNA Targeting IL18

Sequence specific RNAs targeting IL18 are shown in Tables 24 and 25. The CRN in Tables 24 and 25 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:316-320 will complex with one of the antisense

sequences SEQ ID NOs:321-325, respectively, in other words, SEQ ID NO:316 will complex with SEQ ID NO:321, SEQ ID NO:317 will complex with SEQ ID NO:322, and so forth.

Table 24: RNA Targeting IL18

SEQ ID NO:	Sense Sequence (5' to 3')
316	CAGGAAUAAAGAUGGCUGCUGAACcrnC
317	AAUUUGAAUGACCAAGUUCUCUUCcrnA
318	AUGUAUAAAGAUAGCCAGCCUAGAcrnG
319	GGCUGUAACUAUCUCUGUGAAGUGcrnU
320	UCUGUGAAGUGUGAGAAAAUUUCAcrnA

Table 25: RNA Targeting IL18

SEQ ID NO:	Antisense Sequence (5' to 3')
321	GGUUCAGCAGCCAUCUUUAUUCCUGCG
322	UGAAGAGAACUUGGUCAUUCAAAUUUC
323	CUCUAGGCUGGCUAUCUUUAUACAUAC
324	ACACUUCACAGAGAUAGUUACAGCCAU
325	UUGAAAUUUUCUCACACUUCACAGAGA

EXAMPLE 12

RNA Targeting IL6

Sequence specific RNAs targeting IL6 are shown in Tables 26 and 27. The CRN in Tables 26 and 27 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:326-330 will complex with one of the antisense sequences SEQ ID NOs:331-335, respectively, in other words, SEQ ID NO:326 will complex with SEQ ID NO:331, SEQ ID NO:327 will complex with SEQ ID NO:332, and so forth.

Table 26: RNA Targeting IL6

SEQ ID NO:	Sense Sequence (5' to 3')
326	ACGAAAGAGAAGCUCUAUCUcrnCGCCU
327	CUCCACAAGCGCCUUCGGUCCcrnAGUU
328	GAGAAGAUUCCAAAGAUGUAGCcrnCGC
329	AAUCUGGAUUCAAUGAGGAGACUcrnUG
330	AGAACAGAUUUGAGAGUAGUGAGGcrnA

Table 27: RNA Targeting IL6

SEQ ID NO:	Antisense Sequence (5' to 3')
331	AGGCGAGAUAGAGCUUCUCUUUCGUUC
332	AACUGGACCGAAGGCGCUUGUGGAGAA
333	GCGGCUACAUCUUUGGAAUCUUCUCCU
334	CAAGUCUCCUCAUUGAAUCCAGAUUGG
335	UCCUCACUACUCUCAAAUCUGUUCUGG

EXAMPLE 13

RNA Targeting MAP2K1

Sequence specific RNAs targeting MAP2K1 are shown in Tables 28 and 29. The CRN in Tables 28 and 29 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:336-340 will complex with one of the antisense sequences SEQ ID NOs:341-345, respectively, in other words, SEQ ID NO:336 will complex with SEQ ID NO:341, SEQ ID NO:337 will complex with SEQ ID NO:342, and so forth.

Table 28: RNA Targeting MAP2K1

SEQ ID NO:	Sense Sequence (5' to 3')
336	crnCcrnAcrnUcrnGcrnCcrnUcrnGcrnCcrnUcrnGGCGUCUAAGUGUUUG
337	crnAcrnGcrnAcrnUcrnGUGCAUUUCACCUGUGACAAA
338	crnUcrnCcrnAAAACCUGUGCCAGGCUGAAUUA
339	crnGcrnAAUGUGGGUAGUCAUUCUUACAAU
340	crnAUGUGGGUAGUCAUUCUUACAAUUG

Table 29: RNA Targeting MAP2K1

SEQ ID NO:	Antisense Sequence (5' to 3')
341	CAAACACUUAGACGCCAGCAGCAUGGG
342	UUUGUCACAGGUGAAAUGCACAUCUGA
343	UAAUUCAGCCUGGCACAGGUUUUGAUC
344	AUUGUAAGAAUGACUACCCACAUUCAC
345	CAAUUGUAAGAAUGACUACCCACAUUC

EXAMPLE 14

RNA Targeting MAPK1

Sequence specific RNAs targeting MAPK1 are shown in Tables 30 and 31. The CRN in Tables 30 and 31 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:346-350 will complex with one of the antisense sequences SEQ ID NOs:351-355, respectively, in other words, SEQ ID NO:346 will complex with SEQ ID NO:351, SEQ ID NO:347 will complex with SEQ ID NO:352, and so forth.

Table 30: RNA Targeting MAPK1

SEQ ID NO:	Sense Sequence (5' to 3')
346	CAcrnUAcrnUCcrnCUcrnUGcrnGCcrnUAcrnCUcrnAAcrnCAcrnUCcrnUGcrnG
347	UACcrnUAAcrnCAUcrnCUGcrnGAGcrnACUcrnGUGcrnAGCcrnU
348	CAUAcrnAGUUcrnGUGUcrnGCUUcrnUUUAcrnUUAAcrnU
349	GCAUCcrnAUUUUcrnGGCUCcrnUUCUUcrnACAUU
350	GCUCUUcrnCUUACAcrnUUUGUAcrnAAAAUGcrnU

Table 31: RNA Targeting MAPK1

SEQ ID NO:	Antisense Sequence (5' to 3')
351	CCAGAUGUUAGUAGCCAAGGAUAUGGU
352	AGCUCACAGUCUCCAGAUGUUAGUAGC
353	AUUAAUAAAAAGCACACAACUUAUGGC
354	AAUGUAAGAAGAGCCAAAAUGAUGCAU
355	ACAUUUUUACAAAUGUAAGAAGAGCCA

EXAMPLE 15

RNA Targeting MAPK14-1

Sequence specific RNAs targeting MAPK14-1 are shown in Tables 32 and 33. The CRN in Tables 32 and 33 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:356-360 will complex with one of the antisense sequences SEQ ID NOs:361-365, respectively, in other words, SEQ ID NO:356 will complex with SEQ ID NO:361, SEQ ID NO:357 will complex with SEQ ID NO:362, and so forth.

Table 32: RNA Targeting MAPK14-1

SEQ ID NO:	Sense Sequence (5' to 3')
356	UCGGAAAcrnCAAGUUAUUCUCUUCACU
357	ACUCCCAAcrnUAACUAAUGCUAAGAAA
358	AAUGCUAAGcrnAAAUGCUGAAAAUCAA
359	crnGUCUUUCUCUAAAUAUGAUUACUUU
360	crnUGAAUUUCAGGCAUUUUGUUCUACA

Table 33: RNA Targeting MAPK14-1

SEQ ID NO:	Antisense Sequence (5' to 3')
361	AGUGAAGAGAAUAACUUGUUUCCGAAG
362	UUUCUUAGCAUUAGUUAUUGGGAGUGA
363	UUGAUUUUCAGCAUUUCUUAGCAUUAG
364	AAAGUAAUCAUAUUUAGAGAAAGACAG
365	UGUAGAACAAAAUGCCUGAAAUUCAGC

EXAMPLE 16

RNA Targeting PDGFA

Sequence specific RNAs targeting PDGFA are shown in Tables 34 and 35. The CRN in Tables 34 and 35 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:366-370 will complex with one of the antisense

sequences SEQ ID NOs:371-375, respectively, in other words, SEQ ID NO:366 will complex with SEQ ID NO:371, SEQ ID NO:367 will complex with SEQ ID NO:372, and so forth.

