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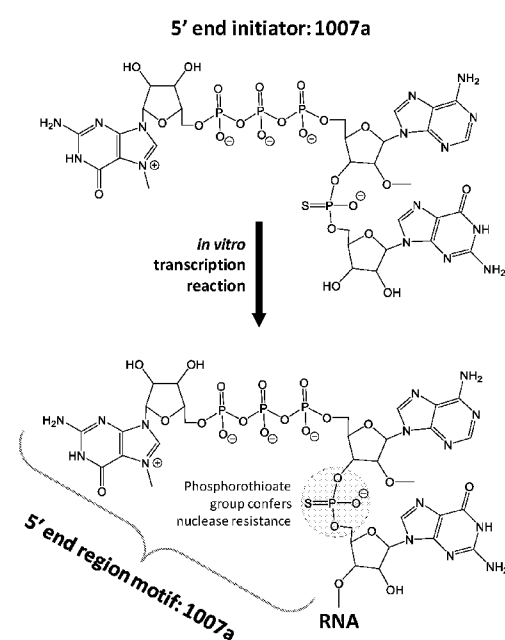


FIG. 1A

(57) Abstract: Provided herein are compositions and methods for preparation of 5' end region-modified mRNAs. In particular, the instant disclosure relates to novel mRNA 5' end region motifs and sequence initiators therefore together with assays that are capable of measuring the aspects of the functionality of those motifs and sequence initiators. Further provided herein are compositions and methods of treating conditions related to coronary disease.

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COMPOSITIONS AND METHODS FOR CAPPING RNAS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/074,993, filed September 04, 2020, which is herein incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] The instant disclosure relates to RNA and in particular the 5' end- region of an mRNA molecule, including for example, novel mRNA 5' end region motifs (or mRNA Caps) and initiators thereof.

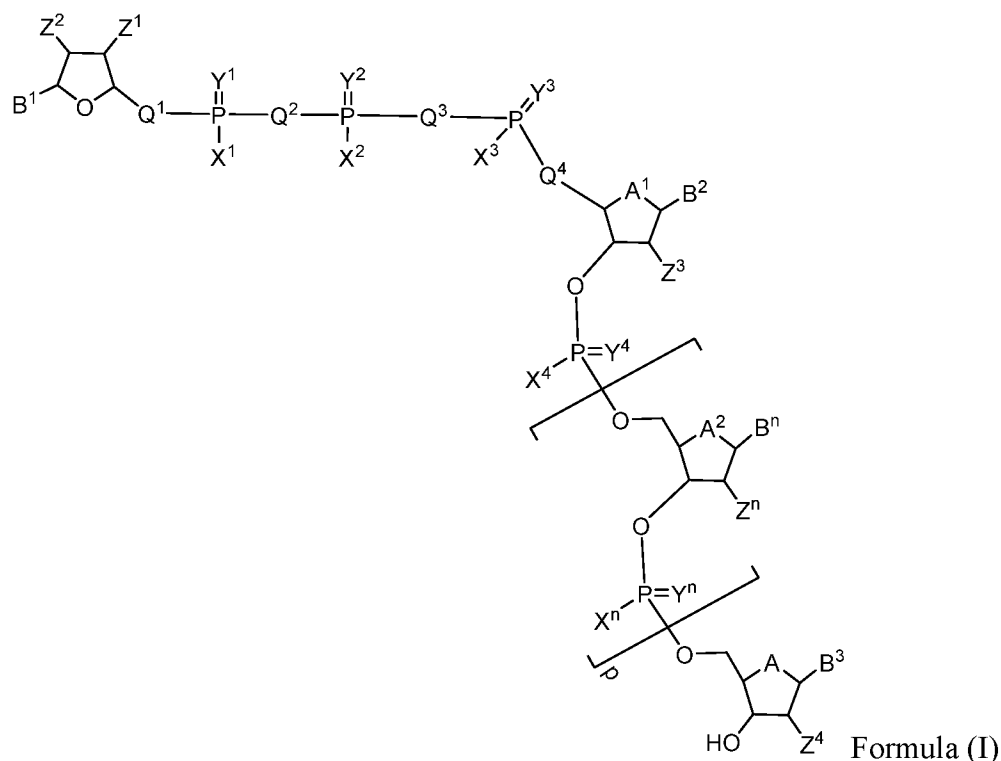
BACKGROUND

[0003] The 5' end region of an mRNA can be an important structural and/or functional feature of eukaryotic mRNA molecules as it is capable of providing stability to the mRNA (e.g., by providing protection against 5' exonucleases) and being involved in RNA splicing, mRNA transport, and other activities that support protein translation. A structural element of a conventional mRNA Cap frequently comprises an inverted 7-methylguanosine (m^7G) linked at the 5' end to a triphosphate (ppp) bridge, which phosphate bridge is in turn linked to the first nucleotide (N_1) of the mRNA transcript. The 5' end region mRNA motifs and sequence initiators thereof described here differ from the conventional mRNA Caps in several respects, including, for example, that they comprise a chemically modified inverted 7-methylguanosine (m^7G) nucleoside structure and/or modified triphosphate (ppp) linkage. Conventional Caps are often one of the most expensive components in the manufacture of mRNA molecules. Accordingly, alternatives to conventional Caps while maintaining or improving capping efficiencies and/or mRNA yields are each independently important aspects to the field.

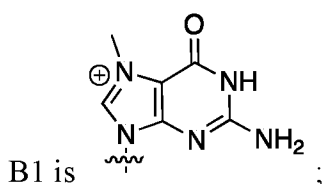
SUMMARY

[0004] Novel mRNA 5' end region motifs and initiators therefore are described herein.

[0005] In one aspect, described herein is an in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (I) or a salt or solvate thereof:



wherein



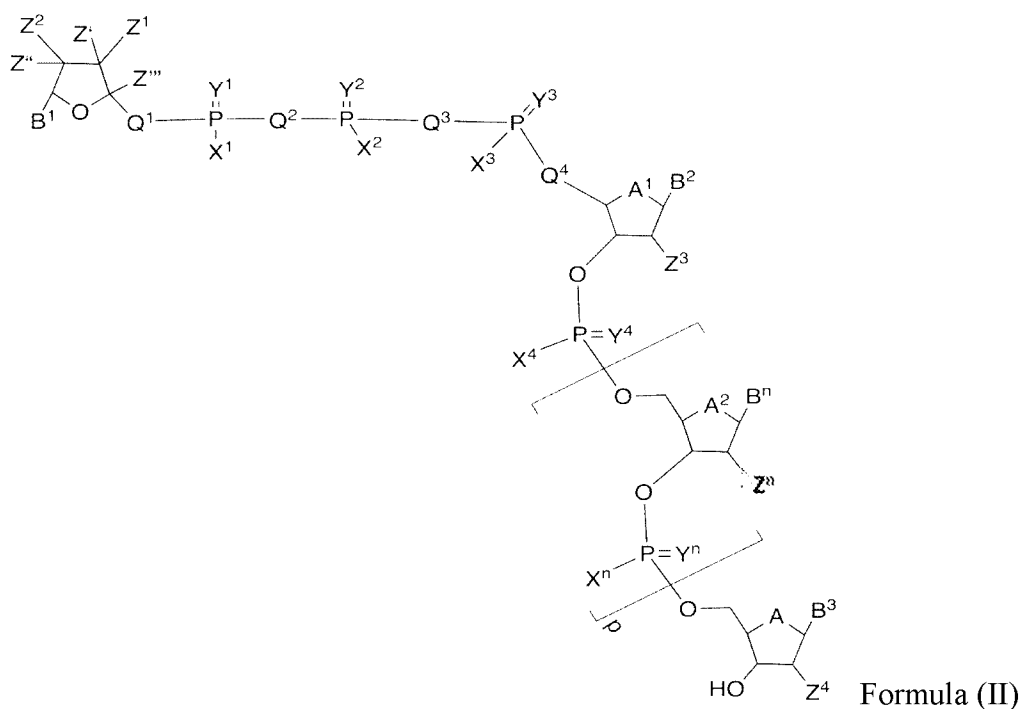
each B2, B3, and Bn is independently a natural, a modified, or an unnatural nucleobase;
 each Z1 and Z2 is independently hydrogen, fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -OCH2CH3, -SCH3, -NH2, NHCH3, or NHC(=O)CH3;
 each Z3, Z4, and Zn is independently hydrogen, fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -NH2, -NHCH3, -NH(C(=O)CH3), -OCH2CH3, -OCH2OCH3, -OCH2CH2CH3, -OCH(CH3)2, -SCH3, or -OCH2CH2OCH3;
 each Q1 and Q4 is independently -CH2-, -CH=CH-, -CH2O-, -CH2S-, -CH2CH2-, -CH2CF2-, -CH2NH2-, -CH2NH(CH3)-, or -CH2N(C(=O)CH3)-;
 each Q2 and Q3 is independently -O-, -S-, -CH2-, -CF2-, -NH-, -N(CH3)-, or -N(C(=O)CH3)-;
 each X1, X2, X3, X4, and Xn is independently -OH, -SH, -O-, -S-, -NH2, -NHCH3, -NH(C(=O)CH3), -CH3, -CH2CH3, -CH2CH2CH3, -CH(CH3)2, -OCH3, or -OCH2CH3;
 each Y1, Y2, Y3, Y4, and Yn is independently =O, =S, =NH, or =NCH3;
 each A, A1, and A2 is independently -O-, -S-, -CH2-, -NH-, -N(CH3)- or -N(C(=O)CH3)-; and
 p = 0, 1, 2, 3, 4, 5 or 6,

[0006] In another aspect, described herein the compound of Formula (I) satisfies one or more of the following proviso (i) to (iii): (i) at least one of X1, X2, X3, X4, and Xn is -SH or -S-; (ii) at

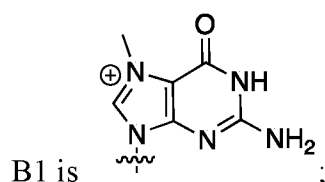
least one of Y1, Y2, Y3, Y4, and Yn is =S; and (iii) at least one of A, A1, and A2 is -S-.

[0007] In another aspect, the IVT mRNA sequence initiator satisfies at least one of X1, X2, X3, X4, and Xn is -SH or -S-; at least one of Y1, Y2, Y3, Y4, and Yn is =S; or at least one of A, A1, and A2 is -S-.

[0008] In one aspect, described herein is an in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B2, B3, and Bn is independently a natural, a modified, or an unnatural nucleobase;

each Z1 and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -NH(CH3), -NH2, -NH(C(=O)CH3), or -SCH3;

each Z2 and Z'' is independently fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -SCH3, -OCH2CH3, -NH2, NHCH3, or NHC(=O)CH3;

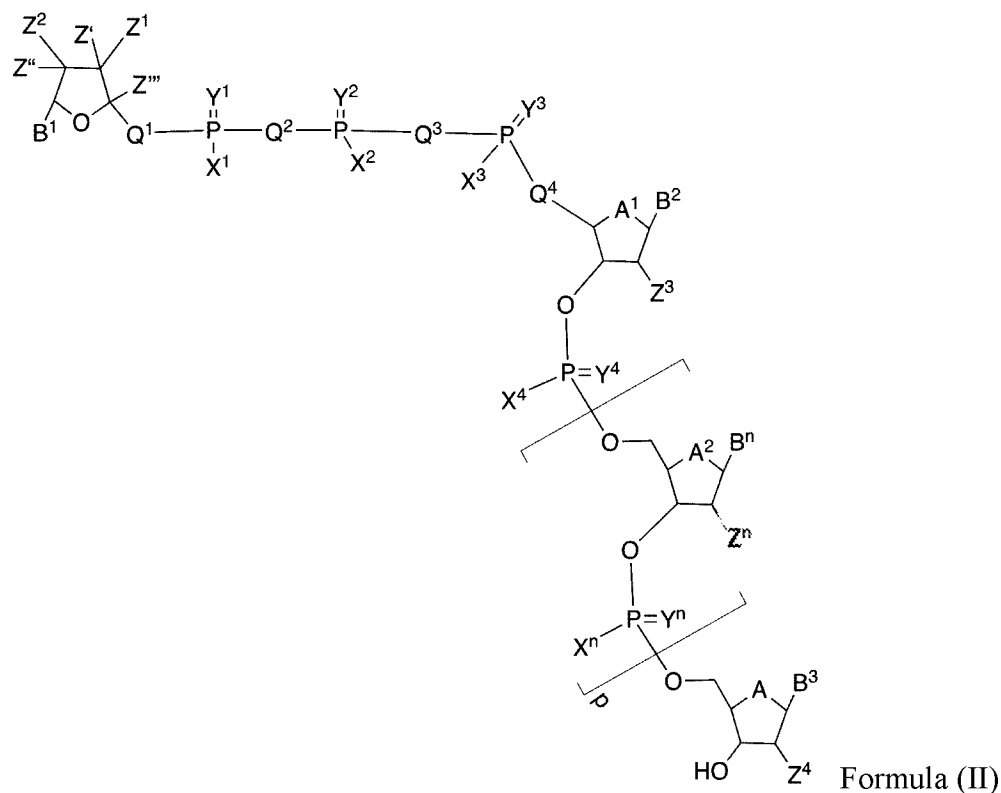
Z''' is hydrogen, fluorine, -CH3, -CH2CH3, -OCH3, or -OCH2CH3;

each Z3, Z4, and Zn is independently hydrogen, fluorine, -OH, -CH3, -CH2CH3, -OCH3, -NH2, -NHCH3, -NH(C(=O)CH3), -OCH2CH3, -OCH2OCH3, -OCH2CH2CH3, -OCH(CH3)2, -SCH3, or -OCH2CH2OCH3;

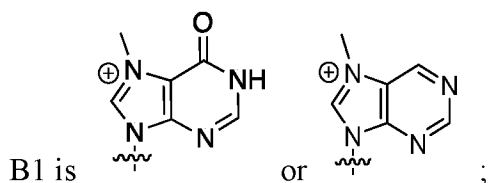
each Q1 and Q4 is independently -CH=CH-, -CH2-, -CH2O-, -CH2S-, -CH2CH2-, -CH2CF2-, -CH2NH2-, -CH2NH(CH3)-, or -CH2N(C(=O)CH3)-;

each Q2 and Q3 is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;
 each X1, X2, X3, X4, and X_n is independently -OH, -SH, -O-, -S-, -NH₂, -NHCH₃, -
 NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;
 each Y1, Y2, Y3, Y4, and Y_n is independently =O, =S, =NH, or =NCH₃;
 each A, A1, and A2 is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and
 p = 0, 1, 2, 3, 4, 5 or 6.

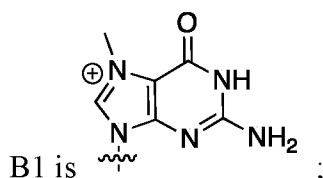
[0009] In one aspect, described herein is an in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B2, B3, and B_n is independently a natural, a modified, or an unnatural nucleobase;
 each Z' and Z'' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -
 NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;
 Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;
 each Z1 and Z2 is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃,
 -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;
 each Z3, Z4, and Z_n is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -



each B2, B3, and Bn is independently a natural, a modified, or an unnatural nucleobase;

each Z1 and Z2 is independently hydrogen, fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -OCH2CH3, -SCH3, -NH2, NHCH3, or NHC(=O)CH3;

each Z3, Z4, and Zn is independently hydrogen, fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -NH2, -NHCH3, -NH(C(=O)CH3), -OCH2CH3, -OCH2OCH3, -OCH2CH2CH3, -OCH(CH3)2, -SCH3, or -OCH2CH2OCH3;

each Q1 and Q4 is independently -CH2-, -CH=CH-, -CH2O-, -CH2S-, -CH2CH2-, -CH2CF2-, -CH2NH2-, -CH2NH(CH3)-, or -CH2N(C(=O)CH3)-;

each Q2 and Q3 is independently -O-, -S-, -CH2-, -CF2-, -NH-, -N(CH3)-, or -N(C(=O)CH3)-;

each X1, X2, X3, X4, and Xn is independently -OH, -SH, -O-, -S-, -NH2, -NHCH3, -NH(C(=O)CH3), -CH3, -CH2CH3, -CH2CH2CH3, -CH(CH3)2, -OCH3, or -OCH2CH3;

each Y1, Y2, Y3, Y4, and Yn is independently =O, =S, =NH, or =NCH3;

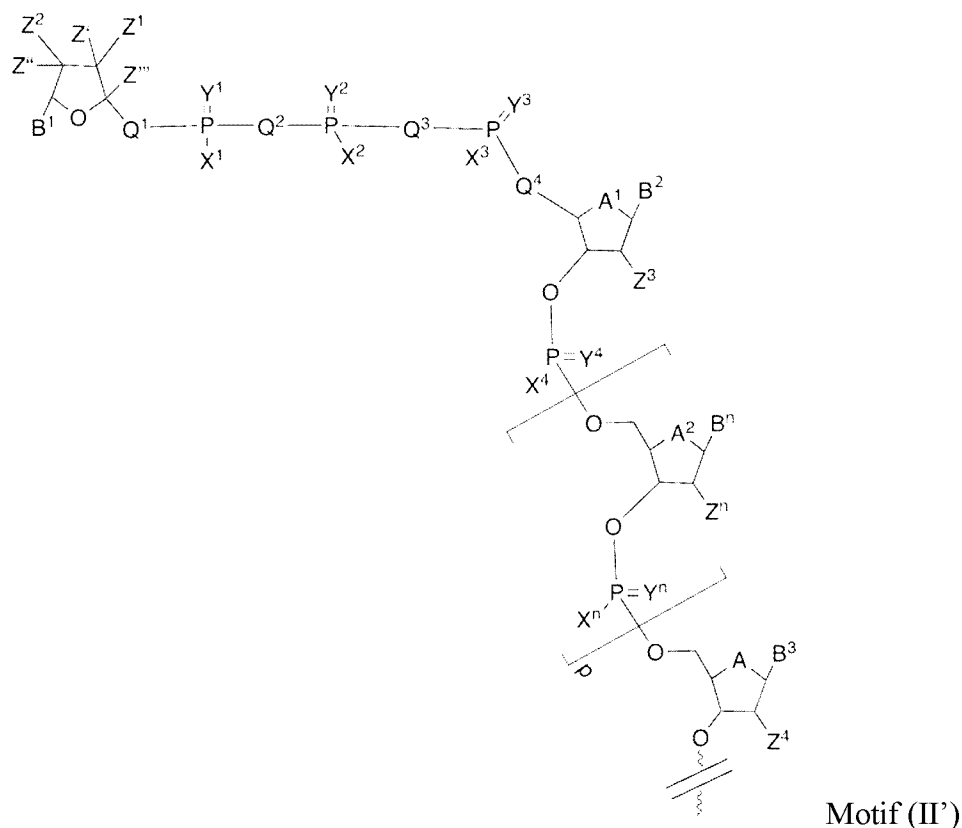
each A, A1, and A2 is independently -O-, -S-, -CH2-, -NH-, -N(CH3)- or -N(C(=O)CH3)-; and

p = 0, 1, 2, 3, 4, 5 or 6,

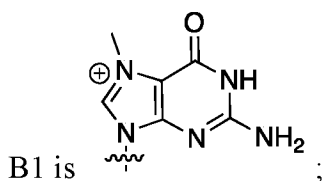
[0012] In another aspect, Formula (I) satisfies one or more of the following proviso (i) to (iii):

(i) at least one of X1, X2, X3, X4, and Xn is -SH or -S-; (ii) at least one of Y1, Y2, Y3, Y4, and Yn is =S; and (iii) at least one of A, A1, and A2 is -S-. In another aspect, at least one of X1, X2, X3, X4, and Xn is -SH or -S-; at least one of Y1, Y2, Y3, Y4, and Yn is =S; or at least one of A, A1, and A2 is -S-.

[0013] In one aspect, described herein, an mRNA sequence having a 5' end region motif (II'):



wherein



each B2, B3, and Bn is independently a natural, a modified, or an unnatural nucleobase;

each Z1 and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -NH(CH3), -NH2, -NH(C(=O)CH3), or -SCH3;

each Z2 and Z'' is independently fluorine, -OH, -SH, -CH3, -CH2CH3, -OCH3, -SCH3, -OCH2CH3, -NH2, NHCH3, or NHC(=O)CH3;

Z''' is hydrogen, fluorine, -CH3, -CH2CH3, -OCH3, or -OCH2CH3;

each Z3, Z4, and Zn is independently hydrogen, fluorine, -OH, -CH3, -CH2CH3, -OCH3, -NH2, -NHCH3, -NH(C(=O)CH3), -OCH2CH3, -OCH2OCH3, -OCH2CH2CH3, -OCH(CH3)2, -SCH3, or -OCH2CH2OCH3;

each Q1 and Q4 is independently -CH=CH-, -CH2-, -CH2O-, -CH2S-, -CH2CH2-, -CH2CF2-, -CH2NH2-, -CH2NH(CH3)-, or -CH2N(C(=O)CH3)-;

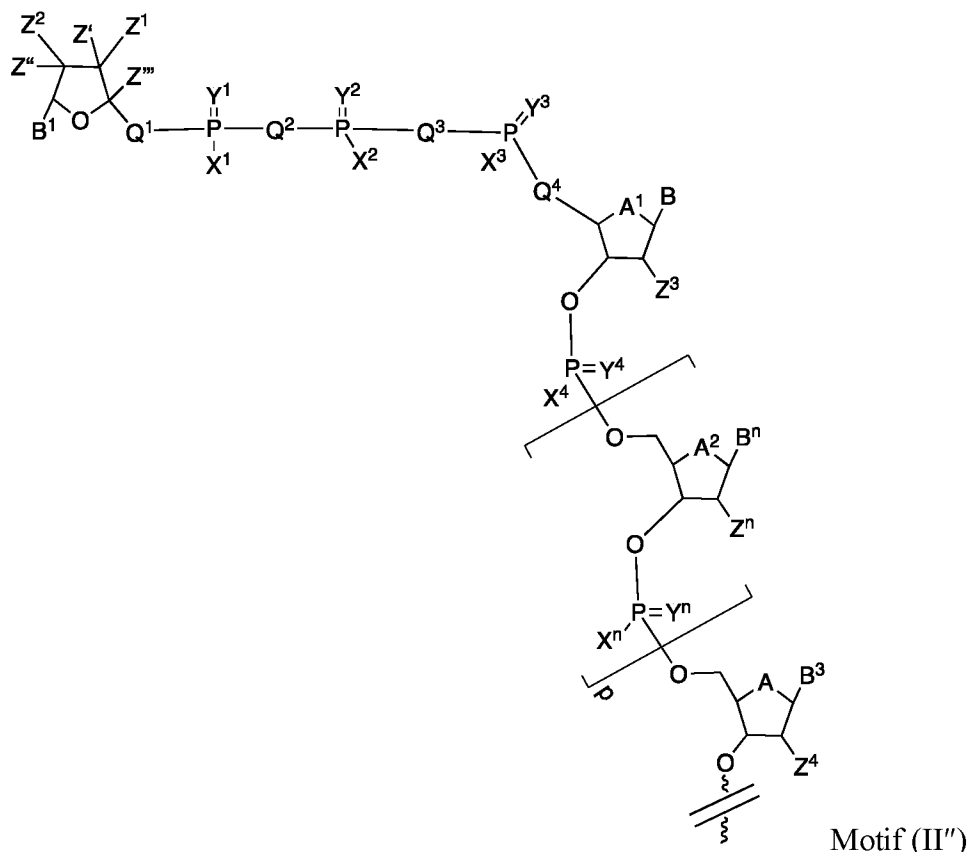
each Q2 and Q3 is independently -O-, -S-, -CH2-, -CF2-, -NH-, -N(CH3)-, or -N(C(=O)CH3)-;

each X1, X2, X3, X4, and Xn is independently -OH, -SH, -O-, -S-, -NH2, -NHCH3, -NH(C(=O)CH3), -CH3, -CH2CH3, -CH2CH2CH3, -CH(CH3)2, -OCH3 or -OCH2CH3;

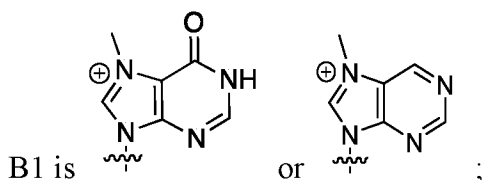
each Y1, Y2, Y3, Y4, and Yn is independently =O, =S, =NH, or =NCH₃;

each A, A1, and A2 is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and
p = 0, 1, 2, 3, 4, 5 or 6.

[0014] In one aspect, described herein, an mRNA sequence having a 5'-end region motif (II''):



wherein



each B2, B3, and Bn is independently a natural, a modified, or an unnatural nucleobase;

each Z' and Z'' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z1 and Z2 is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z3, Z4, and Zn is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q1 and Q4 is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -

CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q₂ and Q₃ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X₁, X₂, X₃, X₄, and X_n is independently -OH, -SH, -O-, -S-, -NH₂, -NHCH₃, -

NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y₁, Y₂, Y₃, Y₄, and Y_n is independently =O, =S, =NH, or =NCH₃;

each A, A₁, and A₂ is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

p = 0, 1, 2, 3, 4, 5 or 6.

[0015] In one aspect, described herein is a mRNA sequence having a 5'-end region motif, wherein the 5'-end region motif is a compound from Table 1, or a salt or solvate thereof.

[0016] In another aspect, described herein is a mRNA sequence having a 5'-end region motif, wherein the 5'-end region motif is a compound from Table 2, or a salt or solvate thereof.

[0017] In another aspect, described herein is a mRNA sequence having a 5'-end region motif, wherein the 5'-end region motif is a compound from Table 3, or a salt or solvate thereof.

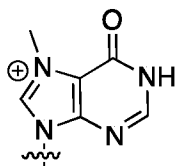
[0018] In another aspect of the mRNA sequence having a 5'-end region motif, Z³ is hydrogen, fluorine, -OH, -OCH₃, - or -OCH₂CH₃.

[0019] In another aspect of the mRNA sequence having a 5'-end region, Z³ is -OCH₃.

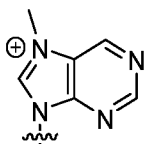
[0020] In another aspect of the mRNA sequence having a 5'-end region motif, each Z⁴ and Zⁿ is independently -OH or -OCH₃.

[0021] In another aspect of the mRNA sequence having a 5'-end region motif, each Z³, Z⁴, and Zⁿ is independently -OH or -OCH₃.

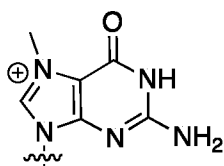
[0022] In another aspect of the mRNA sequence having a 5'-end region motif, B¹ is



[0023] In another aspect of the mRNA sequence having a 5'-end region motif, B¹ is



[0024] In another aspect of the mRNA sequence having a 5'-end region motif, B¹ is



[0025] In another aspect of the mRNA sequence having a 5'-end region motif, Z¹ is fluorine, -

OH, or -OCH₃.

[0026] In another aspect of the mRNA sequence having a 5'-end region motif, Z¹ is fluorine.

[0027] In another aspect of the mRNA sequence having a 5'-end region motif, Z¹ is -OH.

[0028] In another aspect of the mRNA sequence having a 5'-end region motif, Z¹ is -OCH₃.

[0029] In another aspect of the mRNA sequence having a 5'-end region motif, Z² is fluorine, -OH, or -OCH₃.

[0030] In another aspect of the mRNA sequence having a 5'-end region motif, Z² is fluorine.

[0031] In another aspect of the mRNA sequence having a 5'-end region motif, Z² is -OH.

[0032] In another aspect of the mRNA sequence having a 5'-end region motif, Z² is -OCH₃.

[0033] In another aspect of the mRNA sequence having a 5'-end region motif, Q¹ and Q⁴ is -CH₂O-.

[0034] In another aspect of the mRNA sequence having a 5'-end region motif, each Q² and Q³ is -O-.

[0035] In another aspect of the mRNA sequence having a 5'-end region motif, each Y¹ and Y³ is =O.

[0036] In another aspect of the mRNA sequence having a 5'-end region motif, each Y², Y⁴, and Yⁿ is independently =O or =S.

[0037] In another aspect of the mRNA sequence having a 5'-end region motif, one or more of Y¹, Y², Y³, Y⁴, and Yⁿ is =S.

[0038] In another aspect of the mRNA sequence having a 5'-end region motif, Y² is =S.

[0039] In another aspect of the mRNA sequence having a 5'-end region motif, Y⁴ is =S.

[0040] In another aspect of the mRNA sequence having a 5'-end region motif, each Y¹, Y², Y³, Y⁴, and Yⁿ is =O.

[0041] In another aspect of the mRNA sequence having a 5'-end region motif, each X¹, X⁴, and Xⁿ is -O[•].

[0042] In another aspect of the mRNA sequence having a 5'-end region motif, each X² and X³ is independently -O[•] or -S[•].

[0043] In another aspect of the mRNA sequence having a 5'-end region motif, X³ is -O[•].

[0044] In another aspect of the mRNA sequence having a 5'-end region motif, one or more of X¹, X², X³, X⁴, and Xⁿ is -S[•].

[0045] In another aspect of the mRNA sequence having a 5'-end region motif, X² is -S[•].

[0046] In another aspect of the mRNA sequence having a 5'-end region motif, X⁴ is -S[•].

[0047] In another aspect of the mRNA sequence having a 5'-end region motif, each X¹, X², X³, X⁴, and Xⁿ is -O[•].

[0048] In another aspect of the mRNA sequence having a 5'-end region motif, each A, A¹, and A² is -O-.

[0049] In another aspect of the mRNA sequence having a 5'-end region motif, one or more of A, A¹, and A² is -S-.

[0050] In another aspect of the mRNA sequence having a 5'-end region motif, A is -S- and A¹ and A² is -O-.

[0051] In another aspect of the mRNA sequence having a 5'-end region motif, A² is -S- and A and A¹ is -O-.

[0052] In another aspect of the mRNA sequence having a 5'-end region motif, A, A¹, and A² is -O-.

[0053] In another aspect of the mRNA sequence having a 5'-end region motif, p is 0.

[0054] In another aspect of the mRNA sequence having a 5'-end region motif, p is 1.

[0055] In another aspect of the mRNA sequence having a 5'-end region motif, p is 2.

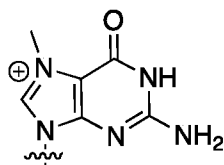
[0056] In another aspect of the e mRNA sequence having a 5'-end region motif, wherein each B², B³, and Bⁿ is independently adenine, cytosine, guanine, uracil, thymine, hypoxanthine, or purine.

[0057] In another aspect of the mRNA sequence having a 5'-end region motif, B² is adenine and B³ is guanine.

[0058] In another aspect of the mRNA sequence having a 5'-end region motif, B² is guanine and B³ is adenine.

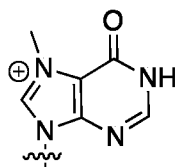
[0059] In another aspect of the mRNA sequence having a 5'-end region motif, protein expression is increased.

[0060] In another aspect of the mRNA sequence having a 5'-end region motif, Q¹ and Q⁴ are -CH₂O-; Q² and Q³ are -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently



=O or =S; and B¹ is

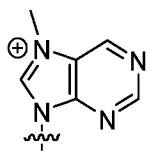
[0061] In another aspect of the mRNA sequence having a 5'-end region motif, Q¹ and Q⁴ are -CH₂O-; Q² and Q³ are -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently



=O or =S; and B¹ is

[0062] In another aspect of the mRNA sequence having a 5'-end region motif, Q¹ and Q⁴ are -

CH₂O-; Q² and Q³ are -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently



=O or =S; and B¹ is

[0063] In another aspect, described herein is a complex comprising an mRNA sequence having a 5'-end region motif and a DNA template, wherein the mRNA sequence having a 5'-end region motif comprises a compound described herein, wherein the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1, a second nucleotide at nucleotide position +2, and a third nucleotide at nucleotide position +3; and wherein the mRNA sequence having a 5'-end region motif is hybridized to the DNA template at least at nucleotide positions +1, +2, and +3.

[0064] In another aspect, described herein is a complex comprising an mRNA sequence having a 5'-end region motif and a DNA template, wherein the mRNA sequence having a 5'-end region motif comprises a compound described herein, wherein the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1 and a second nucleotide at nucleotide position +2; and wherein the mRNA sequence having a 5'-end region motif is hybridized to the DNA template at least at nucleotide positions +1 and +2.

[0065] In another aspect, described herein is a RNA molecule comprising the mRNA sequence having a 5'-end region motif. In another aspect, the RNA comprises a guide RNA or a nuclease mRNA. In another aspect, the RNA comprises an mRNA.

[0066] In another aspect, described herein is a method of expressing an mRNA comprising introducing the mRNA described herein into a cell lysate to express the mRNA. In another aspect, the method further comprises measuring the expression level of the mRNA. In another aspect, described herein in the method, the expression level of the mRNA is at least 2-fold, 3-fold, 4-fold, 6-fold, 8-fold, or 20-fold greater compared to a corresponding mRNA without the the mRNA sequence having a 5'-end region motif. In another aspect, described herein, the method involves a HeLa cell.

[0067] In another aspect, described herein is a method of detecting cellular immune stimulation resulting from mRNA comprising (a) contacting a formulation comprising capped mRNA according the compounds described herein with a cell reporter line and (b) measuring RIG-I activation in said cell reporter line. In another aspect, the reporter line is HEK-Lucia RIG-I model. In another aspect, described herein the cellular immune stimulation is reduced compared to an uncapped mRNA by at least 20%, 50%, 70%, 100%, and 150%.

[0068] In another aspect, described herein is a method of producing an mRNA sequence having

a 5'-end region motif described herein using an IVT reaction comprising (a) mixing a DNA template, polymerase enzyme, mRNA sequence motif comprising a phosphorothioate group (PS), and nucleoside triphosphates (NTPs) at a specified molar ratio of said mRNA sequence motif to said NTP to generate a mixture (b) incubating said mixture at a specified temperature and duration and (c) harvesting and purifying said mRNA sequence having a 5'-end region motif from said mixture. In another aspect, the molar ratio is 1:5, and the method is capable of producing a yield of at least 80% with a capping efficiency of at least 80%. In another aspect, the molar ratio is 1:2.5, and the method is capable of producing a yield of at least 80% with a capping efficiency of at least 85%. In another aspect, the molar ratio is 1:1.67, and the method is capable of producing a yield of at least 80% with a capping efficiency of at least 90%. In another aspect, the molar ratio is 1:1.25, and the method is capable of producing a yield of at least 80% with a capping efficiency of at least 90%. In another aspect, the molar ratio is 1.0:1.0, and the method is capable of producing a yield of at least 80% with a capping efficiency of at least 80%. In another aspect, the molar ratio is 1:5, and the method is capable of producing a yield of at least 3 mg of mRNA per milliliter (mL) of IVT reaction with a capping efficiency of at least 80%. In another aspect, the molar ratio is 1:2.5, and the method is capable of producing a yield of at least 3 mg of mRNA per milliliter (mL) of IVT reaction with a capping efficiency of at least 85%. In another aspect, the molar ratio is 1:1.67, and the method is capable of producing a yield of at least 3 mg of mRNA per milliliter (mL) of IVT reaction with a capping efficiency of at least 90%. In another aspect, the molar ratio is 1:1.25, and the method is capable of producing a yield of at least 3 mg of mRNA per milliliter (mL) of IVT reaction with a capping efficiency of at least 90%. In another aspect, the molar ratio is 1.0:1.0, and the method is capable of producing a yield of at least 3 mg of mRNA per milliliter (mL) of IVT reaction with a capping efficiency of at least 80%. In another aspect, the NTP is GTP, ATP, CTP, UTP, a modified NTP, or a combination thereof. In another aspect, the modified NTP is N1-methyl pseudouridine.

[0069] In another aspect, described herein is a cell containing an RNA molecule comprising the mRNA sequence having a 5' end region motif described herein.

[0070] In another aspect, described herein is a cell containing a polypeptide translated from an RNA molecule comprising the mRNA sequence having a 5' end region motif described herein.

[0071] In another aspect, described herein is a pharmaceutical composition comprising an RNA molecule comprising the mRNA sequence having a 5' end region motif described herein and one or more of pharmaceutically acceptable excipients. In another aspect, the pharmaceutical comprises lipid nanoparticles. In another aspect, the pharmaceutical composition is encapsulated in a lipid nanoparticle. In another aspect, the pharmaceutical composition further comprises one or more

single guide RNAs designed to target one or more specific locations of one or more genes of interest to elicit pharmacological effect upon administration into a mammal.

[0072] In another aspect, described herein is a method for synthesizing an RNA molecule comprising: introducing the mRNA sequence having a 5' end region motif described herein into a mixture comprising an RNA polymerase, and incubating the mixture for a time sufficient to allow for transcription of the RNA molecule. In another aspect, the mixture further comprises a DNA template and nucleoside triphosphates.

[0073] In another aspect, described herein is a method of gene editing comprising introducing into a cell an RNA molecule, or pharmaceutical composition, wherein the RNA molecule comprises guide RNA or a nuclease mRNA, wherein the RNA molecule is translated in the cell.

[0074] In another aspect, described herein is a method for reducing the risk of coronary disease in a subject in need thereof, comprising administering to the subject an effective amount of a pharmaceutical composition described herein.

INCORPORATION BY REFERENCE

[0075] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0076] Novel features of the invention are set forth with particularity in the appended claims and embodied in the mRNA 5' end-region structures described herein. A better understanding of the features and advantages of the present invention will be obtained by reference to the detailed description that sets forth illustrative embodiments of the 5' end-region structures or compounds (sometimes referred herein as motifs) in which the principles of the inventions are utilized, and the accompanying drawings of which:

[0077] FIG. 1A shows phosphorothioate-modified 5' end initiators and the corresponding *in vitro* transcribed mRNAs with 5' end region motifs identified in the specification as 1007a.

[0078] FIG. 1B shows phosphorothioate-modified 5' end initiators and the corresponding *in vitro* transcribed mRNAs with 5' end region motifs identified in the specification as 1107a.

[0079] FIG. 2 illustrates a comparison of production yields for mRNAs that were prepared using different 5' end initiators.

[0080] FIG. 3 illustrates a comparison of mRNA full-length purity between mRNAs that were

prepared using different 5' end initiators.

[0081] FIG. 4 illustrates a comparison of mRNA capping efficiency between mRNAs that were prepared using different 5' end initiators.

[0082] FIG. 5 illustrates protein expression of mRNAs comprising different 5' end region motifs in HeLa cell lysate.

[0083] FIG. 6 illustrates protein expression of mRNAs comprising different 5' end region motifs in primary human hepatocyte cells.

[0084] FIG. 7 illustrates a comparison of ABE base editing using the protein encoded by mRNAs comprising different 5' end-region motifs *in vivo* in mouse.

[0085] FIG. 8 illustrates immune stimulation of mRNA comprising different 5' end-regions motifs in HEK293 cells.

DETAILED DESCRIPTION

[0086] Certain specific details of this description are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the present disclosure may be practiced without these details. In other instances, well-known structures and/or methods have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed disclosure. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0087] Messenger RNA (mRNA), encoding physiologically important proteins for therapeutic applications, has shown significant advantages over DNA-based plasmid and viral vectors for delivering genetic material. Such important advantages include: (i) potentially improved levels of safety when compared to the potential genome damage that can result from viral or plasmid integration, (ii) more immediate protein expression upon mRNA delivery (unlike delayed responses that generally occur with plasmids), (iii) robust dose-dependent control over expression of proteins, and (iv) is capable of facilitating simplification of large scale synthesis of mRNAs as compared to manufacturing of plasmid and viral vectors.

[0088] Messenger RNAs can be encoded for virtually any known protein and can be delivered to specific cells, tissues and organs by a variety of methods known to those skilled in the art. Once delivered, such mRNAs are capable of direct ribosomal protein expression within targeted cell or

tissue resulting in the production of potentially many hundreds copies of the encoded proteins from a single mRNA molecule.

[0089] Several structural elements, present in active mRNA molecule, are utilized to translate the encoded proteins efficiently. One of these elements is the 5'-end region of mRNAs. In naturally occurring mRNA, the 5' end-region comprises a Cap structure, which is an important feature of eukaryotic mRNA molecules (and some viruses). Such Cap structures are known to be involved in protein translation, 5' exonuclease protection, splicing, and mRNA transport. A consistent structural element of a naturally occurring 5' Cap is an inverted 7-methylguanosine (m^7G) linked at the 5' end of the mRNA through a triphosphate (ppp) bridge, and this phosphate bridge is linked to the first nucleotide (N_1) of the mRNA transcript. This 5' Cap moiety generally represented by $m^7G(ppp)N_1$ is called cap-0. Methylation of the 2'-hydroxyl on N_1 ribose ring (*i.e.*, cap-1) is known to be capable of providing an identifier of self-RNA, which thereby serves to shield the mRNA from the innate immune system, which in turn is capable of improving protein expression. This $m^7G(ppp)N_1$ cap-1 structure is a known conventional cap moiety used in *in vitro* transcription (IVT) of mRNAs.

[0090] Here we present novel mRNA 5' end region motifs and initiators. These novel designs include modification of the purine base of the m^7G moiety; phosphorothioate (PS) substitution in the triphosphate bridge and chemical modifications of phosphodiester linkages, substitution of the 5' end region nucleotides with non-canonical bases, extension of the 5' end region nucleotide oligomer, as well as chemical modification of the ribose rings. Specifically, these mRNA 5' end region structures serve as the terminal 5' end region of an mRNA and provide stability to the mRNA. The chemical structures of the motifs are capable of facilitating and/or modulating mRNA activity and rates of translation initiation and elongation; protecting mRNA by creating a barrier that prevents or interferes with mRNA decapping by 5' exonuclease activity; impacting capping efficiency and reducing the formation of immune-stimulatory by-products, which can improve mRNA safety; and facilitating the mRNA manufacturability by modulating the binding affinity for DNA template during an IVT reaction.

Definitions

[0091] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All references cited herein are incorporated by reference in their entirety as

though fully set forth. Singleton et al., Dictionary of Microbiology and Molecular Biology 3rd ed., J. Wiley & Sons (New York, NY 2001); March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 5th ed., J. Wiley & Sons (New York, NY 2001); and Sambrook and Russel, Molecular Cloning: A Laboratory Manual 3rd ed., Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

[0092] As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0093] When indicating the number of substituents, the term “one or more” refers to the range from one substituent to the highest possible number of substitution, e.g. replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0094] The term “optional” or “optionally” denotes that a subsequently described event or circumstance can but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

[0095] The term “nucleic acid” as used herein generally refers to one or more nucleobases, nucleosides, or nucleotides, and the term includes polynucleobases, polynucleosides, and polynucleotides. A nucleic acid can include polynucleotides, mononucleotides, and oligonucleotides. A nucleic acid can include DNA, RNA, or a mixture thereof, and can be single stranded, double stranded, or partially single or double stranded, and can form secondary structures. In some embodiments, a nucleic acid has multiple double-stranded segments and single stranded segments. For example, a nucleic acid may comprise a polynucleotide, e.g. a mRNA, with multiple double stranded segments within it.

[0096] The terms “mRNA sequence initiator”, “IVT mRNA sequence initiator” and “initiator” are used interchangeably herein to generally refer to a ribo- or deoxyribo- or chimeric ribo/deoxyribo-oligonucleotide, single stranded, may be naturally occurring or synthetic, and usually include a sequence of between about 2 to about 10 nucleotides, about 3 to about 8 nucleotides or about 3 to about 5 nucleotides. mRNA sequence initiators may contain one or more modification groups. mRNA sequence initiators may be primers, e.g. oligonucleotide primers. mRNA sequence initiators, for example, oligonucleotide primers, may include RNA, DNA, and/or other modified nucleosides. The skilled artisan is capable of designing and preparing mRNA sequence initiators that are appropriate for transcription of DNA template sequence.

[0097] mRNA sequence initiators may be capped primers or capped oligonucleotide analogs.