Table 34: RNA Targeting PDGFA

SEQ ID NO:	Sense Sequence (5' to 3')
366	AAUGUGACAUCAAAGCAAGUAUUGcrnU
367	CAUCAAAGCAAGUAUUGUAGCACUcrnC
368	AGAGAGAGAAAACAAAACCACAAAcrnU
369	UCGCUGUAGUAUUUAAGCCCAUACcrnA
370	CGCUGUAGUAUUUAAGCCCAUACAcrnG

Table 35: RNA Targeting PDGFA

SEQ ID NO:	Antisense Sequence (5' to 3')
371	ACAAUACUUGCUUUGAUGUCACAUUAA
372	GAGUGCUACAAUACUUGCUUUGAUGUC
373	AUUUGUGGUUUUGUUUUCUCUCUCUCU
374	UGUAUGGGCUUAAAUACUACAGCGAGG
375	CUGUAUGGGCUUAAAUACUACAGCGAG

EXAMPLE 17

RNA Targeting PDGFRA

Sequence specific RNAs targeting PDGFRA are shown in Tables 36 and 37. The CRN in Tables 36 and 37 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:376-380 will complex with one of the antisense sequences SEQ ID NOs:381-385, respectively, in other words, SEQ ID NO:376 will complex with SEQ ID NO:381, SEQ ID NO:377 will complex with SEQ ID NO:382, and so forth.

Table 36: RNA Targeting PDGFRA

SEQ ID NO:	Sense Sequence (5' to 3')
376	crnCcrnUcrnGUUCUGAUCGGCCAGUUUUCGGA
377	crnAcrnAcrnAUAAUUUGAACUUUGGAACAGGG
378	crnUGCGACCUUAAUUUAACUUUCCAGU
379	crnCUGAGAAAGCUAAAGUUUGGUUUUG
380	crnAGUAAAGAUGCUACUUCCCACUGUA

Table 37: RNA Targeting PDGFRA

SEQ ID NO:	Antisense Sequence (5' to 3')
381	UCCGAAAACUGGCCGAUCAGAACAGCC
382	CCCUGUUCCAAAGUUCAAAUUAUUUGU
383	ACUGGAAAGUUAAAUUAAGGUCGCAAU
384	CAAAACCAAACUUUAGCUUUCUCAGCC
385	UACAGUGGGAAGUAGCAUCUUUACUUU

EXAMPLE 18

RNA Targeting PDGFRA

Sequence specific RNAs targeting PDGFRA are shown in Tables 38 and 39. The CRN in Tables 38 and 39 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:386-390 will complex with one of the antisense sequences SEQ ID NOs:391-395, respectively, in other words, SEQ ID NO:386 will complex with SEQ ID NO:391, SEQ ID NO:387 will complex with SEQ ID NO:392, and so forth.

Table 38: RNA Targeting PDGFRA

SEQ ID NO:	Sense Sequence (5' to 3')
386	CUGUUCUGAUCGGCCAGUUUUCcrnGGA
387	AAAUAAUUUGAACUUUGGAACAGcrnGG
388	UGCGACCUUAAUUUAACUUUCCAGcrnU
389	crnCUGAGAAAcrnGCUAAAGUUUGGUUUUcrnG
390	crnAGUAAAGAUcrnGCUACUUCCCACUGcrnUA

Table 39: RNA Targeting PDGFRA

SEQ ID NO:	Antisense Sequence (5' to 3')
391	UCCGAAAACUGGCCGAUCAGAACAGCC
392	CCCUGUUCCAAAGUUCAAAUUAUUUGU
393	ACUGGAAAGUUAAAUUAAGGUCGCAAU
394	CAAAACCAAACUUUAGCUUUCUCAGCC
395	UACAGUGGGAAGUAGCAUCUUUACUUU

EXAMPLE 19

RNA Targeting PIK3CA

Sequence specific RNAs targeting PIK3CA are shown in Tables 40 and 41. The CRN in Tables 40 and 41 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:396-400 will complex with one of the antisense sequences SEQ ID NOs:401-405, respectively, in other words, SEQ ID NO:396 will complex with SEQ ID NO:401, SEQ ID NO:397 will complex with SEQ ID NO:402, and so forth.

Table 40: RNA Targeting PIK3CA

SEQ ID NO:	Sense Sequence (5' to 3')
396	crnGAAUCCUAGUAGAAUGUUUACUACC
397	GAAAGGGcrnAAGAAUUUUUUGAUGAAA
398	UAUCGGCAcrnUGCCAGUGUGUGAAUUU
399	CACCUCAUcrnAcrnGUAGAGCAAUGUAUGU
400	CCAGAAUcrnUcrnGcrnCCAAAGCACAUAUAUA

Table 41: RNA Targeting PIK3CA

SEQ ID NO:	Antisense Sequence (5' to 3')
401	GGUAGUAAACAUUCUACUAGGAUUCUU
402	UUUCAUCAAAAAAUUCUUCCCUUUCUG
403	AAAUUCACACACUGGCAUGCCGAUAGC
404	ACAUACAUUGCUCUACUAUGAGGUGAA
405	UAUAUAUGUGCUUUGGCAAUUCUGGUG

EXAMPLE 20

RNA Targeting PKN3

Sequence specific RNAs targeting PKN3 are shown in Tables 42 and 43. The CRN in Tables 42 and 43 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:406-410 will complex with one of the antisense sequences SEQ ID NOs:411-415, respectively, in other words, SEQ ID NO:406 will complex with SEQ ID NO:411, SEQ ID NO:407 will complex with SEQ ID NO:412, and so forth.

Table 42: RNA Targeting PKN3

SEQ ID NO:	Sense Sequence (5' to 3')
406	UGCAGUUCUUACACGAGAAGAAGAcrnU
407	ACGAGAAGAAGAUCAUUUACAGcrnGGA
408	CGAcrnGAAGAAGAUCAUUUACAGGGAC
409	AAGAAGAUcrnCAUUUACAGGGACCUGA
410	AGAGGAAGAGGUGUUUGACUGCAUC

Table 43: RNA Targeting PKN3

SEQ ID NO:	Antisense Sequence (5' to 3')
411	AUCUUCUUCUCGUGUAAGAACUGCAGC
412	UCCCUGUAAAUGAUCUUCUUCUCGUGU
413	GUCCCUGUAAAUGAUCUUCUUCUCGUG
414	UCAGGUCCCUGUAAAUGAUCUUCUUCU
415	GAUGCAGUCAAACACCUCUUCCUCUGU

EXAMPLE 21

RNA Targeting RAF1

Sequence specific RNAs targeting RAF1 are shown in Tables 44 and 45. The CRN in Tables 44 and 45 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:416-420 will complex with one of the antisense

sequences SEQ ID NOs:421-425, respectively, in other words, SEQ ID NO:416 will complex with SEQ ID NO:421, SEQ ID NO:417 will complex with SEQ ID NO:422, and so forth.

Table 44: RNA Targeting RAF1

SEQ ID NO:	Sense Sequence (5' to 3')
416	UGCAGUAAAcrnGAUCCUAAAGGUUGUC
417	AGUAAAGAcrnUCCUAAAGGUUGUCGAC
418	UGACAAAGGAcrnCAACCUGGCAAUUGU
419	GCAAUUGUGACCCAGUGGUGCGAGcrnG
420	crnAACAUCAUCCAUAGAGACAUGAAAU

Table 45: RNA Targeting RAF1

SEQ ID NO:	Antisense Sequence (5' to 3')
421	GACAACCUUUAGGAUCUUUACUGCAAC
422	GUCGACAACCUUUAGGAUCUUUACUGC
423	ACAAUUGCCAGGUUGUCCUUUGUCAUG
424	CCUCGCACCACUGGGUCACAAUUGCCA
425	AUUUCAUGUCUCUAUGGAUGAUGUUCU

EXAMPLE 22

RNA Targeting SRD5A1

Sequence specific RNAs targeting SRD5A1 are shown in Tables 46 and 47. The CRN in Tables 46 and 47 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:426-430 will complex with one of the antisense sequences SEQ ID NOs:431-435, respectively, in other words, SEQ ID NO:426 will complex with SEQ ID NO:431, SEQ ID NO:427 will complex with SEQ ID NO:432, and so forth.

Table 46: RNA Targeting SRD5A1

SEQ ID NO:	Sense Sequence (5' to 3')
426	AAUGGAGGUUGAAUAUCCUACUGUcrnG
427	GGAGGUUGAAUAUCCUACUGUGUcrnAA
428	AUUUUGAGUUUUCCCUUGUAGUcrnGUA
429	crnUAUCCUGUUUGUUCUUUGUUGAUUG
430	CcrnCUGUUUGUUCUUUGUUGAUUGAAA

Table 47: RNA Targeting SRD5A1

SEQ ID NO:	Antisense Sequence (5' to 3')
431	CACAGUAGGAUAUUCAACCUCCAUUUC
432	UUACACAGUAGGAUAUUCAACCUCCAU
433	UACACUACAAGGGAAAACUCAAAAUCU
434	CAAUCAACAAAGAACAAACAGGAUAAA
435	UUUCAAUCAACAAAGAACAAACAGGAU

EXAMPLE 23

RNA Targeting TNF

Sequence specific RNAs targeting TNF are shown in Tables 48 and 49. The CRN in Tables 48 and 49 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:436-440 will complex with one of the antisense sequences SEQ ID NOs:441-445, respectively, in other words, SEQ ID NO:436 will complex with SEQ ID NO:441, SEQ ID NO:437 will complex with SEQ ID NO:442, and so forth.

Table 48: RNA Targeting TNF

SEQ ID NO:	Sense Sequence (5' to 3')
436	crnAAGAGGGAGAGAAGCAACUACAGAC
437	CGUCUCCUACCAGACCAAGGUCAcrnAC
438	GAUCAAUCGcrnGCCCGACUAUCUCGAC
439	GGACGAACAcrnUCCAACCUUCCCAAAC
440	AGGGUCGGAcrnACCCAAGCUUAGAACU

Table 49: RNA Targeting TNF

SEQ ID NO:	Antisense Sequence (5' to 3')
441	GUCUGUAGUUGCUUCUCUCCCUCUUAG
442	GUUGACCUUGGUCUGGUAGGAGACGGC
443	GUCGAGAUAGUCGGGCCGAUUGAUCUC
444	GUUUGGGAAGGUUGGAUGUUCGUCCUC
445	AGUUCUAAGCUUGGGUUCCGACCCUAA

EXAMPLE 24

RNA Targeting TNFSF13B

Sequence specific RNAs targeting TNFSF13B are shown in Tables 50 and 51. The CRN in Tables 50 and 51 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:446-450 will complex with one of the antisense sequences SEQ ID NOs:451-455, respectively, in other words, SEQ ID NO:446 will complex with SEQ ID NO:451, SEQ ID NO:447 will complex with SEQ ID NO:452, and so forth.

Table 50: RNA Targeting TNFSF13B

SEQ ID NO:	Sense Sequence (5' to 3')
446	AAACACAGAUAACAGGAAAUGAUCC
447	CUUAAGAAAAGAGAAGAAAUGAAAC
448	CUGAAGGAGUGUGUUUCCAUCCUCC
449	UCACCGCGGGACUGAAAAUCUUUGA
450	AGCAGAAAUAAGCGUGCCGUUCAGG

Table 51: RNA Targeting TNFSF13B

SEQ ID NO:	Antisense Sequence (5' to 3')
451	crnGGAUCAUUUCCUGUUAUCUGUGUUUGU
452	crnGUUUCAUUUCUUCUCUUUUCUUAAGGC
453	GcrnGAGGAUGGAAACACACUCCUUCAGUU
454	UcrnCAAAGAUUUUCAGUCCCGCGGUGACA
455	CCcrnUGAACGGCACGCUUAUUUCUGCUGU

EXAMPLE 25

RNA Targeting VEGFA-1

Sequence specific RNAs targeting VEGFA-1 are shown in Tables 52 and 53. The CRN in Tables 52 and 53 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:456-460 will complex with one of the antisense sequences SEQ ID NOs:461-465, respectively, in other words, SEQ ID NO:456 will complex with SEQ ID NO:461, SEQ ID NO:457 will complex with SEQ ID NO:462, and so forth.

Table 52: RNA Targeting VEGFA-1

SEQ ID NO:	Sense Sequence (5' to 3')
456	CAAAGAAAGAUAGAGCAAGACAAGcrnA
457	AAGAAAGAUAGAGCAAGACAAGAcrnAA
458	GAAAGCAUUUGUUUGUACAAGAcrnUCC
459	UGAGUUAAACGAACGUACUUGCcrnAcrnGA
460	ACUGAUACAGAACGAUCGAUACcrnAcrnGcrnA

Table 53: RNA Targeting VEGFA-1

SEQ ID NO:	Antisense Sequence (5' to 3')
461	UCUUGUCUUGCUCUAUCUUUCUUUGGU
462	UUUCUUGUCUUGCUCUAUCUUUCUUUG
463	GGAUCUUGUACAAACAAAUGCUUUCUC
464	UCUGCAAGUACGUUCGUUUAACUCAAG
465	UCUGUAUCGAUCGUUCUGUAUCAGUCU

EXAMPLE 26

Increased melting temperature of a CRN-containing duplex

A CRN-containing RNA duplex targeted to ApoB (SEQ ID NOs:468-469) was prepared and its melting temperature was compared to the same RNA duplex targeted to ApoB that did not contain the CRN (SEQ ID NOs:466-467). The CRN used in this experiment was crnU.

ApoB

Passenger Strand: (SEQ ID NO:466) 5'-CAUCACACUGAAUACCAAUTT

Guide Strand: (SEQ ID NO:467) 5'-AUUGGUAUUCAGUGUGAUGTT

CRN-ApoB

Passenger Strand: (SEQ ID NO:468) 5'-CAUCACACcrnUGAAUACCAAUTT

Guide Strand: (SEQ ID NO:469) 5'-AUUGGUAUUCAGUGUGAUGTT

The CRN-containing RNA duplex targeted to ApoB (SEQ ID NOs:468-469) had a melting temperature of 68.5°C, while the same RNA duplex targeted to ApoB that did not contain the CRN had a melting temperature of 67.1°C. Thus, the use of a single conformationally restricted nucleomonomer crnU increased the melting temperature of the duplex by 1.4°C.