For example, a capped mRNA sequence initiator may contain initiating capped oligonucleotide analogs or initiating capped oligonucleotides with Cap 0, Cap 1, Cap 2 or TMG-Cap structure on 5'-end. In some instances, a capped initiator, e.g., a capped primer or capped oligonucleotide analog has an unmodified or open 3'-OH group and it may be extended by RNA polymerase through the incorporation of an NTP onto the 3'-end. In some instances, an initiator as described herein can initiate in vitro transcription under the control of a promoter in a transcription system containing necessary components: DNA template (e.g. DNA plasmid), RNA polymerase, nucleoside 5'-triphosphates and appropriate buffer. An initiator may be a oligonucleotide carrying a terminal 3'-OH group that is a valid substrate for RNA polymerase. In certain embodiments, an initiator is a substrate for RNA polymerase and may be elongated by incorporation of NTP onto the 3'-end. In some embodiments, an initiator is complementary to the DNA template at the initiation site.

[0098] The term “unsubstituted” or “unmodified” in the context of mRNA sequence initiators and nucleoside triphosphates (NTPs) as used herein generally refers to an initiating capped initiator and NTPs that have not been modified.

[0099] The term “modified initiating capped initiator” as used herein generally refers to an initiating capped mRNA sequence initiator that contains one or more additional modification group(s) or moiety/moieties within the sequence initiator.

[0100] The term “modification group(s) or moiety/moieties” as used herein generally refers to any chemical moiety that may be attached or substituted to the mRNA sequence initiator, e.g., an initiating primer at locations, which include, but are not limited to, the sugar, nucleoside base, triphosphate bridge, and/or internucleotide phosphate (e.g., U.S. Patent Application No. 20070281308). The modification group of a capped initiator may be a group of any nature that is compatible with the process of transcription.

[0101] The term “internucleotide linkage” as used herein generally refers to the bond or bonds that connect two nucleosides of an initiator, e.g. an oligonucleotide primer or a nucleic acid and may be a natural phosphodiester linkage or a chemically modified nucleic acid backbone linkage.

[0102] The term “polynucleotide”, as used herein generally refers to a molecule comprising two or more linked nucleic acid subunits, e.g., nucleotides, and can be used interchangeably with “oligonucleotide”. For example, a polynucleotide may include one or more nucleotides selected from corresponding nucleosides carrying the nucleobase- adenine (A), cytosine (C), guanine (G), thymine (T) and uracil (U), or variants and combinations thereof. A nucleotide generally includes a nucleoside and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphate (PO₃) groups. A nucleotide can include a nucleobase, a five-carbon sugar (either ribose or deoxyribose), and one or more phosphate groups. Ribonucleotides include nucleotides in which the sugar is ribose.

Deoxyribonucleotides include nucleotides in which the sugar is deoxyribose. A nucleotide can be a nucleoside monophosphate, nucleoside diphosphate, nucleoside triphosphate or a nucleoside polyphosphate. For example, a nucleotide can be a deoxyribonucleoside polyphosphate, such as a deoxyribonucleoside triphosphate (dNTP). Exemplary dNTPs include deoxyadenosine triphosphate (dATP), deoxycytidine triphosphate (dCTP), deoxyguanosine triphosphate (dGTP), uridine triphosphate (dUTP) and deoxythymidine triphosphate (dTTP). dNTPs can also include detectable tags, such as luminescent tags or markers (*e.g.*, fluorophores). For example, a nucleotide can be a purine (*e.g.*, A or G, or variant thereof) or a pyrimidine (*e.g.*, C, T or U, or variant thereof). In some examples, a polynucleotide is deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or derivatives or variants thereof. Exemplary polynucleotides include, but are not limited to, short interfering RNA (siRNA), a microRNA (miRNA), a plasmid DNA (pDNA), a short hairpin RNA (shRNA), small nuclear RNA (snRNA), messenger RNA (mRNA), precursor mRNA (pre-mRNA), antisense RNA (asRNA), and heteronuclear RNA (hnRNA), and encompasses both the nucleotide sequence and any structural embodiments thereof, such as single-stranded, double-stranded, triple-stranded, helical, hairpin, stem loop, bulge, etc. In some cases, a polynucleotide is circular. A polynucleotide can have various lengths. For example, a polynucleotide can have a length of at least about 7 bases, 8 bases, 9 bases, 10 bases, 20 bases, 30 bases, 40 bases, 50 bases, 100 bases, 200 bases, 300 bases, 400 bases, 500 bases, 1 kilobase (kb), 2 kb, 3 kb, 4 kb, 5 kb, 10 kb, 50 kb, or more. A polynucleotide can be isolated from a cell or a tissue. For example, polynucleotide sequences may comprise isolated and purified DNA/RNA molecules, synthetic DNA/RNA molecules, and/or synthetic DNA/RNA analogs.

[0103] Polynucleotides can include one or more nucleotide variants, including nonstandard nucleotide(s), non-natural nucleotide(s), nucleotide analog(s) and/or modified nucleotides including acyclic and carbocyclic nucleotides. Examples of modified nucleotides include, but are not limited to diaminopurine, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (*v*), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil,

(acp3)w, 2,6-diaminopurine and the like. In some cases, nucleotides may include modifications in their phosphate moieties, including modifications to a triphosphate moiety. Non-limiting examples of such modifications include phosphate chains of greater length (*e.g.*, a phosphate chain having, 4, 5, 6, 7, 8, 9, 10 or more phosphate moieties) and modifications with thiol moieties (*e.g.*, alpha-thiotriphosphate and beta-thiotriphosphates). Nucleic acid molecules may also be modified at the base moiety (*e.g.*, at one or more atoms that typically are available to form a hydrogen bond with a complementary nucleotide and/or at one or more atoms that are not typically capable of forming a hydrogen bond with a complementary nucleotide), sugar moiety or phosphate backbone. Nucleic acid molecules may also contain amine-modified groups, such as amino ally 1-dUTP (aa-dUTP) and aminohexylacrylamide-dCTP (aha-dCTP) to allow covalent attachment of amine reactive moieties, such as N-hydroxysuccinimide esters (NHS). Alternatives to standard DNA base pairs or RNA base pairs in the oligonucleotides of the present disclosure can provide higher density in bits per cubic mm, higher safety (resistant to accidental or purposeful synthesis of natural toxins), easier discrimination in photo-programmed polymerases, or lower secondary structure. Such alternative base pairs compatible with natural and mutant polymerases for *de novo* and/or amplification synthesis are described in Betz K, Malyshev DA, Lavergne T, Welte W, Diederichs K, Dwyer TJ, Ordoukhanian P, Romesberg FE, Marx A. *Nat. Chem. Biol.* 2012, 8(7):612-4, which is herein incorporated by reference for all purposes.

[0104] As used herein, the terms “polypeptide”, “protein” and “peptide” are used interchangeably and refer to a polymer of amino acid residues linked via peptide bonds and which may be composed of two or more polypeptide chains. The terms “polypeptide”, “protein” and “peptide” refer to a polymer of at least two amino acid monomers joined together through amide bonds. An amino acid may be the L-optical isomer or the D-optical isomer. More specifically, the terms “polypeptide”, “protein” and “peptide” refer to a molecule composed of two or more amino acids in a specific order; for example, the order as determined by the base sequence of nucleotides in the gene or RNA coding for the protein. Proteins are essential for the structure, function, and regulation of the body’s cells, tissues, and organs, and each protein has unique functions. Examples are hormones, enzymes, antibodies, and any fragments thereof. In some cases, a protein can be a portion of the protein, for example, a domain, a subdomain, or a motif of the protein. In some cases, a protein can be a variant (or mutation) of the protein, wherein one or more amino acid residues are inserted into, deleted from, and/or substituted into the naturally occurring (or at least a known) amino acid sequence of the protein. A protein or a variant thereof can be naturally occurring or recombinant.

[0105] As used herein, “hybridize” refers to a process where initiating a capped mRNA

sequence initiator anneals to a DNA template in accordance with Watson-Crick base pairing rules under appropriately stringent conditions during a transcription reaction. Nucleic acid hybridization techniques are well known in the art. See, e.g., Sambrook, et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, Plainview, N.Y. Those skilled in the art understand how to determine the appropriate stringency of hybridization/washing conditions such that sequences having at least a desired level of complementarity will stably hybridize, while those having lower complementarity will not. For examples of hybridization conditions and parameters, see, e.g., Sambrook, et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Press, Plainview, N.Y.; Ausubel, F. M. et al. 1994, *Current Protocols in Molecular Biology*. John Wiley & Sons, Secaucus, N.J, all of which are incorporated herein by reference in their entireties. In certain embodiments, hybridizations may occur between nucleic acid molecules of 20-100 nucleotides in length. In some embodiments, hybridization may occur between at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 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 consecutive nucleotides. In some embodiments, the hybridizing nucleic acid molecules may contain up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mismatches that are tolerated.

[0106] As used herein, “complement,” “complementary,” or “complementarity” in the context of a complex of, for example, an initiating capped oligonucleotide primer and a DNA template refers to standard Watson/Crick base pairing rules. For example, the sequence “5'-A-G-T-C-3'” is complementary to the sequence “3'-T-C-A-G-5'.” Certain non-natural or synthetic nucleotides may be included in the nucleic acids described herein; these include but not limited to, base and sugar modified nucleosides, nucleotides, and nucleic acids, such as inosine, 7-deazaguanosine, 2'-O-methylguanosine, 2'-fluoro-2'-deoxycytidine, pseudouridine, Locked Nucleic Acids (LNA), and Peptide Nucleic Acids (PNA). Complementarity does not need to be perfect; duplexes may contain mismatched base pairs, degenerative, or unmatched nucleotides. Those skilled in the art can determine duplex stability empirically considering a number of variables including, for example, the length of the oligonucleotide, base composition and sequence of the oligonucleotide, incidence of mismatched base pairs, ionic strength, components of the hybridization buffer and reaction conditions.

[0107] Complementarity may be “complete” or “total” where all of the nucleotide bases of two nucleic acid strands are matched according to recognized base pairing rules, it may be “partial” in which only some of the nucleotide bases of an capped mRNA sequence initiator and a DNA target

are matched according to recognized base pairing rules or it may be “absent” where none of the nucleotide bases of two nucleic acid strands are matched according to recognized base pairing rules. The degree of complementarity between a capped mRNA sequence initiator, e.g. a capped primer, and a DNA template may have a significant effect on the strength of hybridization between the initiating capped oligonucleotide and the DNA template and correspondingly the efficiency of the reaction. The term complementarity may also be used in reference to individual nucleotides. For example, a particular nucleotide within an oligonucleotide may be noted for its complementarity, or lack thereof, to a nucleotide within another strand, in contrast or comparison to the complementarity between the rest of an capped mRNA sequence initiator and a DNA strand.

[0108] As used herein the term “complete”, “total” or “perfectly” complementary means that each of the nucleotide bases of a capped mRNA sequence initiator and a DNA target are matched exactly according to recognized base pairing rules.

[0109] As used herein, the term “substantially complementary” refers to two sequences that hybridize under stringent hybridization conditions. Those skilled in the art will understand that substantially complementary sequences need not hybridize along their entire length. In particular, substantially complementary sequences may comprise a contiguous sequence of bases that do not hybridize to a target sequence and may be positioned 3' or 5' to a contiguous sequence of bases that hybridize under stringent hybridization conditions to the target sequence.

[0110] As used herein, the term “nucleoside” includes all naturally occurring nucleosides, including all forms of nucleoside bases and furanosides found in nature. Base rings most commonly found in naturally occurring nucleosides are purine and pyrimidine rings. Naturally occurring purine rings include, for example, adenine, guanine, and N⁶-methyladenine. Naturally occurring pyrimidine rings include, for example, cytosine, thymine, 5-methylcytosine, pseudouracyl. Naturally occurring nucleosides for example include, but are not limited to, ribo, 2'-O-methyl or 2'-deoxyribo derivatives of adenosine, guanosine, cytidine, thymidine, uridine, inosine, 7-methylguanosine or pseudouridine.

[0111] As used herein, the terms “nucleoside analogs,” “modified nucleosides,” or “nucleoside derivatives” include synthetic nucleosides as described herein. Nucleoside derivatives also include nucleosides having modified base or/and sugar moieties, with or without protecting groups and include, for example, 2'-deoxy-2'-fluorouridine, 5-fluorouridine and the like. The compounds and methods provided herein include such base rings and synthetic analogs thereof, as well as unnatural heterocycle-substituted base sugars, and acyclic substituted base sugars. Other nucleoside derivatives that may be utilized with the present disclosure include, for example, LNA nucleosides, halogen-substituted purines (e.g., 6-fluoropurine), halogen-substituted pyrimidines, N⁶-

ethyladenine, N⁴-(alkyl)-cytosines, 5-ethylcytosine, and the like (U.S. Pat. No. 6,762,298).

[0112] As used herein, the terms “universal base,” “degenerate base,” “universal base analog” and “degenerate base analog” include, for example, a nucleoside analog with an artificial base which is, in certain embodiments, recognizable by RNA polymerase as a substitute for one of the natural NTPs (e.g., ATP, UTP, CTP and GTP) or other specific NTP. Universal bases or degenerate bases are disclosed in Loakes, D., *Nucleic Acids Res.*, 29:2437-2447 (2001); Crey-Desbiolles, C., et. al., *Nucleic Acids Res.*, 33:1532-1543 (2005); Kincaid, K., et. al., *Nucleic Acids Res.*, 33:2620-2628 (2005); Preparata, F P, Oliver, J S, *J. Comput. Biol.* 753-765 (2004); and Hill, F., et. al., *Proc Natl Acad. Sci. USA*, 95:4258-4263 (1998)).

[0113] As used herein, the term “modified NTP” refers to a nucleoside 5'-triphosphate having a chemical moiety group bound at any position, including the sugar, base, triphosphate chain, or any combination of these three locations. Examples of such NTPs can be found, for example in “Nucleoside Triphosphates and Their Analogs: Chemistry, Biotechnology and Biological Applications,” Vaghefi, M., ed., Taylor and Francis, Boca Raton (2005).

[0114] As used herein, the term “specific” when used in reference to a 5' capped mRNA sequence initiator sequence and its ability to hybridize to a DNA template is a sequence that has at least 50% sequence identity with a portion of the DNA template when the capped mRNA sequence initiator and DNA strand are aligned. Higher levels of sequence identity that may be preferred include at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, and most preferable 100% sequence identity.

[0115] In addition to “unmodified” or “natural” nucleobases such as the purine nucleobases adenine (A) and guanine (G), and the pyrimidine nucleobases thymine (T), cytosine (C) and uracil (U), many modified nucleobases or nucleobase mimetics known to those skilled in the art are amenable with the compounds described herein. The unmodified or natural nucleobases can be modified or replaced to provide oligonucleotides having improved properties. For example, nuclease resistant oligonucleotides can be prepared with these bases or with synthetic and natural nucleobases (e.g., inosine, xanthine, hypoxanthine, nebularine, isoguanisine, or tubercidine) and any one of the oligomer modifications described herein. Alternatively, substituted or modified analogs of any of the above bases and “universal bases” can be employed. When a natural base is replaced by a non-natural and/or universal base, the nucleotide is said to comprise a modified nucleobase and/or a nucleobase modification herein. Modified nucleobase and/or nucleobase modifications also include natural, non-natural and universal bases, which comprise conjugated moieties, e.g. a ligand described herein. Preferred conjugate moieties for conjugation with nucleobases include cationic amino groups which can be conjugated to the nucleobase via an

appropriate alkyl, alkenyl or a linker with an amide linkage.

[0116] As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Exemplary modified nucleobases include, but are not limited to, other synthetic and natural nucleobases such as inosine, xanthine, hypoxanthine, nubularine, isoguanisine, tubercidine, 2-(halo)adenine, 2-(alkyl)adenine, 2-(propyl)adenine, 2-(amino)adenine, 2-(aminoalkyl)adenine, 2-(aminopropyl)adenine, 2-(methylthio)-N6-(isopentenyl)adenine, 6-(alkyl)adenine, 6-(methyl)adenine, 7-(deaza)adenine, 8-(alkenyl)adenine, 8-(alkyl)adenine, 8-(alkynyl)adenine, 8-(amino)adenine, 8-(halo)adenine, 8-(hydroxyl)adenine, 8-(thioalkyl)adenine, 8-(thiol)adenine, N6-(isopentyl)adenine, N6-(methyl)adenine, N6, N6-(dimethyl)adenine, 2-(alkyl)guanine, 2-(propyl)guanine, 6-(alkyl)guanine, 6-(methyl)guanine, 7-(alkyl)guanine, 7-(methyl)guanine, 7-(deaza)guanine, 8-(alkyl)guanine, 8-(alkenyl)guanine, 8-(alkynyl)guanine, 8-(amino)guanine, 8-(halo)guanine, 8-(hydroxyl)guanine, 8-(thioalkyl)guanine, 8-(thiol)guanine, N-(methyl)guanine, 2-(thio)cytosine, 3-(deaza)-5-(aza)cytosine, 3-(alkyl)cytosine, 3-(methyl)cytosine, 5-(alkyl)cytosine, 5-(alkynyl)cytosine, 5-(halo)cytosine, 5-(methyl)cytosine, 5-(propynyl)cytosine, 5-(propynyl)cytosine, 5-(trifluoromethyl)cytosine, 6-(azo)cytosine, N4-(acetyl)cytosine, 3-(3-amino-3-carboxypropyl)uracil, 2-(thio)uracil, 5-(methyl)-2-(thio)uracil, 5-(methylaminomethyl)-2-(thio)uracil, 4-(thio)uracil, 5-(methyl)-4-(thio)uracil, 5-(methylaminomethyl)-4-(thio)uracil, 5-(methyl)-2,4-(dithio)uracil, 5-(methylaminomethyl)-2,4-(dithio)uracil, 5-(2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5-(aminoallyl)uracil, 5-(aminoalkyl)uracil, 5-(guanidiniumalkyl)uracil, 5-(1,3-diazole-1-alkyl)uracil, 5-(cyanoalkyl)uracil, 5-(dialkylaminoalkyl)uracil, 5-(dimethylaminoalkyl)uracil, 5-(halo)uracil, 5-(methoxy)uracil, uracil-5-oxyacetic acid, 5-(methoxycarbonylmethyl)-2-(thio)uracil, 5-(methoxycarbonyl-methyl)uracil, 5-(propynyl)uracil, 5-(propynyl)uracil, 5-(trifluoromethyl)uracil, 6-(azo)uracil, dihydrouracil, N-(methyl)uracil, 5-uracil (i.e., pseudouracil), 2-(thio)pseudouracil, 4-(thio)pseudouracil, 2,4-(dithio)pseudouracil, 5-(alkyl)pseudouracil, 5-(methyl)pseudouracil, 5-(alkyl)-2-(thio)pseudouracil, 5-(methyl)-2-(thio)pseudouracil, 5-(alkyl)-4-(thio)pseudouracil, 5-(methyl)-4-(thio)pseudouracil, 5-(alkyl)-2,4-(dithio)pseudouracil, 5-(methyl)-2,4-(dithio)pseudouracil, 1-methylpseudouracil (N1-methylpseudouracil), 1-substituted pseudouracil, 1-substituted 2-(thio)-pseudouracil, 1-substituted 4-(thio)pseudouracil, 1-substituted 2,4-(dithio)pseudouracil, 1-(aminocarbonylethynyl)-pseudouracil, 1-(aminocarbonylethynyl)-2-(thio)-pseudouracil, 1-(aminocarbonylethynyl)-4-(thio)pseudouracil, 1-(aminocarbonylethynyl)-2,4-(dithio)pseudouracil, 1-(aminoalkylaminocarbonylethynyl)-pseudouracil, 1-(aminoalkylamino-carbonylethynyl)-2-(thio)-pseudouracil, 1-(aminoalkylaminocarbonylethynyl)-4-(thio)pseudouracil, 1-

(aminoalkylaminocarbonylethylene)-2,4-(dithio)pseudouracil, 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-substituted 1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-substituted 1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaz)-2-(oxo)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 1,3,5-(triaz)-2,6-(diox)-naphthalene, inosine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, inosinyl, 2-aza-inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl, nitrobenzimidazolyl, nitroindazolyl, aminoindolyl, pyrrolopyrimidinyl, 3-(methyl)isocarbostyryl, 5-(methyl)isocarbostyryl, 3-(methyl)-7-(propynyl)isocarbostyryl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, imidizopyridinyl, 9-(methyl)-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyryl, 7-(propynyl)isocarbostyryl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, naphthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenyl, tetracenyl, pentacenyl, difluorotolyl, 4-(fluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo)thymine, 2-pyridinone, 5-nitroindole, 3-nitropyrrole, 6-(aza)pyrimidine, 2-(amino)purine, 2,6-(diamino)purine, 5-substituted pyrimidines, N2-substituted purines, N6-substituted purines, O6-substituted purines, substituted 1,2,4-triazoles, pyrrolo-pyrimidin-2-on-3-yl, 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ori/zo-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ori/zo-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ori/zo-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ori/zo-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl, 2-oxo-pyridopyrimidine-3-yl, or any O-alkylated or N-alkylated derivatives thereof. Alternatively, substituted or modified analogs of any of the above bases and "universal bases" can be employed. A universal nucleobase is any nucleobase that can base pair with all of the four naturally occurring nucleobases without substantially affecting the melting behavior, recognition by intracellular enzymes or activity of the oligonucleotide duplex. Some exemplary universal nucleobases include, but are not limited to, 2,4-difluorotoluene, nitropyrrolyl, nitroindolyl, 8-aza-7-deazaadenine, 4-fluoro-6-methylbenzimidazole, 4-methylbenzimidazole, 3-methyl isocarbostyryl, 5-methyl isocarbostyryl, 3-methyl-7-propynyl isocarbostyryl, 7-

azaindolyl, 6-methyl-7-azaindolyl, imidizopyridinyl, 9-methyl-imidizopyridinyl, pyrrolopyridinyl, isocarbostyryl, 7-propynyl isocarbostyryl, propynyl-7-azaindolyl, 2,4,5-trimethylphenyl, 4-methylinolyl, 4,6-dimethylindolyl, phenyl, naphthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenyl, tetracenyl, pentacenyl, and structural derivatives thereof (see for example, Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447, incorporated herein by reference in its entirety). Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808; those disclosed in International Application No. PCT US09/038425, filed March 26, 2009; those disclosed in the Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I, ed. John Wiley & Sons, 1990; those disclosed by English et al, *Angewandte Chemie*, International Edition, 1991, 30, 613; those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijin, P.Ed. Wiley-VCH, 2008; and those disclosed by Sanghvi, Y.S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Crooke, S.T. and Lebleu, B., Eds., CRC Press, 1993. Contents of all of the above are herein incorporated by reference.

[0117] As used herein, the term “biological sample” means any biological material from which polynucleotides, polypeptides, biomarkers, and/or metabolites can be prepared or can be extracted out and examined. Non-limiting examples encompasses whole blood, plasma, saliva, cheek swab, fecal specimen, urine specimen, cell mass, or any other bodily fluid or tissue.

[0118] The terms “administer,” “administering,” “administration,” and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes (p.o.), intraduodenal routes (i.d.), parenteral injection (including intravenous (i.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), intravascular or infusion (inf.)), topical (top.) and rectal (p.r.) administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0119] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0120] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated; for example a reduction and/or alleviation of one or more signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses

can be an amount of an agent that provides a clinically significant decrease in one or more disease symptoms. An appropriate “effective” amount may be determined using techniques, such as a dose escalation study, in individual cases.

[0121] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in amount, potency or duration a desired effect.

[0122] As used herein, “carbohydrate” refers to a compound which is either a carbohydrate per se made up of one or more monosaccharide units having at least 6 carbon atoms (which may be linear, branched or cyclic) with an oxygen, nitrogen or sulfur atom bonded to each carbon atom; or a compound having as a part thereof a carbohydrate moiety made up of one or more monosaccharide units each having at least six carbon atoms (which may be linear, branched or cyclic), with an oxygen, nitrogen or sulfur atom bonded to each carbon atom. Representative carbohydrates include the sugars (mono-, di-, tri- and oligosaccharides containing from about 4-9 monosaccharide units), and polysaccharides such as starches, glycogen, cellulose and polysaccharide gums. Specific monosaccharides include C5 and above (preferably C5-C8) sugars; di- and trisaccharides include sugars having two or three monosaccharide units (preferably C5-C8).

[0123] The term “monosaccharide” embraces radicals of allose, altrose, arabinose, cladinose, erythrose, erythrulose, fructose, D-fucitol, L-fucitol, fucosamine, fucose, fuculose, galactosamine, D-galactosaminitol, N-acetyl-galctosamine, galactose, glucosamine, N-acetyl-glucosamine, glucosaminitol, glucose, glucose-6-phosphate gulose glyceraldehyde, L-glycero-D-mannose-heprose, glycerol, glycerone, gulose idose, lyxose, mannosamine, mannose, mannose-6-phosphate, psicose, quinovose, quinovosamine, rhamnitol, rhamnosamine, rhamnose, ribose, ribulose, sedoheptulose, sorbose, tagatose, talose, tararic acid, throse, xylose and xylulose. The monosaccharide can be in D- or L-configuration. The monosaccharide may further be a deoxy sugar (alcoholic hydroxy group replaced by hydrogen), amino sugar (alcoholic hydroxy group replaced by amino group), a thio sugar (alcoholic hydroxy group replaced by thiol, or C=O replaced by C=S, or a ring oxygen of cyclic form replaced by sulfur), a seleno sugar, a telluro sugar, an aza sugar (ring carbon replaced by nitrogen), a imino sugar (ring oxygen replaced by nitrogen), a phosphano sugar (ring oxygen replaced with phosphorus), a phospho sugar (ring carbon replaced with phosphorus), a C-substituted monosaccharide (hydrogen at a non-terminal carbon atom replaced with carbon), an unsaturated monosaccharide, an alditol (carbonyl group replaced with CHOH group), aldonic acid (aldehydic group replaced by carboxy group), a ketoaldonic acid, a uronic acid, an aldaric acid, and so forth. Amino sugars include amino monosaccharides, preferably galactosamine, glusamine, mannosamine, fucosmine, quinavosamine, neuraminic acid, muramic acid, lactosediamine, acosamine, bacillosamine, daunosamine, desosamine, forosamine,

garosamine, kanosamine, kanosamine, mycaminose, myosamine, persosamine, pneumosamine, purpurosamine, rhodosmine. It is understood that the monosaccharide and the like can be further substituted.

[0124] The terms “disaccharide”, “trisaccharide” and “polysaccharide” embrace radicals of abequose, acrabose, amictose, amylopectin, amylose, apiose, arcanose, ascarylose, ascorbic acid, boivinos, cellobiose, cellotriose, cellulose, chacotriose, chalcose, chitin, colitose, cyclodextrin, cymarose, dextrin, 2-deoxyribose, 2-deoxyglucose diginose, digitalose, digitoxose, evalose, evemitrose, fructooligosaccharide, galto-oligosaccharide, gentianose, genitobiose, glucan, gluicogen, glycogen, hamamelose, heparin, inulin, isolevoglucosenone, isomaltose, isomaltotriose, isopanose, kojibiose, lactose, lactosamine, lactosediamine, laminarabiose, levoglucosan, levoglucosenone, β -maltose, maltriose, mannan-oligosaccharide, amnninotriose, melezitose, melibiose, muramic acid, mycarose, mycinose, neuaminic acid, migerose, nojirimycin, noviose, oleandrose, panose, paratose, planteose, primeverose, raffinose, rhodone, rutinose, oleandrose, panose, paratose, planteose, primeverose, raffinose, rhodinose, rutinose, sarmentose, sedoheptulose, sedoheptulosan, solatriose, sophorose, stachyose, streptose, sucrose, α,α -trehalose, trahalosamine, turanose, tyvelose, xylobiose, umbelliferose and the like. Further, it is understood that the “disaccharide”, “trisaccharide” and “polysaccharide” and the like can further substituted. Disaccharide also includes amino sugars and their derivatives, particularly, a mycaminose derivatized at the C-4' position or a 4 deoxy-3-amino-glucose derivatized at the C-6' position.

[0125] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human. The term “animal” as used herein comprises human beings and non-human animals. In one embodiment, a “non-human animal” is a mammal, for example a rodent such as rat or a mouse. In one embodiment, a non-human animal is a mouse.

[0126] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, *e.g.*, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically. The term “treating” further encompasses the concept of “prevent,” “preventing,” and “prevention,” as stated below. It is appreciated that, although not

precluded, treating a disorder or condition does not require that the disorder, condition, or symptoms associated therewith be completely eliminated.

[0127] The term “preventing” or “prevention” of a disease state denotes causing the clinical symptoms of the disease state not to develop in a subject that can be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.

[0128] The terms “pharmaceutical composition” and “pharmaceutical formulation” (or “formulation”) are used interchangeably and denote a mixture or a solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with one or more pharmaceutically acceptable excipients to be administered to a subject, *e.g.*, a human in need thereof.

[0129] The term “pharmaceutical combination” as used herein, means a product that results from mixing or combining more than one pharmaceutically active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, *e.g.*, a compound described herein and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, *e.g.* a compound described herein and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.*, administration of three or more active ingredients.

[0130] The term “pharmaceutically acceptable” denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use. “Pharmaceutically acceptable” can refer a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, *e.g.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0131] The terms “pharmaceutically acceptable excipient”, “pharmaceutically acceptable carrier”, “pharmaceutically acceptable vehicle” and “therapeutically inert excipient” can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents, excipients, preservatives or lubricants used in formulating

pharmaceutical products

[0132] The term "base editing" and "base correction" are used interchangeably to indicate a base change or mutation at a target sequence within the target gene leading to base modification. In certain embodiments, base editing occurs at a single base of the target sequence. In preferred embodiments, base editing does not involve double strand breaks of the target sequence.

[0133] As used herein, the term "siRNA" refers to an agent that mediates the targeted cleavage of an RNA transcript. These agents associate with a cytoplasmic multi-protein complex known as RNAi-induced silencing complex (RISC). Agents that are effective in inducing RNA interference are also referred to as siRNA, RNAi agent, or iRNA agent, herein. As used herein, the term siRNA includes microRNAs and pre-microRNAs. As used herein, the terms "siRNA activity" and "RNAi activity" refer to gene silencing by an siRNA.

[0134] The term "2'-O-methoxyethyl" (also 2'-MOE, 2'-O(CH₂)₂—OCH₃ and 2'-O-(2-methoxyethyl)) refers to an O-methoxy-ethyl modification of the 2' position of a furosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

[0135] The term "2'-O-methoxyethyl nucleotide" means a nucleotide comprising a 2'-O-methoxyethyl modified sugar moiety.

[0136] The term "5-methylcytosine" means a cytosine modified with a methyl group attached to the 5' position. A 5-methylcytosine is a modified nucleobase.

[0137] The term "oxo" refers to the =O substituent.

[0138] The term "alkyl" refers to a straight or branched hydrocarbon chain radical, having from one to twenty carbon atoms, and which is attached to the rest of the molecule by a single bond. An alkyl comprising up to 10 carbon atoms is referred to as a C₁-C₁₀ alkyl, likewise, for example, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl. Alkyls (and other moieties defined herein) comprising other numbers of carbon atoms are represented similarly. Alkyl groups include, but are not limited to, C₁-C₁₀ alkyl, C₁-C₉ alkyl, C₁-C₈ alkyl, C₁-C₇ alkyl, C₁-C₆ alkyl, C₁-C₅ alkyl, C₁-C₄ alkyl, C₁-C₃ alkyl, C₁-C₂ alkyl, C₂-C₈ alkyl, C₃-C₈ alkyl and C₄-C₈ alkyl. Representative alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*i*-propyl), *n*-butyl, *i*-butyl, *s*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, 1-ethyl-propyl, and the like. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, the alkyl is -CH(CH₃)₂ or -C(CH₃)₃. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below. "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group. In some embodiments, the alkylene is -CH₂-, -CH₂CH₂-, or -CH₂CH₂CH₂-. In some embodiments, the alkylene is -CH₂-. In some embodiments, the alkylene is -CH₂CH₂-. In some embodiments, the

alkylene is $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

[0139] The term “alkoxy” refers to a radical of the formula $-\text{OR}$ where R is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below. Representative alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy. In some embodiments, the alkoxy is methoxy. In some embodiments, the alkoxy is ethoxy.

[0140] The term “alkylamino” refers to a radical of the formula $-\text{NHR}$ or $-\text{NRR}$ where each R is, independently, an alkyl radical as defined above. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted as described below.

[0141] The term “alkenyl” refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula $-\text{C}(\text{R})=\text{CR}_2$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include $-\text{CH}=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{CH}=\text{CHCH}_3$, $-\text{C}(\text{CH}_3)=\text{CHCH}_3$, and $-\text{CH}_2\text{CH}=\text{CH}_2$. Depending on the structure, an alkenyl group can be monovalent or divalent (*i.e.*, an alkenylene group).

[0142] The term “alkynyl” refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. Accordingly, “alkynylene” can refer to a divalent alkynyl group. In one embodiment, an alkenyl group has the formula $-\text{C}\equiv\text{C}-\text{R}$, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non-limiting examples of an alkynyl group include $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, $-\text{C}\equiv\text{CCH}_2\text{CH}_3$, $-\text{CH}_2\text{C}\equiv\text{CH}$.

[0143] The term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthyl. In some embodiments, the aryl is phenyl. Depending on the structure, an aryl group can be monovalent or divalent (*i.e.*, an “arylene” group). Unless stated otherwise specifically in the specification, the term “aryl” or the prefix “ar-” (such as in “aralkyl”) is meant to include aryl radicals that are optionally substituted. In some embodiments, an aryl group is partially reduced to form a cycloalkyl group defined herein. In some embodiments, an aryl group is fully reduced to form a cycloalkyl group defined herein. In some embodiments, an aryl group is a C_6 - C_{14} aryl. In some embodiments, an aryl group is a C_6 - C_{10} aryl.

[0144] The term “cycloalkyl” refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (*i.e.* skeletal atoms) is a carbon atom. In some embodiments,

cycloalkyls are saturated or partially unsaturated. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, or from three to five carbon atoms. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, the monocyclic cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl or cyclohexenyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl. Polycyclic radicals include, for example, adamantyl, 1,2-dihydronaphthalenyl, 1,4-dihydronaphthalenyl, tetralinyl, decalinyl, 3,4-dihydronaphthalenyl-1(2H)-one, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted. Depending on the structure, a cycloalkyl group can be monovalent or divalent (i.e., a cycloalkylene group).

[0145] The term “haloalkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl. The term “perhaloalkyl” denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms.

[0146] The term “heteroalkylene” refers to an alkyl radical as described above where one or more carbon atoms of the alkyl is replaced with a O, N or S atom. “Heteroalkylene” or “heteroalkylene chain” refers to a straight or branched divalent heteroalkyl chain linking the rest of the molecule to a radical group. Unless stated otherwise specifically in the specification, the heteroalkyl or heteroalkylene group may be optionally substituted as described below. Representative heteroalkylene groups include, but are not limited to -OCH₂CH₂O-, -OCH₂CH₂OCH₂CH₂O-, or -OCH₂CH₂OCH₂CH₂OCH₂CH₂O-.

[0147] The term “heterocycloalkyl” refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, or bicyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. The nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized. The nitrogen atom may be optionally

quaternized. The heterocycloalkyl radical is partially or fully saturated. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides and oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 12 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 1 or 2 N atoms. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 3 or 4 N atoms. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 0-2 N atoms, 0-2 O atoms, 0-2 P atoms, and 0-1 S atoms in the ring. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 1-3 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted. As used herein, the term “heterocycloalkylene” can refer to a divalent heterocycloalkyl group.

[0148] The term “heteroaryl” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. The heteroaryl is monocyclic or bicyclic. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, furazanyl, indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Illustrative examples of bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl,

thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0-6 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 4-6 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, 0-1 P atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C₁-C₉ heteroaryl. In some embodiments, monocyclic heteroaryl is a C₁-C₅ heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, a bicyclic heteroaryl is a C₆-C₉ heteroaryl. In some embodiments, a heteroaryl group is partially reduced to form a heterocycloalkyl group defined herein. In some embodiments, a heteroaryl group is fully reduced to form a heterocycloalkyl group defined herein. Depending on the structure, a heteroaryl group can be monovalent or divalent (i.e., a “heteroarylene” group).

[0149] The term “substituted,” “substituent” or the like, unless otherwise indicated, can refer to the replacement of one or more hydrogen radicals in a given structure individually and independently with the radical of a specified substituent including, but not limited to: D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄ alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄ alkyl), -C(=O)N(C₁-C₄ alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄ alkyl), -S(=O)₂N(C₁-C₄ alkyl)₂, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ fluoroalkyl, C₁-C₄ heteroalkyl, C₁-C₄ alkoxy, C₁-C₄ fluoroalkoxy, -SC₁-C₄ alkyl, -S(=O)C₁-C₄ alkyl, and -S(=O)₂(C₁-C₄ alkyl). In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -NH(cyclopropyl), -CH₃, -CH₂CH₃, -CF₃, -OCH₃, and -OCF₃. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[0150] The term “unsubstituted” means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term “one or more” means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0151] “About” means within $\pm 10\%$ of a value. For example, if it is stated, “a marker may be increased by about 50%”, it is implied that the marker may be increased between 45%-55%.

[0152] “Active pharmaceutical agent” means the substance or substances in a pharmaceutical composition that provide a therapeutic benefit when administered to an individual.

[0153] “Dosage unit” means a form in which a pharmaceutical agent is provided, e.g. pill, tablet, or other dosage unit known in the art. In certain embodiments, a dosage unit is a vial containing lyophilized antisense oligonucleotide. In certain embodiments, a dosage unit is a vial containing reconstituted antisense oligonucleotide.

[0154] “Dose” means a specified quantity of a pharmaceutical agent provided in a single administration, or in a specified time period. In certain embodiments, a dose can be administered in one, two, or more boluses, tablets, or injections. For example, in certain embodiments where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection, therefore, two or more injections can be used to achieve the desired dose. In certain embodiments, the pharmaceutical agent is administered by infusion over an extended period of time or continuously. Doses can be stated as the amount of pharmaceutical agent per hour, day, week, or month. Doses can also be stated as the mass of pharmaceutical drug product or drug substance per mass of subject tissue (e.g., mg/kg or g/kg).

[0155] “Modified internucleoside linkage” refers to a substitution or any change from a naturally occurring internucleoside bond. For example, a phosphorothioate linkage is a modified internucleoside linkage.

[0156] “Modified nucleobase” refers to any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. For example, 5-methylcytosine is a modified nucleobase. An “unmodified nucleobase” means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C), and uracil (U).

[0157] “Modified nucleoside” means a nucleoside having at least one modified sugar moiety, and/or modified nucleobase.

[0158] “Modified nucleotide” means a nucleotide having at least one modified sugar moiety, modified internucleoside linkage and/or modified nucleobase.

[0159] “Modified oligonucleotide” means an oligonucleotide comprising at least one modified nucleotide.

[0160] “Modified sugar” refers to a substitution or change from a natural sugar. For example, a 2'-O-methoxyethyl modified sugar is a modified sugar.

[0161] “Motif” means the pattern of chemically distinct regions in an antisense compound.

[0162] “Statin” means an agent that inhibits the activity of HMG-CoA reductase.

[0163] “Symptom of cardiovascular disease or disorder” means a phenomenon that arises from and accompanies the cardiovascular disease or disorder and serves as an indication of it. For example, angina; chest pain; shortness of breath; palpitations; weakness; dizziness; nausea; sweating; tachycardia; bradycardia; arrhythmia; atrial fibrillation; swelling in the lower extremities; cyanosis; fatigue; fainting; numbness of the face; numbness of the limbs; claudication or cramping of muscles; bloating of the abdomen; or fever are symptoms of cardiovascular disease or disorder.

[0164] “Target nucleic acid,” and “target sequence” refer to a nucleic acid capable of being targeted by a genome editing composition. For example, a target DNA sequence within or adjacent to the ANGPTL3 gene may be targeted by a guide nucleotide associated with a Cas9 nuclease.

[0165] Methods for detection and/or measurement of polypeptides in biological material are well known in the art and include, but are not limited to, Western-blotting, flow cytometry, ELISAs, RIAs, and various proteomics techniques. An exemplary method to measure or detect a polypeptide is an immunoassay, such as an ELISA. This type of protein quantitation can be based on an antibody capable of capturing a specific antigen, and a second antibody capable of detecting the captured antigen. Exemplary assays for detection and/or measurement of polypeptides are described in Harlow, E. and Lane, D. *Antibodies: A Laboratory Manual*, (1988), Cold Spring Harbor Laboratory Press.

[0166] Methods for detection and/or measurement of RNA in biological material are well known in the art and include, but are not limited to, Northern-blotting, RNA protection assay, RT PCR. Suitable methods are described in *Molecular Cloning: A Laboratory Manual (Fourth Edition)* By Michael R. Green, Joseph Sambrook, Peter MacCallum 2012, 2,028 pp, ISBN 978-1-936113-42-2.

[0167] A ribonucleoprotein (RNP) refers to a nucleoprotein that contains RNA. A RNP can be a complex of a ribonucleic acid and an RNA-binding protein. Such a combination can also be referred to as a protein-RNA complex. These complexes can function in a number of biological functions that include, but are not limited to, DNA replication, DNA modification, gene expression, metabolism and modification of RNA, and pre-mRNA splicing.

[0168] As used herein, the term “biomarker” or “marker” are used interchangeably to refer to any biochemical marker, serological marker, genetic marker, or other clinical or echographic characteristic that can be used to classify a sample from a patient as being associated with an pathological condition, such as a cardiovascular disease or disorder.

[0169] As used herein, the term “antibody” includes but is not limited to a population of immunoglobulin molecules, which can be polyclonal or monoclonal and of any class and isotype, or a fragment of an immunoglobulin molecule. There are five major classes of immunoglobulins:

IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 (human), IgA2 (human), IgAa (canine), IgAb (canine), IgAc (canine), and IgAd (canine). Such fragment generally comprises the portion of the antibody molecule that specifically binds an antigen. For example, a fragment of an immunoglobulin molecule known in the art as Fab, Fab' or F(ab')₂ is included within the meaning of the term antibody.

[0170] The term "label," as used herein, refers to a detectable compound, composition, or solid support, which can be conjugated directly or indirectly (e.g., via covalent or non-covalent means, alone or encapsulated) to a monoclonal antibody or a protein. The label may be detectable by itself (e.g., radioisotope labels, chemiluminescent dye, electrochemical labels, metal chelates, latex particles, or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable (e.g., enzymes such as horseradish peroxidase, alkaline phosphatase, and the like). The label employed in the current disclosure could be, but is not limited to alkaline phosphatase; glucose-6-phosphate dehydrogenase ("G6PDH"); horseradish peroxidase (HRP); chemiluminescers such as isoluminol, fluorescers such as fluorescein and rhodamine compounds; ribozymes; and dyes. The label may also be a specific binding molecule which itself may be detectable (e.g., biotin, avidin, streptavidin, digoxigenin, maltose, oligohistidine, e.g., hex-histidine, 2, 4-dinitrobenzene, phenylarsenate, ssDNA, dsDNA, and the like). The utilization of a label produces a signal that may be detected by means such as detection of electromagnetic radiation or direct visualization, and that can optionally be measured.

[0171] "Substantial binding" or "substantially binding" refer to an amount of specific binding or recognizing between molecules in an assay mixture under particular assay conditions. In its broadest aspect, substantial binding relates to the difference between a first molecule's incapability of binding or recognizing a second molecule, and the first molecule's capability of binding or recognizing a third molecule, such that the difference is sufficient to allow a meaningful assay to be conducted to distinguish specific binding under a particular set of assay conditions, which includes the relative concentrations of the molecules, and the time and temperature of an incubation. In another aspect, one molecule is substantially incapable of binding or recognizing another molecule in a cross-reactivity sense where the first molecule exhibits a reactivity for a second molecule that is less than 25%, e.g. less than 10%, e.g., less than 5% of the reactivity exhibited toward a third molecule under a particular set of assay conditions, which includes the relative concentration and incubation of the molecules. Specific binding can be tested using a number of widely known methods, e.g., an immunohistochemical assay, an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay (RIA), or a western blot assay.

[0172] As used herein, the term "substantially the same amino acid sequence" includes an amino acid sequence that is similar, but not identical to, the naturally-occurring amino acid sequence. For example, an amino acid sequence, e.g., polypeptide, that has substantially the same amino acid sequence as a flagellin protein can have one or more modifications such as amino acid additions, deletions, or substitutions relative to the amino acid sequence of the naturally-occurring flagellin protein, provided that the modified polypeptide retains substantially at least one biological activity of flagellin such as immunoreactivity. The "percentage similarity" between two sequences is a function of the number of positions that contain matching residues or conservative residues shared by the two sequences divided by the number of compared positions times 100. In this regard, conservative residues in a sequence is a residue that is physically or functionally similar to the corresponding reference residue, e.g., that has a similar size, shape, electric charge, chemical properties, including the ability to form covalent or hydrogen bonds, or the like.

[0173] The term "targeting moiety" refers to any molecule that provides an enhanced affinity for a selected target, e.g., a cell, cell type, tissue, organ, region of the body, or a compartment, e.g., a cellular, tissue or organ compartment. Some exemplary targeting moieties include, but are not limited to, antibodies, antigens, carbohydrate base moieties, folates, receptor ligands, carbohydrates, aptamers, integrin receptor ligands, chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL and HDL ligands.

[0174] The term "heterologous" refers to any two or more nucleic acid or polypeptide sequences that are not normally found in the same relationship to each other in nature. For instance, a heterologous nucleic acid is typically recombinantly produced, having two or more sequences, e.g., from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous polypeptide will often refer to two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[0175] As used herein, the term "fragment" includes a peptide, polypeptide or protein segment of amino acids of the full-length protein, provided that the fragment retains reactivity with at least one antibody in sera of disease patients.

[0176] An "epitope" is the antigenic determinant on a polypeptide that is recognized for binding by a paratope on antibodies specific to the polypeptide, for example, an IBD-associated antibody.

[0177] The term "clinical factor" includes a symptom in a patient that is associated with a disease. Examples of clinical factors for cardiovascular disease include, without limitation, , angina; chest pain; shortness of breath; palpitations; weakness; dizziness; nausea; sweating; tachycardia; bradycardia; arrhythmia; atrial fibrillation; swelling in the lower extremities; cyanosis;

fatigue; fainting; numbness of the face; numbness of the limbs; claudication or cramping of muscles; bloating of the abdomen; or fever. In some embodiments, a diagnosis of a cardiovascular disease is based upon a combination of analyzing the presence or level of one or more markers in a patient using statistical algorithms and determining whether the patient has one or more clinical factors.

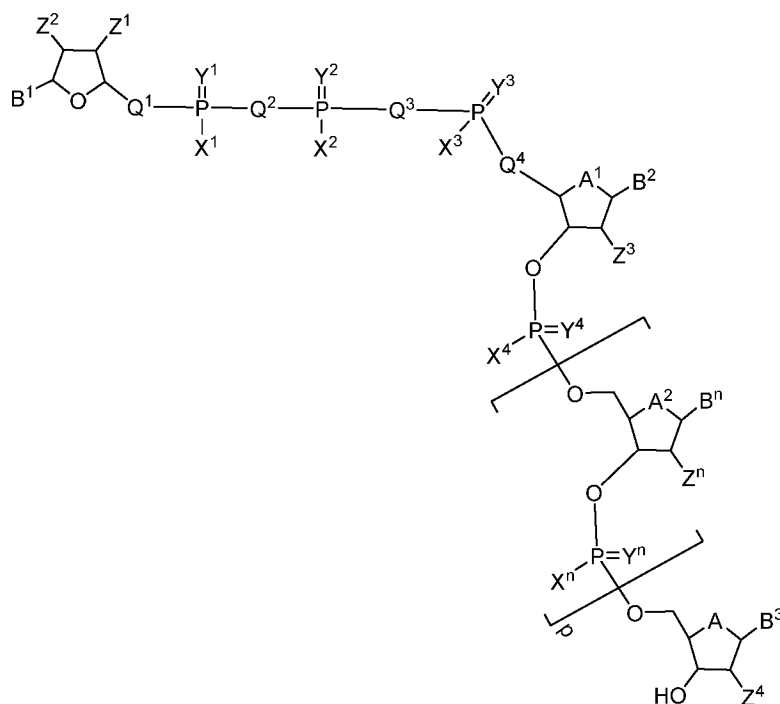
[0178] The term "prognosis" includes a prediction of the probable course and outcome of a pathological condition, for example a cardiovascular disease, or the likelihood of recovery from the disease. In some embodiments, the use of statistical algorithms provides a prognosis of cardiovascular disease in a patient. For example, the prognosis can be surgery, development of one or more clinical factors, development of intestinal cancer, or recovery from the disease.

[0179] The term "CRISPR-Cas system" referred herein includes a CRISPR-associated protein translated from an mRNA encoding the said protein and a single guide RNA. In some embodiments, the CRISPR-associated protein may have inherent endonucleolytic activity. In some embodiments, the CRISPR-Cas system facilitate guide RNA mediated gene alteration. protein or proteins produced from protein-encoded mRNA can facilitate base or nucleobase and/or gene editing within a targeted segment of a gene of interest.

[0180] Provided herein are methods and compositions for targeted delivery of therapeutic agents such as nucleic acid agents. The therapeutic agents as used herein may be connected to or associated with a targeting moiety to assist targeted delivery. For example, the therapeutic agent and the targeting moiety may form a conjugate. The therapeutic agent may comprise a nucleic acid guided programmable nuclease system complexed with nucleic acids, such as guide RNAs. In some embodiments, the guide RNAs may be chemically modified. In some embodiments, the modified guide RNAs can be used for the preparation of a medicament for the treatment of any disease, disorder or condition relating to a gene where the gene may be altered, manipulated, edited, and modified by insertion or deletion of DNA. According to a further aspect of the disclosure, the modified guide RNA may be used for altering genes by deleting, substituting, repairing or inserting on or more nucleotide or a segment of DNA. This can be done in microorganisms, or animals, in particular mammals and more particularly in humans. Human cells or tissue may be genetically altered or amended using the guide RNAs of the present disclosure and the CRISPR/Cas system known in the art in vitro and then inserted back into the patient in need thereof. In another aspect of the disclosure there is provided a pharmaceutical composition comprising a modified guide RNA according to the disclosure and a CRISPR-Cas system and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may include a vector or a cell with the modified guide RNA of the disclosure.

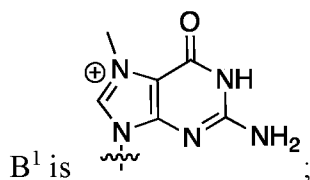
Compounds

[0181] In one aspect, described herein is an IVT mRNA sequence initiator of Formula (I) or a salt or solvate thereof:



Formula (I)

wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃;

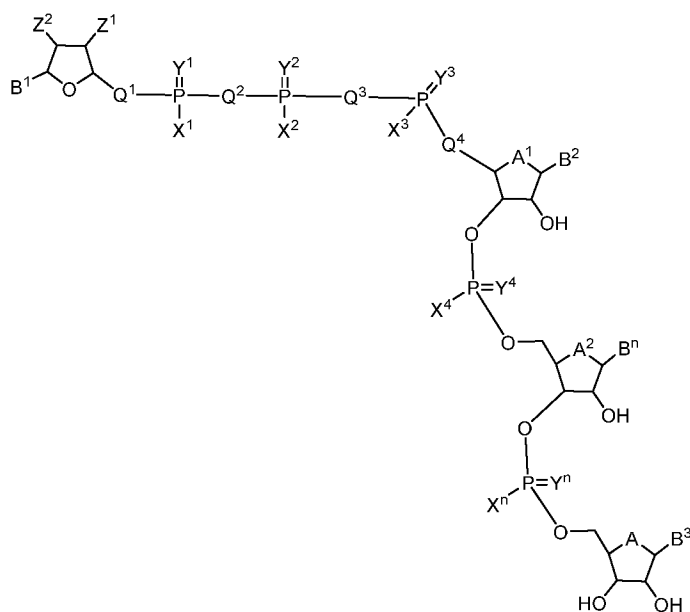
each Y¹, Y², Y³, Y⁴, and Yⁿ is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

$p = 0, 1, 2, 3, 4, 5$ or 6 ,

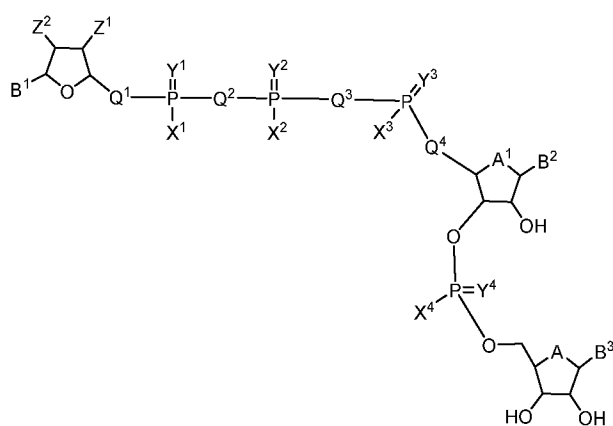
provided that (i) Z^1 , Z^2 , and Z^3 are hydrogen; (ii) Q^1 and Q^4 are $-\text{CH}_2\text{O}-$; (iii) Q^2 and Q^3 are oxygen; (iv) at least one of X^1 , X^2 , X^3 , X^4 , and X^n is $-\text{SH}$ or $-\text{S}^-$; (v) at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is $=\text{S}$; or (vi) at least one of A , A^1 , and A^2 is $-\text{S}-$.

[0182] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-a):



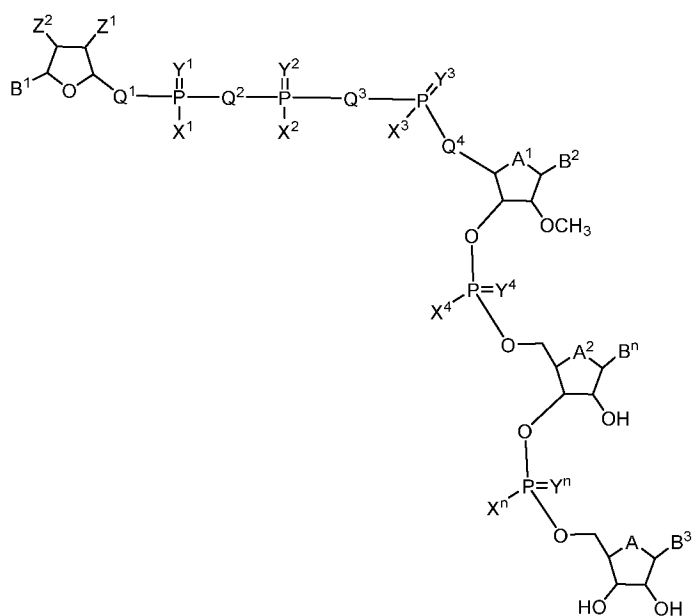
Formula (I-a).

[0183] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-b):



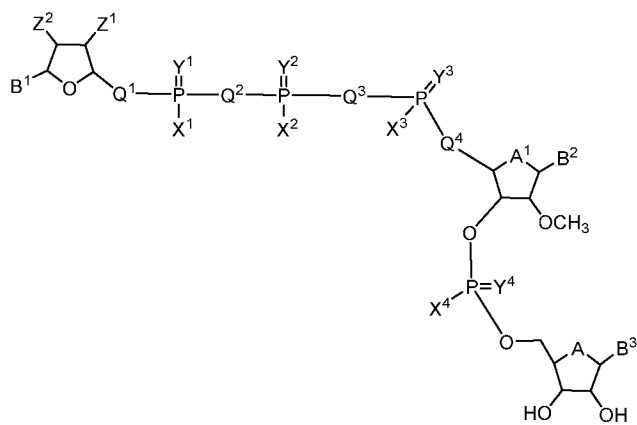
Formula (I-b).

[0184] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-c):



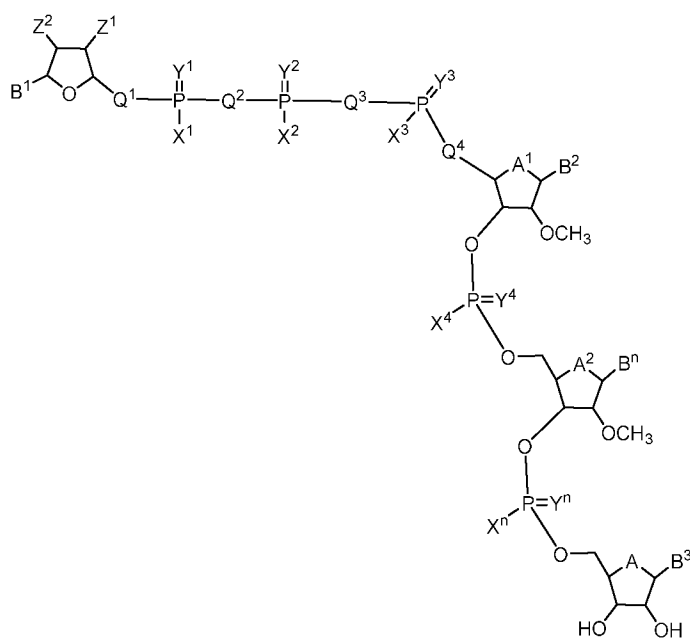
Formula (I-c).

[0185] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-d):



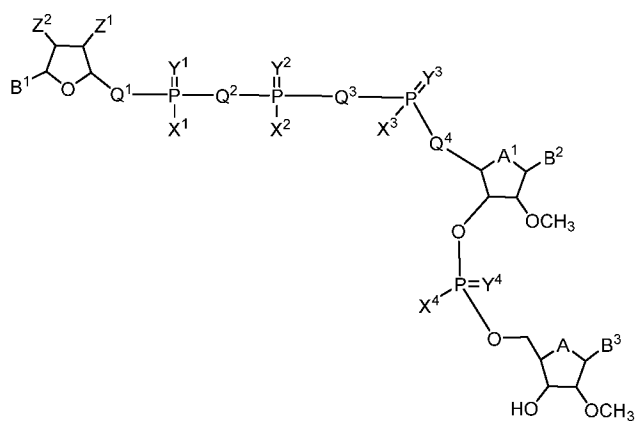
Formula (I-d).

[0186] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-e):



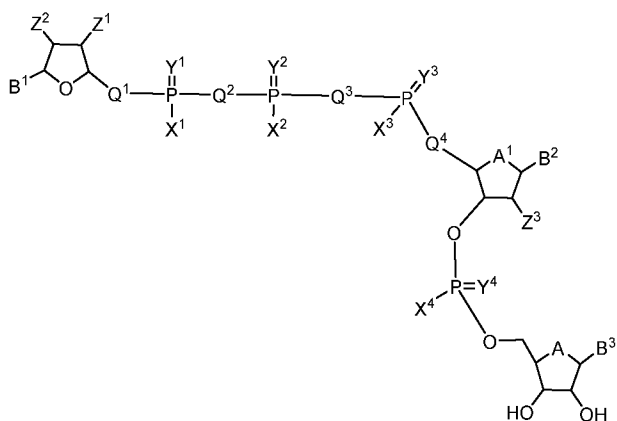
Formula (I-e).

[0187] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-f):



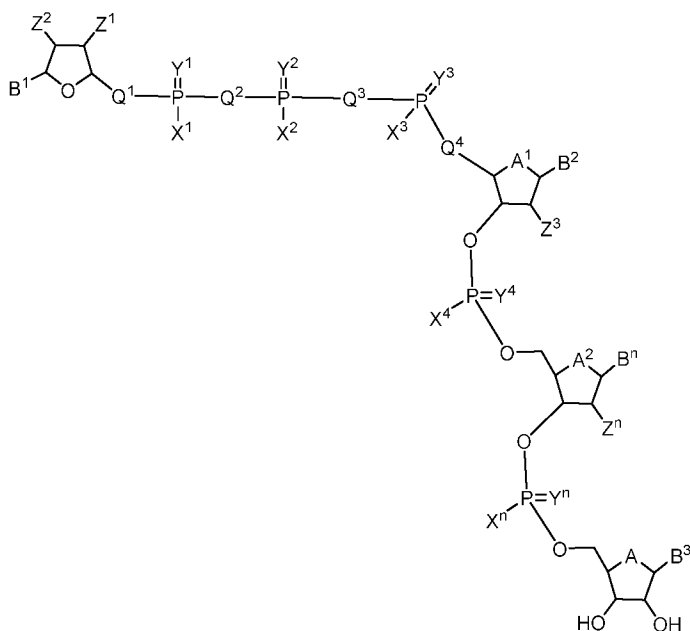
Formula (I-f).

[0188] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-g):



Formula (I-g).

[0189] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (I-h):



Formula (I-h).

[0190] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Z^1 is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z^1 is hydrogen. In some embodiments, Z^1 is F. In some embodiments, Z^1 is -OH. In some embodiments, Z^1 is -SH. In some embodiments, Z^1 is -CH₃. In some embodiments, Z^1 is -CH₂CH₃. In some embodiments, Z^1 is -OCH₃. In some embodiments, Z^1 is -OCH₂CH₃. In some embodiments, Z^1 is -SCH₃. In some embodiments, Z^1 is -NH₂. In some embodiments, Z^1 is NHCH₃. In some embodiments, Z^1 is NHC(=O)CH₃.

[0191] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-a), (I-d), (I-e), (I-f), (I-g) or (I-h), Z^2 is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z^2 is hydrogen. In some embodiments, Z^2 is F. In some embodiments, Z^2 is -OH. In some embodiments, Z^2 is -SH. In some embodiments, Z^2 is -CH₃. In some embodiments, Z^2 is -CH₂CH₃. In some embodiments, Z^2 is -OCH₃. In some embodiments, Z^2 is -OCH₂CH₃. In some embodiments, Z^2 is -SCH₃. In some embodiments, Z^2 is -NH₂. In some embodiments, Z^2 is NHCH₃. In some embodiments, Z^2 is NHC(=O)CH₃.

[0192] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Z^3 is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z^3 is hydrogen. In some embodiments, Z^3 is fluorine. In some embodiments, Z^3 is -OH. In some embodiments, Z^3 is -SH. In some embodiments, Z^3 is -CH₃. In some embodiments, Z^3 is -CH₂CH₃. In some embodiments, Z^3 is -OCH₂OCH₃. In some embodiments, Z^3 is -OCH₂CH₂CH₃. In some embodiments, Z^3 is -OCH(CH₃)₂. In some embodiments, Z^3 is -SCH₃. In some embodiments, Z^3 is -OCH₂CH₂OCH₃.

[0193] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Z^4 is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z^4 is hydrogen. In some embodiments, Z^4 is fluorine. In some embodiments, Z^4 is -OH. In some embodiments, Z^4 is -SH. In some embodiments, Z^4 is -CH₃. In some embodiments, Z^4 is -CH₂CH₃. In some embodiments, Z^4 is -OCH₂OCH₃. In some embodiments, Z^4 is -OCH₂CH₂CH₃. In some embodiments, Z^4 is -OCH(CH₃)₂. In some embodiments, Z^4 is -SCH₃. In some embodiments, Z^4 is -OCH₂CH₂OCH₃.

[0194] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Z^n is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z^n is hydrogen. In some embodiments, Z^n is fluorine. In some embodiments, Z^n is -OH. In some embodiments, Z^n is -SH. In some embodiments, Z^n is -CH₃. In some embodiments, Z^n is -CH₂CH₃. In some embodiments, Z^n is -OCH₂OCH₃. In some embodiments, Z^n is -OCH₂CH₂CH₃. In some embodiments, Z^n is -OCH(CH₃)₂. In some embodiments, Z^n is -SCH₃. In some embodiments, Z^n is -OCH₂CH₂OCH₃.

[0195] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), B^2 is independently a natural, a modified, or an unnatural nucleobase. In some embodiments B^2 is guanine. In some embodiments B^2 is adenine. In some embodiments, B^2 is cytosine. In some embodiments, B^2 is uracil, In some embodiments, B^2 is thymine, In some embodiments, B^2 is hypoxanthine. In some embodiments, B^2 is purine.

[0196] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), B^3 is independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B^3 is guanine. In some embodiments, B^3 is adenine. In some embodiments, B^3 is cytosine. In some embodiments, B^3 is uracil, In some embodiments, B^3 is thymine, In some embodiments, B^3 is hypoxanthine. In some embodiments, B^3 is purine.

[0197] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), B^n is independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B^n is guanine. In some embodiments, B^n is adenine. In some embodiments, B^n is cytosine. In some embodiments, B^n is uracil, In some embodiments, B^n is thymine, In some embodiments, B^n is hypoxanthine. In some embodiments, B^n is purine.

[0198] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), at least one of B^2 , B^3 , and B^n is adenine. In some embodiments, at least one of B^2 , B^3 ,

and Bⁿ is guanine. In some embodiments B² is adenine. In some embodiments, B³ is adenine

[0199] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Q¹ is -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q¹ is -CH₂-. In some embodiments, Q¹ is -CH=CH-. In some embodiments, Q¹ is -CH₂O-. In some embodiments, Q¹ is -CH₂S-. In some embodiments, Q¹ is -CH₂CH₂-. In some embodiments, Q¹ is -CH₂CF₂-. In some embodiments, Q¹ is -CH₂NH₂-. In some embodiments, Q¹ is -CH₂NH(CH₃)-. In some embodiments, Q¹ is -CH₂N(C(=O)CH₃)-. In some

[0200] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Q⁴ is -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q⁴ is -CH₂-. In some embodiments, Q⁴ is -CH=CH-. In some embodiments, Q⁴ is -CH₂O-. In some embodiments, Q⁴ is -CH₂S-. In some embodiments, Q⁴ is -CH₂CH₂-. In some embodiments, Q⁴ is -CH₂CF₂-. In some embodiments, Q⁴ is -CH₂NH₂-. In some embodiments, Q⁴ is -CH₂NH(CH₃)-. In some embodiments, Q⁴ is -CH₂N(C(=O)CH₃)-. In some

[0201] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Q² is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments, Q² is -O-. In some embodiments, Q² is -S-. In some embodiments, Q² is -CH₂-. In some embodiments, Q² is -CF₂-. In some embodiments, Q² is -NH-. In some embodiments, Q² is -N(CH₃)-. In some embodiments, Q² is -N(C(=O)CH₃)-. In some

[0202] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Q³ is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments, Q³ is -O-. In some embodiments, Q³ is -S-. In some embodiments, Q³ is -CH₂-. In some embodiments, Q³ is -CF₂-. In some embodiments, Q³ is -NH-. In some embodiments, Q³ is -N(CH₃)-. In some embodiments, Q³ is -N(C(=O)CH₃)-. In some

[0203] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), X¹ is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X¹ is -OH. In some embodiments, X¹ is -SH. In some embodiments, X¹ is -O⁻. In some embodiments, X¹ is -S⁻. In some embodiments, X¹ is -NH₂. In some embodiments, X¹ is -NHCH₃. In some embodiments, X¹ is -NH(C(=O)CH₃). In some embodiments, X¹ is -CH₃. In some embodiments, X¹ is -CH₂CH₃. In some embodiments, X¹ is -CH₂CH₂CH₃. In some embodiments, X¹ is -CH(CH₃)₂. In some embodiments, X¹ is -OCH₃. In some embodiments, X¹ is -OCH₂CH₃.

[0204] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f),

(I-g) or (I-h), X^2 is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X^2 is -OH. In some embodiments, X^2 is -SH. In some embodiments, X^2 is -O⁻. In some embodiments, X^2 is -S⁻. In some embodiments, X^2 is -NH₂. In some embodiments, X^2 is -NHCH₃. In some embodiments, X^2 is -NH(C(=O)CH₃). In some embodiments, X^2 is -CH₃. In some embodiments, X^2 is -CH₂CH₃. In some embodiments, X^2 is -CH₂CH₂CH₃. In some embodiments, X^2 is -CH(CH₃)₂. In some embodiments, X^2 is -OCH₃. In some embodiments, X^2 is -OCH₂CH₃.

[0205] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), X^3 is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X^3 is -OH. In some embodiments, X^3 is -SH. In some embodiments, X^3 is -O⁻. In some embodiments, X^3 is -S⁻. In some embodiments, X^3 is -NH₂. In some embodiments, X^3 is -NHCH₃. In some embodiments, X^3 is -NH(C(=O)CH₃). In some embodiments, X^3 is -CH₃. In some embodiments, X^3 is -CH₂CH₃. In some embodiments, X^3 is -CH₂CH₂CH₃. In some embodiments, X^3 is -CH(CH₃)₂. In some embodiments, X^3 is -OCH₃. In some embodiments, X^3 is -OCH₂CH₃.

[0206] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), X^4 is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X^4 is -OH. In some embodiments, X^4 is -SH. In some embodiments, X^4 is -O⁻. In some embodiments, X^4 is -S⁻. In some embodiments, X^4 is -NH₂. In some embodiments, X^4 is -NHCH₃. In some embodiments, X^4 is -NH(C(=O)CH₃). In some embodiments, X^4 is -CH₃. In some embodiments, X^4 is -CH₂CH₃. In some embodiments, X^4 is -CH₂CH₂CH₃. In some embodiments, X^4 is -CH(CH₃)₂. In some embodiments, X^4 is -OCH₃. In some embodiments, X^4 is -OCH₂CH₃.

[0207] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), X^n is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X^n is -OH. In some embodiments, X^n is -SH. In some embodiments, X^n is -O⁻. In some embodiments, X^n is -S⁻. In some embodiments, X^n is -NH₂. In some embodiments, X^n is -NHCH₃. In some embodiments, X^n is -NH(C(=O)CH₃). In some embodiments, X^n is -CH₃. In some embodiments, X^n is -CH₂CH₃. In some embodiments, X^n is -CH₂CH₂CH₃. In some embodiments, X^n is -CH(CH₃)₂. In some embodiments, X^n is -OCH₃. In some embodiments, X^n is -OCH₂CH₃.

[0208] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Y^1 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^1 is =O. In some embodiments, Y^1 is =S. In some embodiments, Y^1 is =NH. In some embodiments, Y^1 is =NHCH₃.

[0209] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Y^2 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^2 is =O. In some embodiments, Y^2 is =S. In some embodiments, Y^2 is =NH. In some embodiments, Y^2 is =NHCH₃.

[0210] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Y^3 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^3 is =O. In some embodiments, Y^3 is =S. In some embodiments, Y^3 is =NH. In some embodiments, Y^3 is =NHCH₃.

[0211] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Y^4 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^4 is =O. In some embodiments, Y^4 is =S. In some embodiments, Y^4 is =NH. In some embodiments, Y^4 is =NHCH₃.

[0212] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), Y^n is =O, =S, =NH, or =NCH₃. In some embodiments, Y^n is =O. In some embodiments, Y^n is =S. In some embodiments, Y^n is =NH. In some embodiments, Y^n is =NHCH₃.

[0213] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), A is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A is -O-. In some embodiments, A is -S-. In some embodiments, A is -CH₂-. In some embodiments, A is -NH-. In some embodiments, A is -N(CH₃)-. In some embodiments, A is -N(C(=O)CH₃)-.

[0214] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), A^1 is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A^1 is -O-. In some embodiments, A^1 is -S-. In some embodiments, A^1 is -CH₂-. In some embodiments, A^1 is -NH-. In some embodiments, A^1 is -N(CH₃)-. In some embodiments, A^1 is -N(C(=O)CH₃)-.

[0215] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), A^2 is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A^2 is -O-. In some embodiments, A^2 is -S-. In some embodiments, A^2 is -CH₂-. In some embodiments, A^2 is -NH-. In some embodiments, A^2 is -N(CH₃)-. In some embodiments, A^2 is -N(C(=O)CH₃)-.

[0216] In some embodiments of a compound of Formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h), p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6.

[0217] In some embodiments of a compound of Formula (I), at least one of X^1 , X^2 , X^3 , X^4 , and X^n is -SH.

[0218] In some embodiments of a compound of Formula (I), at least one of X^1 , X^2 , X^3 , X^4 , and X^n is -S-.

[0219] In some embodiments of a compound of Formula (I), at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S.

[0220] In some embodiments of a compound of Formula (I), at least one of A, A¹, and A² is -S-.

[0221] In some embodiments of a compound of Formula (I), at least one of Z¹, Z², Z³, Z⁴, and Zⁿ is -OCH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z³ and Z¹ are -OCH₃. In some embodiments of a compound of Formula (I), at least one of Z¹, Z², Z³, Z⁴, and Zⁿ is -OH. In some embodiments, Z¹, Z², and Z⁴ are -OH. In some embodiments, Z² and Z⁴ are -OH.

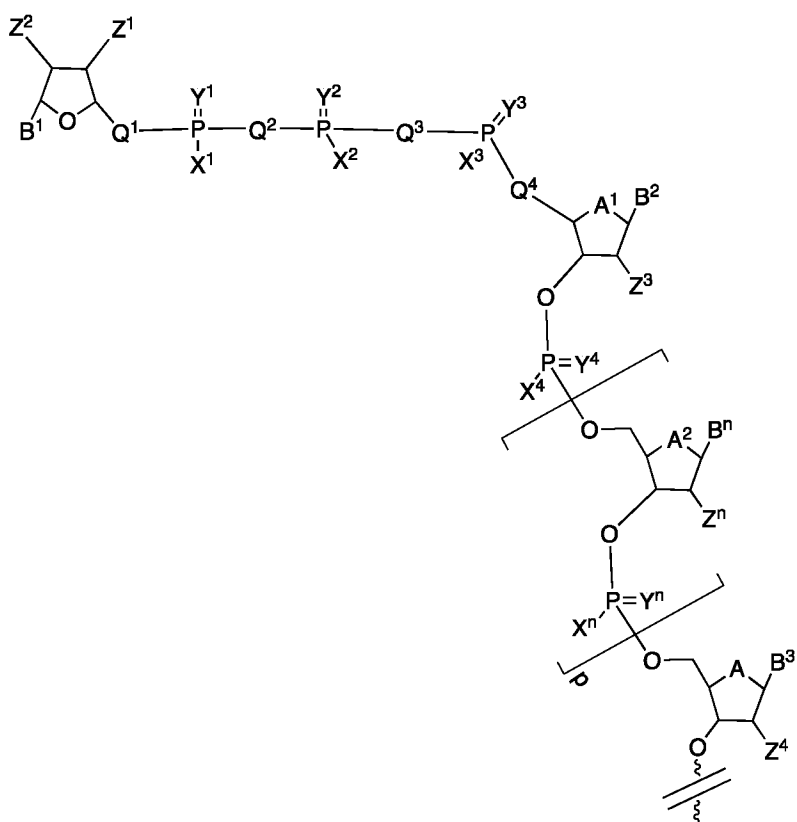
[0222] In some embodiments of a compound of Formula (I), at least one of Q¹, Q², Q³, and Q⁴ is -OCH₃. In some embodiments of a compound of Formula (I), at least one of Q¹, Q², Q³, and Q⁴ is -O-. In some embodiments, Q¹ and Q⁴ are -OCH₃. In some embodiments, Q² and Q³ are -O-.

[0223] In some embodiments of a compound of Formula (I), at least one of Y¹, Y², Y³, Y⁴, and Yⁿ is =O. In some embodiments, Y¹, Y², Y³, and Y⁴ are =O. In some embodiments, Y¹, Y², Y³, Y⁴, and Yⁿ is =S. In some embodiments, Y² is =S. In some embodiments, Y⁴ is =S.

[0224] In some embodiments of a compound of Formula (I), at least one of X¹, X², X³, X⁴, and Xⁿ is -O-. In some embodiments, X¹, X², X³, and X⁴ are -O-. In some embodiments, X¹ is -S-. In some embodiments, X² is -S-. In some embodiments, X³ is -S-. In some embodiments, X⁴ is -S-.

[0225] In some embodiments of a compound of Formula (I), In some embodiments of a compound of Formula (I), at least one of A, A¹, and A² is -O-. In some embodiments, A, A¹, and A² are -O-.

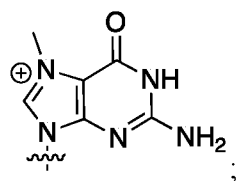
[0226] In one aspect, described herein is a mRNA sequence having a 5'-end region motif of Motif (I'):



Motif (I')

[0227]

[0228] wherein

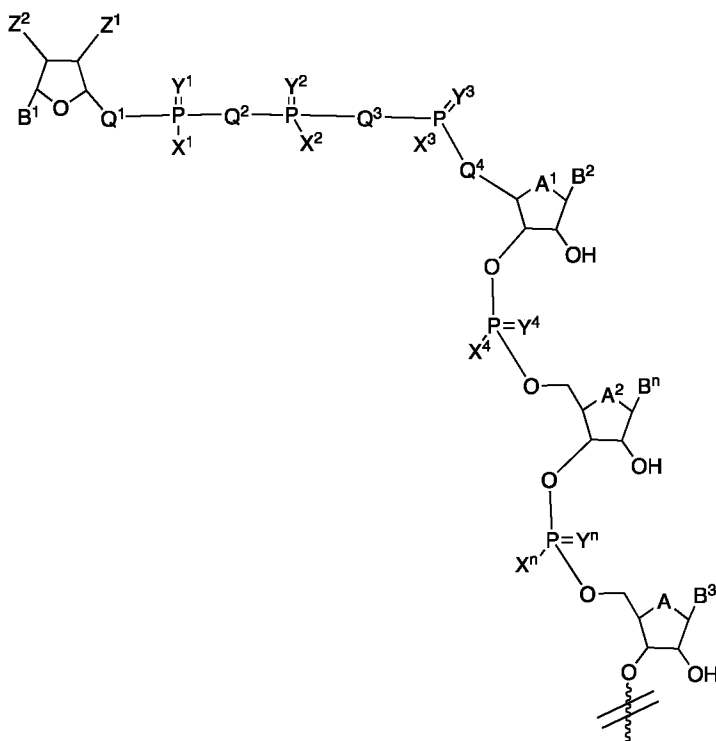
[0229] B¹ is[0230] each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;[0231] each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;[0232] each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;[0233] each Q¹ and Q⁴ is independently -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-[0234] each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-[0235] each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃;[0236] each Y¹, Y², Y³, Y⁴, and Yⁿ is independently =O, =S, =NH, or =NCH₃;[0237] each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)-, or -

$\text{N}(\text{C}(=\text{O})\text{CH}_3)-$; and

[0238] $p = 0, 1, 2, 3, 4, 5$ or 6 ,

[0239] provided that (i) Z^1, Z^2 , and Z^3 are hydrogen; (ii) Q^1 and Q^4 are $-\text{CH}_2\text{O}-$; (iii) Q^2 and Q^3 are oxygen; (iv) at least one of X^1, X^2, X^3, X^4 , and X^n is $-\text{SH}$ or $-\text{S}^-$; (v) at least one of Y^1, Y^2, Y^3, Y^4 , and Y^n is $=\text{S}$; or (vi) at least one of A, A^1 , and A^2 is $-\text{S}-$.

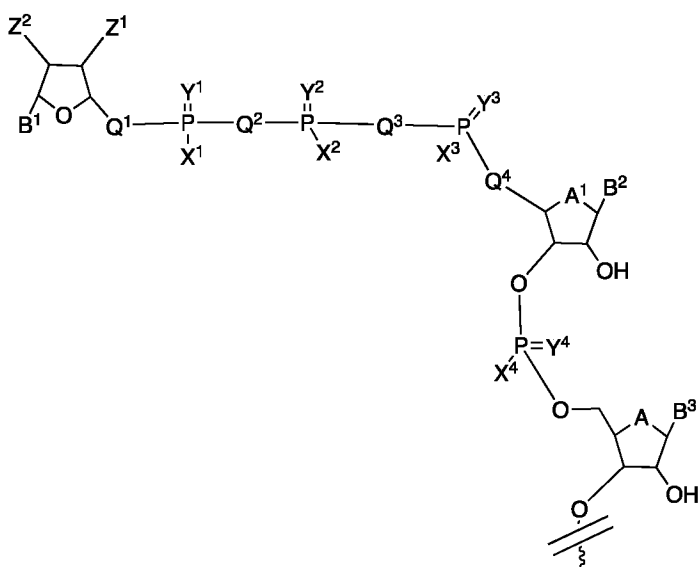
[0240] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-a):



Motif (I'-a)

[0241]

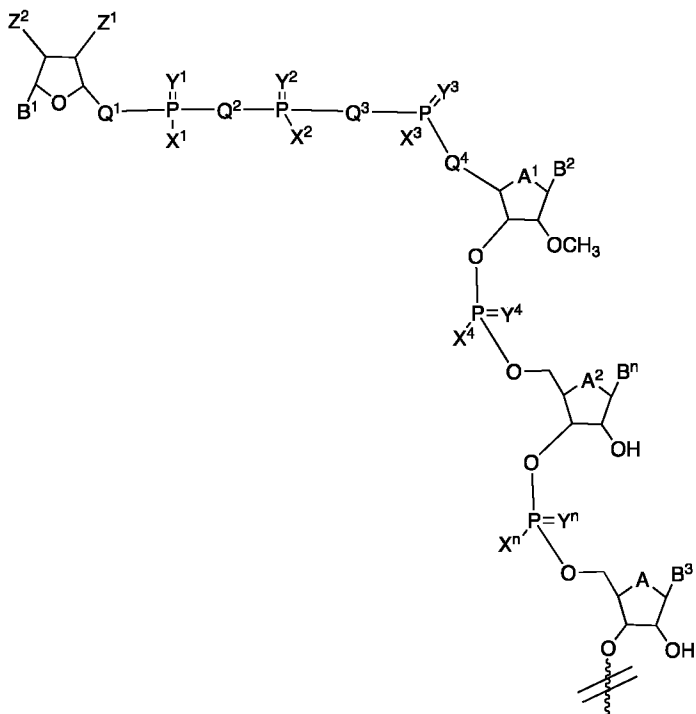
[0242] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-b):



Motif (I'-b)

[0243]

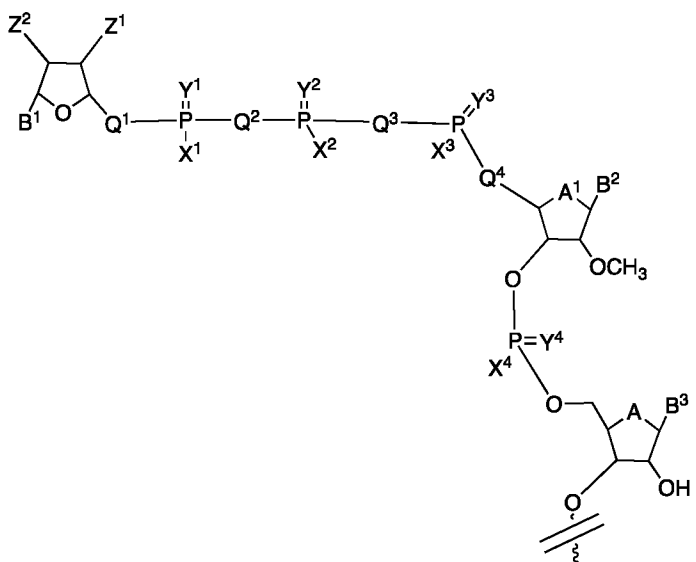
[0244] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-c):



[0245]

Motif (I'-c)

[0246] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-d):

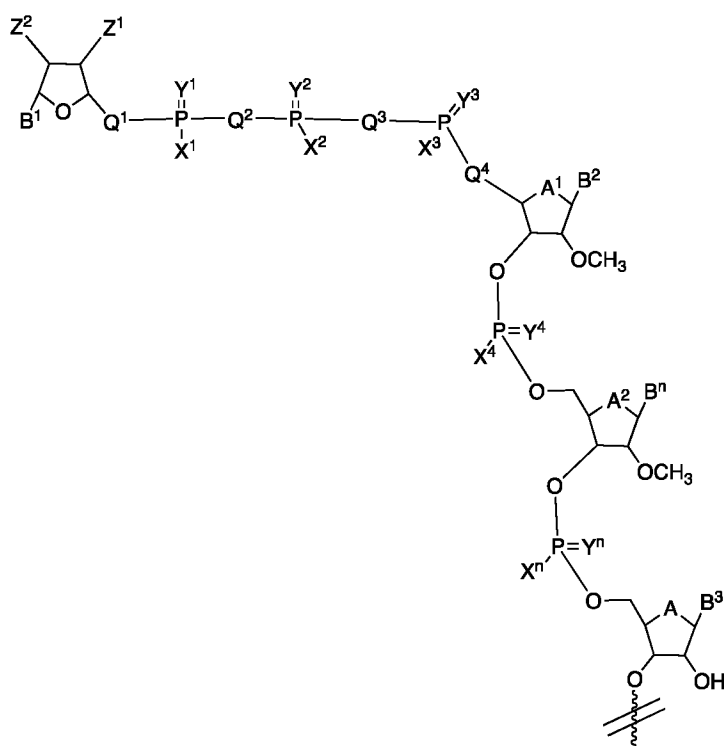


[0247]

Motif (I'-d)

[0248]

[0249] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-e):

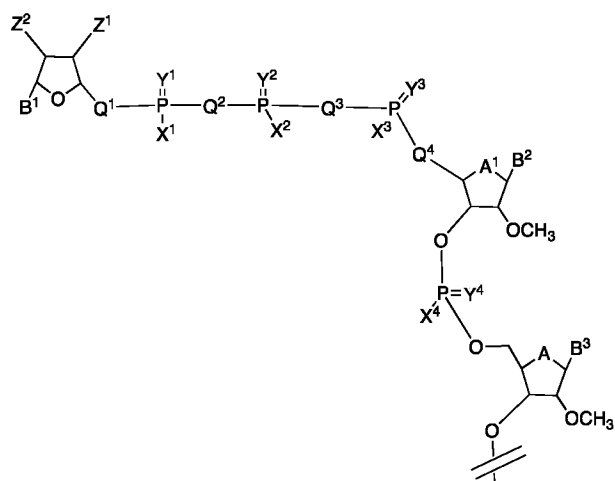


Motif (I'-e)

[0250]

[0251]

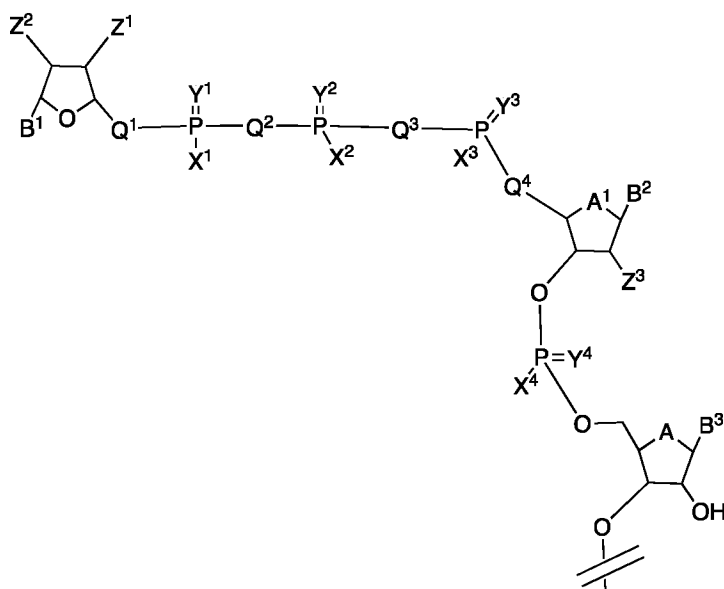
[0252] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-f):



Motif (I'-f)

[0253]

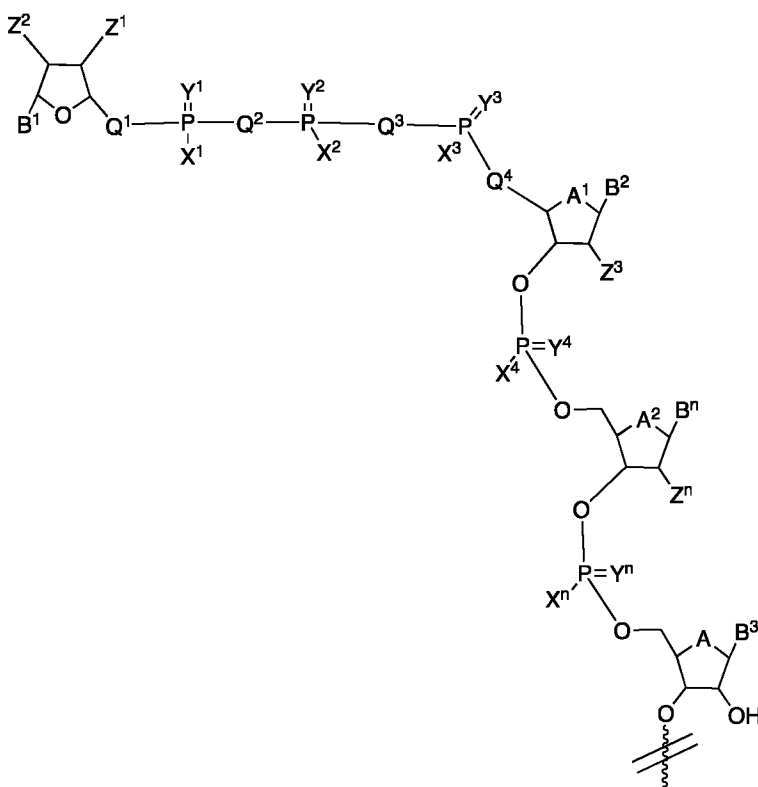
[0254] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-g):



[0255]

Motif (I'-g)

[0256] In some embodiments, the mRNA sequence having a 5'-end region motif has a structure of Motif (I'-h):



[0257]

Motif (I'-h)

[0258] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Z¹ is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z¹ is hydrogen. In some embodiments, Z¹ is F. In some embodiments, Z¹ is -OH. In some embodiments, Z¹ is -SH. In some embodiments, Z¹ is -CH₃. In some embodiments, Z¹ is -CH₂CH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments, Z¹ is -OCH₂CH₃. In some embodiments, Z¹ is -SCH₃. In some

embodiments, Z^1 is $-\text{NH}_2$. In some embodiments, Z^1 is NHCH_3 . In some embodiments, Z^1 is $\text{NHC}(=\text{O})\text{CH}_3$.