A CRN-containing RNA duplex test sequence (SEQ ID NOs:472-473) was prepared and its melting temperature was compared to the same RNA duplex test sequence that did not contain the CRN (SEQ ID NOs:470-471). The CRN used in this experiment was crnU.

Test Sequence

Passenger Strand: (SEQ ID NO:470) 5'-UUGUUGUUGUUGUUGUUGU

Guide Strand: (SEQ ID NO:471) 5'-ACAACAACAACAACAACAA

CRN-Test Sequence

Passenger Strand: (SEQ ID NO:472) 5'-UUGUUGUcrnUGUUGUUGUUGU

Guide Strand: (SEQ ID NO:473) 5'-ACAACAACAACAACAACAA

The CRN-containing RNA duplex test sequence had a melting temperature of 63.6°C, while the same RNA duplex test sequence that did not contain the CRN had a melting temperature of 59.8°C. Thus, the use of a single conformationally restricted nucleomonomer crnU increased the melting temperature of the test sequence RNA duplex by 3.8°C.

EXAMPLE 27

RNA Targeting Factor VII

Sequence specific RNAs targeting Factor VII are shown in Tables 54 and 55. The CRN in Tables 54 and 55 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:474-484 will complex with one of the antisense sequences SEQ ID NOs:485-495, respectively, in other words, SEQ ID NO:474 will complex with SEQ ID NO:485, SEQ ID NO:475 will complex with SEQ ID NO:486, and so forth. The designation "unaU" refers to an hydroxymethyl substituted nucleomonomer (unlocked

nucleomonomer, UNA) having a U nucleobase. The designation "mU" refers to modified nucleotide "um" which is 2'-O-methyluridine.

Table 54: RNA Targeting Factor VII

SEQ ID NO:	Sense Sequence (5' to 3')
474	CCAUGUGGAAAAAUACCUAcrnUmU
475	CUGGAUUUCUUACAGUGAUmUcrnU
476	AGUGGCUGCAAAAGCUCAUcrnUcrnU
477	crnGGCAGGUCCUGUUGUUGGUmUmU
478	CcrnCAGGGUCUCCCAGUACAUmUmU
479	crnUcrnCGAGUGGCUGCAAAAGCUmUmU
480	crnGCcrnGGCUGUGAGCAGUACUGmUmU
481	crnAGGAUGAcrnCCAGCUGAUCUGmUmU
482	crnCGAUGCUGACUCCAUGUGUmUmU
483	crnGGCGGUUGUUUAGCUCUCAmUmU
484	crnUGUCUUGGUUUCAAUUAAAunaUunaU

Table 55: RNA Targeting Factor VII

SEQ ID NO:	Antisense Sequence (5' to 3')
485	UAGGUAUUUUUCCACAUGGmUmU
486	AUCACUGUAAGAAAUCCAGmUmU
487	AUGAGCUUUUGCAGCCACUmUmU
488	ACCAACAACAGGACCUGCCmUmU
489	AUGUACUGGGAGACCCUGGmUmU
490	AGCUUUUGCAGCCACUCGAmUmU
491	CAGUACUGCUCACAGCCGCmUmU
492	CAGAUCAGCUGGUCAUCCUmUmU
493	ACACAUGGAGUCAGCAUCGmUmU
494	UGAGAGCUAAACAACCGCCmUmU
495	UUUAAUUGAAACCAAGACAunaUunaU

EXAMPLE 28

RNA Targeting ApoB

Sequence specific RNAs targeting ApoB are shown in Tables 56 and 57. The CRN in Tables 56 and 57 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:496-501 will complex with one of the antisense sequences SEQ ID NOs:502-507, respectively, in other words, SEQ ID NO:496 will complex with SEQ ID NO:502, SEQ ID NO:497 will complex with SEQ ID NO:503, and so forth.

Table 56: RNA Targeting ApoB

SEQ ID NO:	Sense Sequence (5' to 3')
496	GGACAUUCAGAACAAGAAAUcrnU
497	ACAGAGUCCCUCAAACAGAcrnUU
498	CAUCACACUGAAUACCAAUcrnUcrnU
499	AAGGGAAUCUUAUAUUUGAUCCAcrnAcrnA
500	crnACAGAGUCCCUCAAACAGACAUGAC
501	GcrnUCUCAAAAGGUUUACUAAUAUUCcrnG

Table 57: RNA Targeting ApoB

SEQ ID NO:	Antisense Sequence (5' to 3')
502	UUUCUUGUUCUGAAUGUCCUU
503	UCUGUUUGAGGGACUCUGUUU
504	AUUGGUAUUCAGUGUGAUGUU
505	UUUGGAUCAAAUAUAAGAUUCCCUUCU
506	GUCAUGUCUGUUUGAGGGACUCUGUGA
507	CGAAUAUUAGUAAACCUUUUGAGACUG

EXAMPLE 29

RNA Targeting TTR

Sequence specific RNAs targeting TTR are shown in Tables 58 and 59. The CRN in Tables 58 and 59 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:508-512 will complex with one of the antisense sequences SEQ ID NOs:513-517, respectively, in other words, SEQ ID NO:508 will complex with SEQ ID NO:513, SEQ ID NO:509 will complex with SEQ ID NO:514, and so forth.

Table 58: RNA Targeting TTR

SEQ ID NO:	Sense Sequence (5' to 3')
508	GUCCUCUGAUGGUCAAAGUUcrnU
509	GACUGGUAUUUGUGUCUGAUcrnU
510	UGGACUGGUAUUUGUGUCUUcrnU
511	CACUCAUUCUUGGCAGGAUUcrnU
512	CCUUGCUGGACUGGUAUUUUU

Table 59: RNA Targeting TTR

SEQ ID NO:	Antisense Sequence (5' to 3')
513	ACUUUGACCAUCAGAGGACUU
514	UCAGACACAAAUACCAGUCUU
515	AGACACAAAUACCAGUCCAUU
516	AUCCUGCCAAGAAUGAGUGUU
517	AAAUACCAGUCCAGCAAGGUU

EXAMPLE 30

RNA Targeting DGAT2

Sequence specific RNAs targeting DGAT2 are shown in Tables 60 and 61. The CRN in Tables 60 and 61 is based on Monomer R, Monomer Q, or a combination of Monomers R and Q. Each one of sense sequences SEQ ID NOs:518-522 will complex with one of the antisense

sequences SEQ ID NOs:523-527, respectively, in other words, SEQ ID NO:518 will complex with SEQ ID NO:523, SEQ ID NO:519 will complex with SEQ ID NO:524, and so forth.

Table 60: RNA Targeting DGAT2

SEQ ID NO:	Sense Sequence (5' to 3')
518	crnUCUCUGUCACCUGGCUCAAUAGGdTdC
519	CcrnGAGACUACUUUCCCAUCCAGCUdGdG
520	GAcrnAGACACACAACCUGCUGACCAdCdC
521	UGAcrnCCACCAGGAACUAUAUCUUUdGdG
522	GACcrnCACcrnCAGcrnGAACUAUAUCUUUGdGdA

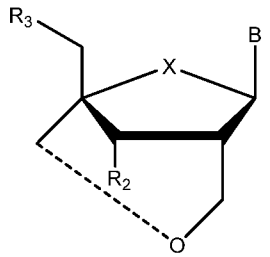
Table 61: RNA Targeting DGAT2

SEQ ID NO:	Antisense Sequence (5' to 3')
523	GACCUAUUGAGCCAGGUGACAGAGAAG
524	CCAGCUGGAUGGGAAAGUAGUCUCGAA
525	GGUGGUCAGCAGGUUGUGUGUCUUCAC
526	CCAAAGAUAUAGUUCCUGGUGGUCAGC
527	UCCAAAGAUAUAGUUCCUGGUGGUCAG

WHAT IS CLAIMED IS:

1. A nucleic acid compound comprising a first strand having from 10 to 60 nucleomonomers, wherein from 1 to 45 of the nucleomonomers of the first strand are the same or different conformationally restricted nucleomonomers each independently selected from

Monomer R having the formula:

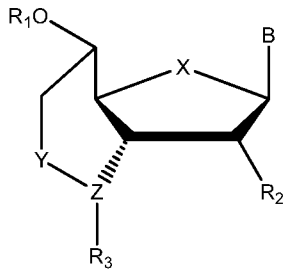


wherein X is independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF or CF_2;

R_2 and R_3 are phosphodiester linkages of the nucleic acid compound; and

B is a nucleobase or nucleobase analog; and

Monomer Q having the formula:



wherein X and Y are independently for each occurrence selected from O, S, CH_2, C=O, C=S, $C=CH_2$, CHF, CF_2 ;

Z is independently for each occurrence selected from N or CH;

R_2 is independently for each occurrence selected from hydrogen, -F, -OH, $-OCH_3$, $-OCH_3OCH_3$, $-OCH_2CH_3OCH_3$, $-CH_2CH_3OCH_3$, $-CH(OCH_3)CH_3$, allyl;

R_1 and R_3 are phosphodiester linkages of the nucleic acid compound; and

B is a nucleobase or nucleobase analog;

wherein each nucleobase or nucleobase analog in the strand is independently selected from adenine, cytosine, guanine, uracil, hypoxanthine, thymine, 7-deazaadenine, inosine, C-phenyl, C-naphthyl, inosine, an azole carboxamide, nebularine, a nitropyrrole, a nitroindole, 2-aminopurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, 5-methyluridine, 5-propynylcytidine, isocytidine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-

thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 2-thioribothymidine, 5,6-dihydrouracil, 4-methylindole, ethenoadenine, deoxyuridine, and any existing deoxy analogs of the foregoing.

2. The compound of claim 1, wherein the compound contains two or more of the same or different Monomer R.

3. The compound of claim 1, wherein the compound contains two or more of the same or different Monomer Q.

4. The compound of claim 1, wherein the first strand has from 19 to 27 nucleomonomers.

5. The compound of claim 1, wherein the nucleic acid is RNA.

6. The compound of claim 1, wherein the nucleic acid is RNA and DNA.

7. The compound of claim 1, further comprising one or more hydroxymethyl substituted nucleomonomers.

8. The compound of claim 1, further comprising one or two additional strands each having from 7 to 60 nucleomonomers, wherein at least a portion of each of the additional strands is complementary to a portion of the first strand, wherein the first strand and the one or two additional complementary strands can anneal to form one or more duplex portions having a total of from 8 to 60 base pairs in the duplex portions, and wherein one or more of the nucleomonomers of the one or two additional strands is a conformationally restricted nucleomonomer.

9. The compound of claim 8, wherein any one or more of the strands includes a sequence for PLK1 selected from SEQ ID NOs:161-220.

10. The compound of claim 8, wherein any one or more of the strands includes a sequence for Survivin BIRC5 selected from SEQ ID NOs:1-160.

11. The compound of claim 8, wherein any one or more of the strands includes a sequence for Factor VII selected from SEQ ID NOs:474-495.

12. The compound of claim 8, wherein any one or more of the strands includes a sequence for ApoB selected from SEQ ID NOs:496-507.

13. The compound of claim 8, wherein any one or more of the strands includes a sequence selected from SEQ ID NOs:221-230, 231-245, 246-255, 256-265, 266-275, 276-285, 286-295, 296-305, 306-315, 316-325, 326-335, 336-345, 346-355, 356-365, 366-375, 376-385, 386-395, 396-405, 406-415, 416-425, 426-435, 436-445, 446-455, 456-465, 508-517, and 518-527.

14. The compound of claim 8, wherein the conformationally restricted nucleomonomers are only present in either of the one or more additional strands, and the first strand does not contain any conformationally restricted nucleomonomers.

15. The compound of claim 8, wherein the melting temperature of the compound is increased by at least 1°C over the same compound that does not contain any conformationally restricted nucleomonomers.

16. The compound of claim 8, wherein the compound is an siRNA.

17. The compound of claim 8, wherein the compound is an mdRNA.

18. The compound of claim 8, wherein the compound is RNA and DNA.

19. The compound of claim 8, wherein one of the additional strands has one or more nicks.

20. The compound of claim 8, wherein the compound has one or more duplex gaps that are each independently from 1 to 10 unpaired nucleomonomers in length.

21. The compound of claim 8, wherein the compound has a blunt end.

22. The compound of claim 8, wherein the compound has a 3'-end overhang.

23. The compound of claim 8, further comprising one or more hydroxymethyl substituted nucleomonomers.

24. The compound according to any one of claims 1-23 for use in delivering an RNA agent into a cell or an organism.

25. The compound according to any one of claims 1-23 for use in mediating nucleic acid modification of a target nucleic acid in a cell or an organism.

26. The compound according to any one of claims 1-23 for use in decreasing expression levels of a target mRNA in a cell or an organism.

27. The compound according to any one of claims 1-23 for use in inhibiting an endogenous nucleic acid-based regulatory system in a cell or an organism.

28. The compound according to any one of claims 1-23 for use in gene regulation, gene analysis, or RNA interference.

29. The compound according to any one of claims 1-23 for use in the manufacture of a medicament for a therapeutic target, including targets for cancers, metabolic diseases, inflammatory diseases, and viral infections.

30. The compound according to any one of claims 1-23 for use in treating a disease, condition or disorder, including cancers, metabolic diseases, inflammatory diseases, and viral infections.

31. A method for treating a disease, condition or disorder in a subject including cancers, metabolic diseases, inflammatory diseases, and viral infections, the method comprising administering to the subject a compound according to any one of claims 1-23.