[0259] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Z^2 is hydrogen, fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SCH}_3$, $-\text{NH}_2$, NHCH_3 , or $\text{NHC}(=\text{O})\text{CH}_3$. In some embodiments, Z^2 is hydrogen. In some embodiments, Z^2 is F. In some embodiments, Z^2 is $-\text{OH}$. In some embodiments, Z^2 is $-\text{SH}$. In some embodiments, Z^2 is $-\text{CH}_3$. In some embodiments, Z^2 is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z^2 is $-\text{OCH}_3$. In some embodiments, Z^2 is $-\text{OCH}_2\text{CH}_3$. In some embodiments, Z^2 is $-\text{SCH}_3$. In some embodiments, Z^2 is $-\text{NH}_2$. In some embodiments, Z^2 is NHCH_3 . In some embodiments, Z^2 is $\text{NHC}(=\text{O})\text{CH}_3$.

[0260] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Z^3 is hydrogen, fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{SCH}_3$, or $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, Z^3 is hydrogen. In some embodiments, Z^3 is fluorine. In some embodiments, Z^3 is $-\text{OH}$. In some embodiments, Z^3 is $-\text{SH}$. In some embodiments, Z^3 is $-\text{CH}_3$. In some embodiments, Z^3 is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z^3 is $-\text{OCH}_2\text{OCH}_3$. In some embodiments, Z^3 is $-\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, Z^3 is $-\text{OCH}(\text{CH}_3)_2$. In some embodiments, Z^3 is $-\text{SCH}_3$. In some embodiments, Z^3 is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$.

[0261] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Z^4 is hydrogen, fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{SCH}_3$, or $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, Z^4 is hydrogen. In some embodiments, Z^4 is fluorine. In some embodiments, Z^4 is $-\text{OH}$. In some embodiments, Z^4 is $-\text{SH}$. In some embodiments, Z^4 is $-\text{CH}_3$. In some embodiments, Z^4 is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z^4 is $-\text{OCH}_2\text{OCH}_3$. In some embodiments, Z^4 is $-\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, Z^4 is $-\text{OCH}(\text{CH}_3)_2$. In some embodiments, Z^4 is $-\text{SCH}_3$. In some embodiments, Z^4 is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$.

[0262] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Z^n is hydrogen, fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{SCH}_3$, or $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, Z^n is hydrogen. In some embodiments, Z^n is fluorine. In some embodiments, Z^n is $-\text{OH}$. In some embodiments, Z^n is $-\text{SH}$. In some embodiments, Z^n is $-\text{CH}_3$. In some embodiments, Z^n is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z^n is $-\text{OCH}_2\text{OCH}_3$. In some embodiments, Z^n is $-\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, Z^n is $-\text{OCH}(\text{CH}_3)_2$. In some embodiments, Z^n is $-\text{SCH}_3$. In some embodiments, Z^n is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$.

[0263]

[0264] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), B² is independently a natural, a modified, or an unnatural nucleobase. In some embodiments B² is guanine. In some embodiments B² is adenine. In some embodiments, B² is cytosine. In some embodiments, B² is uracil, In some embodiments, B² is thymine, In some embodiments, B² is hypoxanthine. In some embodiments, B² is purine.

[0265] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), B³ is independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B³ is guanine. In some embodiments, B³ is adenine. In some embodiments, B³ is cytosine. In some embodiments, B³ is uracil, In some embodiments, B³ is thymine, In some embodiments, B³ is hypoxanthine. In some embodiments, B³ is purine.

[0266] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Bⁿ is independently a natural, a modified, or an unnatural nucleobase. In some embodiments, Bⁿ is guanine. In some embodiments, Bⁿ is adenine. In some embodiments, Bⁿ is cytosine. In some embodiments, Bⁿ is uracil, In some embodiments, Bⁿ is thymine, In some embodiments, Bⁿ is hypoxanthine. In some embodiments, Bⁿ is purine.

[0267] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), at least one of B², B³, and Bⁿ is adenine. In some embodiments, at least one of B², B³, and Bⁿ is guanine. In some embodiments B² is adenine. In some embodiments, B³ is adenine

[0268] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Q¹ is -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q¹ is -CH₂-. In some embodiments, Q¹ is -CH=CH-. In some embodiments, Q¹ is -CH₂O-. In some embodiments, Q¹ is -CH₂S-. In some embodiments, Q¹ is -CH₂CH₂-. In some embodiments, Q¹ is -CH₂CF₂-. In some embodiments, Q¹ is -CH₂NH₂-. In some embodiments, Q¹ is -CH₂NH(CH₃)-. In some embodiments, Q¹ is -CH₂N(C(=O)CH₃)-. In some

[0269] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Q⁴ is -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q⁴ is -CH₂-. In some embodiments, Q⁴ is -CH=CH-. In some embodiments, Q⁴ is -CH₂O-. In some embodiments, Q⁴ is -CH₂S-. In some embodiments, Q⁴ is -CH₂CH₂-. In some embodiments, Q⁴ is -CH₂CF₂-. In some embodiments, Q⁴ is -CH₂NH₂-. In some embodiments, Q⁴ is -CH₂NH(CH₃)-. In some embodiments, Q⁴ is -CH₂N(C(=O)CH₃)-. In some

[0270] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-

f), (I'-g) or (I'-h), Q² is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments, Q² is -O-. In some embodiments, Q² is -S-. In some embodiments, Q² is -CH₂-. In some embodiments, Q² is -CF₂-. In some embodiments, Q² is -NH-. In some embodiments, Q² is -N(CH₃)-. In some embodiments, Q² is -N(C(=O)CH₃)-.

[0271] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Q³ is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments, Q³ is -O-. In some embodiments, Q³ is -S-. In some embodiments, Q³ is -CH₂-. In some embodiments, Q³ is -CF₂-. In some embodiments, Q³ is -NH-. In some embodiments, Q³ is -N(CH₃)-. In some embodiments, Q³ is -N(C(=O)CH₃).

[0272] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), X¹ is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X¹ is -OH. In some embodiments, X¹ is -SH. In some embodiments, X¹ is -O⁻. In some embodiments, X¹ is -S⁻. In some embodiments, X¹ is -NH₂. In some embodiments, X¹ is -NHCH₃. In some embodiments, X¹ is -NH(C(=O)CH₃). In some embodiments, X¹ is -CH₃. In some embodiments, X¹ is -CH₂CH₃. In some embodiments, X¹ is -CH₂CH₂CH₃. In some embodiments, X¹ is -CH(CH₃)₂. In some embodiments, X¹ is -OCH₃. In some embodiments, X¹ is -OCH₂CH₃.

[0273] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), X² is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X² is -OH. In some embodiments, X² is -SH. In some embodiments, X² is -O⁻. In some embodiments, X² is -S⁻. In some embodiments, X² is -NH₂. In some embodiments, X² is -NHCH₃. In some embodiments, X² is -NH(C(=O)CH₃). In some embodiments, X² is -CH₃. In some embodiments, X² is -CH₂CH₃. In some embodiments, X² is -CH₂CH₂CH₃. In some embodiments, X² is -CH(CH₃)₂. In some embodiments, X² is -OCH₃. In some embodiments, X² is -OCH₂CH₃.

[0274] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), X³ is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X³ is -OH. In some embodiments, X³ is -SH. In some embodiments, X³ is -O⁻. In some embodiments, X³ is -S⁻. In some embodiments, X³ is -NH₂. In some embodiments, X³ is -NHCH₃. In some embodiments, X³ is -NH(C(=O)CH₃). In some embodiments, X³ is -CH₃. In some embodiments, X³ is -CH₂CH₃. In some embodiments, X³ is -CH₂CH₂CH₃. In some embodiments, X³ is -CH(CH₃)₂. In some embodiments, X³ is -OCH₃. In some embodiments, X³ is -OCH₂CH₃.

[0275] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-

f), (I'-g) or (I'-h), X^4 is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X^4 is -OH. In some embodiments, X^4 is -SH. In some embodiments, X^4 is -O⁻. In some embodiments, X^4 is -S⁻. In some embodiments, X^4 is -NH₂. In some embodiments, X^4 is -NHCH₃. In some embodiments, X^4 is -NH(C(=O)CH₃). In some embodiments, X^4 is -CH₃. In some embodiments, X^4 is -CH₂CH₃. In some embodiments, X^4 is -CH₂CH₂CH₃. In some embodiments, X^4 is -CH(CH₃)₂. In some embodiments, X^4 is -OCH₃. In some embodiments, X^4 is -OCH₂CH₃.

[0276] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), X^n is -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃. In some embodiments, X^n is -OH. In some embodiments, X^n is -SH. In some embodiments, X^n is -O⁻. In some embodiments, X^n is -S⁻. In some embodiments, X^n is -NH₂. In some embodiments, X^n is -NHCH₃. In some embodiments, X^n is -NH(C(=O)CH₃). In some embodiments, X^n is -CH₃. In some embodiments, X^n is -CH₂CH₃. In some embodiments, X^n is -CH₂CH₂CH₃. In some embodiments, X^n is -CH(CH₃)₂. In some embodiments, X^n is -OCH₃. In some embodiments, X^n is -OCH₂CH₃.

[0277] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Y^1 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^1 is =O. In some embodiments, Y^1 is =S. In some embodiments, Y^1 is =NH. In some embodiments, Y^1 is =NHCH₃.

[0278] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Y^2 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^2 is =O. In some embodiments, Y^2 is =S. In some embodiments, Y^2 is =NH. In some embodiments, Y^2 is =NHCH₃.

[0279] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Y^3 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^3 is =O. In some embodiments, Y^3 is =S. In some embodiments, Y^3 is =NH. In some embodiments, Y^3 is =NHCH₃.

[0280] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Y^4 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^4 is =O. In some embodiments, Y^4 is =S. In some embodiments, Y^4 is =NH. In some embodiments, Y^4 is =NHCH₃.

[0281] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), Y^n is =O, =S, =NH, or =NCH₃. In some embodiments, Y^n is =O. In some embodiments, Y^n is =S. In some embodiments, Y^n is =NH. In some embodiments, Y^n is =NHCH₃.

[0282] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), A is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A is -O-. In some embodiments, A is -S-. In some embodiments, A is -CH₂-. In some embodiments, A is -NH-. In some embodiments, A is -N(CH₃)-. In some embodiments, A is -N(C(=O)CH₃)-.

[0283] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), A¹ is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A¹ is -O-. In some embodiments, A¹ is -S-. In some embodiments, A¹ is -CH₂-. In some embodiments, A¹ is -NH-. In some embodiments, A¹ is -N(CH₃)-. In some embodiments, A¹ is -N(C(=O)CH₃)-.

[0284] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), A² is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A² is -O-. In some embodiments, A² is -S-. In some embodiments, A² is -CH₂-. In some embodiments, A² is -NH-. In some embodiments, A² is -N(CH₃)-. In some embodiments, A² is -N(C(=O)CH₃)-.

[0285] In some embodiments of a compound of Motif (I'), (I'-a), (I'-b), (I'-c), (I'-d), (I'-e), (I'-f), (I'-g) or (I'-h), p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6.

[0286] In some embodiments of a compound of Motif (I'), at least one of X¹, X², X³, X⁴, and Xⁿ is -SH.

[0287] In some embodiments of a compound of Motif (I'), at least one of X¹, X², X³, X⁴, and Xⁿ is -S-.

[0288] In some embodiments of a compound of Motif (I'), at least one of Y¹, Y², Y³, Y⁴, and Yⁿ is =S.

[0289] In some embodiments of a compound of Motif (I'), at least one of A, A¹, and A² is -S-.

[0290] In some embodiments of a compound of Motif (I'), at least one of Z¹, Z², Z³, Z⁴, and Zⁿ is -OCH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z³ and Z¹ are -OCH₃. In some embodiments of a compound of Motif (I'), at least one of Z¹, Z², Z³, Z⁴, and Zⁿ is -OH. In some embodiments, Z¹, Z², and Z⁴ are -OH. In some embodiments, Z² and Z⁴ are -OH.

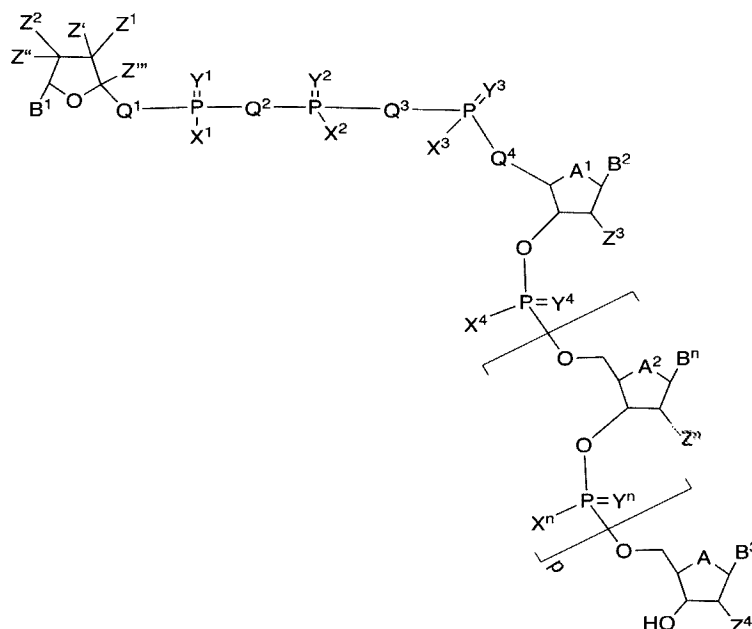
[0291] In some embodiments of a compound of Motif (I'), at least one of Q¹, Q², Q³, and Q⁴ is -OCH₃. In some embodiments of a compound of Formula (I), at least one of Q¹, Q², Q³, and Q⁴ is -O-. In some embodiments, Q¹ and Q⁴ are -OCH₃. In some embodiments, Q² and Q³ are -O-.

[0292] In some embodiments of a compound of Motif (I'), at least one of Y¹, Y², Y³, Y⁴, and Yⁿ is =O. In some embodiments, Y¹, Y², Y³, and Y⁴ are =O. In some embodiments, Y¹, Y², Y³, Y⁴, and Yⁿ is =S. In some embodiments, Y² is =S. In some embodiments, Y⁴ is =S.

[0293] In some embodiments of a compound of Motif (I'), at least one of X¹, X², X³, X⁴, and Xⁿ is -O-. In some embodiments, X¹, X², X³, and X⁴ are -O-. In some embodiments, X¹ is -S-. In some embodiments, X² is -S-. In some embodiments, X³ is -S-. In some embodiments, X⁴ is -S-.

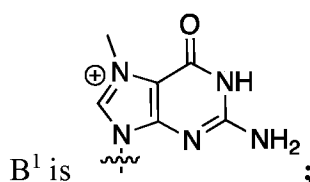
[0294] In some embodiments of a compound of Motif (I'), In some embodiments of a compound of Motif (I'), at least one of A, A¹, and A² is -O-. In some embodiments, A, A¹, and A² are -O-.

[0295] In one aspect, described herein is an mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



Formula (II)

wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z¹ and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

each Z² and Z'' is independently fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X^1 , X^2 , X^3 , X^4 , and X^n is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

p = 0, 1, 2, 3, 4, 5 or 6.

[0296] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), B² independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B² is adenine. In some embodiments, B² is guanine. In some embodiments, B² is cytosine. In some embodiments, B² is uracil, In some embodiments, B² is thymine, In some embodiments, B² is hypoxanthine. In some embodiments, B² is purine.

[0297] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), B³ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B³ is adenine. In some embodiments, B³ is guanine. In some embodiments, B³ is cytosine. In some embodiments, B³ is uracil, In some embodiments, B³ is thymine, In some embodiments, B³ is hypoxanthine. In some embodiments, B³ is purine.

[0298] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Bⁿ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, Bⁿ is adenine. In some embodiments, Bⁿ is guanine. In some embodiments, Bⁿ is cytosine. In some embodiments, Bⁿ is uracil, In some embodiments, Bⁿ is thymine, In some embodiments, Bⁿ is hypoxanthine. In some embodiments, Bⁿ is purine.

[0299] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z¹ is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z¹ is hydrogen. In some embodiments, Z¹ is fluorine. In some embodiments, Z¹ is -OH. In some embodiments, Z¹ is -SH. In some embodiments, Z¹ is -CH₃. In some embodiments, Z¹ is -CH₂CH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments, Z¹ is -NH(CH₃), In some embodiments, Z¹ is -NH₂-. In some embodiments, Z¹ is -NH(C(=O)CH₃). In some embodiments, Z¹ is -SCH₃.

[0300] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z' is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -

NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z' is hydrogen. In some embodiments, Z' is fluorine. In some embodiments, Z' is -OH. In some embodiments, Z' is -SH. In some embodiments, Z' is -CH₃. In some embodiments, Z' is -CH₂CH₃. In some embodiments, Z' is -OCH₃. In some embodiments, Z' is -NH(CH₃). In some embodiments, Z' is -NH₂-. In some embodiments, Z' is -NH(C(=O)CH₃). In some embodiments, Z' is -SCH₃.

[0301] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z² is fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z² is fluorine. In some embodiments, Z² is -OH. In some embodiments, Z² is -SH. In some embodiments, Z² is -CH₃. In some embodiments, Z² is -CH₂CH₃. In some embodiments, Z² is -OCH₃. In some embodiments, Z² is -SCH₃. In some embodiments, Z² is -OCH₂CH₃. In some embodiments, Z² is -NH₂. In some embodiments, Z² is NHCH₃. In some embodiments, Z² is NHC(=O)CH₃.

[0302] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z'' is fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z'' is fluorine. In some embodiments, Z'' is -OH. In some embodiments, Z'' is -SH. In some embodiments, Z'' is -CH₃. In some embodiments, Z'' is -CH₂CH₃. In some embodiments, Z'' is -OCH₃. In some embodiments, Z'' is -SCH₃. In some embodiments, Z'' is -OCH₂CH₃. In some embodiments, Z'' is -NH₂. In some embodiments, Z'' is NHCH₃. In some embodiments, Z'' is NHC(=O)CH₃.

[0303] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃. In some embodiments, Z''' is hydrogen. In some embodiments, Z''' is fluorine. In some embodiments, Z''' is -CH₃. In some embodiments, Z''' is -CH₂CH₃. In some embodiments, Z''' is -OCH₃. In some embodiments, Z''' is -OCH₂CH₃.

[0304] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z³ is hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z³ is hydrogen. In some embodiments, Z³ is fluorine. In some embodiments, Z³ is -OH. In some embodiments, Z³ is -CH₃. In some embodiments, Z³ is -CH₂CH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z³ is -NH₂. In some embodiments, Z³ is -

NHCH₃. In some embodiments, Z³ is -NH(C(=O)CH₃). In some embodiments, Z³ is -OCH₂CH₃. In some embodiments, Z³ is -OCH₂OCH₃. In some embodiments, Z³ is -OCH₂CH₂CH₃. In some embodiments, Z³ is -OCH(CH₃)₂. In some embodiments, Z³ is -SCH₃. In some embodiments, Z³ is -OCH₂CH₂OCH₃.

[0305] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z^4 is hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z^4 is hydrogen. In some embodiments, Z^4 is fluorine. In some embodiments, Z^4 is -OH. In some embodiments, Z^4 is -CH₃. In some embodiments, Z^4 is -CH₂CH₃. In some embodiments, Z^4 is -OCH₃. In some embodiments, Z^4 is -NH₂. In some embodiments, Z^4 is -NHCH₃. In some embodiments, Z^4 is -NH(C(=O)CH₃). In some embodiments, Z^4 is -OCH₂CH₃. In some embodiments, Z^4 is -OCH₂OCH₃. In some embodiments, Z^4 is -OCH₂CH₂CH₃. In some embodiments, Z^4 is -OCH(CH₃)₂. In some embodiments, Z^4 is -SCH₃. In some embodiments, Z^4 is -OCH₂CH₂OCH₃.

[0306] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Z^n is hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z^n is hydrogen. In some embodiments, Z^n is fluorine. In some embodiments, Z^n is -OH. In some embodiments, Z^n is -CH₃. In some embodiments, Z^n is -CH₂CH₃. In some embodiments, Z^n is -OCH₃. In some embodiments, Z^n is -NH₂. In some embodiments, Z^n is -NHCH₃. In some embodiments, Z^n is -NH(C(=O)CH₃). In some embodiments, Z^n is -OCH₂CH₃. In some embodiments, Z^n is -OCH₂OCH₃. In some embodiments, Z^n is -OCH₂CH₂CH₃. In some embodiments, Z^n is -OCH(CH₃)₂. In some embodiments, Z^n is -SCH₃. In some embodiments, Z^n is -OCH₂CH₂OCH₃.

[0307] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Q¹ is -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q¹ is -CH=CH-. In some embodiments, Q¹ is -CH₂-. In some embodiments, Q¹ is -CH₂O-. In some embodiments, Q¹ is -CH₂S-. In some embodiments, Q¹ is -CH₂CH₂-. In some embodiments, Q¹ is -CH₂CF₂-. In some embodiments, Q¹ is -CH₂NH₂-. In some embodiments, Q¹ is -CH₂NH(CH₃)-. In some embodiments, Q¹ is -CH₂N(C(=O)CH₃)-.

[0308] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e),

(II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Q^4 is $-\text{CH}=\text{CH}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CF}_2-$, $-\text{CH}_2\text{NH}_2-$, $-\text{CH}_2\text{NH}(\text{CH}_3)-$, or $-\text{CH}_2\text{N}(\text{C}(=\text{O})\text{CH}_3)-$. In some embodiments, Q^4 is $-\text{CH}=\text{CH}-$. In some embodiments, Q^4 is $-\text{CH}_2-$. In some embodiments, Q^4 is $-\text{CH}_2\text{O}-$. In some embodiments, Q^4 is $-\text{CH}_2\text{S}-$. In some embodiments, Q^4 is $-\text{CH}_2\text{CH}_2-$. In some embodiments, Q^4 is $-\text{CH}_2\text{CF}_2-$. In some embodiments, Q^4 is $-\text{CH}_2\text{NH}_2-$. In some embodiments, Q^4 is $-\text{CH}_2\text{NH}(\text{CH}_3)-$. In some embodiments, Q^4 is $-\text{CH}_2\text{N}(\text{C}(=\text{O})\text{CH}_3)-$.

[0309] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Q^2 is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, or $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$. In some embodiments Q^2 is $-\text{O}-$. In some embodiments Q^2 is $-\text{S}-$. In some embodiments Q^2 is $-\text{CH}_2-$. In some embodiments Q^2 is $-\text{CF}_2-$. In some embodiments Q^2 is $-\text{NH}-$. In some embodiments Q^2 is $-\text{N}(\text{CH}_3)-$. In some embodiments Q^2 is $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$.

[0310] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Q^3 is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, or $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$. In some embodiments Q^3 is $-\text{O}-$. In some embodiments Q^3 is $-\text{S}-$. In some embodiments Q^3 is $-\text{CH}_2-$. In some embodiments Q^3 is $-\text{CF}_2-$. In some embodiments Q^3 is $-\text{NH}-$. In some embodiments Q^3 is $-\text{N}(\text{CH}_3)-$. In some embodiments Q^3 is $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$.

[0311] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), X^1 is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^1 is $-\text{OH}$. In some embodiments, X^1 is $-\text{SH}$. In some embodiments, X^1 is $-\text{O}^\cdot$. In some embodiments, X^1 is $-\text{S}^\cdot$. In some embodiments, X^1 is $-\text{NH}_2$. In some embodiments, X^1 is $-\text{NHCH}_3$. In some embodiments, X^1 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^1 is $-\text{CH}_3$. In some embodiments, X^1 is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^1 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^1 is $-\text{OCH}_3$. In some embodiments, X^1 is $-\text{OCH}_2\text{CH}_3$.

[0312] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), X^2 is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^2 is $-\text{OH}$. In some embodiments, X^2 is $-\text{SH}$. In some embodiments, X^2 is $-\text{O}^\cdot$. In some embodiments, X^2 is $-\text{S}^\cdot$. In some embodiments, X^2 is $-\text{NH}_2$. In some embodiments, X^2 is $-\text{NHCH}_3$. In some embodiments, X^2 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^2 is $-\text{CH}_3$. In some embodiments, X^2 is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^2 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^2 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^2 is $-\text{OCH}_3$. In some embodiments, X^2 is $-\text{OCH}_2\text{CH}_3$.

$\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^2 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^2 is $-\text{OCH}_3$. In some embodiments, X^2 is $-\text{OCH}_2\text{CH}_3$.

[0313] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), X^3 is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^3 is $-\text{OH}$. In some embodiments, X^3 is $-\text{SH}$. In some embodiments, X^3 is $-\text{O}^\cdot$. In some embodiments, X^3 is $-\text{S}^\cdot$. In some embodiments, X^3 is $-\text{NH}_2$. In some embodiments, X^3 is $-\text{NHCH}_3$. In some embodiments, X^3 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^3 is $-\text{CH}_3$. In some embodiments, X^3 is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^3 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^3 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^3 is $-\text{OCH}_3$. In some embodiments, X^3 is $-\text{OCH}_2\text{CH}_3$.

[0314] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), X^4 is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^4 is $-\text{OH}$. In some embodiments, X^4 is $-\text{SH}$. In some embodiments, X^4 is $-\text{O}^\cdot$. In some embodiments, X^4 is $-\text{S}^\cdot$. In some embodiments, X^4 is $-\text{NH}_2$. In some embodiments, X^4 is $-\text{NHCH}_3$. In some embodiments, X^4 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^4 is $-\text{CH}_3$. In some embodiments, X^4 is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^4 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^4 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^4 is $-\text{OCH}_3$. In some embodiments, X^4 is $-\text{OCH}_2\text{CH}_3$.

[0315] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), X^n is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^n is $-\text{OH}$. In some embodiments, X^n is $-\text{SH}$. In some embodiments, X^n is $-\text{O}^\cdot$. In some embodiments, X^n is $-\text{S}^\cdot$. In some embodiments, X^n is $-\text{NH}_2$. In some embodiments, X^n is $-\text{NHCH}_3$. In some embodiments, X^n is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^n is $-\text{CH}_3$. In some embodiments, X^n is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^n is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^n is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^n is $-\text{OCH}_3$. In some embodiments, X^n is $-\text{OCH}_2\text{CH}_3$.

[0316] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Y^1 is $=\text{O}$, $=\text{S}$, $=\text{NH}$, or $=\text{NCH}_3$. In some embodiments, Y^1 is $=\text{O}$. In some embodiments, Y^1 is $=\text{S}$. In some embodiments, Y^1 is $=\text{NH}$. In some embodiments, Y^1 is $=\text{NCH}_3$.

[0317] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e),

(II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Y^2 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^2 is =O. In some embodiments, Y^2 is =S. In some embodiments, Y^2 is =NH. In some embodiments, Y^2 is =NCH₃.

[0318] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Y^3 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^3 is =O. In some embodiments, Y^3 is =S. In some embodiments, Y^3 is =NH. In some embodiments, Y^3 is =NCH₃.

[0319] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Y^4 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^4 is =O. In some embodiments, Y^4 is =S. In some embodiments, Y^4 is =NH. In some embodiments, Y^4 is =NCH₃.

[0320] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), Y^n is =O, =S, =NH, or =NCH₃. In some embodiments, Y^n is =O. In some embodiments, Y^n is =S. In some embodiments, Y^n is =NH. In some embodiments, Y^n is =NCH₃.

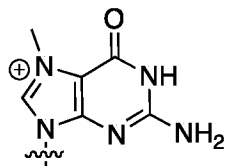
[0321] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), A is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A is -O-. In some embodiments, A is -S-. In some embodiments, A is -CH₂-. In some embodiments, A is -NH-. In some embodiments, A is -N(CH₃)-. In some embodiments, A is -N(C(=O)CH₃)-.

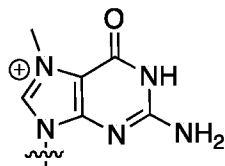
[0322] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), A¹ is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A¹ is -O-. In some embodiments, A¹ is -S-. In some embodiments, A¹ is -CH₂-. In some embodiments, A¹ is -NH-. In some embodiments, A¹ is -N(CH₃)-. In some embodiments, A¹ is -N(C(=O)CH₃)-.

[0323] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), A² is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A² is -O-. In some embodiments, A² is -S-. In some embodiments, A² is -CH₂-. In some embodiments, A² is -NH-. In some embodiments, A² is -N(CH₃)-. In some embodiments, A² is -N(C(=O)CH₃)-.

[0324] In some embodiments of a compound of Formula (II), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (II-l), (II-m), (II-n), (II-o), (II-p), (II-q), (II-r), (II-s), (II-t), or (II-u), p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some

embodiments, p is 5. In some embodiments, p is 6.



[0325] In some embodiments, B¹ is . In some embodiments, each B² and B³ is independently adenine or guanine. In some embodiments, B² is adenine. In some embodiments, B³ is guanine.

[0326] In some embodiments, each Z¹, Z², Z³, and Z⁴ is independently -OH or -OCH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments Z² is -OH. In some embodiments, Z¹, Z², and Z⁴ are -OH and Z³ is -OCH₃. In some embodiments, Z¹ and Z³ are -OCH₃ and Z² and Z⁴ are -OH. In some embodiments, Z', Z'', and Z''' are hydrogen.

[0327] In some embodiments, Q¹ and Q⁴ are -OCH₂-. In some embodiments Q² and Q³ are -O-.

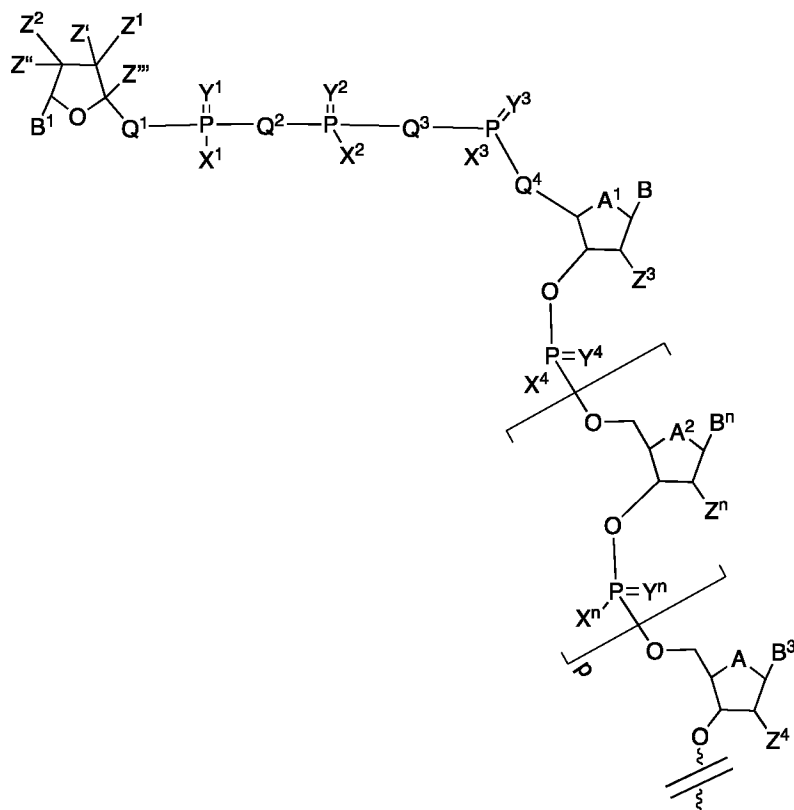
[0328] In some embodiments, X¹, X², X³, and X⁴ are -O-. In some embodiments, X¹, X², X³, and X⁴ are -S-. In some embodiments, X¹, X³, X⁴ are -O- and X² is -S-.

[0329] In some embodiments, Y¹, Y², Y³, and Y⁴ are =O. In some embodiments, Y¹, Y², Y³, and Y⁴ are =S. In some embodiments, Y¹, Y³, and Y⁴ are =O and Y² is =S. In some embodiments, Y¹, Y², Y³ are =O and Y⁴ is =S.

[0330] In some embodiments, A, A¹, and A² are -O-.

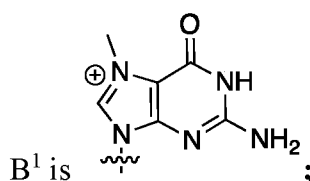
[0331] In some embodiments, p is 0.

[0332] In one aspect, described herein is an mRNA sequence having a 5'-end region motif (Motif (II')) :



Motif (II')

wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z¹ and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

each Z² and Z'' is independently fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-

each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

p = 0, 1, 2, 3, 4, 5 or 6.

[0333] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), B² independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B² is adenine. In some embodiments, B² is guanine. In some embodiments, B² is cytosine. In some embodiments, B² is uracil, In some embodiments, B² is thymine, In some embodiments, B² is hypoxanthine. In some embodiments, B² is purine.

[0334] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), B³ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B³ is adenine. In some embodiments, B³ is guanine. In some embodiments, B³ is cytosine. In some embodiments, B³ is uracil, In some embodiments, B³ is thymine, In some embodiments, B³ is hypoxanthine. In some embodiments, B³ is purine.

[0335] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Bⁿ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, Bⁿ is adenine. In some embodiments, Bⁿ is guanine. In some embodiments, Bⁿ is cytosine. In some embodiments, Bⁿ is uracil, In some embodiments, Bⁿ is thymine, In some embodiments, Bⁿ is hypoxanthine. In some embodiments, Bⁿ is purine.

[0336] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Z¹ is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z¹ is hydrogen. In some embodiments, Z¹ is fluorine. In some embodiments, Z¹ is -OH. In some embodiments, Z¹ is -SH. In some embodiments, Z¹ is -CH₃. In some embodiments, Z¹ is -CH₂CH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments, Z¹ is -NH(CH₃), In some embodiments, Z¹ is -NH₂-. In some embodiments, Z¹ is -NH(C(=O)CH₃). In some embodiments, Z¹ is -SCH₃.

[0337] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Z' is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z' is hydrogen. In some embodiments, Z' is fluorine. In some embodiments, Z' is -OH. In some embodiments, Z' is -SH. In some

embodiments, Z' is $-\text{CH}_3$. In some embodiments, Z' is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z' is $-\text{OCH}_3$. In some embodiments, Z' is $-\text{NH}(\text{CH}_3)$. In some embodiments, Z' is $-\text{NH}_2$. In some embodiments, Z' is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, Z' is $-\text{SCH}_3$.

[0338] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Z^2 is fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{SCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NH}_2$, NHCH_3 , or $\text{NHC}(=\text{O})\text{CH}_3$. In some embodiments, Z^2 is fluorine. In some embodiments, Z^2 is $-\text{OH}$. In some embodiments, Z^2 is $-\text{SH}$. In some embodiments, Z^2 is $-\text{CH}_3$. In some embodiments, Z^2 is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z^2 is $-\text{OCH}_3$. In some embodiments, Z^2 is $-\text{SCH}_3$. In some embodiments, Z^2 is $-\text{OCH}_2\text{CH}_3$. In some embodiments, Z^2 is $-\text{NH}_2$. In some embodiments, Z^2 is NHCH_3 . In some embodiments, Z^2 is $\text{NHC}(=\text{O})\text{CH}_3$.

[0339] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Z'' is fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{SCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NH}_2$, NHCH_3 , or $\text{NHC}(=\text{O})\text{CH}_3$. In some embodiments, Z'' is fluorine. In some embodiments, Z'' is $-\text{OH}$. In some embodiments, Z'' is $-\text{SH}$. In some embodiments, Z'' is $-\text{CH}_3$. In some embodiments, Z'' is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z'' is $-\text{OCH}_3$. In some embodiments, Z'' is $-\text{SCH}_3$. In some embodiments, Z'' is $-\text{OCH}_2\text{CH}_3$. In some embodiments, Z'' is $-\text{NH}_2$. In some embodiments, Z'' is NHCH_3 . In some embodiments, Z'' is $\text{NHC}(=\text{O})\text{CH}_3$.

[0340] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Z''' is hydrogen, fluorine, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, or $-\text{OCH}_2\text{CH}_3$. In some embodiments, Z''' is hydrogen. In some embodiments, Z''' is fluorine. In some embodiments, Z''' is $-\text{CH}_3$. In some embodiments, Z''' is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z''' is $-\text{OCH}_3$. In some embodiments, Z''' is $-\text{OCH}_2\text{CH}_3$.

[0341] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Z^3 is hydrogen, fluorine, $-\text{OH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{SCH}_3$, or $-\text{OCH}_2\text{CH}_2\text{OCH}_3$. In some embodiments, Z^3 is hydrogen. In some embodiments, Z^3 is fluorine. In some embodiments, Z^3 is $-\text{OH}$. In some embodiments, Z^3 is $-\text{CH}_3$. In some embodiments, Z^3 is $-\text{CH}_2\text{CH}_3$. In some embodiments, Z^3 is $-\text{OCH}_3$. In some embodiments, Z^3 is $-\text{NH}_2$. In some embodiments, Z^3 is $-\text{NHCH}_3$. In some embodiments, Z^3 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, Z^3 is $-\text{OCH}_2\text{CH}_3$. In some embodiments, Z^3 is $-\text{OCH}_2\text{OCH}_3$. In some embodiments, Z^3 is $-\text{OCH}_2\text{CH}_2\text{CH}_3$. In some embodiments, Z^3 is $-\text{OCH}(\text{CH}_3)_2$. In some embodiments, Z^3 is $-\text{SCH}_3$. In some embodiments, Z^3 is $-\text{OCH}_2\text{CH}_2\text{OCH}_3$.

(II'-s), (II'-t), or (II'-u), Q⁴ is -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q¹ is -CH=CH-. In some embodiments, Q⁴ is -CH₂-. In some embodiments, Q⁴ is -CH₂O-. In some embodiments, Q⁴ is -CH₂S-. In some embodiments, Q⁴ is -CH₂CH₂-. In some embodiments, Q⁴ is -CH₂CF₂-. In some embodiments, Q⁴ is -CH₂NH₂-. In some embodiments, Q⁴ is -CH₂NH(CH₃)-. In some embodiments, Q⁴ is -CH₂N(C(=O)CH₃)-.

[0346] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Q² is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments Q² is -O-. In some embodiments Q² is -S-. In some embodiments Q² is -CH₂-. In some embodiments Q² is -CF₂-. In some embodiments Q² is -NH-. In some embodiments Q² is -N(CH₃)-. In some embodiments Q² is -N(C(=O)CH₃)-.

[0347] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Q³ is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments Q³ is -O-. In some embodiments Q³ is -S-. In some embodiments Q³ is -CH₂-. In some embodiments Q³ is -CF₂-. In some embodiments Q³ is -NH-. In some embodiments Q³ is -N(CH₃)-. In some embodiments Q³ is -N(C(=O)CH₃)-.

[0348] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), X¹ is -OH, -SH, -O[•], -S[•], -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃. In some embodiments, X¹ is -OH. In some embodiments, X¹ is -SH. In some embodiments, X¹ is -O[•]. In some embodiments, X¹ is -S[•]. In some embodiments, X¹ is -NH₂. In some embodiments, X¹ is -NHCH₃. In some embodiments, X¹ is -NH(C(=O)CH₃). In some embodiments, X¹ is -CH₃. In some embodiments, X¹ is -CH₂CH₃. In some embodiments, X¹ is -CH₂CH₂CH₃. In some embodiments, X¹ is -CH(CH₃)₂. In some embodiments, X¹ is -OCH₃. In some embodiments, X¹ is -OCH₂CH₃.

[0349] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), X² is -OH, -SH, -O[•], -S[•], -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃. In some embodiments, X² is -OH. In some embodiments, X² is -SH. In some embodiments, X² is -O[•]. In some embodiments, X² is -S[•]. In some embodiments, X² is -NH₂. In some embodiments, X² is -NHCH₃. In some embodiments, X² is -NH(C(=O)CH₃). In some embodiments, X² is -CH₃. In some embodiments, X² is -CH₂CH₃. In

some embodiments, X^2 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^2 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^2 is $-\text{OCH}_3$. In some embodiments, X^2 is $-\text{OCH}_2\text{CH}_3$.

[0350] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), X^3 is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^3 is $-\text{OH}$. In some embodiments, X^3 is $-\text{SH}$. In some embodiments, X^3 is $-\text{O}^\cdot$. In some embodiments, X^3 is $-\text{S}^\cdot$. In some embodiments, X^3 is $-\text{NH}_2$. In some embodiments, X^3 is $-\text{NHCH}_3$. In some embodiments, X^3 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^3 is $-\text{CH}_3$. In some embodiments, X^3 is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^3 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^3 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^3 is $-\text{OCH}_3$. In some embodiments, X^3 is $-\text{OCH}_2\text{CH}_3$.

[0351] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), X^4 is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^4 is $-\text{OH}$. In some embodiments, X^4 is $-\text{SH}$. In some embodiments, X^4 is $-\text{O}^\cdot$. In some embodiments, X^4 is $-\text{S}^\cdot$. In some embodiments, X^4 is $-\text{NH}_2$. In some embodiments, X^4 is $-\text{NHCH}_3$. In some embodiments, X^4 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^4 is $-\text{CH}_3$. In some embodiments, X^4 is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^4 is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^4 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^4 is $-\text{OCH}_3$. In some embodiments, X^4 is $-\text{OCH}_2\text{CH}_3$.

[0352] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), X^n is $-\text{OH}$, $-\text{SH}$, $-\text{O}^\cdot$, $-\text{S}^\cdot$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$. In some embodiments, X^n is $-\text{OH}$. In some embodiments, X^n is $-\text{SH}$. In some embodiments, X^n is $-\text{O}^\cdot$. In some embodiments, X^n is $-\text{S}^\cdot$. In some embodiments, X^n is $-\text{NH}_2$. In some embodiments, X^n is $-\text{NHCH}_3$. In some embodiments, X^n is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$. In some embodiments, X^n is $-\text{CH}_3$. In some embodiments, X^n is $-\text{CH}_2\text{CH}_3$. In some embodiments, X^n is $-\text{CH}_2\text{CH}_2\text{CH}_3$. In some embodiments, X^n is $-\text{CH}(\text{CH}_3)_2$. In some embodiments, X^n is $-\text{OCH}_3$. In some embodiments, X^n is $-\text{OCH}_2\text{CH}_3$.

[0353] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Y^1 is $=\text{O}$, $=\text{S}$, $=\text{NH}$, or $=\text{NCH}_3$. In some embodiments, Y^1 is $=\text{O}$. In some embodiments, Y^1 is $=\text{S}$. In some embodiments, Y^1 is $=\text{NH}$. In some embodiments, Y^1 is $=\text{NCH}_3$.

[0354] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-

e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Y^2 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^2 is =O. In some embodiments, Y^2 is =S. In some embodiments, Y^2 is =NH. In some embodiments, Y^2 is =NCH₃.

[0355] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Y^3 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^3 is =O. In some embodiments, Y^3 is =S. In some embodiments, Y^3 is =NH. In some embodiments, Y^3 is =NCH₃.

[0356] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Y^4 is =O, =S, =NH, or =NCH₃. In some embodiments, Y^4 is =O. In some embodiments, Y^4 is =S. In some embodiments, Y^4 is =NH. In some embodiments, Y^4 is =NCH₃.

[0357] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), Y^n is =O, =S, =NH, or =NCH₃. In some embodiments, Y^n is =O. In some embodiments, Y^n is =S. In some embodiments, Y^n is =NH. In some embodiments, Y^n is =NCH₃.

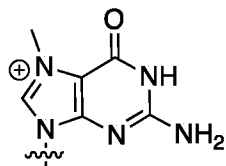
[0358] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), A is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A is -O-. In some embodiments, A is -S-. In some embodiments, A is -CH₂-. In some embodiments, A is -NH-. In some embodiments, A is -N(CH₃)-. In some embodiments, A is -N(C(=O)CH₃)-.

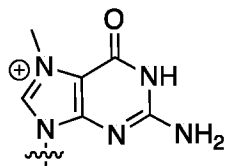
[0359] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), A¹ is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A¹ is -O-. In some embodiments, A¹ is -S-. In some embodiments, A¹ is -CH₂-. In some embodiments, A¹ is -NH-. In some embodiments, A¹ is -N(CH₃)-. In some embodiments, A¹ is -N(C(=O)CH₃)-.

[0360] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), A² is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A² is -O-. In some embodiments, A² is -S-. In some embodiments, A² is -CH₂-. In some embodiments, A² is -NH-. In some embodiments, A² is -N(CH₃)-. In some embodiments, A² is -N(C(=O)CH₃)-.

[0361] In some embodiments of a compound of Motif (II'), (II'-a), (II'-b), (II'-c), (II'-d), (II'-

e), (II'-f), (II'-g), (II'-h), (II'-i), (II'-j), (II'-k), (II'-l), (II'-m), (II'-n), (II'-o), (II'-p), (II'-q), (II'-r), (II'-s), (II'-t), or (II'-u), p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6.



[0362] In some embodiments, B¹ is . In some embodiments, each B² and B³ is independently adenine or guanine. In some embodiments, B² is adenine. In some embodiments, B³ is guanine.

[0363] In some embodiments, each Z¹, Z², Z³, and Z⁴ is independently -OH or -OCH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments Z² is -OH. In some embodiments, Z¹, Z², and Z⁴ are -OH and Z³ is -OCH₃. In some embodiments, Z¹ and Z³ are -OCH₃ and Z² and Z⁴ are -OH. In some embodiments, Z', Z'', and Z''' are hydrogen.

[0364] In some embodiments, Q¹ and Q⁴ are -OCH₂-. In some embodiments Q² and Q³ are -O-.

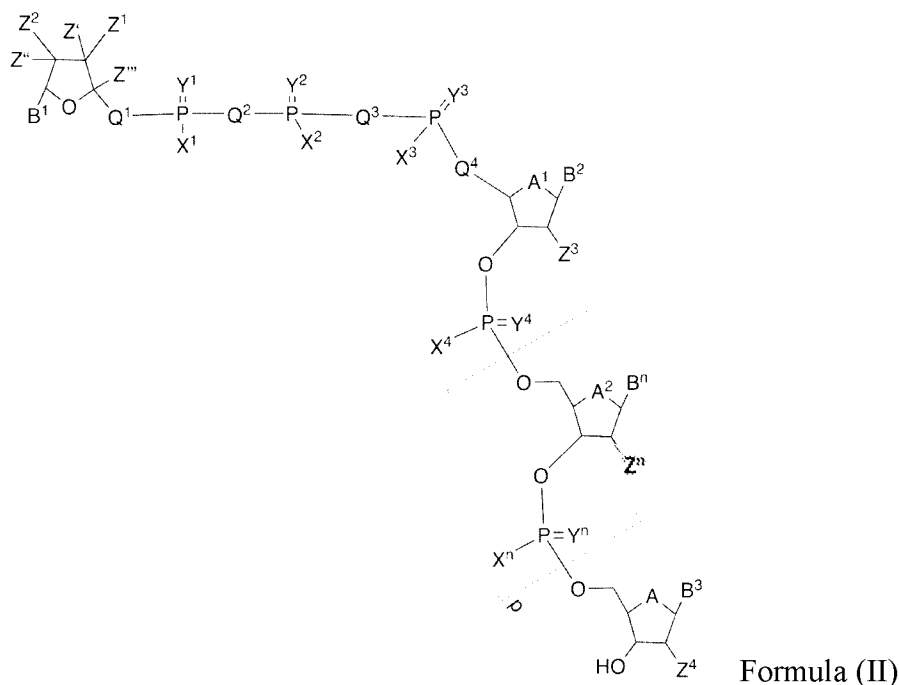
[0365] In some embodiments, X¹, X², X³, and X⁴ are -O-. In some embodiments, X¹, X², X³, and X⁴ are -S-. In some embodiments, X¹, X³, X⁴ are -O- and X² is -S-.

[0366] In some embodiments, Y¹, Y², Y³, and Y⁴ are =O. In some embodiments, Y¹, Y², Y³, and Y⁴ are =S. In some embodiments, Y¹, Y³, and Y⁴ are =O and Y² is =S. In some embodiments, Y¹, Y², Y³ are =O and Y⁴ is =S.

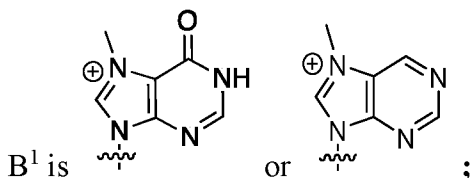
[0367] In some embodiments, A, A¹, and A² are -O-.

[0368] In some embodiments, p is 0.

[0369] In one aspect, described herein is an mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z¹ and Z² is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

Z³ is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

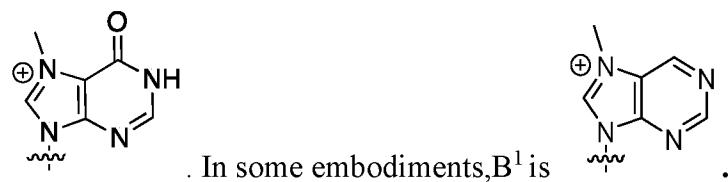
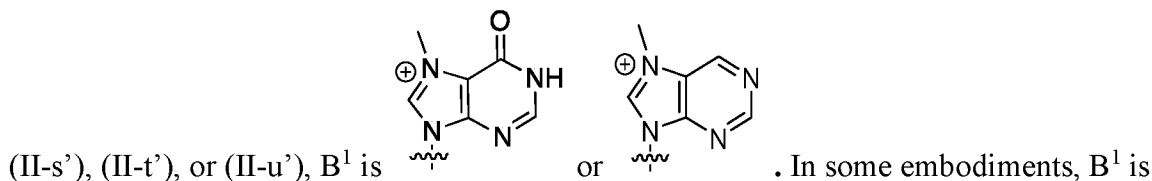
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y¹, Y², Y³, Y⁴, and Yⁿ is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

p = 0, 1, 2, 3, 4, 5 or 6.

[0370] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'),



[0371] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), B² independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B² is adenine. In some embodiments, B² is guanine. In some embodiments, B² is cytosine. In some embodiments, B² is uracil, In some embodiments, B² is thymine, In some embodiments, B² is hypoxanthine. In some embodiments, B² is purine.

[0372] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), B³ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B³ is adenine. In some embodiments, B³ is guanine. In some embodiments, B³ is cytosine. In some embodiments, B³ is uracil, In some embodiments, B³ is thymine, In some embodiments, B³ is hypoxanthine. In some embodiments, B³ is purine.

[0373] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Bⁿ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, Bⁿ is adenine. In some embodiments, Bⁿ is guanine. In some embodiments, Bⁿ is cytosine. In some embodiments, Bⁿ is uracil, In some embodiments, Bⁿ is thymine, In some embodiments, Bⁿ is hypoxanthine. In some embodiments, Bⁿ is purine.

[0374] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z' is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z' is hydrogen. In some embodiments, Z' is fluorine. In some embodiments, Z' is -OH. In some embodiments, Z' is -SH. In some embodiments, Z' is -CH₃. In some embodiments, Z' is -CH₂CH₃. In some embodiments, Z' is -OCH₃. In some embodiments, Z' is -NH(CH₃), In some embodiments, Z' is -NH₂. In some

embodiments, Z' is $\text{-NH(C(=O)CH}_3\text{)}$. In some embodiments, Z' is -SCH_3 .

[0375] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z'' is hydrogen, fluorine, -OH , -SH , -CH_3 , $\text{-CH}_2\text{CH}_3$, -OCH_3 , $\text{-NH(CH}_3\text{)}$, -NH_2 , $\text{-NH(C(=O)CH}_3\text{)}$, or -SCH_3 . In some embodiments, Z'' is hydrogen. In some embodiments, Z'' is fluorine. In some embodiments, Z'' is -OH . In some embodiments, Z'' is -SH . In some embodiments, Z'' is -CH_3 . In some embodiments, Z'' is $\text{-CH}_2\text{CH}_3$. In some embodiments, Z'' is -OCH_3 . In some embodiments, Z'' is $\text{-NH(CH}_3\text{)}$. In some embodiments, Z'' is -NH_2 . In some embodiments, Z'' is $\text{-NH(C(=O)CH}_3\text{)}$. In some embodiments, Z'' is -SCH_3 .

[0376] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z''' is hydrogen, fluorine, -CH_3 , $\text{-CH}_2\text{CH}_3$, -OCH_3 , or $\text{-OCH}_2\text{CH}_3$. In some embodiments, Z''' is hydrogen. In some embodiments, Z''' is fluorine. In some embodiments, Z''' is -CH_3 . In some embodiments, Z''' is $\text{-CH}_2\text{CH}_3$. In some embodiments, Z''' is -OCH_3 . In some embodiments, Z''' is $\text{-OCH}_2\text{CH}_3$.

[0377] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z^1 is hydrogen, fluorine, -OH , -SH , -CH_3 , $\text{-CH}_2\text{CH}_3$, -OCH_3 , -SCH_3 , $\text{-OCH}_2\text{CH}_3$, -NH_2 , NHCH_3 , or NHC(=O)CH_3 . In some embodiments, Z^1 is hydrogen. In some embodiments, Z^1 is fluorine. In some embodiments, Z^1 is -OH . In some embodiments, Z^1 is -SH . In some embodiments, Z^1 is -CH_3 . In some embodiments, Z^1 is $\text{-CH}_2\text{CH}_3$. In some embodiments, Z^1 is -OCH_3 . In some embodiments, Z^1 is -SCH_3 . In some embodiments, Z^1 is $\text{-OCH}_2\text{CH}_3$. In some embodiments, Z^1 is -NH_2 . In some embodiments, Z^1 is NHCH_3 . In some embodiments, Z^1 is NHC(=O)CH_3 .

[0378] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z^2 is hydrogen, fluorine, -OH , -SH , -CH_3 , $\text{-CH}_2\text{CH}_3$, -OCH_3 , -SCH_3 , $\text{-OCH}_2\text{CH}_3$, -NH_2 , NHCH_3 , or NHC(=O)CH_3 . In some embodiments, Z^2 is hydrogen. In some embodiments, Z^2 is fluorine. In some embodiments, Z^2 is -OH . In some embodiments, Z^2 is -SH . In some embodiments, Z^2 is -CH_3 . In some embodiments, Z^2 is $\text{-CH}_2\text{CH}_3$. In some embodiments, Z^2 is -OCH_3 . In some embodiments, Z^2 is -SCH_3 . In some embodiments, Z^2 is $\text{-OCH}_2\text{CH}_3$. In some embodiments, Z^2 is -NH_2 . In some embodiments, Z^2 is NHCH_3 . In some embodiments, Z^2 is NHC(=O)CH_3 .

[0379] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-

e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z³ is hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z³ is hydrogen. In some embodiments, Z³ is fluorine. In some embodiments, Z³ is -OH. In some embodiments, Z³ is -CH₃. In some embodiments, Z³ is -CH₂CH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z³ is -NH₂. In some embodiments, Z³ is -NHCH₃. In some embodiments, Z³ is -NH(C(=O)CH₃). In some embodiments, Z³ is -OCH₂CH₃. In some embodiments, Z³ is -OCH₂OCH₃. In some embodiments, Z³ is -OCH₂CH₂CH₃. In some embodiments, Z³ is -OCH(CH₃)₂. In some embodiments, Z³ is -SCH₃. In some embodiments, Z³ is -OCH₂CH₂OCH₃.

[0380] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Z⁴ is hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Z⁴ is hydrogen. In some embodiments, Z⁴ is fluorine. In some embodiments, Z⁴ is -OH. In some embodiments, Z⁴ is -CH₃. In some embodiments, Z⁴ is -CH₂CH₃. In some embodiments, Z⁴ is -OCH₃. In some embodiments, Z⁴ is -NH₂. In some embodiments, Z⁴ is -NHCH₃. In some embodiments, Z⁴ is -NH(C(=O)CH₃). In some embodiments, Z⁴ is -OCH₂CH₃. In some embodiments, Z⁴ is -OCH₂OCH₃. In some embodiments, Z⁴ is -OCH₂CH₂CH₃. In some embodiments, Z⁴ is -OCH(CH₃)₂. In some embodiments, Z⁴ is -SCH₃. In some embodiments, Z⁴ is -OCH₂CH₂OCH₃.

[0381] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Zⁿ is hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃. In some embodiments, Zⁿ is hydrogen. In some embodiments, Zⁿ is fluorine. In some embodiments, Zⁿ is -OH. In some embodiments, Zⁿ is -CH₃. In some embodiments, Zⁿ is -CH₂CH₃. In some embodiments, Zⁿ is -OCH₃. In some embodiments, Zⁿ is -NH₂. In some embodiments, Zⁿ is -NHCH₃. In some embodiments, Zⁿ is -NH(C(=O)CH₃). In some embodiments, Zⁿ is -OCH₂CH₃. In some embodiments, Zⁿ is -OCH₂OCH₃. In some embodiments, Zⁿ is -OCH₂CH₂CH₃. In some embodiments, Zⁿ is -OCH(CH₃)₂. In some embodiments, Zⁿ is -SCH₃. In some embodiments, Zⁿ is -OCH₂CH₂OCH₃.

[0382] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'),

(II-s'), (II-t'), or (II-u'), Q¹ is -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q¹ is -CH=CH-. In some embodiments, Q¹ is -CH₂-. In some embodiments, Q¹ is -CH₂O-. In some embodiments, Q¹ is -CH₂S-. In some embodiments, Q¹ is -CH₂CH₂-. In some embodiments, Q¹ is -CH₂CF₂-. In some embodiments, Q¹ is -CH₂NH₂-. In some embodiments, Q¹ is -CH₂NH(CH₃)-. In some embodiments, Q¹ is -CH₂N(C(=O)CH₃)-.

[0383] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Q⁴ is -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-. In some embodiments, Q⁴ is -CH=CH-. In some embodiments, Q⁴ is -CH₂-. In some embodiments, Q⁴ is -CH₂O-. In some embodiments, Q⁴ is -CH₂S-. In some embodiments, Q⁴ is -CH₂CH₂-. In some embodiments, Q⁴ is -CH₂CF₂-. In some embodiments, Q⁴ is -CH₂NH₂-. In some embodiments, Q⁴ is -CH₂NH(CH₃)-. In some embodiments, Q⁴ is -CH₂N(C(=O)CH₃)-.

[0384] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Q² is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments Q² is -O-. In some embodiments Q² is -S-. In some embodiments Q² is -CH₂-. In some embodiments Q² is -CF₂-. In some embodiments Q² is -NH-. In some embodiments Q² is -N(CH₃)-. In some embodiments Q² is -N(C(=O)CH₃)-.

[0385] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Q³ is -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-. In some embodiments Q³ is -O-. In some embodiments Q³ is -S-. In some embodiments Q³ is -CH₂-. In some embodiments Q³ is -CF₂-. In some embodiments Q³ is -NH-. In some embodiments Q³ is -N(CH₃)-. In some embodiments Q³ is -N(C(=O)CH₃)-.

[0386] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), X¹ is -OH, -SH, -O[•], -S[•], -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃. In some embodiments, X¹ is -OH. In some embodiments, X¹ is -SH. In some embodiments, X¹ is -O[•]. In some embodiments, X¹ is -S[•]. In some embodiments, X¹ is -NH₂. In some embodiments, X¹ is -NHCH₃. In some embodiments, X¹ is -NH(C(=O)CH₃). In some embodiments, X¹ is -CH₃. In some embodiments, X¹ is -CH₂CH₃. In some embodiments, X¹ is -CH₂CH₂CH₃. In some embodiments, X¹ is -CH(CH₃)₂. In some

embodiments, X^1 is $-OCH_3$. In some embodiments, X^1 is $-OCH_2CH_3$.

[0387] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), X^2 is $-OH$, $-SH$, $-O^\cdot$, $-S^\cdot$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^2 is $-OH$. In some embodiments, X^2 is $-SH$. In some embodiments, X^2 is $-O^\cdot$. In some embodiments, X^2 is $-S^\cdot$. In some embodiments, X^2 is $-NH_2$. In some embodiments, X^2 is $-NHCH_3$. In some embodiments, X^2 is $-NH(C(=O)CH_3)$. In some embodiments, X^2 is $-CH_3$. In some embodiments, X^2 is $-CH_2CH_3$. In some embodiments, X^2 is $-CH_2CH_2CH_3$. In some embodiments, X^2 is $-CH(CH_3)_2$. In some embodiments, X^2 is $-OCH_3$. In some embodiments, X^2 is $-OCH_2CH_3$.

[0388] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), X^3 is $-OH$, $-SH$, $-O^\cdot$, $-S^\cdot$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^3 is $-OH$. In some embodiments, X^3 is $-SH$. In some embodiments, X^3 is $-O^\cdot$. In some embodiments, X^3 is $-S^\cdot$. In some embodiments, X^3 is $-NH_2$. In some embodiments, X^3 is $-NHCH_3$. In some embodiments, X^3 is $-NH(C(=O)CH_3)$. In some embodiments, X^3 is $-CH_3$. In some embodiments, X^3 is $-CH_2CH_3$. In some embodiments, X^3 is $-CH_2CH_2CH_3$. In some embodiments, X^3 is $-CH(CH_3)_2$. In some embodiments, X^3 is $-OCH_3$. In some embodiments, X^3 is $-OCH_2CH_3$.

[0389] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), X^4 is $-OH$, $-SH$, $-O^\cdot$, $-S^\cdot$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^4 is $-OH$. In some embodiments, X^4 is $-SH$. In some embodiments, X^4 is $-O^\cdot$. In some embodiments, X^4 is $-S^\cdot$. In some embodiments, X^4 is $-NH_2$. In some embodiments, X^4 is $-NHCH_3$. In some embodiments, X^4 is $-NH(C(=O)CH_3)$. In some embodiments, X^4 is $-CH_3$. In some embodiments, X^4 is $-CH_2CH_3$. In some embodiments, X^4 is $-CH_2CH_2CH_3$. In some embodiments, X^4 is $-CH(CH_3)_2$. In some embodiments, X^4 is $-OCH_3$. In some embodiments, X^4 is $-OCH_2CH_3$.

[0390] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), X^n is $-OH$, $-SH$, $-O^\cdot$, $-S^\cdot$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^n is $-OH$. In some embodiments, X^n is $-SH$. In some embodiments, X^n is $-O^\cdot$. In some embodiments, X^n is $-S^\cdot$. In some embodiments, X^n is $-NH_2$. In some embodiments, X^n is $-NHCH_3$. In some embodiments, X^n is

-NH(C(=O)CH₃). In some embodiments, Xⁿ is -CH₃. In some embodiments, Xⁿ is -CH₂CH₃. In some embodiments, Xⁿ is -CH₂CH₂CH₃. In some embodiments, Xⁿ is -CH(CH₃)₂. In some embodiments, Xⁿ is -OCH₃. In some embodiments, Xⁿ is -OCH₂CH₃.

[0391] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Y¹ is =O, =S, =NH, or =NCH₃. In some embodiments, Y¹ is =O. In some embodiments, Y¹ is =S. In some embodiments, Y¹ is =NH. In some embodiments, Y¹ is =NCH₃.

[0392] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Y² is =O, =S, =NH, or =NCH₃. In some embodiments, Y² is =O. In some embodiments, Y² is =S. In some embodiments, Y² is =NH. In some embodiments, Y² is =NCH₃.

[0393] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Y³ is =O, =S, =NH, or =NCH₃. In some embodiments, Y³ is =O. In some embodiments, Y³ is =S. In some embodiments, Y³ is =NH. In some embodiments, Y³ is =NCH₃.

[0394] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Y⁴ is =O, =S, =NH, or =NCH₃. In some embodiments, Y⁴ is =O. In some embodiments, Y⁴ is =S. In some embodiments, Y⁴ is =NH. In some embodiments, Y⁴ is =NCH₃.

[0395] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), Yⁿ is =O, =S, =NH, or =NCH₃. In some embodiments, Yⁿ is =O. In some embodiments, Yⁿ is =S. In some embodiments, Yⁿ is =NH. In some embodiments, Yⁿ is =NCH₃.

[0396] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), A is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A is -O-. In some embodiments, A is -S-. In some embodiments, A is -CH₂-. In some embodiments, A is -NH-. In some embodiments, A is -N(CH₃)-. In some embodiments, A is -N(C(=O)CH₃)-.

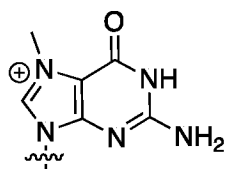
[0397] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), A¹ is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A¹ is -O-. In some embodiments, A¹ is -S-. In some embodiments, A¹ is -CH₂-. In some embodiments, A¹ is -NH-. In some embodiments, A¹ is -N(CH₃)-. In some embodiments, A¹ is

-N(C(=O)CH₃)-.

[0398] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), A² is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-. In some embodiments, A² is -O-. In some embodiments, A² is -S-. In some embodiments, A² is -CH₂-. In some embodiments, A² is -NH-. In some embodiments, A² is -N(CH₃)-. In some embodiments, A² is -N(C(=O)CH₃)-.

[0399] In some embodiments of a compound of Formula (II), (II-a'), (II-b'), (II-c'), (II-d'), (II-e'), (II-f'), (II-g'), (II-h'), (II-i'), (II-j'), (II-k'), (II-l'), (II-m'), (II-n'), (II-o'), (II-p'), (II-q'), (II-r'), (II-s'), (II-t'), or (II-u'), p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6.

[0400]



[0401] In some embodiments, B¹ is . In some embodiments, each B² and B³ is independently adenine or guanine. In some embodiments, B² is adenine. In some embodiments, B³ is guanine.

[0402] In some embodiments, each Z¹, Z², Z³, and Z⁴ is independently -OH or -OCH₃. In some embodiments, Z³ is -OCH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments Z² is -OH. In some embodiments, Z¹, Z², and Z⁴ are -OH and Z³ is -OCH₃. In some embodiments, Z¹ and Z³ are -OCH₃ and Z² and Z⁴ are -OH. In some embodiments, Z', Z'', and Z''' are hydrogen.

[0403] In some embodiments, Q¹ and Q⁴ are -OCH₂-. In some embodiments Q² and Q³ are -O-.

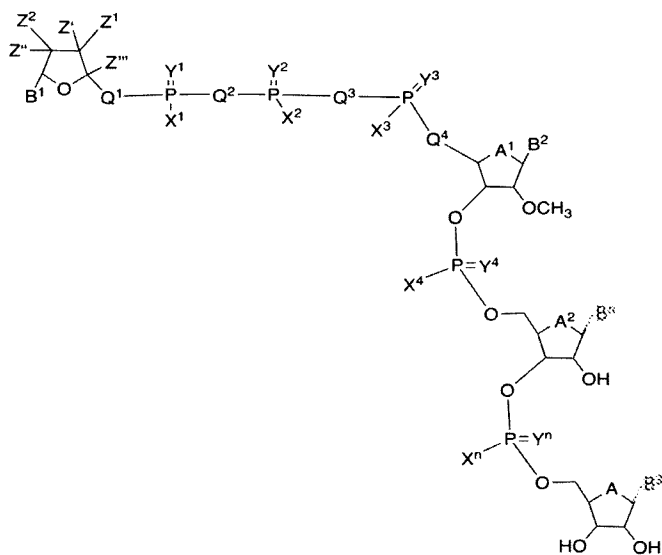
[0404] In some embodiments, X¹, X², X³, and X⁴ are -O-. In some embodiments, X¹, X², X³, and X⁴ are -S-. In some embodiments, X¹, X³, X⁴ are -O- and X² is -S-.

[0405] In some embodiments, Y¹, Y², Y³, and Y⁴ are =O. In some embodiments, Y¹, Y², Y³, and Y⁴ are =S. In some embodiments, Y¹, Y³, and Y⁴ are =O and Y² is =S. In some embodiments, Y¹, Y², Y³ are =O and Y⁴ is =S.

[0406] In some embodiments, A, A¹, and A² are -O-.

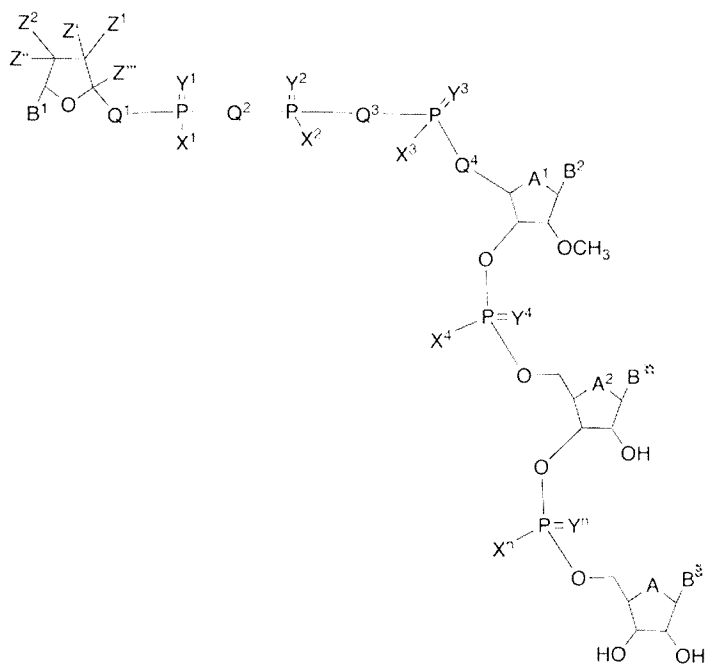
[0407] In some embodiments, p is 0.

[0408] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-a):



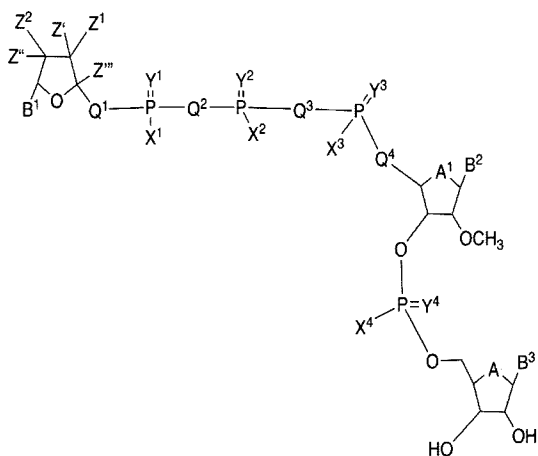
Formula (II-a).

[0409] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-a'):



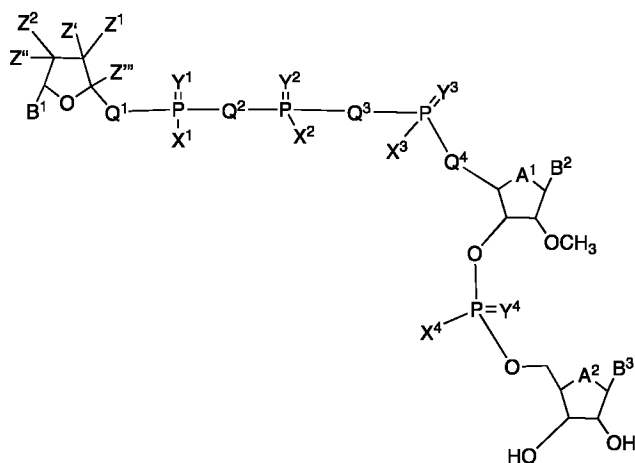
Formula (II-a').

[0410] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-b):



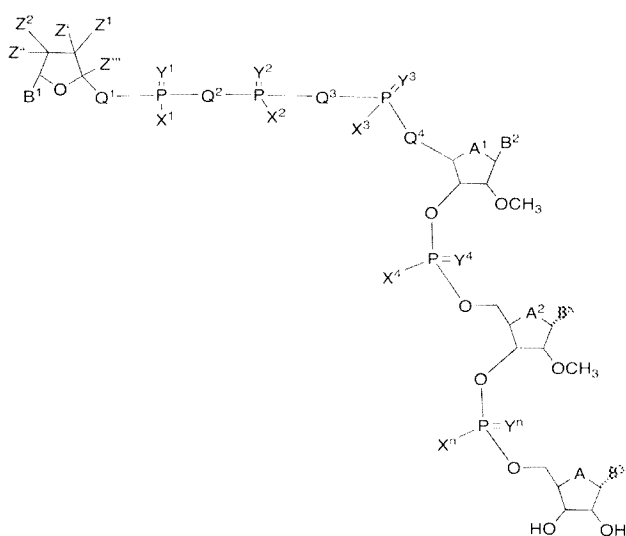
Formula (II-b).

[0411] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-b'):



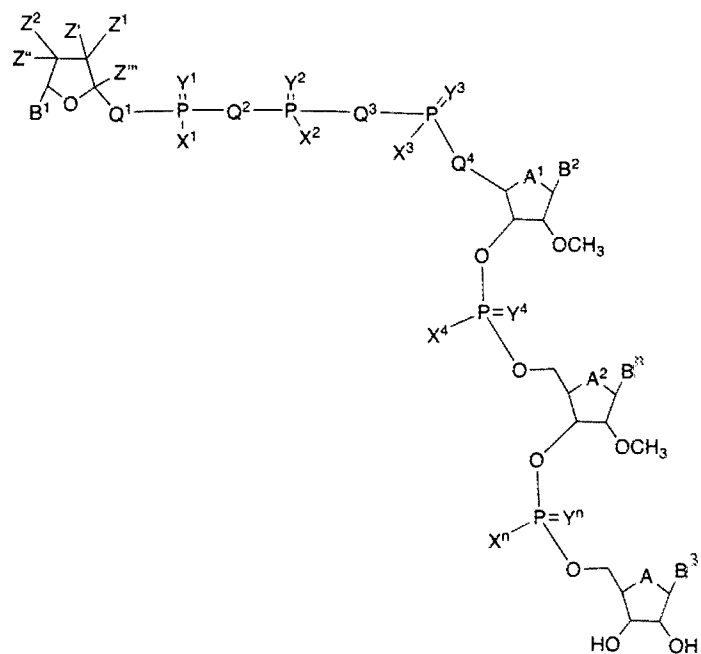
Formula (II-b').

[0412] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-c):



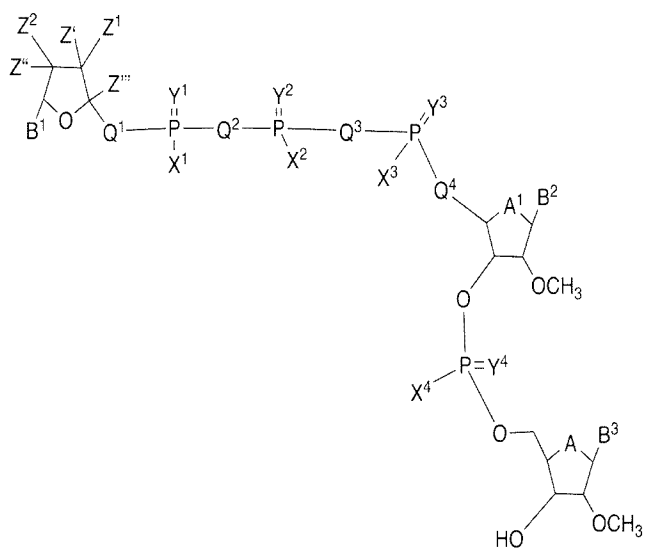
Formula (II-c).

[0413] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-c'):



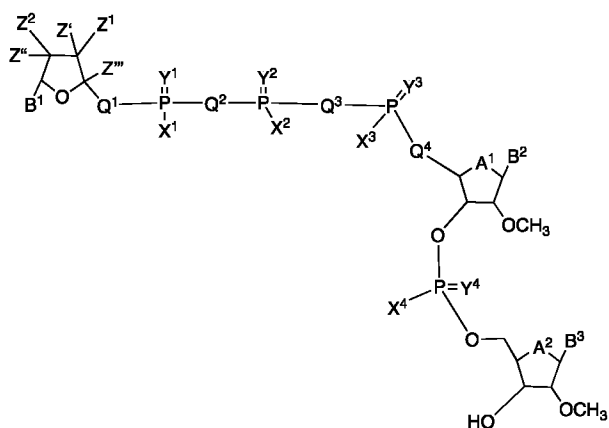
Formula (II-c').

[0414] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-d):



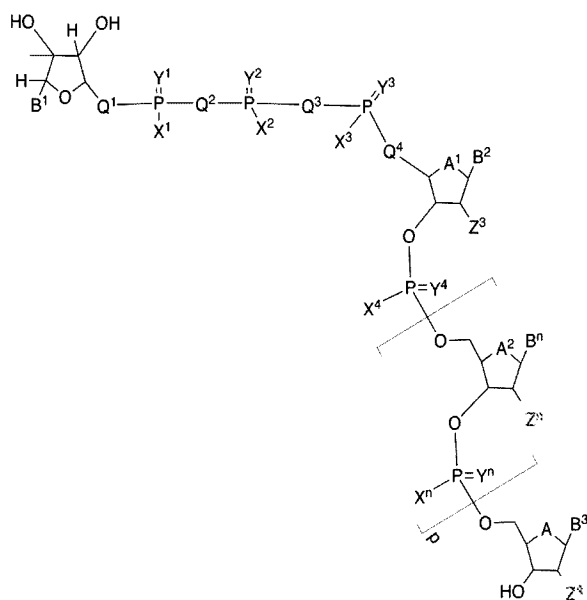
Formula (II-d).

[0415] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-d'):



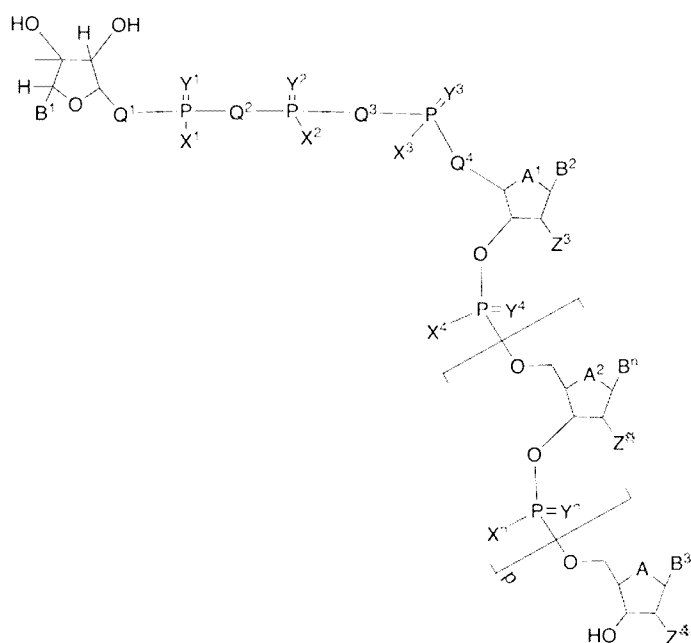
Formula (II-d').

[0416] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-e):



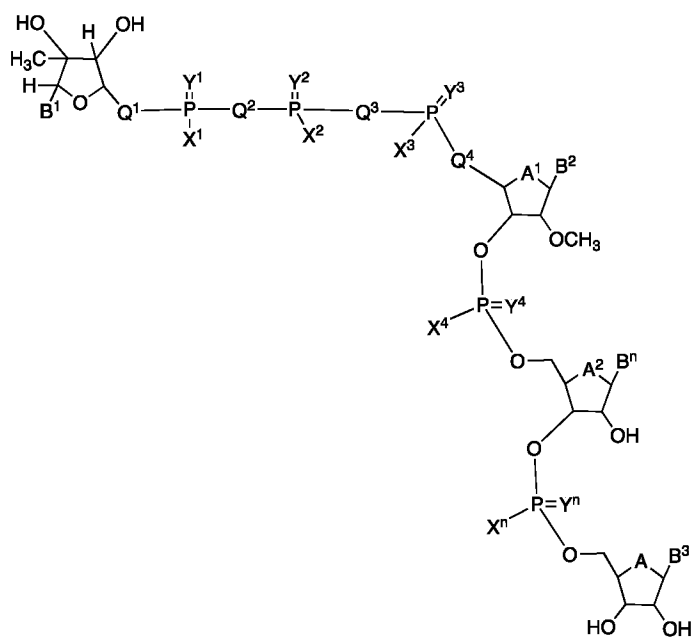
Formula (II-e).

[0417] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-e'):



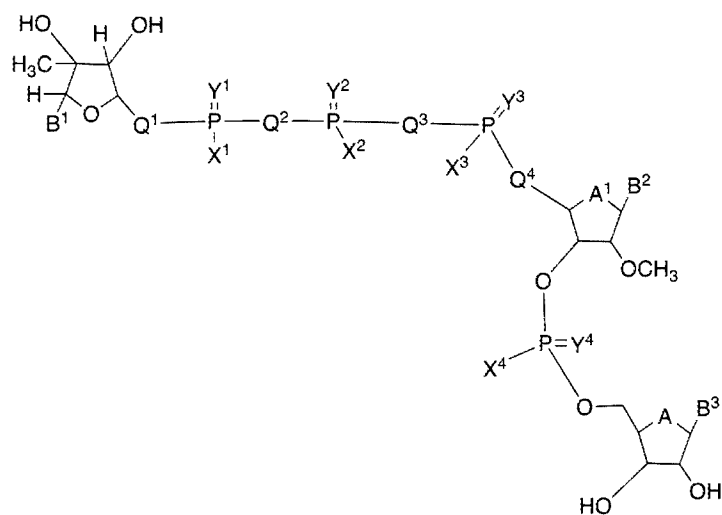
Formula (II-e').

[0418] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-f):



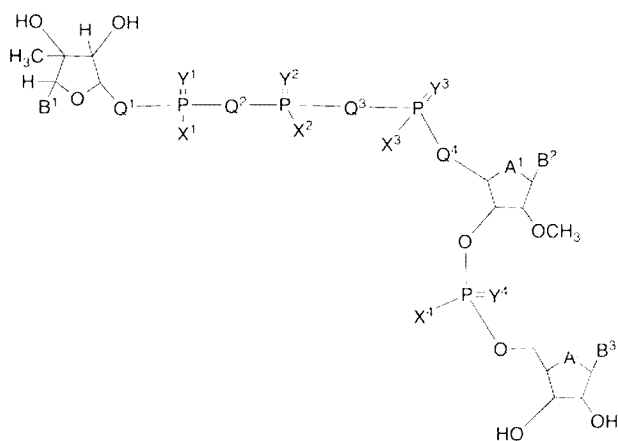
Formula (II-f).

[0419] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-g):



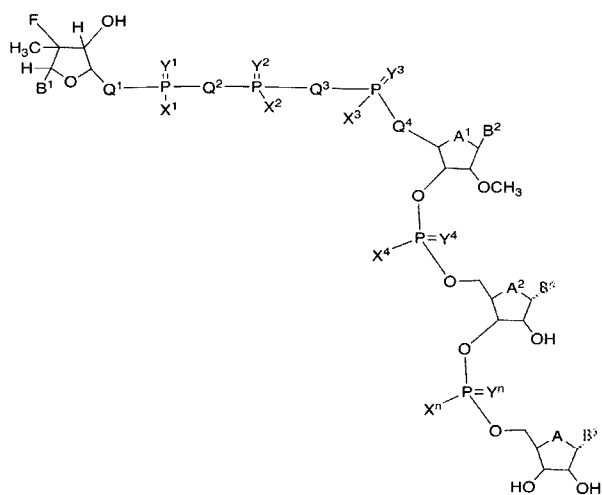
Formula (II-g).

[0420] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-g'):



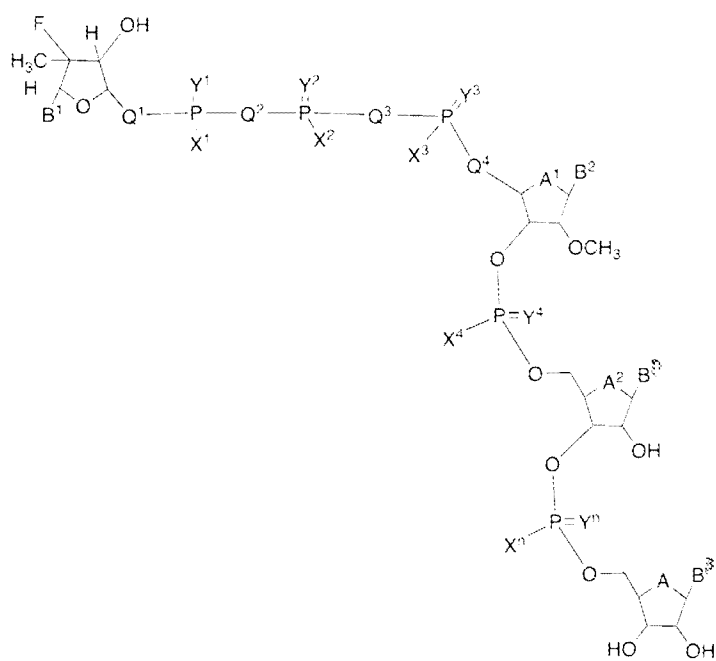
Formula (II-g').

[0421] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-h):



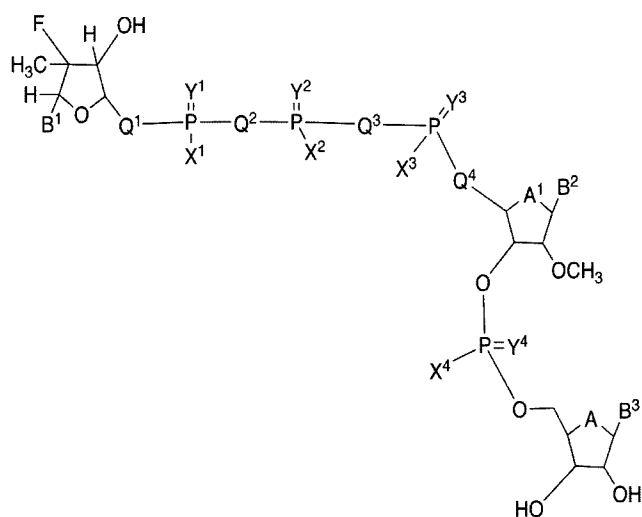
Formula (II-h).