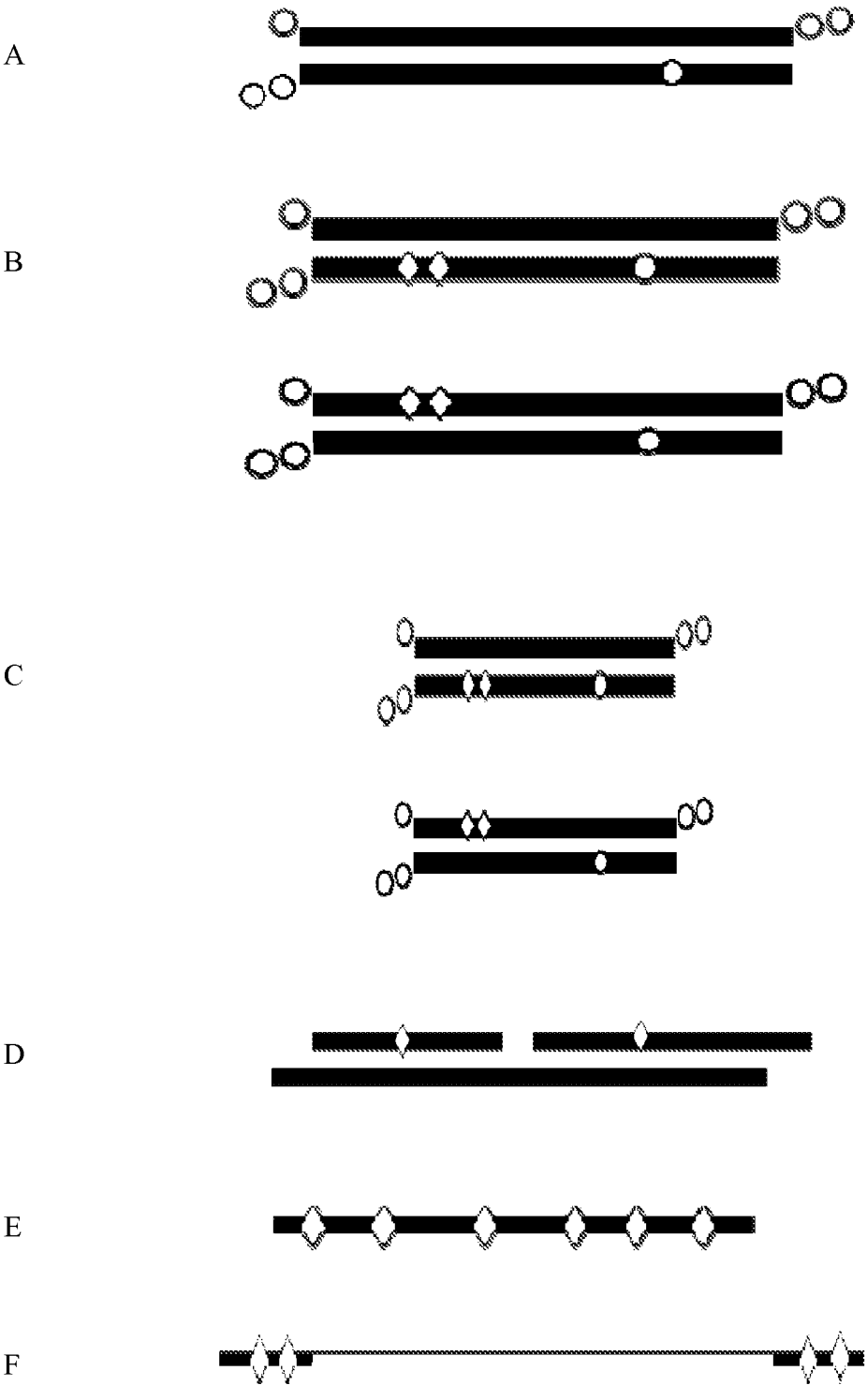
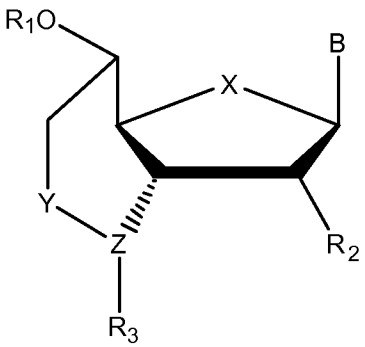
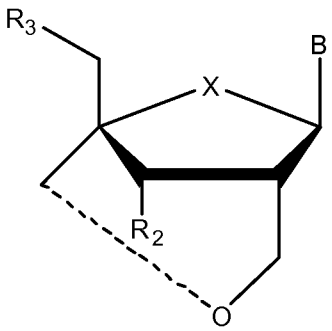