[0422] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-h'):



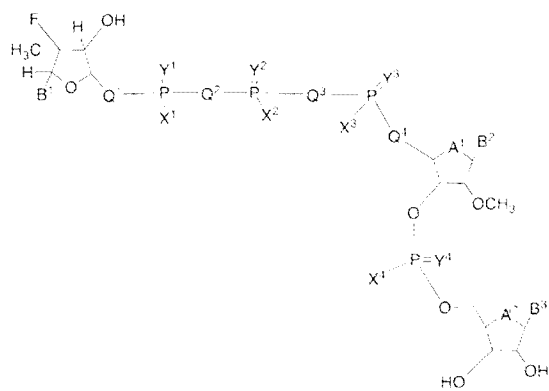
Formula (II-h').

[0423] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-i)



Formula (II-i).

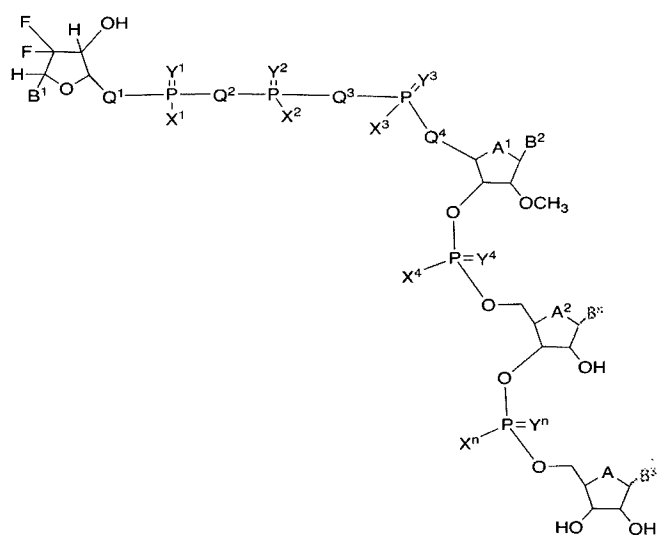
[0424] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-I')



Formula (II-I').

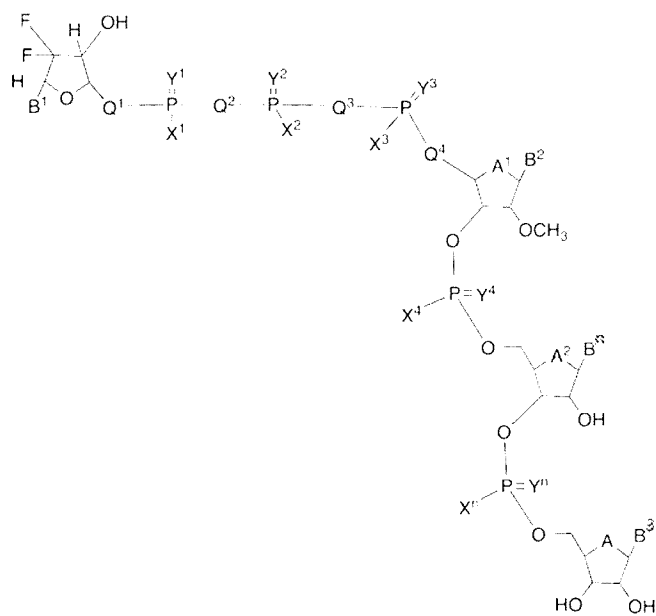
[0425] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-

j):



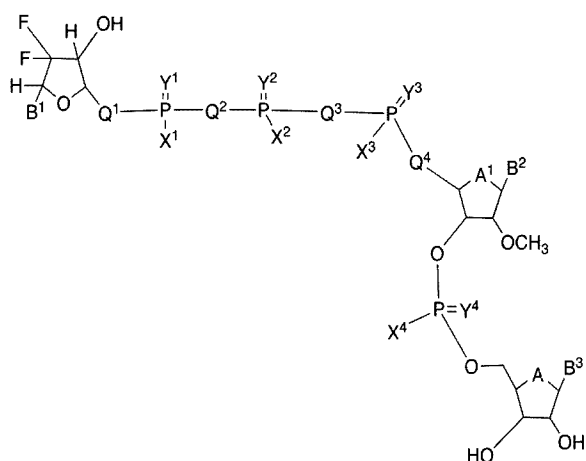
Formula (II-j).

[0426] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-j'):



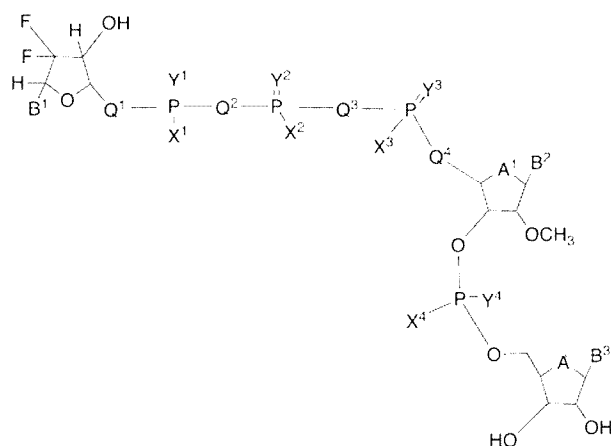
Formula (II-j').

[0427] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-k):



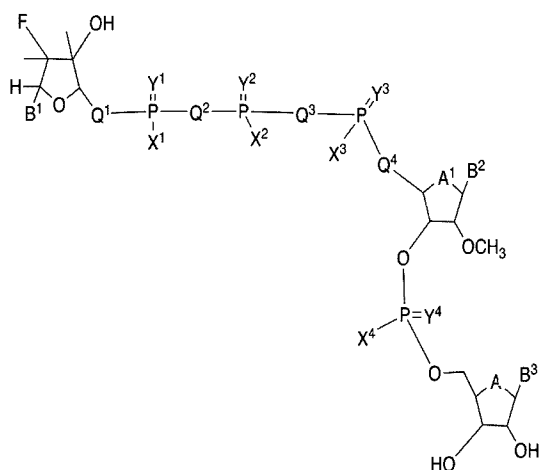
Formula (II-k).

[0428] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-k'):



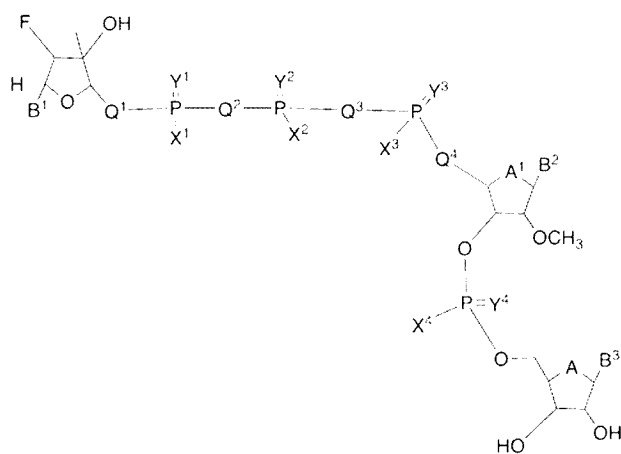
Formula (II-k').

[0429] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-l):



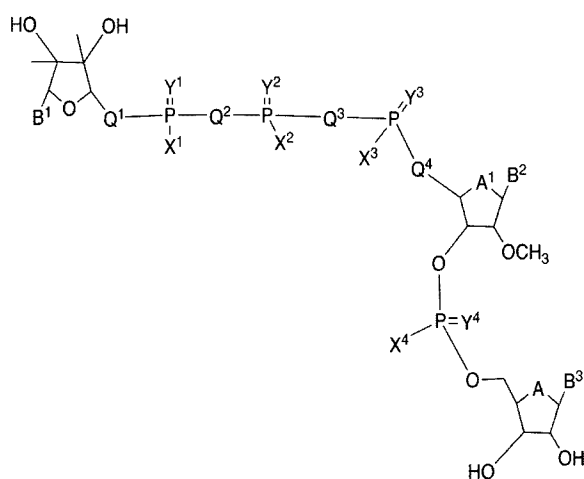
Formula (II-l).

[0430] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-l'):



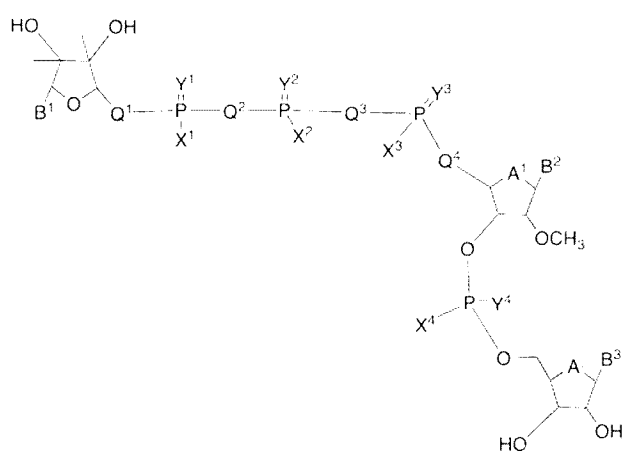
Formula (II-l').

[0431] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-m):



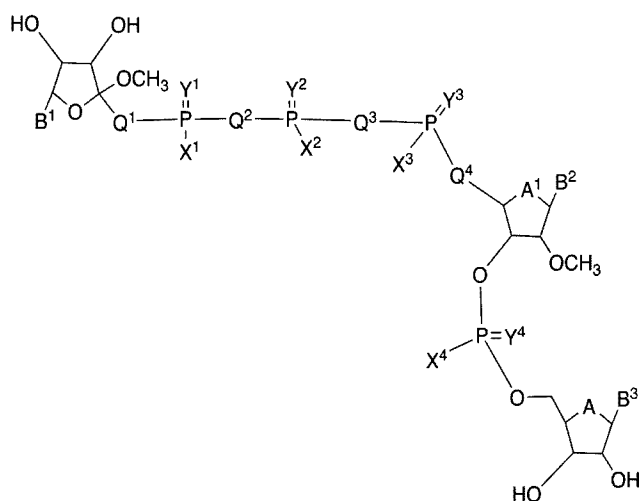
Formula (II-m).

[0432] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-m'):



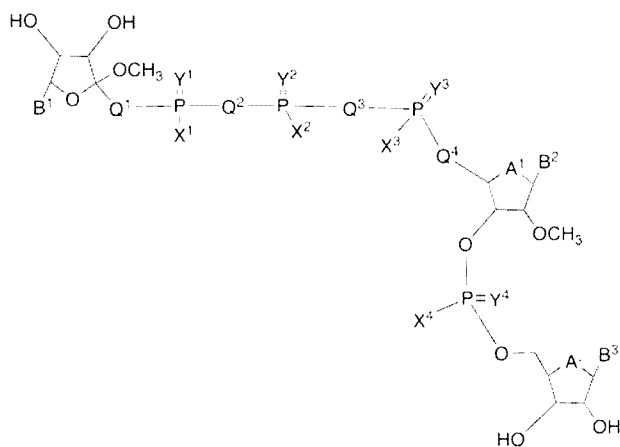
Formula (II-m').

[0433] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-n):



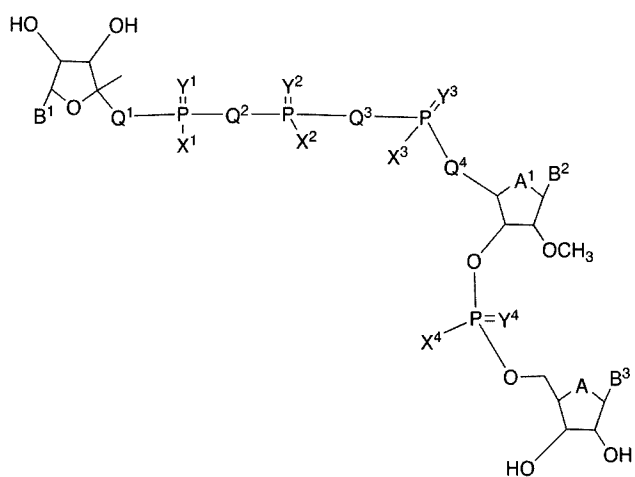
Formula (II-n).

[0434] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-n'):



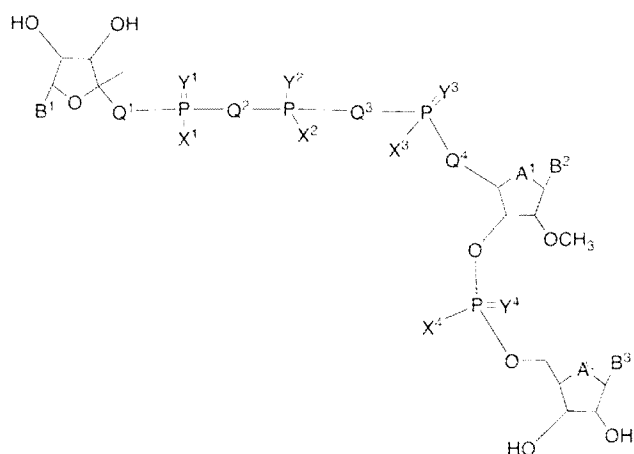
Formula (II-n').

[0435] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-o):



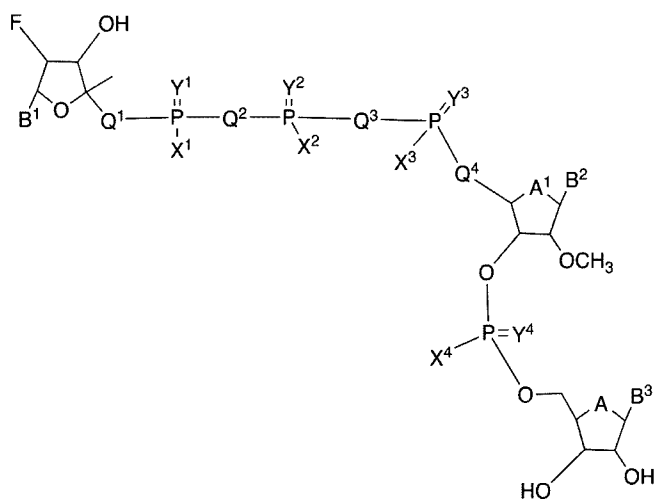
Formula (II-o).

[0436] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-o'):



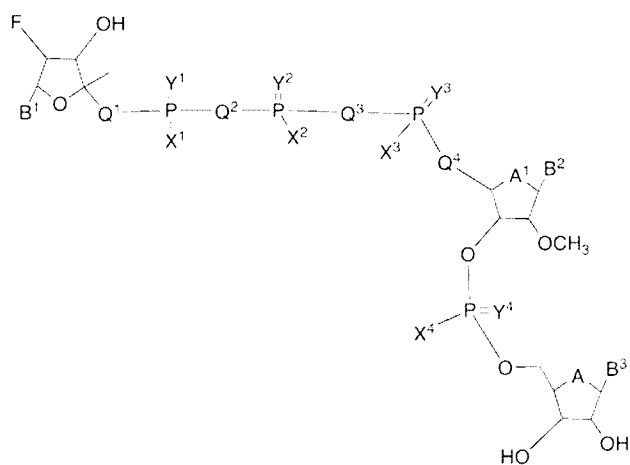
Formula (II-o').

[0437] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-p):



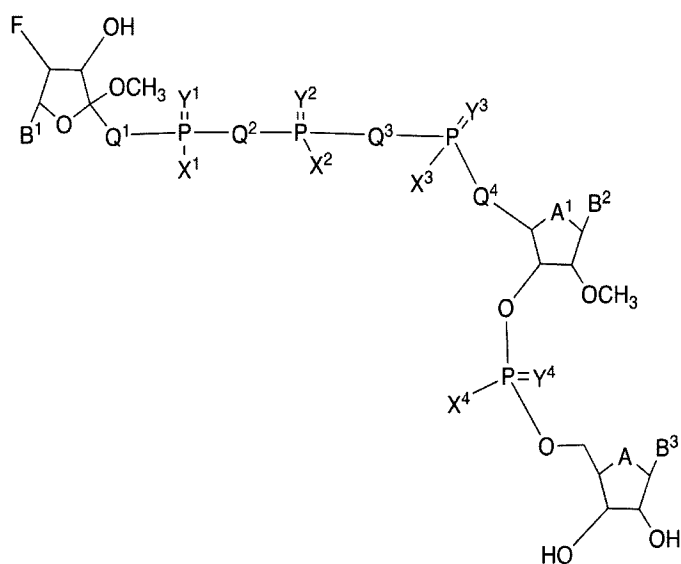
Formula (II-p).

[0438] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-p'):



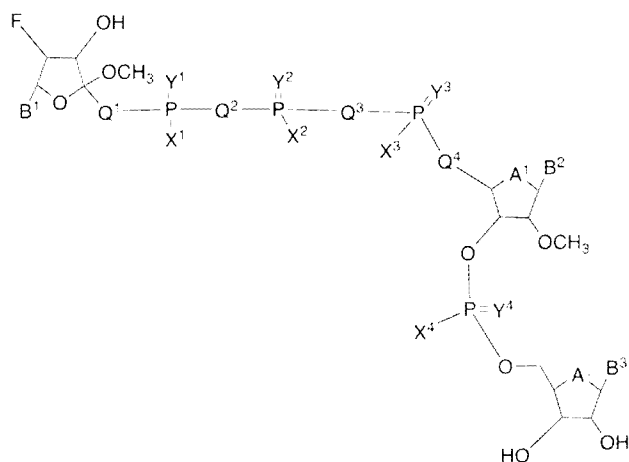
Formula (II-p').

[0439] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-q):



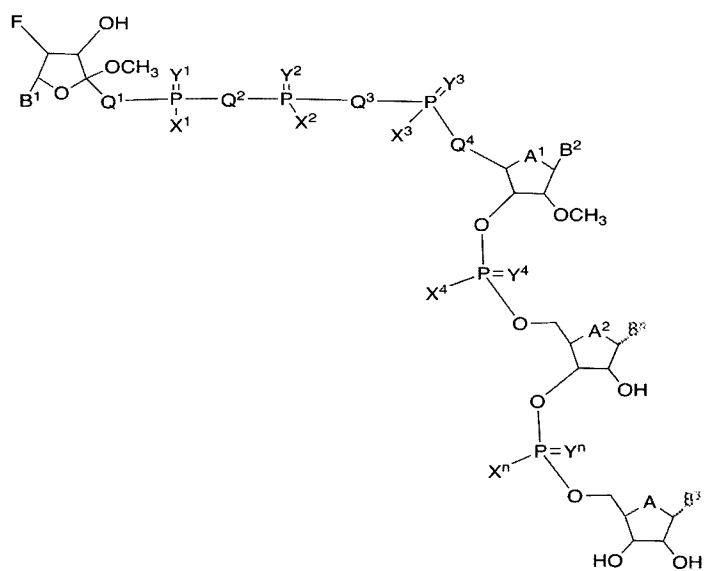
Formula (II-q).

[0440] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-q'):



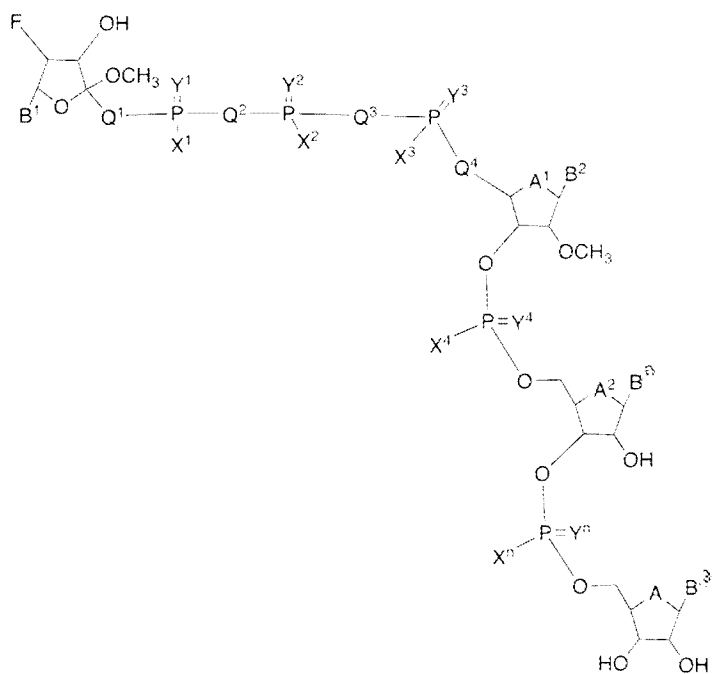
Formula (II-q').

[0441] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-r):



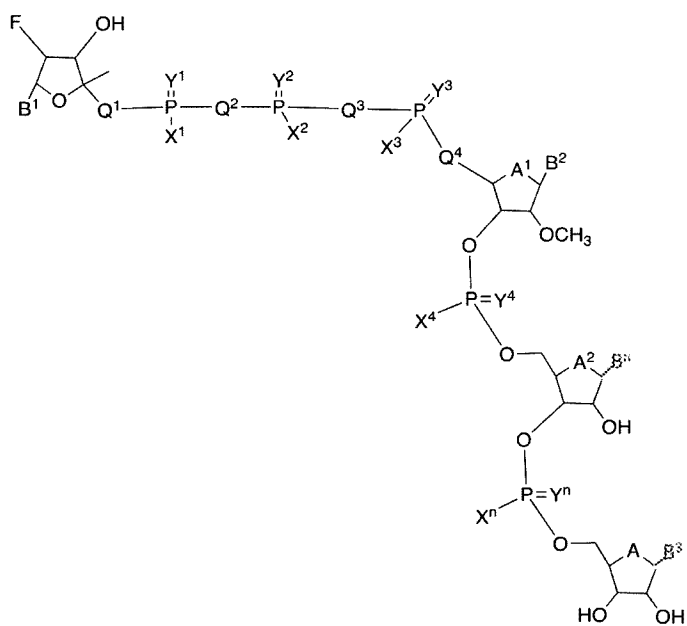
Formula (II-r).

[0442] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-r'):



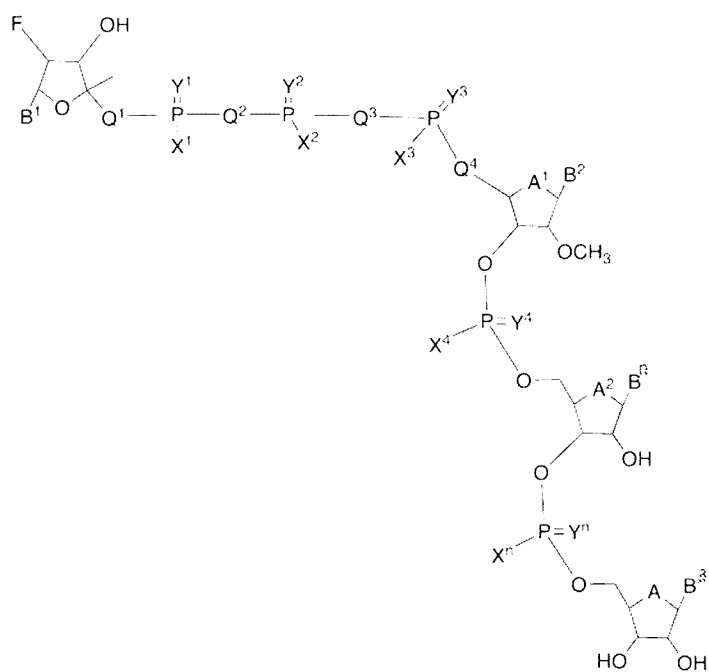
Formula (II-r').

[0443] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-s):



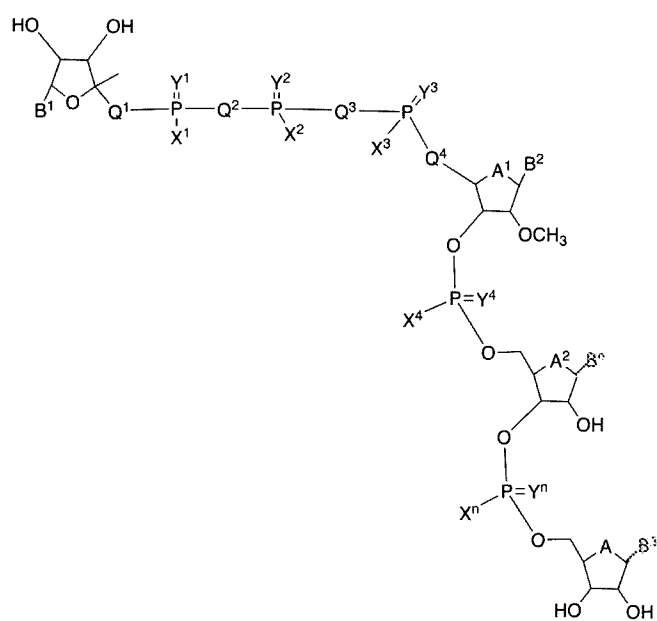
Formula (II-s).

[0444] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-s'):



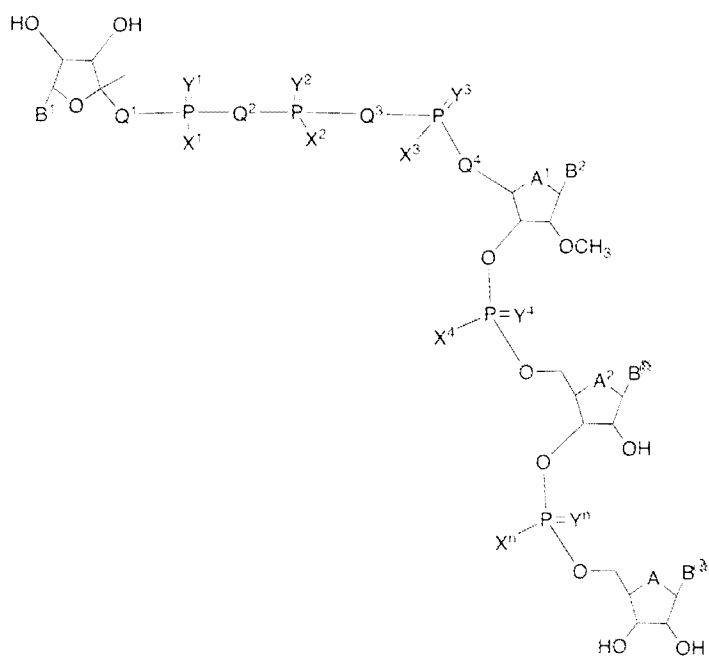
Formula (II-s').

[0445] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-t):



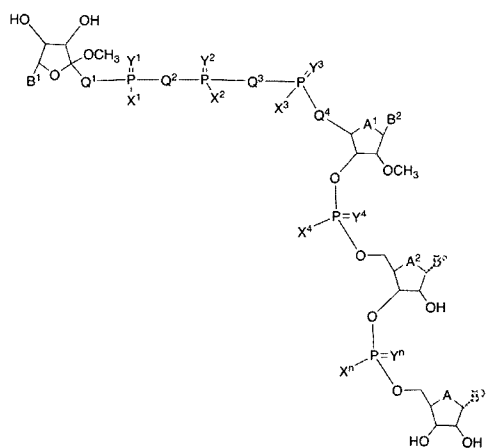
Formula (II-t).

[0446] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-t'):



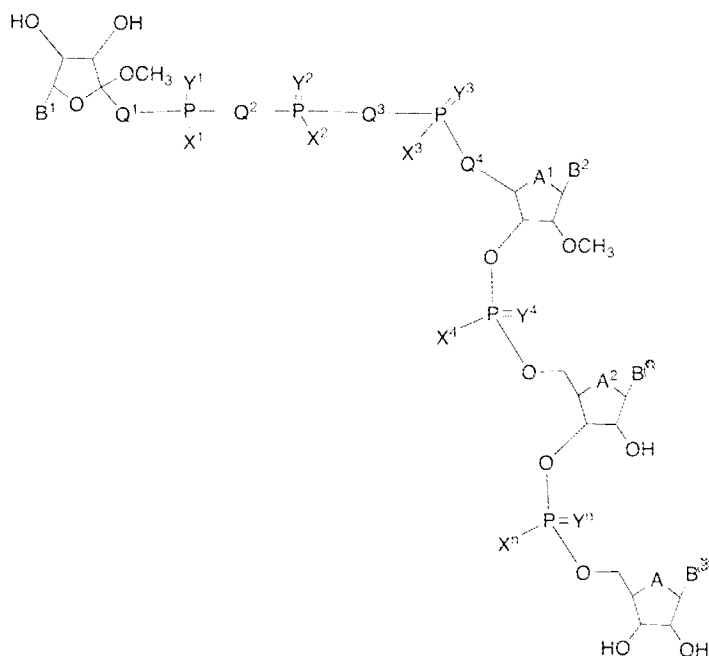
Formula (II-t').

[0447] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-u):



Formula (II-u).

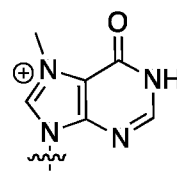
[0448] In some embodiments, the IVT mRNA sequence initiator has a structure of Formula (II-u'):



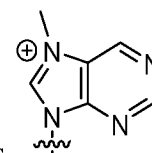
Formula (II-u').

[0449] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each B independently is a natural nucleobase. In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each B independently is a modified nucleobase. In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each B independently is an unnatural nucleobase.

[0450] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B¹ is



[0451] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B¹ is



[0452] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Z¹ is fluorine.

[0453] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Z¹ is -OH.

[0454] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Z¹ is -OCH₃.

[0455] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Z² is fluorine.

[0456] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Z² is -OH.

[0457] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Z² is -OCH₃.

[0458] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q¹ is -CH₂O-.

[0459] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q¹ is -O-.

[0460] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q⁴ is -CH₂O-.

[0461] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q⁴ is -O-.

- [0462] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q^2 is $-O-$.
- [0463] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q^3 is $-O-$.
- [0464] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^1 is $=O$.
- [0465] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^3 is $=O$.
- [0466] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^2 is $=O$.
- [0467] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^4 is $=O$.
- [0468] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^n is $=O$.
- [0469] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), one or more of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is $=S$.
- [0470] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^2 is $=S$.
- [0471] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^4 is $=S$.
- [0472] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Y^n is $=S$.
- [0473] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is $=O$.
- [0474] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each X^1 , X^4 , and X^n is $-O-$.
- [0475] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), X^2 is $-O-$.
- [0476] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), X^3 is $-O-$.
- [0477] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), one or more of X^1 , X^2 , X^3 , X^4 , and X^n is $-S-$.
- [0478] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), X^2 is $-S-$.
- [0479] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), X^4 is $-S-$.
- [0480] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), X^3 is $-S-$.
- [0481] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each X^1 , X^2 , X^3 , X^4 , and X^n is $-O-$.
- [0482] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each A , A^1 , and A^2 is $-O-$.
- [0483] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), one or more of A , A^1 , and A^2 is $-S-$. In some embodiments, A is $-S-$. In some embodiments, A^1 is $-O-$. In some embodiments, A^2 is $-O-$. In some embodiments, A^2 is $-S-$. In some embodiments, A is $-O-$. In some embodiments, A^1 is $-O-$.
- [0484] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), p is 0. In some embodiments, p is 1. In some embodiments, p is 2.
- [0485] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B^2 is adenine,

cytosine, guanine, uracil, thymine, hypoxanthine, or purine.

[0486] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B³ is adenine, cytosine, guanine, uracil, thymine, hypoxanthine, or purine.

[0487] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Bⁿ is adenine, cytosine, guanine, uracil, thymine, hypoxanthine, or purine.

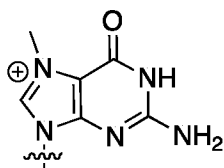
[0488] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q¹ is -CH₂O-. In some embodiments, Q⁴ is -CH₂O-.

[0489] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q² is -O-. In some embodiments, Q³ is -O-.

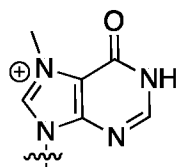
[0490] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each Xⁿ is independently -OH, -SH, O⁻, or S⁻.

[0491] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), each Yⁿ is independently =O or =S.

[0492] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B¹ is

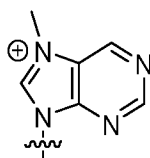


[0493] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q¹ is -CH₂O-; Q⁴ is -CH₂O-; Q² is -O-; Q³ is -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently



=O or =S; B¹ is

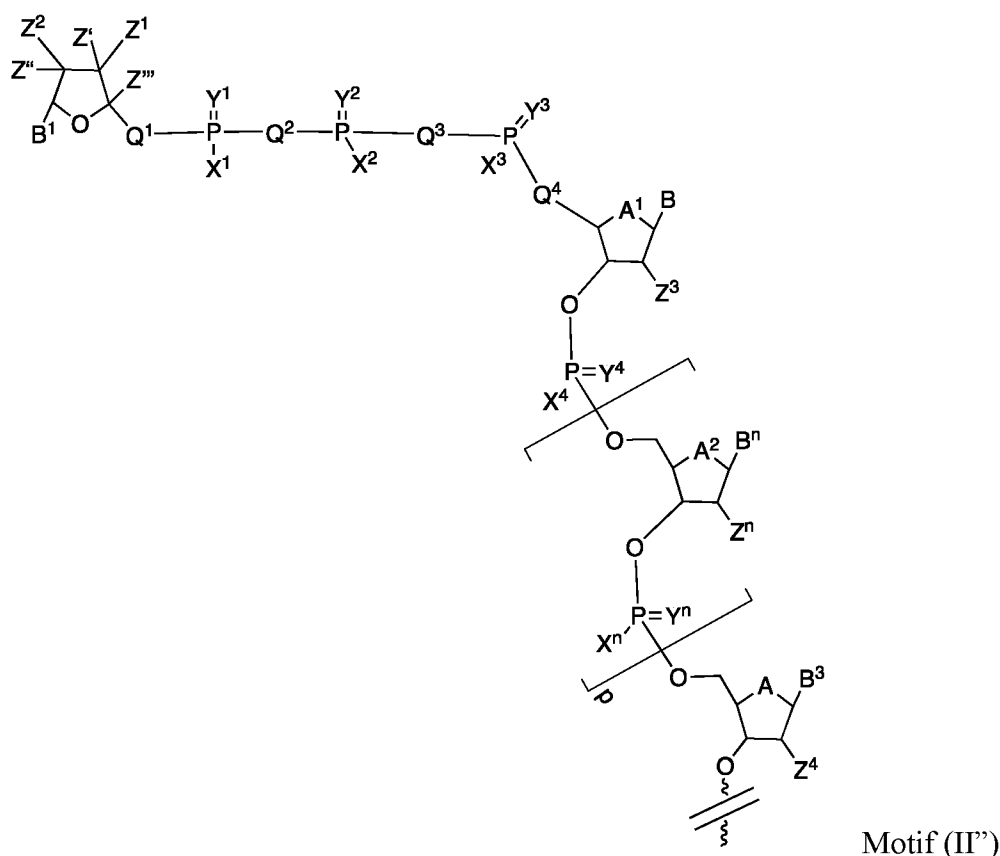
[0494] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), Q¹ is -CH₂O-; Q⁴ is -CH₂O-; Q² is -O-; Q³ is -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently



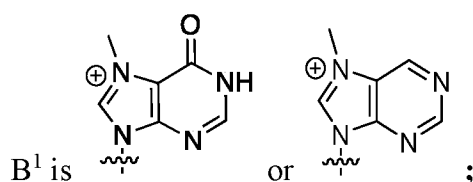
=O or =S; B¹ is

[0495] In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B² is adenine. In some embodiments of Formula (II) or Formulas (II-a) to (II-u'), B³ is guanine.

[0496] In one aspect, described herein is a mRNA sequence having a 5'-end region motif (Motif (II')):



wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z¹ and Z² is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

Z^{'''} is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

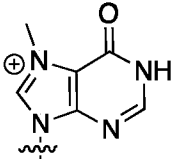
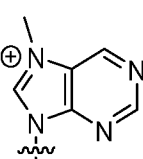
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

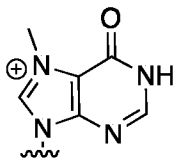
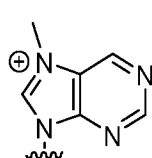
each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

p = 0, 1, 2, 3, 4, 5 or 6.

[0497] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-

p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), B¹ is  or . In some

embodiments, B¹ is . In some embodiments, B¹ is .

[0498] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), B² independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B² is adenine. In some embodiments, B² is guanine. In some embodiments, B² is cytosine. In some embodiments, B² is uracil, In some embodiments, B² is thymine, In some embodiments, B² is hypoxanthine. In some embodiments, B² is purine.

[0499] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), B³ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, B³ is adenine. In some embodiments, B³ is guanine. In some embodiments, B³ is cytosine. In some embodiments, B³ is uracil, In some embodiments, B³ is thymine, In some embodiments, B³ is hypoxanthine. In some embodiments, B³ is purine.

[0500] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Bⁿ independently a natural, a modified, or an unnatural nucleobase. In some embodiments, Bⁿ is adenine. In some embodiments, Bⁿ is guanine. In some embodiments, Bⁿ is cytosine. In some embodiments, Bⁿ is uracil, In some embodiments, Bⁿ is thymine, In some embodiments, Bⁿ is hypoxanthine. In some embodiments, Bⁿ is purine.

[0501] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z' is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z' is

hydrogen. In some embodiments, Z' is fluorine. In some embodiments, Z' is -OH. In some embodiments, Z' is -SH. In some embodiments, Z' is -CH₃. In some embodiments, Z' is -CH₂CH₃. In some embodiments, Z' is -OCH₃. In some embodiments, Z' is -NH(CH₃). In some embodiments, Z' is -NH₂-. In some embodiments, Z' is -NH(C(=O)CH₃). In some embodiments, Z' is -SCH₃.

[0502] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z'' is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂-, -NH(C(=O)CH₃), or -SCH₃. In some embodiments, Z'' is hydrogen. In some embodiments, Z'' is fluorine. In some embodiments, Z'' is -OH. In some embodiments, Z'' is -SH. In some embodiments, Z'' is -CH₃. In some embodiments, Z'' is -CH₂CH₃. In some embodiments, Z'' is -OCH₃. In some embodiments, Z'' is -NH(CH₃). In some embodiments, Z'' is -NH₂-. In some embodiments, Z'' is -NH(C(=O)CH₃). In some embodiments, Z'' is -SCH₃.

[0503] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃. In some embodiments, Z''' is hydrogen. In some embodiments, Z''' is fluorine. In some embodiments, Z''' is -CH₃. In some embodiments, Z''' is -CH₂CH₃. In some embodiments, Z''' is -OCH₃. In some embodiments, Z''' is -OCH₂CH₃.

[0504] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z¹ is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z¹ is hydrogen. In some embodiments, Z¹ is fluorine. In some embodiments, Z¹ is -OH. In some embodiments, Z¹ is -SH. In some embodiments, Z¹ is -CH₃. In some embodiments, Z¹ is -CH₂CH₃. In some embodiments, Z¹ is -OCH₃. In some embodiments, Z¹ is -SCH₃. In some embodiments, Z¹ is -OCH₂CH₃. In some embodiments, Z¹ is -NH₂. In some embodiments, Z¹ is NHCH₃. In some embodiments, Z¹ is NHC(=O)CH₃.

[0505] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z² is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃. In some embodiments, Z² is hydrogen. In some embodiments, Z² is fluorine. In some embodiments, Z² is -OH. In some embodiments, Z² is -SH. In some embodiments, Z² is -CH₃. In some embodiments, Z² is -CH₂CH₃. In some embodiments, Z² is -OCH₃. In some embodiments, Z² is -SCH₃. In some embodiments, Z²

is $-OCH_2CH_3$. In some embodiments, Z^2 is $-NH_2$. In some embodiments, Z^2 is $NHCH_3$. In some embodiments, Z^2 is $NHC(=O)CH_3$.

[0506] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z^3 is hydrogen, fluorine, $-OH$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-OCH_2CH_3$, $-OCH_2OCH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-SCH_3$, or $-OCH_2CH_2OCH_3$. In some embodiments, Z^3 is hydrogen. In some embodiments, Z^3 is fluorine. In some embodiments, Z^3 is $-OH$. In some embodiments, Z^3 is $-CH_3$. In some embodiments, Z^3 is $-CH_2CH_3$. In some embodiments, Z^3 is $-OCH_3$. In some embodiments, Z^3 is $-NH_2$. In some embodiments, Z^3 is $-NHCH_3$. In some embodiments, Z^3 is $-NH(C(=O)CH_3)$. In some embodiments, Z^3 is $-OCH_2CH_3$. In some embodiments, Z^3 is $-OCH_2OCH_3$. In some embodiments, Z^3 is $-OCH_2CH_2CH_3$. In some embodiments, Z^3 is $-OCH(CH_3)_2$. In some embodiments, Z^3 is $-SCH_3$. In some embodiments, Z^3 is $-OCH_2CH_2OCH_3$.

[0507] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z^4 is hydrogen, fluorine, $-OH$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-OCH_2CH_3$, $-OCH_2OCH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-SCH_3$, or $-OCH_2CH_2OCH_3$. In some embodiments, Z^4 is hydrogen. In some embodiments, Z^4 is fluorine. In some embodiments, Z^4 is $-OH$. In some embodiments, Z^4 is $-CH_3$. In some embodiments, Z^4 is $-CH_2CH_3$. In some embodiments, Z^4 is $-OCH_3$. In some embodiments, Z^4 is $-NH_2$. In some embodiments, Z^4 is $-NHCH_3$. In some embodiments, Z^4 is $-NH(C(=O)CH_3)$. In some embodiments, Z^4 is $-OCH_2CH_3$. In some embodiments, Z^4 is $-OCH_2OCH_3$. In some embodiments, Z^4 is $-OCH_2CH_2CH_3$. In some embodiments, Z^4 is $-OCH(CH_3)_2$. In some embodiments, Z^4 is $-SCH_3$. In some embodiments, Z^4 is $-OCH_2CH_2OCH_3$.

[0508] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Z^n is hydrogen, fluorine, $-OH$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-OCH_2CH_3$, $-OCH_2OCH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-SCH_3$, or $-OCH_2CH_2OCH_3$. In some embodiments, Z^n is hydrogen. In some embodiments, Z^n is fluorine. In some embodiments, Z^n is $-OH$. In some embodiments, Z^n is $-CH_3$. In some embodiments, Z^n is $-CH_2CH_3$. In some embodiments, Z^n is $-OCH_3$. In some embodiments, Z^n is $-NH_2$. In some embodiments, Z^n is $-NHCH_3$. In some embodiments, Z^n is $-NH(C(=O)CH_3)$. In some embodiments, Z^n is $-OCH_2CH_3$. In some embodiments, Z^n is $-OCH_2OCH_3$. In some embodiments, Z^n is $-OCH_2CH_2CH_3$. In some embodiments, Z^n is $-OCH(CH_3)_2$. In some embodiments, Z^n is $-SCH_3$. In some embodiments, Z^n is $-OCH_2CH_2OCH_3$.

some embodiments, X^1 is $-S^-$. In some embodiments, X^1 is $-NH_2$. In some embodiments, X^1 is $-NHCH_3$. In some embodiments, X^1 is $-NH(C(=O)CH_3)$. In some embodiments, X^1 is $-CH_3$. In some embodiments, X^1 is $-CH_2CH_3$. In some embodiments, X^1 is $-CH_2CH_2CH_3$. In some embodiments, X^1 is $-CH(CH_3)_2$. In some embodiments, X^1 is $-OCH_3$. In some embodiments, X^1 is $-OCH_2CH_3$.