FIG. 1

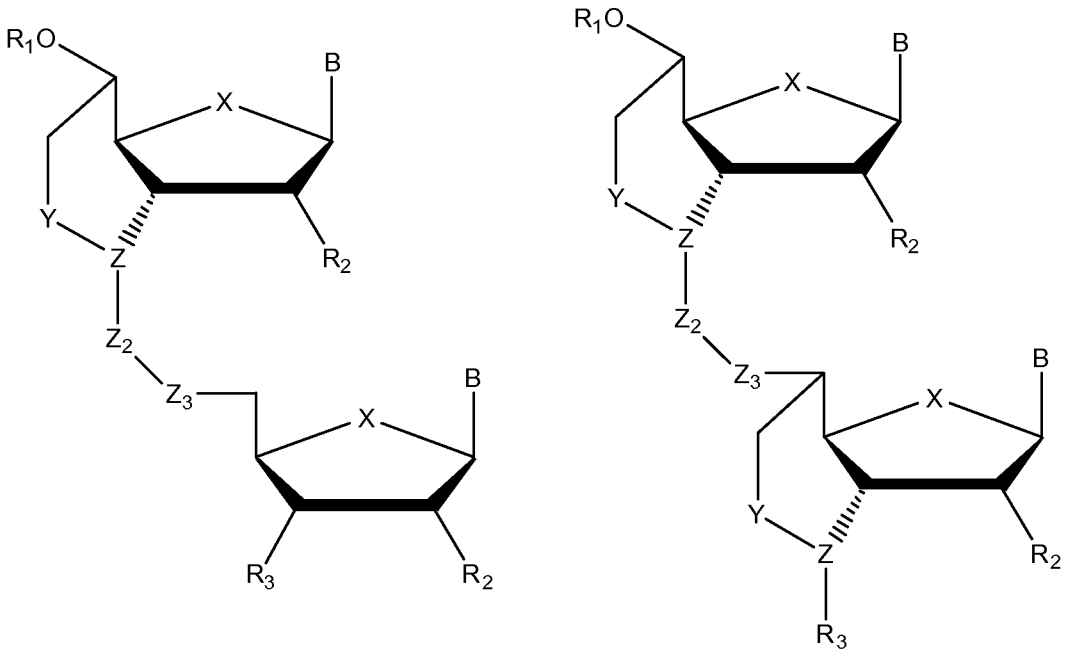


Monomer Q



Monomer R

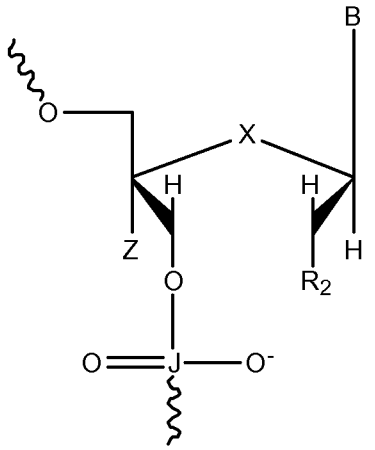
FIG. 2



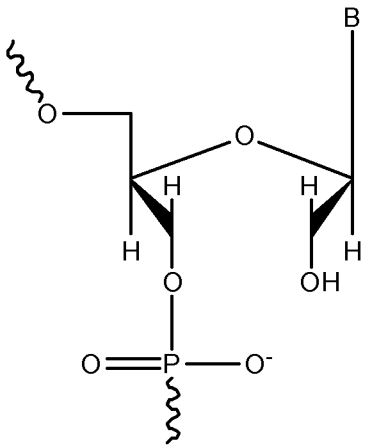
Dimer A

Dimer B

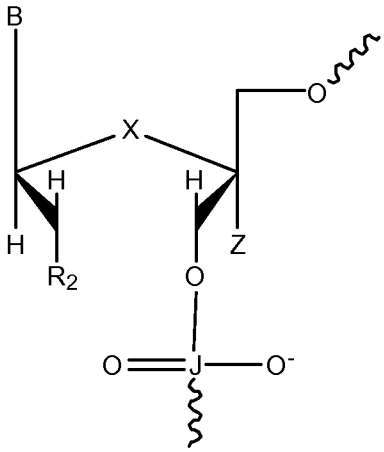
FIG. 3



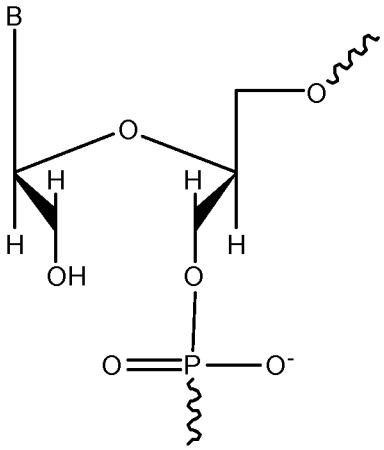
Monomer A



Monomer B

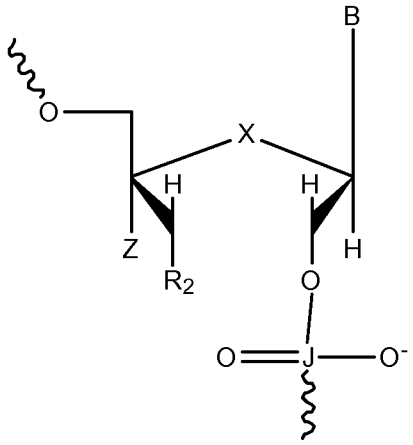


Monomer C

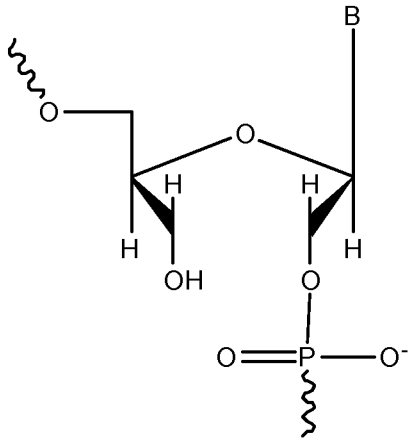


Monomer D

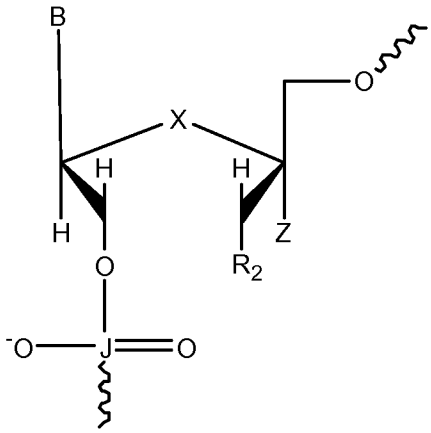
FIG. 4



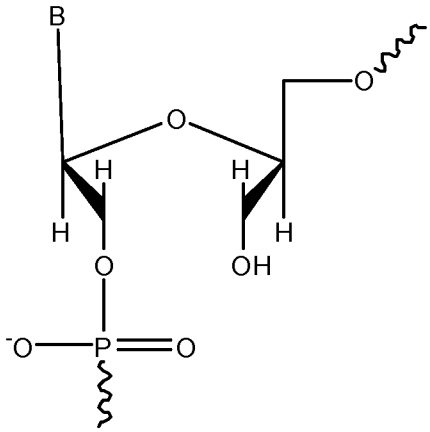
Monomer E



Monomer F

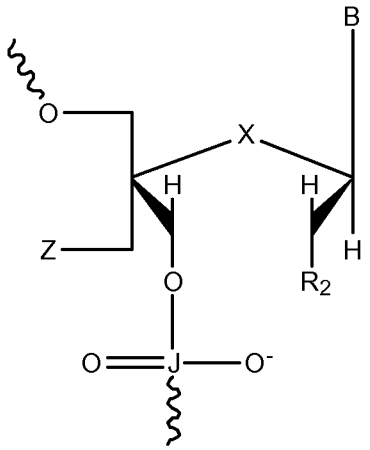


Monomer G

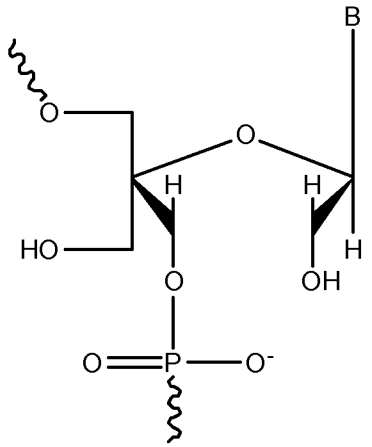


Monomer H

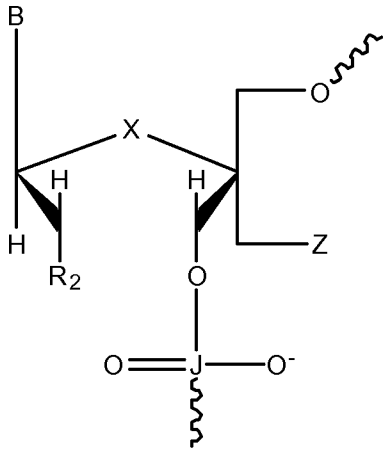
FIG. 5



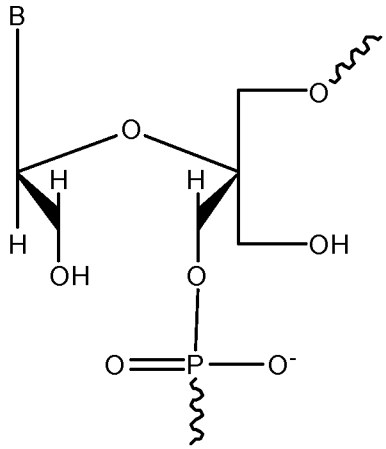
Monomer I



Monomer J

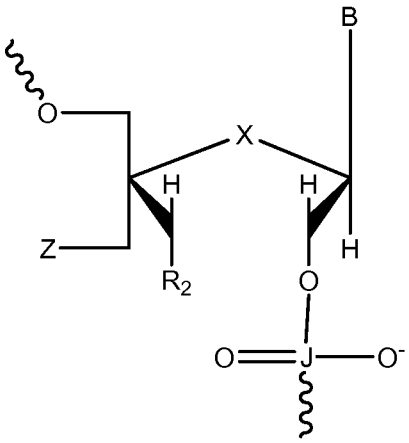


Monomer K

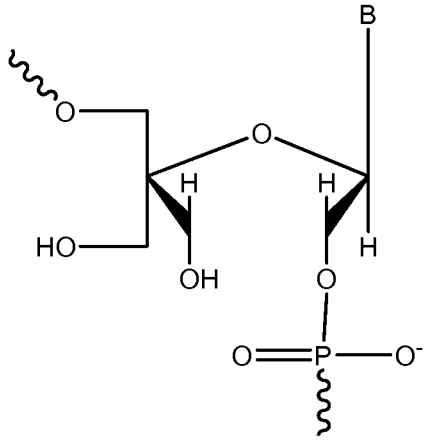


Monomer L

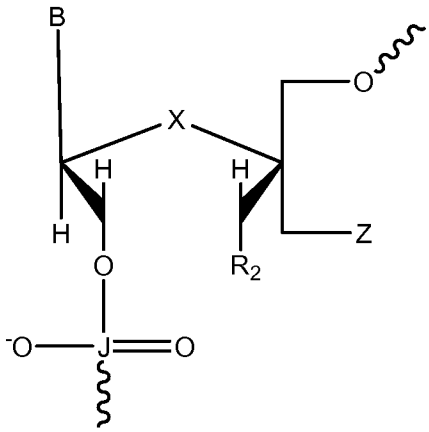
FIG. 6



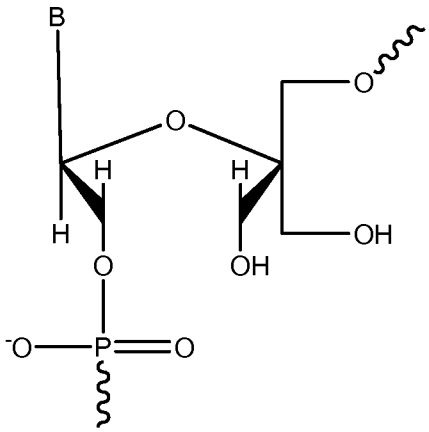
Monomer M



Monomer N



Monomer O



Monomer P

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/033980

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG G ET AL: "Conformationally locked nucleosides. Synthesis and hybridization properties of oligodeoxynucleotides containing 2',4'-C-bridged 2'-deoxynucleosides", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, no. 8, 19 April 1999 (1999-04-19), pages 1147-1150, XP004163984, PERGAMON, ELSEVIER SCIENCE, GB ISSN: 0960-894X, DOI: 10.1016/S0960-894X(99)00146-8	1-8, 14-31
A	the whole document	9

X	US 6 403 566 B1 (WANG GUANGYI [US]) 11 June 2002 (2002-06-11) cited in the application	1-8, 14-31
A	the whole document	9

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2011	05/09/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Spindler, Mark-Peter

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/033980

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

9(completely); 1-8, 14-31(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/033980

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 083 482 A (WANG GUANGYI [US]) 4 July 2000 (2000-07-04) cited in the application	1-8, 14-31
A	the whole document	9

X	WO 2004/044245 A1 (ISIS PHARMACEUTICALS INC [US]; BAKER BRENDA F [US]; ELDRUP ANNE B [US]) 27 May 2004 (2004-05-27)	1-8, 14-31
A	page 1 - page 8 page 131 - page 132; compound 170	9

X	WO 2010/017319 A2 (MDRNA INC [US]; QUAY STEVEN C [US]; VAISH NARENDRA K [US]; FOSNAUGH KA) 11 February 2010 (2010-02-11) page 1 - page 7 page 26 - page 45 examples 10-11; tables 7-11; sequences 1371-1412,1417-1436	1-9, 14-31

X	WO 2009/082817 A1 (PROTIVA BIOTHERAPEUTICS INC [CA]; MACLACHLAN IAN [CA]; JUDGE ADAM [CA]) 9 July 2009 (2009-07-09) page 1 - page 4 claims 1-2,92; tables 1,4,5,7	1-9, 14-31

X	WO 2009/083790 A2 (QIAGEN SCIENCES INC [US]; LADER ERIC [US]) 9 July 2009 (2009-07-09) page 13, line 26 - page 14, line 25; sequences 18-30	1-9, 14-31

X	RACHNA PATEL ET AL: "The Potency of siRNA-Mediated Growth Inhibition Following Silencing of Essential Genes Is Dependent on siRNA Design and Varies With Target Sequence", OLIGONUCLEOTIDES, vol. 19, no. 4, 23 December 2009 (2009-12-23), pages 317-328, XP055000779, ISSN: 1545-4576, DOI: 10.1089/oli.2009.0207 the whole document	1-9, 14-31