[0514] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), X^2 is $-OH$, $-SH$, $-O^-$, $-S^-$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^2 is $-OH$. In some embodiments, X^2 is $-SH$. In some embodiments, X^2 is $-O^-$. In some embodiments, X^2 is $-S^-$. In some embodiments, X^2 is $-NH_2$. In some embodiments, X^2 is $-NHCH_3$. In some embodiments, X^2 is $-NH(C(=O)CH_3)$. In some embodiments, X^2 is $-CH_3$. In some embodiments, X^2 is $-CH_2CH_3$. In some embodiments, X^2 is $-CH_2CH_2CH_3$. In some embodiments, X^2 is $-CH(CH_3)_2$. In some embodiments, X^2 is $-OCH_3$. In some embodiments, X^2 is $-OCH_2CH_3$.

[0515] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), X^3 is $-OH$, $-SH$, $-O^-$, $-S^-$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^3 is $-OH$. In some embodiments, X^3 is $-SH$. In some embodiments, X^3 is $-O^-$. In some embodiments, X^3 is $-S^-$. In some embodiments, X^3 is $-NH_2$. In some embodiments, X^3 is $-NHCH_3$. In some embodiments, X^3 is $-NH(C(=O)CH_3)$. In some embodiments, X^3 is $-CH_3$. In some embodiments, X^3 is $-CH_2CH_3$. In some embodiments, X^3 is $-CH_2CH_2CH_3$. In some embodiments, X^3 is $-CH(CH_3)_2$. In some embodiments, X^3 is $-OCH_3$. In some embodiments, X^3 is $-OCH_2CH_3$.

[0516] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), X^4 is $-OH$, $-SH$, $-O^-$, $-S^-$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$ or $-OCH_2CH_3$. In some embodiments, X^4 is $-OH$. In some embodiments, X^4 is $-SH$. In some embodiments, X^4 is $-O^-$. In some embodiments, X^4 is $-S^-$. In some embodiments, X^4 is $-NH_2$. In some embodiments, X^4 is $-NHCH_3$. In some embodiments, X^4 is $-NH(C(=O)CH_3)$. In some embodiments, X^4 is $-CH_3$. In some embodiments, X^4 is $-CH_2CH_3$. In some embodiments, X^4 is $-CH_2CH_2CH_3$. In some embodiments, X^4 is $-CH(CH_3)_2$. In some embodiments, X^4 is $-OCH_3$. In some embodiments, X^4 is $-OCH_2CH_3$.

[0517] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), X^n is $-OH$, $-SH$, $-O^-$, $-S^-$, $-NH_2$, $-NHCH_3$, $-$

NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃. In some embodiments, Xⁿ is -OH. In some embodiments, Xⁿ is -SH. In some embodiments, Xⁿ is -O[·]. In some embodiments, Xⁿ is -S[·]. In some embodiments, Xⁿ is -NH₂. In some embodiments, Xⁿ is -NHCH₃. In some embodiments, Xⁿ is -NH(C(=O)CH₃). In some embodiments, Xⁿ is -CH₃. In some embodiments, Xⁿ is -CH₂CH₃. In some embodiments, Xⁿ is -CH₂CH₂CH₃. In some embodiments, Xⁿ is -CH(CH₃)₂. In some embodiments, Xⁿ is -OCH₃. In some embodiments, Xⁿ is -OCH₂CH₃.

[0518] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Y¹ is =O, =S, =NH, or =NCH₃. In some embodiments, Y¹ is =O. In some embodiments, Y¹ is =S. In some embodiments, Y¹ is =NH. In some embodiments, Y¹ is =NCH₃.

[0519] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Y² is =O, =S, =NH, or =NCH₃. In some embodiments, Y² is =O. In some embodiments, Y² is =S. In some embodiments, Y² is =NH. In some embodiments, Y² is =NCH₃.

[0520] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Y³ is =O, =S, =NH, or =NCH₃. In some embodiments, Y³ is =O. In some embodiments, Y³ is =S. In some embodiments, Y³ is =NH. In some embodiments, Y³ is =NCH₃.

[0521] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Y⁴ is =O, =S, =NH, or =NCH₃. In some embodiments, Y⁴ is =O. In some embodiments, Y⁴ is =S. In some embodiments, Y⁴ is =NH. In some embodiments, Y⁴ is =NCH₃.

[0522] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), Yⁿ is =O, =S, =NH, or =NCH₃. In some embodiments, Yⁿ is =O. In some embodiments, Yⁿ is =S. In some embodiments, Yⁿ is =NH. In some embodiments, Yⁿ is =NCH₃.

[0523] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), A is -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -

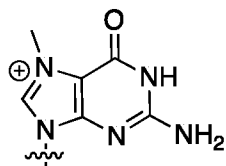
$\text{N}(\text{C}(\text{=O})\text{CH}_3)-$. In some embodiments, A is $-\text{O}-$. In some embodiments, A is $-\text{S}-$. In some embodiments, A is $-\text{CH}_2-$. In some embodiments, A is $-\text{NH}-$. In some embodiments, A is $-\text{N}(\text{CH}_3)-$. In some embodiments, A is $-\text{N}(\text{C}(\text{=O})\text{CH}_3)-$.

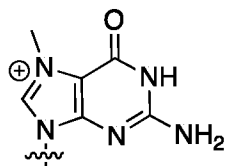
[0524] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), A^1 is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$ or $-\text{N}(\text{C}(\text{=O})\text{CH}_3)-$. In some embodiments, A^1 is $-\text{O}-$. In some embodiments, A^1 is $-\text{S}-$. In some embodiments, A^1 is $-\text{CH}_2-$. In some embodiments, A^1 is $-\text{NH}-$. In some embodiments, A^1 is $-\text{N}(\text{CH}_3)-$. In some embodiments, A^1 is $-\text{N}(\text{C}(\text{=O})\text{CH}_3)-$.

[0525] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), A^2 is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$ or $-\text{N}(\text{C}(\text{=O})\text{CH}_3)-$. In some embodiments, A^2 is $-\text{O}-$. In some embodiments, A^2 is $-\text{S}-$. In some embodiments, A^2 is $-\text{CH}_2-$. In some embodiments, A^2 is $-\text{NH}-$. In some embodiments, A^2 is $-\text{N}(\text{CH}_3)-$. In some embodiments, A^2 is $-\text{N}(\text{C}(\text{=O})\text{CH}_3)-$.

[0526] In some embodiments of a compound of Motif (II''), (II''-a'), (II''-b'), (II''-c'), (II''-d'), (II''-e'), (II''-f'), (II''-g'), (II''-h'), (II''-i'), (II''-j'), (II''-k'), (II''-l'), (II''-m'), (II''-n'), (II''-o'), (II''-p'), (II''-q'), (II''-r'), (II''-s'), (II''-t'), or (II''-u'), p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4. In some embodiments, p is 5. In some embodiments, p is 6.

[0527]



[0528] In some embodiments, B^1 is . In some embodiments, each B^2 and B^3 is independently adenine or guanine. In some embodiments, B^2 is adenine. In some embodiments, B^3 is guanine.

[0529] In some embodiments, each Z^1 , Z^2 , Z^3 , and Z^4 is independently $-\text{OH}$ or $-\text{OCH}_3$. In some embodiments, Z^3 is $-\text{OCH}_3$. In some embodiments, Z^1 is $-\text{OCH}_3$. In some embodiments, Z^2 is $-\text{OH}$. In some embodiments, Z^1 , Z^2 , and Z^4 are $-\text{OH}$ and Z^3 is $-\text{OCH}_3$. In some embodiments, Z^1 and Z^3 are $-\text{OCH}_3$ and Z^2 and Z^4 are $-\text{OH}$. In some embodiments, Z' , Z'' , and Z''' are hydrogen.

[0530] In some embodiments, Q^1 and Q^4 are $-\text{OCH}_2-$. In some embodiments, Q^2 and Q^3 are $-\text{O}-$.

[0531] In some embodiments, X^1 , X^2 , X^3 , and X^4 are $-\text{O}-$. In some embodiments, X^1 , X^2 , X^3 , and X^4 are $-\text{S}-$. In some embodiments, X^1 , X^3 , X^4 are $-\text{O}-$ and X^2 is $-\text{S}-$.

[0532] In some embodiments, Y^1 , Y^2 , Y^3 , and Y^4 are $=\text{O}$. In some embodiments, Y^1 , Y^2 , Y^3 , and

Y^4 are =S. In some embodiments, Y^1 , Y^3 , and Y^4 are =O and Y^2 is =S. In some embodiments, Y^1 , Y^2 , Y^3 are =O and Y^4 is =S.

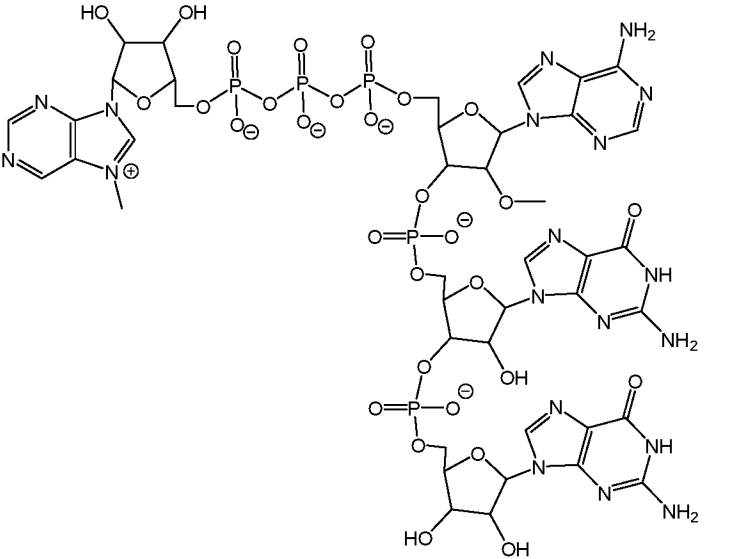
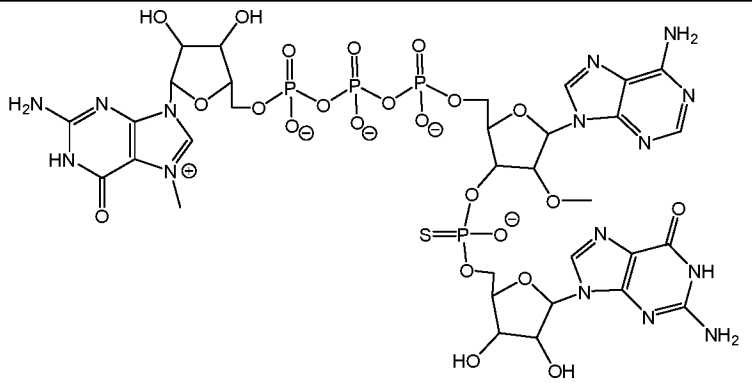
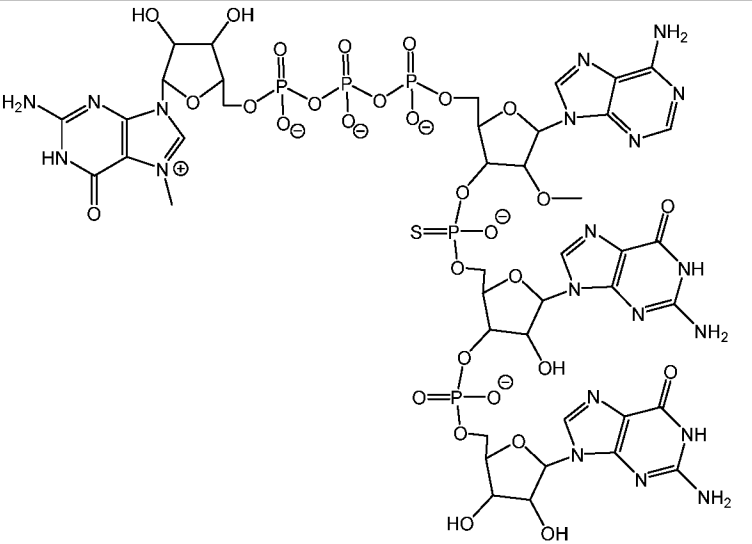
[0533] In some embodiments, A, A^1 , and A^2 are -O-.

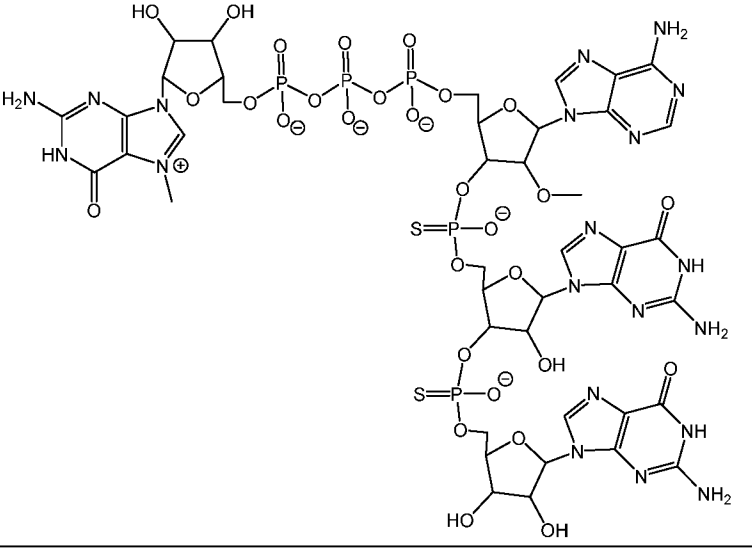
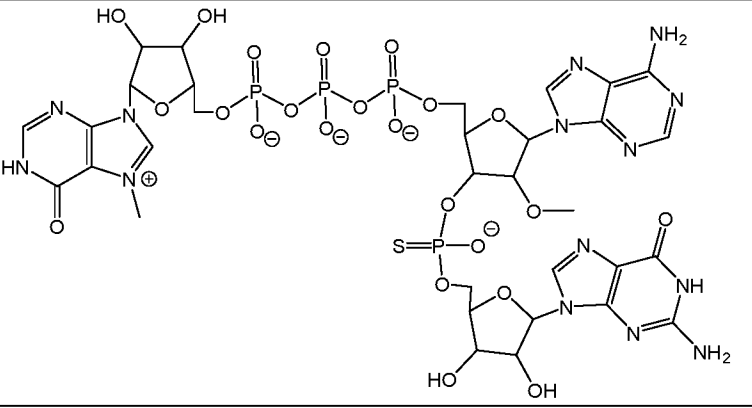
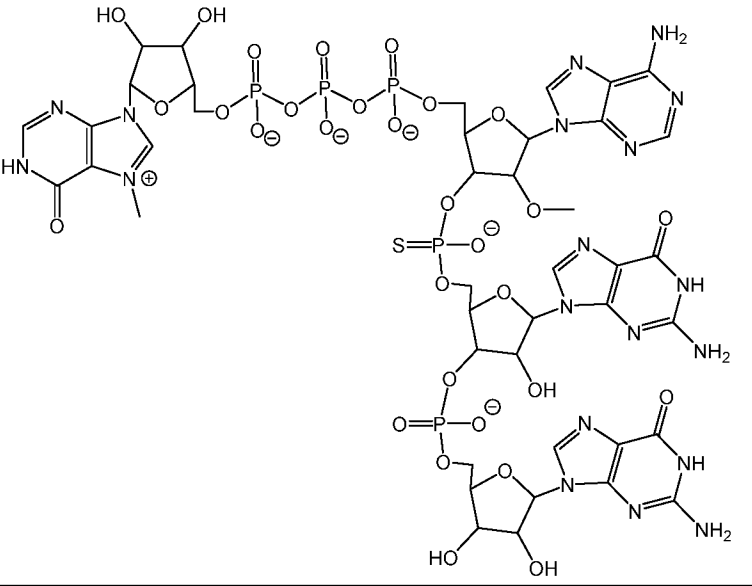
[0534] In some embodiments, p is 0.

[0535] In certain embodiments the sequence initiator compound is as described in Table 1.

Table 1

Compound ID	Name	Chemical Structure
1002e	$m^7I(ppp)Am(p)G$	
1002i	$m^7E(ppp)Am(p)G$	
5201	$m^7I(ppp)Am(p)G(p)G$	

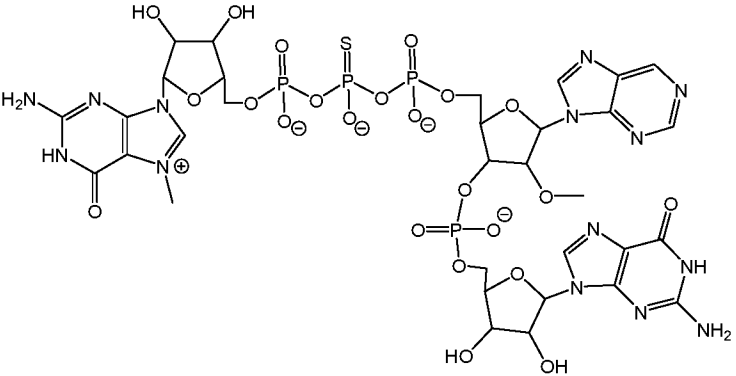
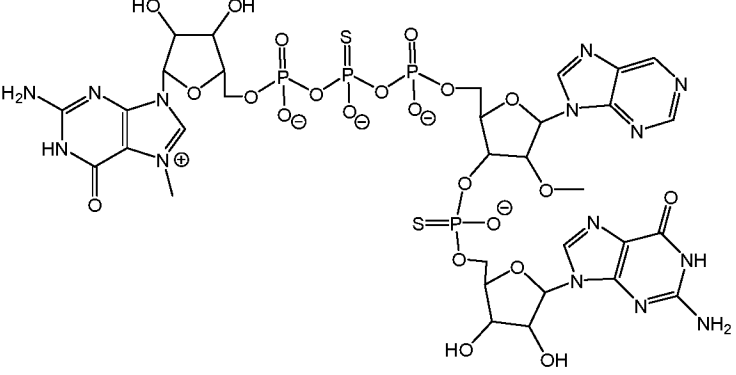
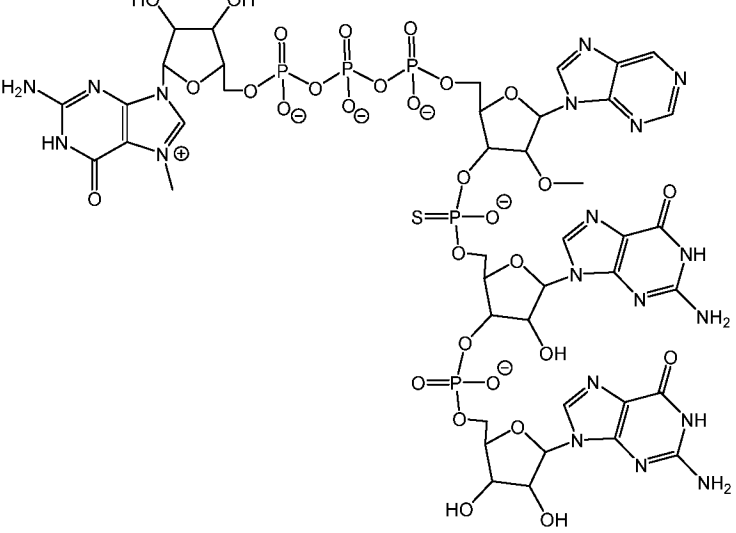
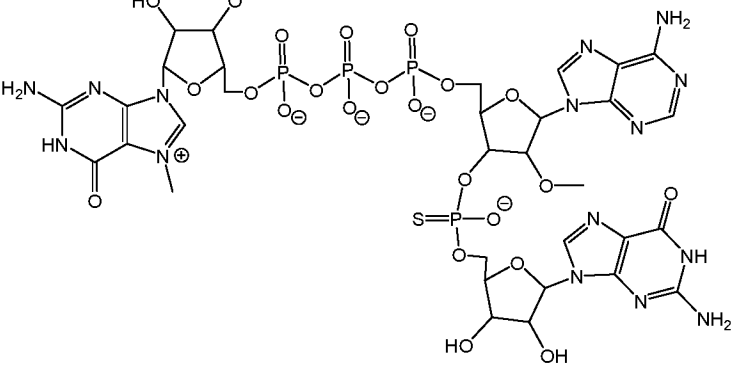
5202	$m^7E(ppp)Am(p)G(p)G$	
1007a	$m^7G(ppp)Am(ps)G$	
5203	$m^7G(ppp)Am(ps)G(p)G$	

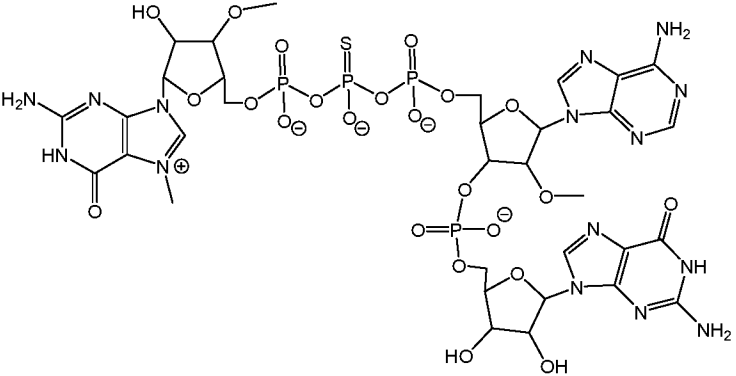
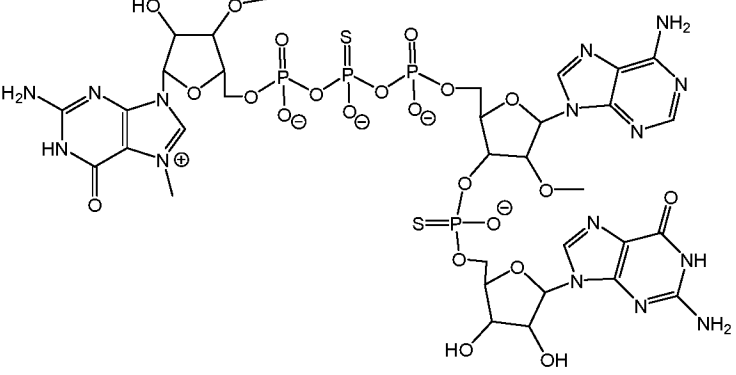
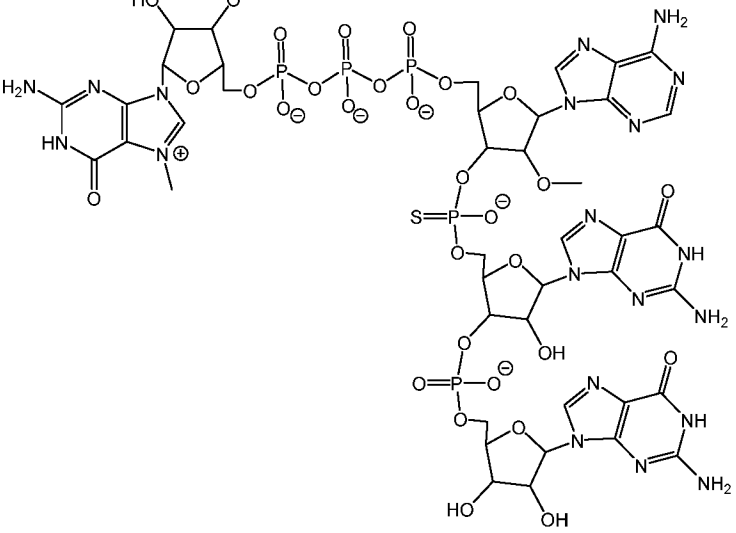
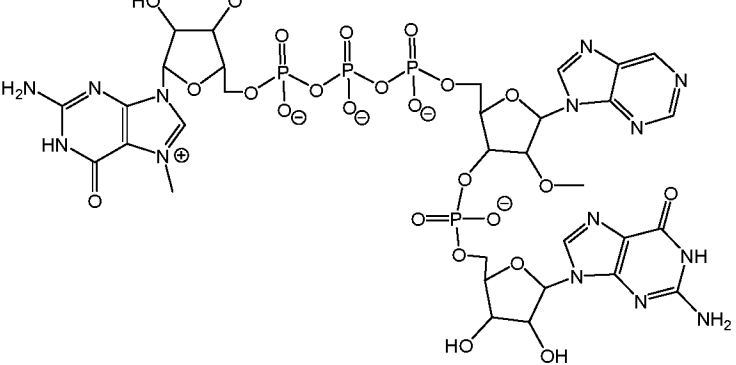
5204	$m^7G(ppp)Am(ps)G(ps)G$	
1007e	$m^7I(ppp)Am(ps)G$	
5205	$m^7I(ppp)Am(ps)G(p)G$	

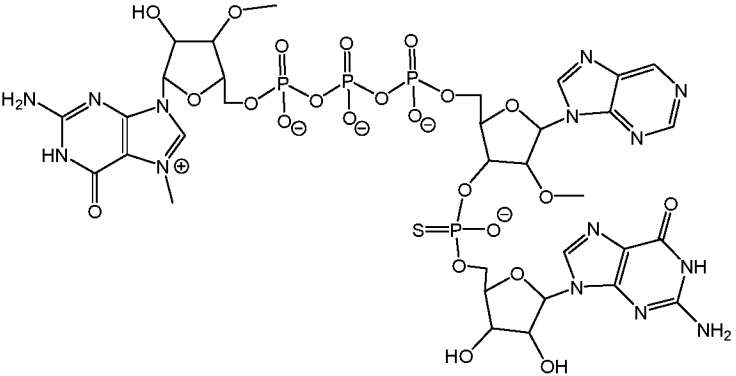
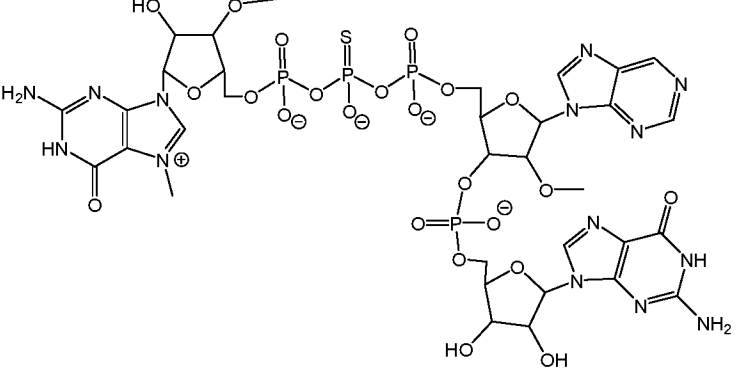
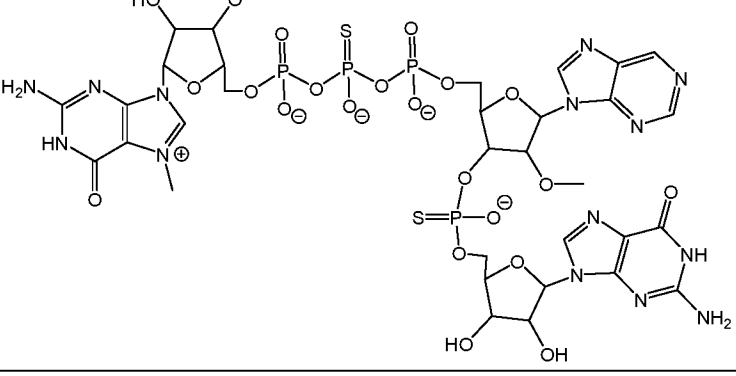
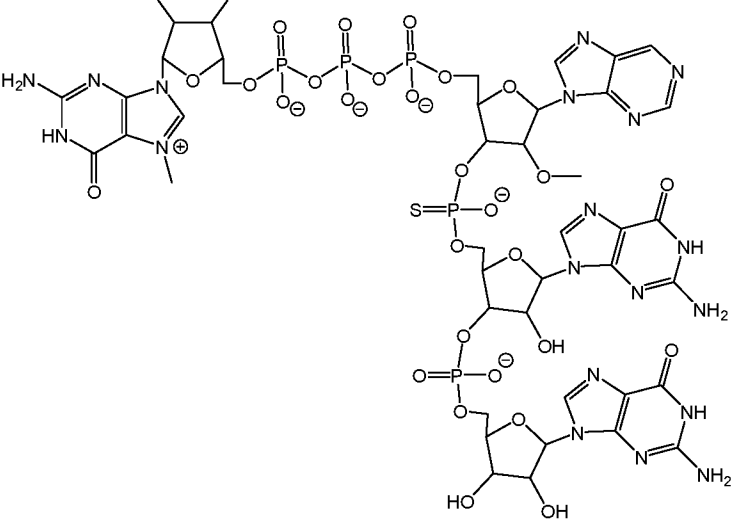
1007i	$m^7E(ppp)Am(ps)G$	
5206	$m^7E(ppp)Am(ps)G(p)G$	
1032a	$m^7G(ppsps)Am(p)G$	
1037a	$m^7G(ppsps)Am(ps)G$	

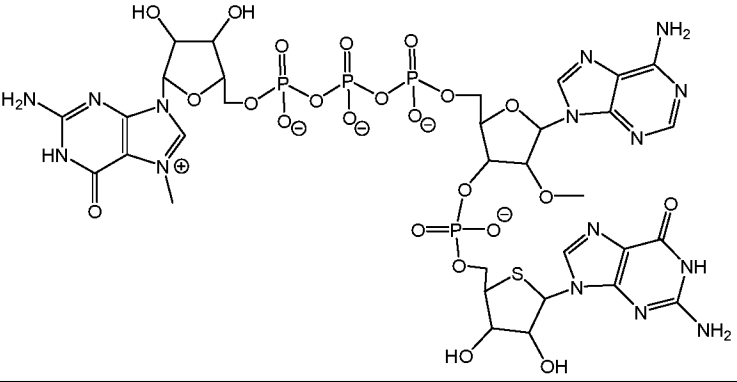
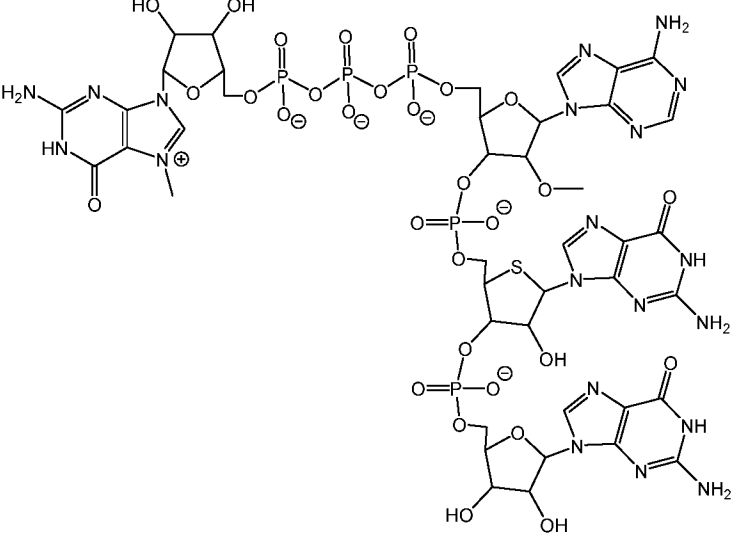
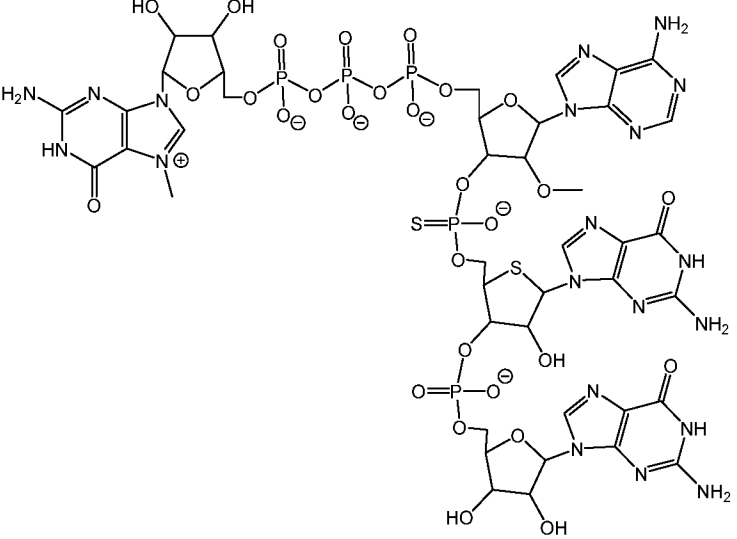
1107a	$m^7G(ppsp)Am(p)G$	
5207	$m^7G(ppsp)Am(p)G(p)G$	
1112a	$m^7G(ppsp)Am(ps)G$	
1137a	$m^7G(ppssp)Am(p)G$	

1141a	$m^7G(ppssp)Am(ps)G$	
5208	$m^7G(ppssp)Am(p)G(p)G$	
3102a	$m^7G(ppp)Em(p)G$	
3107a	$m^7G(ppp)Em(ps)G$	

3207a	$m^7G(ppsp)Em(p)G$	
3212a	$m^7G(ppsp)Em(ps)G$	
5209	$m^7G(ppp)Em(ps)G(p)G$	
1007c	$m^7G(3'OMe)(ppp)Am(ps)G$	

1107c	$m^7G(3'OMe)(ppsp)Am(p)_G$	
1112c	$m^7G(3'OMe)(ppsp)Am(ps)_G$	
5210	$m^7G(3'OMe)(ppp)Am(ps)_G(p)G$	
3102c	$m^7G(3'OMe)(ppp)Em(p)_G$	

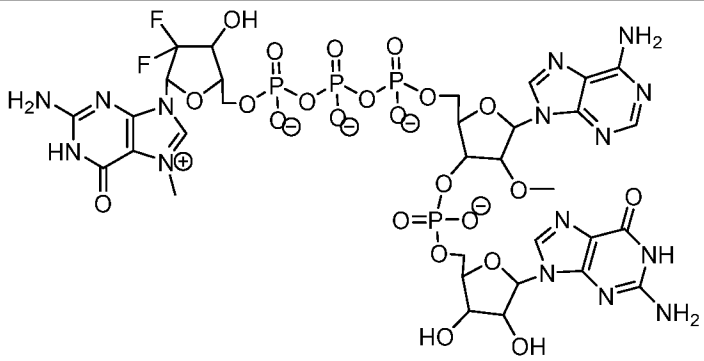
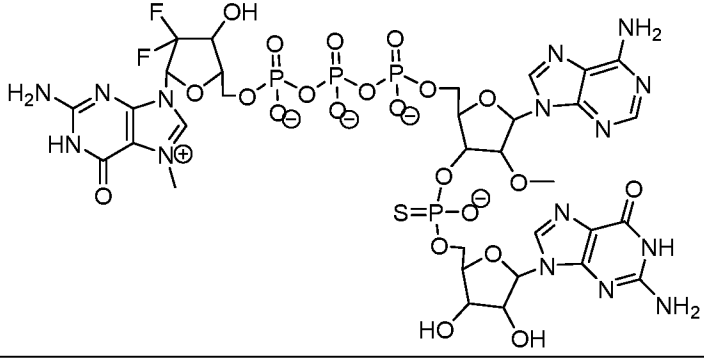
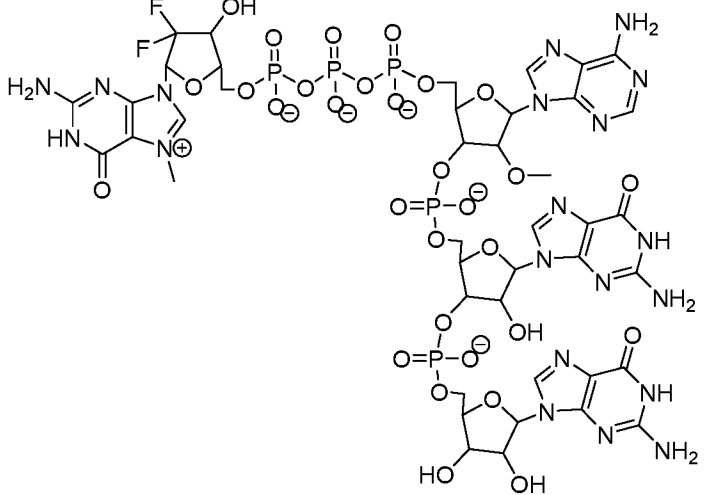
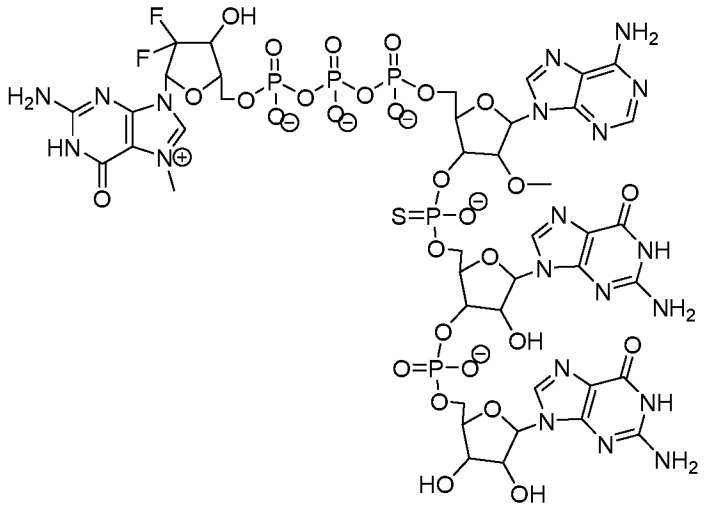
3107c	$m^7G(3'OMe)(ppp)Em(ps)_G$	
3207c	$m^7G(3'OMe)(ppsp)Em(p)_G$	
3212c	$m^7G(3'OMe)(ppsp)Em(ps)_G$	
5211	$m^7G(3'OMe)(ppp)Em(ps)_G(p)G$	

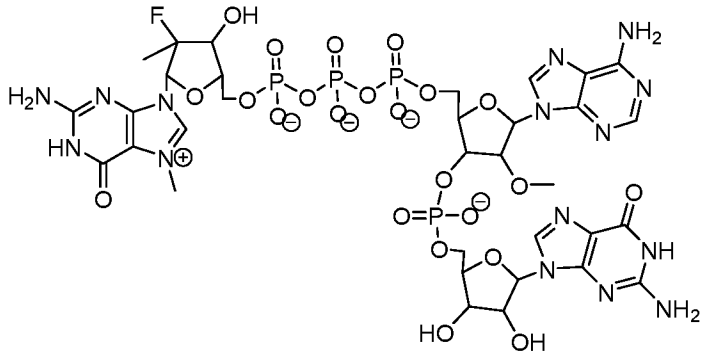
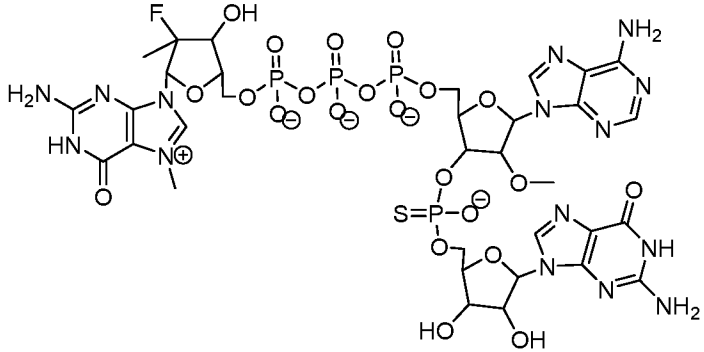
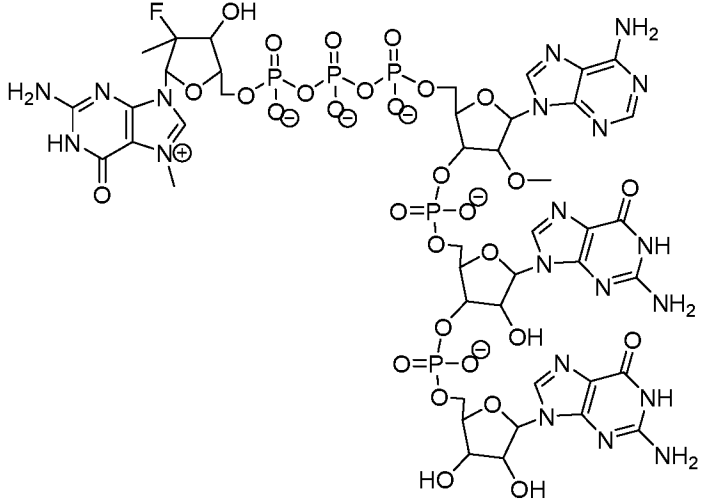
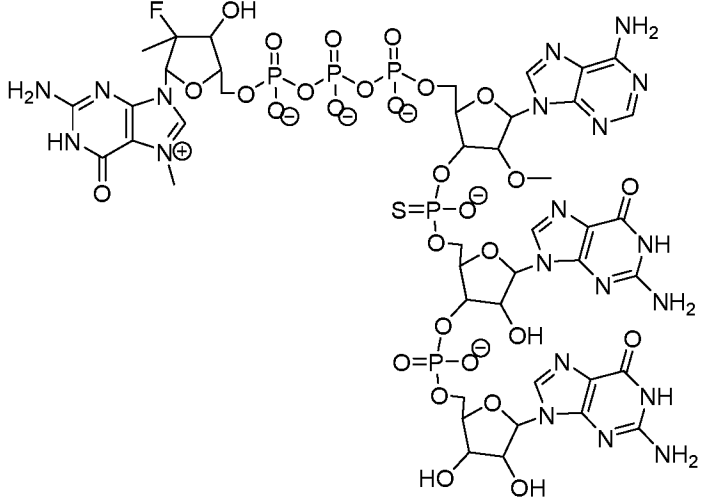
5212	$m^7G(ppp)Am(p)G(4\text{-thio})$	
5213	$m^7G(ppp)Am(p)G(4\text{-thio})(p)G$	
5214	$m^7G(ppp)Am(ps)G(4\text{-thio})(p)G$	

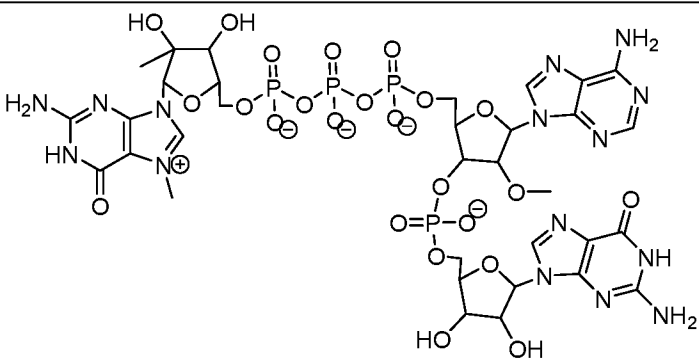
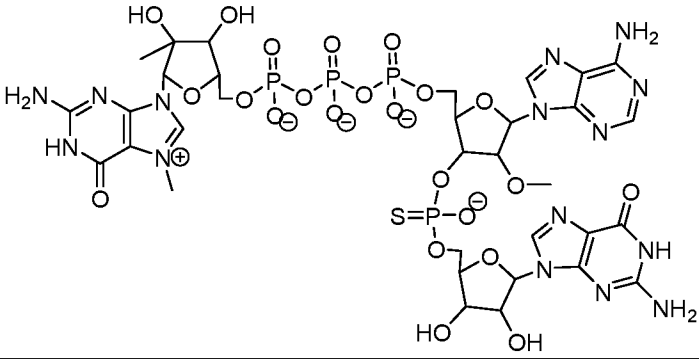
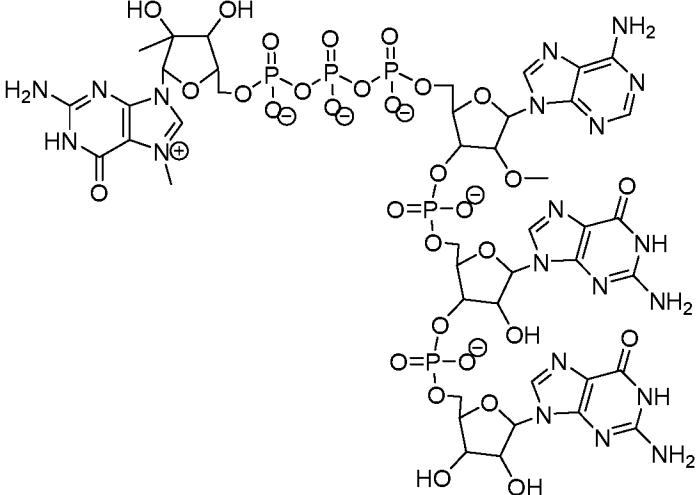
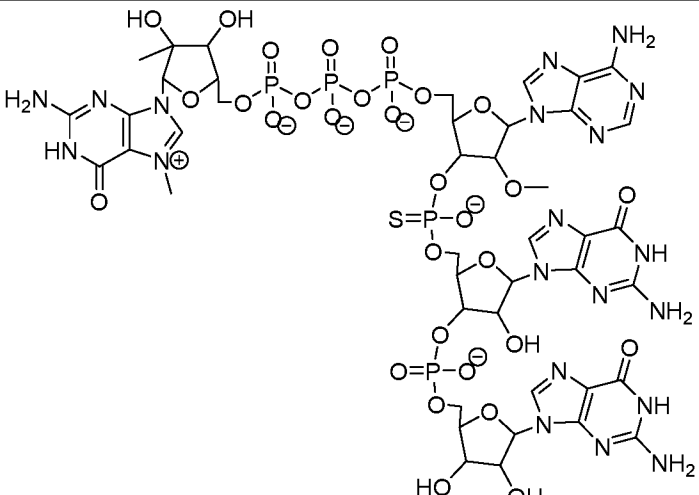
[0536] In some embodiments, disclosed herein is a pharmaceutically acceptable salt or pharmaceutically acceptable solvate or a pharmaceutical composition comprising one or more mRNA(s) which is/are produced/manufactured from one or more sequence initiator compound selected from Table 1, wherein the mRNA encode(s) one or more pharmaceutically active protein(s).