X	WO 2004/011610 A2 (ISIS PHARMACEUTICALS INC [US]; WYATT JACQUELINE R [US]; FREIER SUSAN M) 5 February 2004 (2004-02-05) page 1 - page 4; claim 1; example 15; table 2	1-9, 14-31

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/033980

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MARIA LAURSEN: "Utilization of unlocked nucleic acid (UNA) to enhance siRNA performance in vitro and in vivo", MOLECULAR BIOSYSTEMS, 9 February 2010 (2010-02-09), pages 862-870, XP055000712, the whole document -----	1-8, 14-31
A	WERK D ET AL: "Application of small interfering RNAs modified by unlocked nucleic acid (UNA) to inhibit the heart-pathogenic coxsackievirus B3", FEBS LETTERS, vol. 584, no. 3, 5 February 2010 (2010-02-05), pages 591-598, XP026865080, ELSEVIER, AMSTERDAM, NL ISSN: 0014-5793 [retrieved on 2010-01-13] the whole document -----	1-8, 14-31
A	J. B. BRAMSEN ET AL: "A large-scale chemical modification screen identifies design rules to generate siRNAs with high activity, high stability and low toxicity", NUCLEIC ACIDS RESEARCH, vol. 37, no. 9, 1 May 2009 (2009-05-01), pages 2867-2881, XP055000747, ISSN: 0305-1048, DOI: 10.1093/nar/gkp106 the whole document -----	1-8, 14-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/033980

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6403566 B1	11-06-2002	US 2003028013 A1	06-02-2003
US 6083482 A	04-07-2000	NONE	
WO 2004044245 A1	27-05-2004	AU 2003287503 A1	03-06-2004
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		EP 1546179 A2	29-06-2005
		US 6906186 B1	14-06-2005
		US 2005107328 A1	19-05-2005

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 9(completely); 1-8, 14-31(partially)

nucleic acid compound comprising at least one conformationally restricted nucleomonomer selected from monomer R and monomer Q having a formula as indicated in claim 1; said compound further comprising one or more additional strands and targeting PLK1 wherein one of the strands includes a sequence defined by SEQ ID NO: 161-220; therapeutic implementations of said compound

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2. claims: 10(completely); 1-8, 14-31(partially)

as in 1) the target gene being survivin BIRC5 and one of the strands includes a sequence defined by SEQ ID NO: 1-160

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3. claims: 11(completely); 1-8, 14-31(partially)

as in 1) the target gene being factor VII and one of the strands includes a sequence defined by SEQ ID NO: 474-495

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4. claims: 12(completely); 1-8, 14-31(partially)

as in 1) the target gene being ApoB and one of the strands includes a sequence defined by SEQ ID NO: 496-507

5-29. claims: 1-8, 13-31(all partially)

as in 1) with other target genes wherein one of the strands includes a sequence defined by SEQ ID NO: 221-245, 246-255, 256-265, 266-275, 276-285, 286-295, 296-305, 306-315, 316-325, 326-335, 336-345, 346-355, 356-365, 366-375, 376-385, 386-395, 396-405, 406-415, 416-425, 426-435,436-445, 446-455, 456-465, 508-517, or 518-527, respectively

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