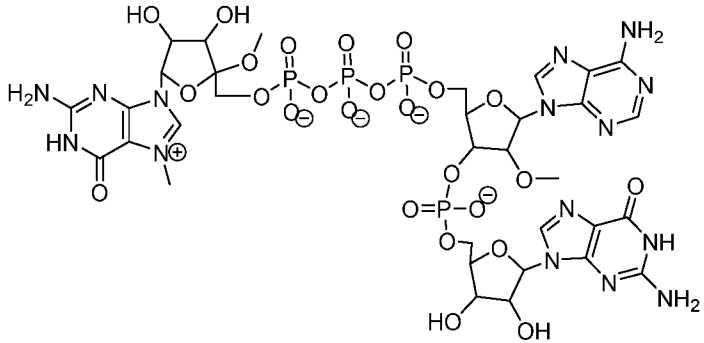
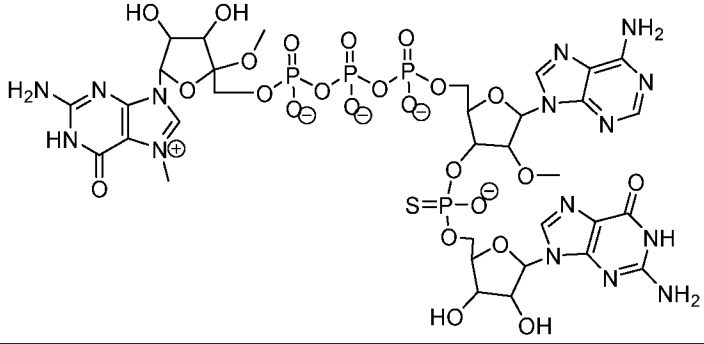
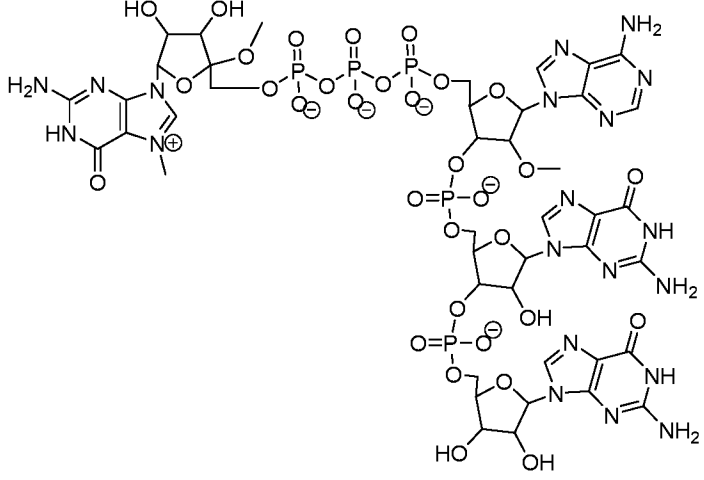
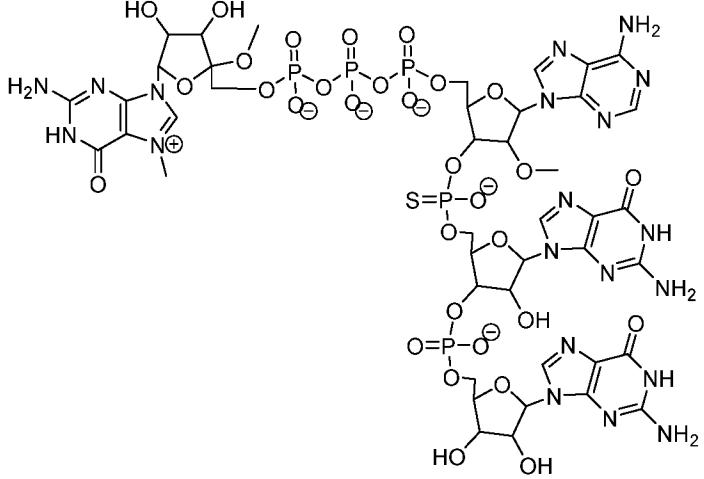
[0537] In certain embodiments the sequence initiator compound is as described in Table 2.

Table 2

5215	$m^7G(2'F-2'F)(ppp)Am(p)G$	
5216	$m^7G(2'F-2'F)(ppp)Am(ps)G$	
5217	$m^7G(2'F-2'F)(ppp)Am(p)G(p)G$	
5218	$m^7G(2'F-2'F)(ppp)Am(ps)G(p)G$	

5219	$m^7G(2'F-2'Me)(ppp)Am(p)G$	
5220	$m^7G(2'F-2'Me)(ppp)Am(ps)G$	
5221	$m^7G(2'F-2'Me)(ppp)Am(p)G(p)G$	
5222	$m^7G(2'F-2'Me)(ppp)Am(ps)G(p)G$	

5223	$m^7G(2'Me-2'OH)(ppp)Am(p)G$	
5224	$m^7G(2'Me-2'OH)(ppp)Am(ps)G$	
5225	$m^7G(2'Me-2'OH)(ppp)Am(p)G(p)G$	
5226	$m^7G(2'Me-2'OH)(ppp)Am(ps)G(p)G$	

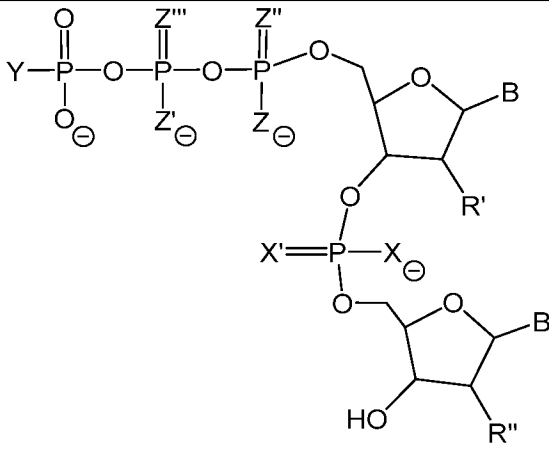
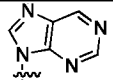
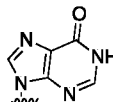
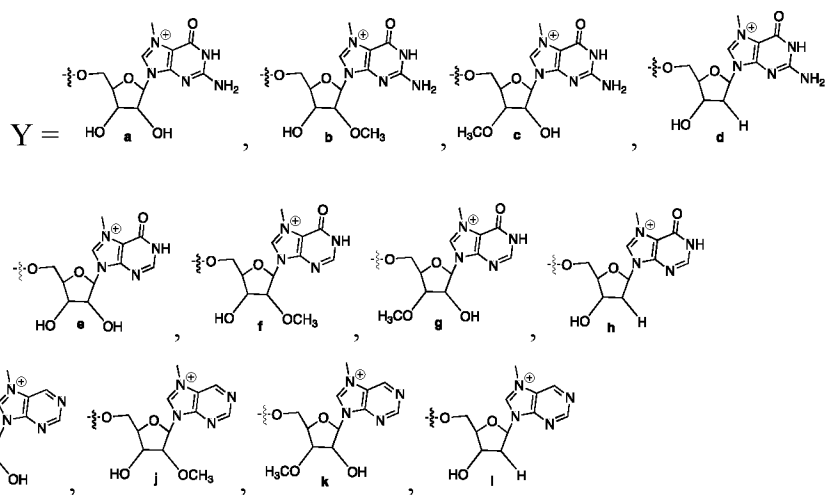
5227	$m^7G(4'OMe)(ppp)Am(p)G$	
5228	$m^7G(4'OMe)(ppp)Am(ps)G$	
5229	$m^7G(4'OMe)(ppp)Am(p)G(p)G$	
5230	$m^7G(4'OMe)(ppp)Am(ps)G(p)G$	

[0538] In some embodiments, disclosed herein is a pharmaceutically acceptable salt or pharmaceutically acceptable solvate or a pharmaceutical composition comprising one or more mRNA(s) which is/are produced/manufactured from one or more sequence initiator compound

selected from Table 2, wherein the mRNA encode(s) one or more pharmaceutically active protein(s).

[0539] In certain embodiments the sequence initiator compound is as described in Table 3.

Table 3

Table 3. CapA Structures for mRNA preparation									
									
Y*NN (1001a-l to 4360a-l) B is Adenine (A), Cytosine (C), Guanine (G), Uracil (U), Thymine (T), Hypoxanthine (I) or Purine (E); X is O or S and X' is O or S; Z is O or S and Z' is O or S and Z'' is O or S and Z''' is O or S; R' is OH, OMe, H, F, or OEt and R'' is OH or OMe Each N in Y*NN indicates nucleotide/nucleoside carrying A, C, G, U, T, I or E, where NN is a dinucleotide moiety of any combination of A, C, G, U, T, I and E									
$\ast = \text{O}=\text{P}(\text{O}^-)-\text{O}-\text{P}(\text{O}^-)(\text{O}^-)-\text{X}-\text{P}(\text{O}^-)(\text{O}^-)(\text{O}^-)-$  Purine (E)  Hypoxanthine (I)		$Y =$ 							
Compound	Sequence	X	X'	Z	Z'	Z''	Z'''	R'	R''
1001a-l	Y*AG	O	O	O	O	O	O	OH	OH
1002a-l	Y*AG	O	O	O	O	O	O	OMe	OH
1003a-l	Y*AG	O	O	O	O	O	O	H	OH
1004a-l	Y*AG	O	O	O	O	O	O	F	OH
1005a-l	Y*AG	O	O	O	O	O	O	OEt	OH

1006a-l	Y*AG	S	O	O	O	O	O	OH	OH
1007a-l	Y*AG	S	O	O	O	O	O	OMe	OH
1008a-l	Y*AG	S	O	O	O	O	O	H	OH
1009a-l	Y*AG	S	O	O	O	O	O	F	OH
1010a-l	Y*AG	S	O	O	O	O	O	OEt	OH
1011a-l	Y*AG	S	S	O	O	O	O	OH	OH
1012a-l	Y*AG	S	S	O	O	O	O	OMe	OH
1013a-l	Y*AG	S	S	O	O	O	O	H	OH
1014a-l	Y*AG	S	S	O	O	O	O	F	OH
1015a-l	Y*AG	S	S	O	O	O	O	OEt	OH
1016a-l	Y*AG	O	O	S	O	O	O	OH	OH
1017a-l	Y*AG	O	O	S	O	O	O	OMe	OH
1018a-l	Y*AG	O	O	S	O	O	O	H	OH
1019a-l	Y*AG	O	O	S	O	O	O	F	OH
1020a-l	Y*AG	O	O	S	O	O	O	OEt	OH
1021a-l	Y*AG	S	O	S	O	O	O	OH	OH
1022a-l	Y*AG	S	O	S	O	O	O	OMe	OH
1023a-l	Y*AG	S	O	S	O	O	O	H	OH
1024a-l	Y*AG	S	O	S	O	O	O	F	OH
1025a-l	Y*AG	S	O	S	O	O	O	OEt	OH
1026a-l	Y*AG	S	S	S	O	O	O	OH	OH
1027a-l	Y*AG	S	S	S	O	O	O	OMe	OH
1028a-l	Y*AG	S	S	S	O	O	O	H	OH
1029a-l	Y*AG	S	S	S	O	O	O	F	OH
1030a-l	Y*AG	S	S	S	O	O	O	OEt	OH
1031a-l	Y*AG	O	O	S	S	O	O	OH	OH
1032a-l	Y*AG	O	O	S	S	O	O	OMe	OH
1033a-l	Y*AG	O	O	S	S	O	O	H	OH
1034a-l	Y*AG	O	O	S	S	O	O	F	OH
1035a-l	Y*AG	O	O	S	S	O	O	OEt	OH
1036a-l	Y*AG	S	O	S	S	O	O	OH	OH
1037a-l	Y*AG	S	O	S	S	O	O	OMe	OH
1038a-l	Y*AG	S	O	S	S	O	O	H	OH
1039a-l	Y*AG	S	O	S	S	O	O	F	OH
1040a-l	Y*AG	S	O	S	S	O	O	OEt	OH
1041a-l	Y*AG	S	S	S	S	O	O	OH	OH
1042a-l	Y*AG	S	S	S	S	O	O	OMe	OH
1043a-l	Y*AG	S	S	S	S	O	O	H	OH
1044a-l	Y*AG	S	S	S	S	O	O	F	OH
1045a-l	Y*AG	S	S	S	S	O	O	OEt	OH
1046a-l	Y*AG	O	O	S	S	S	O	OH	OH
1047a-l	Y*AG	O	O	S	S	S	O	OMe	OH
1048a-l	Y*AG	O	O	S	S	S	O	H	OH
1049a-l	Y*AG	O	O	S	S	S	O	F	OH
1050a-l	Y*AG	O	O	S	S	S	O	OEt	OH
1051a-l	Y*AG	S	O	S	S	S	O	OH	OH
1052a-l	Y*AG	S	O	S	S	S	O	OMe	OH
1053a-l	Y*AG	S	O	S	S	S	O	H	OH
1054a-l	Y*AG	S	O	S	S	S	O	F	OH

1055a-l	Y*AG	S	O	S	S	S	O	OEt	OH
1056a-l	Y*AG	S	S	S	S	S	O	OH	OH
1057a-l	Y*AG	S	S	S	S	S	O	OMe	OH
1058a-l	Y*AG	S	S	S	S	S	O	H	OH
1059a-l	Y*AG	S	S	S	S	S	O	F	OH
1060a-l	Y*AG	S	S	S	S	S	O	OEt	OH
1061a-l	Y*AG	O	O	S	S	S	S	OH	OH
1062a-l	Y*AG	O	O	S	S	S	S	OMe	OH
1063a-l	Y*AG	O	O	S	S	S	S	H	OH
1064a-l	Y*AG	O	O	S	S	S	S	F	OH
1065a-l	Y*AG	O	O	S	S	S	S	OEt	OH
1066a-l	Y*AG	S	O	S	S	S	S	OH	OH
1067a-l	Y*AG	S	O	S	S	S	S	OMe	OH
1068a-l	Y*AG	S	O	S	S	S	S	H	OH
1069a-l	Y*AG	S	O	S	S	S	S	F	OH
1070a-l	Y*AG	S	O	S	S	S	S	OEt	OH
1071a-l	Y*AG	S	S	S	S	S	S	OH	OH
1072a-l	Y*AG	S	S	S	S	S	S	OMe	OH
1073a-l	Y*AG	S	S	S	S	S	S	H	OH
1074a-l	Y*AG	S	S	S	S	S	S	F	OH
1075a-l	Y*AG	S	S	S	S	S	S	OEt	OH
1076a-l	Y*AG	O	O	O	S	S	S	OH	OH
1077a-l	Y*AG	O	O	O	S	S	S	OMe	OH
1078a-l	Y*AG	O	O	O	S	S	S	H	OH
1079a-l	Y*AG	O	O	O	S	S	S	F	OH
1080a-l	Y*AG	O	O	O	S	S	S	OEt	OH
1081a-l	Y*AG	S	O	O	S	S	S	OH	OH
1082a-l	Y*AG	S	O	O	S	S	S	OMe	OH
1083a-l	Y*AG	S	O	O	S	S	S	H	OH
1084a-l	Y*AG	S	O	O	S	S	S	F	OH
1085a-l	Y*AG	S	O	O	S	S	S	OEt	OH
1086a-l	Y*AG	S	S	O	S	S	S	OH	OH
1087a-l	Y*AG	S	S	O	S	S	S	OMe	OH
1088a-l	Y*AG	S	S	O	S	S	S	H	OH
1089a-l	Y*AG	S	S	O	S	S	S	F	OH
1090a-l	Y*AG	S	S	O	S	S	S	OEt	OH
1091a-l	Y*AG	O	O	O	O	S	S	OH	OH
1092a-l	Y*AG	O	O	O	O	S	S	OMe	OH
1093a-l	Y*AG	O	O	O	O	S	S	H	OH
1094a-l	Y*AG	O	O	O	O	S	S	F	OH
1095a-l	Y*AG	O	O	O	O	S	S	OEt	OH
1096a-l	Y*AG	S	O	O	O	S	S	OH	OH
1097a-l	Y*AG	S	O	O	O	S	S	OMe	OH
1098a-l	Y*AG	S	O	O	O	S	S	H	OH
1099a-l	Y*AG	S	O	O	O	S	S	F	OH
1100a-l	Y*AG	S	O	O	O	S	S	OEt	OH
1101a-l	Y*AG	S	S	O	O	S	S	OH	OH
1102a-l	Y*AG	S	S	O	O	S	S	OMe	OH
1103a-l	Y*AG	S	S	O	O	S	S	H	OH

1104a-l	Y*AG	S	S	O	O	S	S	F	OH
1105a-l	Y*AG	S	S	O	O	S	S	OEt	OH
1106a-l	Y*AG	O	O	O	O	O	S	OH	OH
1107a-l	Y*AG	O	O	O	O	O	S	OMe	OH
1108a-l	Y*AG	O	O	O	O	O	S	H	OH
1109a-l	Y*AG	O	O	O	O	O	S	F	OH
1110a-l	Y*AG	O	O	O	O	O	S	OEt	OH
1111a-l	Y*AG	S	O	O	O	O	S	OH	OH
1112a-l	Y*AG	S	O	O	O	O	S	OMe	OH
1113a-l	Y*AG	S	O	O	O	O	S	H	OH
1114a-l	Y*AG	S	O	O	O	O	S	F	OH
1115a-l	Y*AG	S	O	O	O	O	S	OEt	OH
1116a-l	Y*AG	S	S	O	O	O	S	OH	OH
1117a-l	Y*AG	S	S	O	O	O	S	OMe	OH
1118a-l	Y*AG	S	S	O	O	O	S	H	OH
1119a-l	Y*AG	S	S	O	O	O	S	F	OH
1120a-l	Y*AG	S	S	O	O	O	S	OEt	OH
1121a-l	Y*AG	O	O	S	O	S	O	OH	OH
1122a-l	Y*AG	O	O	S	O	S	O	OMe	OH
1123a-l	Y*AG	O	O	S	O	S	O	H	OH
1124a-l	Y*AG	O	O	S	O	S	O	F	OH
1125a-l	Y*AG	O	O	S	O	S	O	OEt	OH
1126a-l	Y*AG	S	O	S	O	S	O	OH	OH
1127a-l	Y*AG	S	O	S	O	S	O	OMe	OH
1128a-l	Y*AG	S	O	S	O	S	O	H	OH
1129a-l	Y*AG	S	O	S	O	S	O	F	OH
1130a-l	Y*AG	S	O	S	O	S	O	OEt	OH
1131a-l	Y*AG	S	S	S	O	S	O	OH	OH
1132a-l	Y*AG	S	S	S	O	S	O	OMe	OH
1133a-l	Y*AG	S	S	S	O	S	O	H	OH
1134a-l	Y*AG	S	S	S	O	S	O	F	OH
1135a-l	Y*AG	S	S	S	O	S	O	OEt	OH
1136a-l	Y*AG	O	O	O	S	O	S	OH	OH
1137a-l	Y*AG	O	O	O	S	O	S	OMe	OH
1138a-l	Y*AG	O	O	O	S	O	S	H	OH
1139a-l	Y*AG	O	O	O	S	O	S	F	OH
1140a-l	Y*AG	O	O	O	S	O	S	OEt	OH
1141a-l	Y*AG	S	O	O	S	O	S	OH	OH
1142a-l	Y*AG	S	O	O	S	O	S	OMe	OH
1143a-l	Y*AG	S	O	O	S	O	S	H	OH
1144a-l	Y*AG	S	O	O	S	O	S	F	OH
1145a-l	Y*AG	S	O	O	S	O	S	OEt	OH
1146a-l	Y*AG	S	S	O	S	O	S	OH	OH
1147a-l	Y*AG	S	S	O	S	O	S	OMe	OH
1148a-l	Y*AG	S	S	O	S	O	S	H	OH
1149a-l	Y*AG	S	S	O	S	O	S	F	OH
1150a-l	Y*AG	S	S	O	S	O	S	OEt	OH
1151a-l	Y*AG	O	O	O	O	O	O	OH	OMe
1152a-l	Y*AG	O	O	O	O	O	O	OMe	OMe

1153a-l	Y*AG	O	O	O	O	O	O	H	OMe
1154a-l	Y*AG	O	O	O	O	O	O	F	OMe
1155a-l	Y*AG	O	O	O	O	O	O	OEt	OMe
1156a-l	Y*AG	S	O	O	O	O	O	OH	OMe
1157a-l	Y*AG	S	O	O	O	O	O	OMe	OMe
1158a-l	Y*AG	S	O	O	O	O	O	H	OMe
1159a-l	Y*AG	S	O	O	O	O	O	F	OMe
1160a-l	Y*AG	S	O	O	O	O	O	OEt	OMe
1161a-l	Y*AG	S	S	O	O	O	O	OH	OMe
1162a-l	Y*AG	S	S	O	O	O	O	OMe	OMe
1163a-l	Y*AG	S	S	O	O	O	O	H	OMe
1164a-l	Y*AG	S	S	O	O	O	O	F	OMe
1165a-l	Y*AG	S	S	O	O	O	O	OEt	OMe
1166a-l	Y*AG	O	O	S	O	O	O	OH	OMe
1167a-l	Y*AG	O	O	S	O	O	O	OMe	OMe
1168a-l	Y*AG	O	O	S	O	O	O	H	OMe
1169a-l	Y*AG	O	O	S	O	O	O	F	OMe
1170a-l	Y*AG	O	O	S	O	O	O	OEt	OMe
1171a-l	Y*AG	S	O	S	O	O	O	OH	OMe
1172a-l	Y*AG	S	O	S	O	O	O	OMe	OMe
1173a-l	Y*AG	S	O	S	O	O	O	H	OMe
1174a-l	Y*AG	S	O	S	O	O	O	F	OMe
1175a-l	Y*AG	S	O	S	O	O	O	OEt	OMe
1176a-l	Y*AG	S	S	S	O	O	O	OH	OMe
1177a-l	Y*AG	S	S	S	O	O	O	OMe	OMe
1178a-l	Y*AG	S	S	S	O	O	O	H	OMe
1179a-l	Y*AG	S	S	S	O	O	O	F	OMe
1180a-l	Y*AG	S	S	S	O	O	O	OEt	OMe
1181a-l	Y*AG	O	O	S	S	O	O	OH	OMe
1182a-l	Y*AG	O	O	S	S	O	O	OMe	OMe
1183a-l	Y*AG	O	O	S	S	O	O	H	OMe
1184a-l	Y*AG	O	O	S	S	O	O	F	OMe
1185a-l	Y*AG	O	O	S	S	O	O	OEt	OMe
1186a-l	Y*AG	S	O	S	S	O	O	OH	OMe
1187a-l	Y*AG	S	O	S	S	O	O	OMe	OMe
1188a-l	Y*AG	S	O	S	S	O	O	H	OMe
1189a-l	Y*AG	S	O	S	S	O	O	F	OMe
1190a-l	Y*AG	S	O	S	S	O	O	OEt	OMe
1191a-l	Y*AG	S	S	S	S	O	O	OH	OMe
1192a-l	Y*AG	S	S	S	S	O	O	OMe	OMe
1193a-l	Y*AG	S	S	S	S	O	O	H	OMe
1194a-l	Y*AG	S	S	S	S	O	O	F	OMe
1195a-l	Y*AG	S	S	S	S	O	O	OEt	OMe
1196a-l	Y*AG	O	O	S	S	S	O	OH	OMe
1197a-l	Y*AG	O	O	S	S	S	O	OMe	OMe
1198a-l	Y*AG	O	O	S	S	S	O	H	OMe
1199a-l	Y*AG	O	O	S	S	S	O	F	OMe
1200a-l	Y*AG	O	O	S	S	S	O	OEt	OMe
1201a-l	Y*AG	S	O	S	S	S	O	OH	OMe

1202a-l	Y*AG	S	O	S	S	S	O	OMe	OMe
1203a-l	Y*AG	S	O	S	S	S	O	H	OMe
1204a-l	Y*AG	S	O	S	S	S	O	F	OMe
1205a-l	Y*AG	S	O	S	S	S	O	OEt	OMe
1206a-l	Y*AG	S	S	S	S	S	O	OH	OMe
1207a-l	Y*AG	S	S	S	S	S	O	OMe	OMe
1208a-l	Y*AG	S	S	S	S	S	O	H	OMe
1209a-l	Y*AG	S	S	S	S	S	O	F	OMe
1210a-l	Y*AG	S	S	S	S	S	O	OEt	OMe
1211a-l	Y*AG	O	O	S	S	S	S	OH	OMe
1212a-l	Y*AG	O	O	S	S	S	S	OMe	OMe
1213a-l	Y*AG	O	O	S	S	S	S	H	OMe
1214a-l	Y*AG	O	O	S	S	S	S	F	OMe
1215a-l	Y*AG	O	O	S	S	S	S	OEt	OMe
1216a-l	Y*AG	S	O	S	S	S	S	OH	OMe
1217a-l	Y*AG	S	O	S	S	S	S	OMe	OMe
1218a-l	Y*AG	S	O	S	S	S	S	H	OMe
1219a-l	Y*AG	S	O	S	S	S	S	F	OMe
1220a-l	Y*AG	S	O	S	S	S	S	OEt	OMe
1221a-l	Y*AG	S	S	S	S	S	S	OH	OMe
1222a-l	Y*AG	S	S	S	S	S	S	OMe	OMe
1223a-l	Y*AG	S	S	S	S	S	S	H	OMe
1224a-l	Y*AG	S	S	S	S	S	S	F	OMe
1225a-l	Y*AG	S	S	S	S	S	S	OEt	OMe
1226a-l	Y*AG	O	O	O	S	S	S	OH	OMe
1227a-l	Y*AG	O	O	O	S	S	S	OMe	OMe
1228a-l	Y*AG	O	O	O	S	S	S	H	OMe
1229a-l	Y*AG	O	O	O	S	S	S	F	OMe
1230a-l	Y*AG	O	O	O	S	S	S	OEt	OMe
1231a-l	Y*AG	S	O	O	S	S	S	OH	OMe
1232a-l	Y*AG	S	O	O	S	S	S	OMe	OMe
1233a-l	Y*AG	S	O	O	S	S	S	H	OMe
1234a-l	Y*AG	S	O	O	S	S	S	F	OMe
1235a-l	Y*AG	S	O	O	S	S	S	OEt	OMe
1236a-l	Y*AG	S	S	O	S	S	S	OH	OMe
1237a-l	Y*AG	S	S	O	S	S	S	OMe	OMe
1238a-l	Y*AG	S	S	O	S	S	S	H	OMe
1239a-l	Y*AG	S	S	O	S	S	S	F	OMe
1240a-l	Y*AG	S	S	O	S	S	S	OEt	OMe
1241a-l	Y*AG	O	O	O	O	S	S	OH	OMe
1242a-l	Y*AG	O	O	O	O	S	S	OMe	OMe
1243a-l	Y*AG	O	O	O	O	S	S	H	OMe
1244a-l	Y*AG	O	O	O	O	S	S	F	OMe
1245a-l	Y*AG	O	O	O	O	S	S	OEt	OMe
1246a-l	Y*AG	S	O	O	O	S	S	OH	OMe
1247a-l	Y*AG	S	O	O	O	S	S	OMe	OMe
1248a-l	Y*AG	S	O	O	O	S	S	H	OMe
1249a-l	Y*AG	S	O	O	O	S	S	F	OMe
1250a-l	Y*AG	S	O	O	O	S	S	OEt	OMe

1251a-l	Y*AG	S	S	O	O	S	S	OH	OMe
1252a-l	Y*AG	S	S	O	O	S	S	OMe	OMe
1253a-l	Y*AG	S	S	O	O	S	S	H	OMe
1254a-l	Y*AG	S	S	O	O	S	S	F	OMe
1255a-l	Y*AG	S	S	O	O	S	S	OEt	OMe
1256a-l	Y*AG	O	O	O	O	O	S	OH	OMe
1257a-l	Y*AG	O	O	O	O	O	S	OMe	OMe
1258a-l	Y*AG	O	O	O	O	O	S	H	OMe
1259a-l	Y*AG	O	O	O	O	O	S	F	OMe
1260a-l	Y*AG	O	O	O	O	O	S	OEt	OMe
1261a-l	Y*AG	S	O	O	O	O	S	OH	OMe
1262a-l	Y*AG	S	O	O	O	O	S	OMe	OMe
1263a-l	Y*AG	S	O	O	O	O	S	H	OMe
1264a-l	Y*AG	S	O	O	O	O	S	F	OMe
1265a-l	Y*AG	S	O	O	O	O	S	OEt	OMe
1266a-l	Y*AG	S	S	O	O	O	S	OH	OMe
1267a-l	Y*AG	S	S	O	O	O	S	OMe	OMe
1268a-l	Y*AG	S	S	O	O	O	S	H	OMe
1269a-l	Y*AG	S	S	O	O	O	S	F	OMe
1270a-l	Y*AG	S	S	O	O	O	S	OEt	OMe
1271a-l	Y*AG	O	O	S	O	S	O	OH	OMe
1272a-l	Y*AG	O	O	S	O	S	O	OMe	OMe
1273a-l	Y*AG	O	O	S	O	S	O	H	OMe
1274a-l	Y*AG	O	O	S	O	S	O	F	OMe
1275a-l	Y*AG	O	O	S	O	S	O	OEt	OMe
1276a-l	Y*AG	S	O	S	O	S	O	OH	OMe
1277a-l	Y*AG	S	O	S	O	S	O	OMe	OMe
1278a-l	Y*AG	S	O	S	O	S	O	H	OMe
1279a-l	Y*AG	S	O	S	O	S	O	F	OMe
1280a-l	Y*AG	S	O	S	O	S	O	OEt	OMe
1281a-l	Y*AG	S	S	S	O	S	O	OH	OMe
1282a-l	Y*AG	S	S	S	O	S	O	OMe	OMe
1283a-l	Y*AG	S	S	S	O	S	O	H	OMe
1284a-l	Y*AG	S	S	S	O	S	O	F	OMe
1285a-l	Y*AG	S	S	S	O	S	O	OEt	OMe
1286a-l	Y*AG	O	O	O	S	O	S	OH	OMe
1287a-l	Y*AG	O	O	O	S	O	S	OMe	OMe
1288a-l	Y*AG	O	O	O	S	O	S	H	OMe
1289a-l	Y*AG	O	O	O	S	O	S	F	OMe
1290a-l	Y*AG	O	O	O	S	O	S	OEt	OMe
1291a-l	Y*AG	S	O	O	S	O	S	OH	OMe
1292a-l	Y*AG	S	O	O	S	O	S	OMe	OMe
1293a-l	Y*AG	S	O	O	S	O	S	H	OMe
1294a-l	Y*AG	S	O	O	S	O	S	F	OMe
1295a-l	Y*AG	S	O	O	S	O	S	OEt	OMe
1296a-l	Y*AG	S	S	O	S	O	S	OH	OMe
1297a-l	Y*AG	S	S	O	S	O	S	OMe	OMe
1298a-l	Y*AG	S	S	O	S	O	S	H	OMe
1299a-l	Y*AG	S	S	O	S	O	S	F	OMe

1300a-l	Y*AG	S	S	O	S	O	S	OEt	OMe
1301a-l	Y*AA	O	O	O	O	O	O	OH	OH
1302a-l	Y*AA	O	O	O	O	O	O	OMe	OH
1303a-l	Y*AA	O	O	O	O	O	O	H	OH
1304a-l	Y*AA	O	O	O	O	O	O	F	OH
1305a-l	Y*AA	O	O	O	O	O	O	OEt	OH
1306a-l	Y*AA	S	O	O	O	O	O	OH	OH
1307a-l	Y*AA	S	O	O	O	O	O	OMe	OH
1308a-l	Y*AA	S	O	O	O	O	O	H	OH
1309a-l	Y*AA	S	O	O	O	O	O	F	OH
1310a-l	Y*AA	S	O	O	O	O	O	OEt	OH
1311a-l	Y*AA	S	S	O	O	O	O	OH	OH
1312a-l	Y*AA	S	S	O	O	O	O	OMe	OH
1313a-l	Y*AA	S	S	O	O	O	O	H	OH
1314a-l	Y*AA	S	S	O	O	O	O	F	OH
1315a-l	Y*AA	S	S	O	O	O	O	OEt	OH
1316a-l	Y*AA	O	O	S	O	O	O	OH	OH
1317a-l	Y*AA	O	O	S	O	O	O	OMe	OH
1318a-l	Y*AA	O	O	S	O	O	O	H	OH
1319a-l	Y*AA	O	O	S	O	O	O	F	OH
1320a-l	Y*AA	O	O	S	O	O	O	OEt	OH
1321a-l	Y*AA	S	O	S	O	O	O	OH	OH
1322a-l	Y*AA	S	O	S	O	O	O	OMe	OH
1323a-l	Y*AA	S	O	S	O	O	O	H	OH
1324a-l	Y*AA	S	O	S	O	O	O	F	OH
1325a-l	Y*AA	S	O	S	O	O	O	OEt	OH
1326a-l	Y*AA	S	S	S	O	O	O	OH	OH
1327a-l	Y*AA	S	S	S	O	O	O	OMe	OH
1328a-l	Y*AA	S	S	S	O	O	O	H	OH
1329a-l	Y*AA	S	S	S	O	O	O	F	OH
1330a-l	Y*AA	S	S	S	O	O	O	OEt	OH
1331a-l	Y*AA	O	O	S	S	O	O	OH	OH
1332a-l	Y*AA	O	O	S	S	O	O	OMe	OH
1333a-l	Y*AA	O	O	S	S	O	O	H	OH
1334a-l	Y*AA	O	O	S	S	O	O	F	OH
1335a-l	Y*AA	O	O	S	S	O	O	OEt	OH
1336a-l	Y*AA	S	O	S	S	O	O	OH	OH
1337a-l	Y*AA	S	O	S	S	O	O	OMe	OH
1338a-l	Y*AA	S	O	S	S	O	O	H	OH
1339a-l	Y*AA	S	O	S	S	O	O	F	OH
1340a-l	Y*AA	S	O	S	S	O	O	OEt	OH
1341a-l	Y*AA	S	S	S	S	O	O	OH	OH
1342a-l	Y*AA	S	S	S	S	O	O	OMe	OH
1343a-l	Y*AA	S	S	S	S	O	O	H	OH
1344a-l	Y*AA	S	S	S	S	O	O	F	OH
1345a-l	Y*AA	S	S	S	S	O	O	OEt	OH
1346a-l	Y*AA	O	O	S	S	S	O	OH	OH
1347a-l	Y*AA	O	O	S	S	S	O	OMe	OH
1348a-l	Y*AA	O	O	S	S	S	O	H	OH

1349a-l	Y*AA	O	O	S	S	S	O	F	OH
1350a-l	Y*AA	O	O	S	S	S	O	OEt	OH
1351a-l	Y*AA	S	O	S	S	S	O	OH	OH
1352a-l	Y*AA	S	O	S	S	S	O	OMe	OH
1353a-l	Y*AA	S	O	S	S	S	O	H	OH
1354a-l	Y*AA	S	O	S	S	S	O	F	OH
1355a-l	Y*AA	S	O	S	S	S	O	OEt	OH
1356a-l	Y*AA	S	S	S	S	S	O	OH	OH
1357a-l	Y*AA	S	S	S	S	S	O	OMe	OH
1358a-l	Y*AA	S	S	S	S	S	O	H	OH
1359a-l	Y*AA	S	S	S	S	S	O	F	OH
1360a-l	Y*AA	S	S	S	S	S	O	OEt	OH
1361a-l	Y*AA	O	O	S	S	S	S	OH	OH
1362a-l	Y*AA	O	O	S	S	S	S	OMe	OH
1363a-l	Y*AA	O	O	S	S	S	S	H	OH
1364a-l	Y*AA	O	O	S	S	S	S	F	OH
1365a-l	Y*AA	O	O	S	S	S	S	OEt	OH
1366a-l	Y*AA	S	O	S	S	S	S	OH	OH
1367a-l	Y*AA	S	O	S	S	S	S	OMe	OH
1368a-l	Y*AA	S	O	S	S	S	S	H	OH
1369a-l	Y*AA	S	O	S	S	S	S	F	OH
1370a-l	Y*AA	S	O	S	S	S	S	OEt	OH
1371a-l	Y*AA	S	S	S	S	S	S	OH	OH
1372a-l	Y*AA	S	S	S	S	S	S	OMe	OH
1373a-l	Y*AA	S	S	S	S	S	S	H	OH
1374a-l	Y*AA	S	S	S	S	S	S	F	OH
1375a-l	Y*AA	S	S	S	S	S	S	OEt	OH
1376a-l	Y*AA	O	O	O	S	S	S	OH	OH
1377a-l	Y*AA	O	O	O	S	S	S	OMe	OH
1378a-l	Y*AA	O	O	O	S	S	S	H	OH
1379a-l	Y*AA	O	O	O	S	S	S	F	OH
1380a-l	Y*AA	O	O	O	S	S	S	OEt	OH
1381a-l	Y*AA	S	O	O	S	S	S	OH	OH
1382a-l	Y*AA	S	O	O	S	S	S	OMe	OH
1383a-l	Y*AA	S	O	O	S	S	S	H	OH
1384a-l	Y*AA	S	O	O	S	S	S	F	OH
1385a-l	Y*AA	S	O	O	S	S	S	OEt	OH
1386a-l	Y*AA	S	S	O	S	S	S	OH	OH
1387a-l	Y*AA	S	S	O	S	S	S	OMe	OH
1388a-l	Y*AA	S	S	O	S	S	S	H	OH
1389a-l	Y*AA	S	S	O	S	S	S	F	OH
1390a-l	Y*AA	S	S	O	S	S	S	OEt	OH
1391a-l	Y*AA	O	O	O	O	S	S	OH	OH
1392a-l	Y*AA	O	O	O	O	S	S	OMe	OH
1393a-l	Y*AA	O	O	O	O	S	S	H	OH
1394a-l	Y*AA	O	O	O	O	S	S	F	OH
1395a-l	Y*AA	O	O	O	O	S	S	OEt	OH
1396a-l	Y*AA	S	O	O	O	S	S	OH	OH
1397a-l	Y*AA	S	O	O	O	S	S	OMe	OH

1398a-l	Y*AA	S	O	O	O	S	S	H	OH
1399a-l	Y*AA	S	O	O	O	S	S	F	OH
1400a-l	Y*AA	S	O	O	O	S	S	OEt	OH
1401a-l	Y*AA	S	S	O	O	S	S	OH	OH
1402a-l	Y*AA	S	S	O	O	S	S	OMe	OH
1403a-l	Y*AA	S	S	O	O	S	S	H	OH
1404a-l	Y*AA	S	S	O	O	S	S	F	OH
1405a-l	Y*AA	S	S	O	O	S	S	OEt	OH
1406a-l	Y*AA	O	O	O	O	O	S	OH	OH
1407a-l	Y*AA	O	O	O	O	O	S	OMe	OH
1408a-l	Y*AA	O	O	O	O	O	S	H	OH
1409a-l	Y*AA	O	O	O	O	O	S	F	OH
1410a-l	Y*AA	O	O	O	O	O	S	OEt	OH
1411a-l	Y*AA	S	O	O	O	O	S	OH	OH
1412a-l	Y*AA	S	O	O	O	O	S	OMe	OH
1413a-l	Y*AA	S	O	O	O	O	S	H	OH
1414a-l	Y*AA	S	O	O	O	O	S	F	OH
1415a-l	Y*AA	S	O	O	O	O	S	OEt	OH
1416a-l	Y*AA	S	S	O	O	O	S	OH	OH
1417a-l	Y*AA	S	S	O	O	O	S	OMe	OH
1418a-l	Y*AA	S	S	O	O	O	S	H	OH
1419a-l	Y*AA	S	S	O	O	O	S	F	OH
1420a-l	Y*AA	S	S	O	O	O	S	OEt	OH
1421a-l	Y*AA	O	O	S	O	S	O	OH	OH
1422a-l	Y*AA	O	O	S	O	S	O	OMe	OH
1423a-l	Y*AA	O	O	S	O	S	O	H	OH
1424a-l	Y*AA	O	O	S	O	S	O	F	OH
1425a-l	Y*AA	O	O	S	O	S	O	OEt	OH
1426a-l	Y*AA	S	O	S	O	S	O	OH	OH
1427a-l	Y*AA	S	O	S	O	S	O	OMe	OH
1428a-l	Y*AA	S	O	S	O	S	O	H	OH
1429a-l	Y*AA	S	O	S	O	S	O	F	OH
1430a-l	Y*AA	S	O	S	O	S	O	OEt	OH
1431a-l	Y*AA	S	S	S	O	S	O	OH	OH
1432a-l	Y*AA	S	S	S	O	S	O	OMe	OH
1433a-l	Y*AA	S	S	S	O	S	O	H	OH
1434a-l	Y*AA	S	S	S	O	S	O	F	OH
1435a-l	Y*AA	S	S	S	O	S	O	OEt	OH
1436a-l	Y*AA	O	O	O	S	O	S	OH	OH
1437a-l	Y*AA	O	O	O	S	O	S	OMe	OH
1438a-l	Y*AA	O	O	O	S	O	S	H	OH
1439a-l	Y*AA	O	O	O	S	O	S	F	OH
1440a-l	Y*AA	O	O	O	S	O	S	OEt	OH
1441a-l	Y*AA	S	O	O	S	O	S	OH	OH
1442a-l	Y*AA	S	O	O	S	O	S	OMe	OH
1443a-l	Y*AA	S	O	O	S	O	S	H	OH
1444a-l	Y*AA	S	O	O	S	O	S	F	OH
1445a-l	Y*AA	S	O	O	S	O	S	OEt	OH
1446a-l	Y*AA	S	S	O	S	O	S	OH	OH

1447a-l	Y*AA	S	S	O	S	O	S	OMe	OH
1448a-l	Y*AA	S	S	O	S	O	S	H	OH
1449a-l	Y*AA	S	S	O	S	O	S	F	OH
1450a-l	Y*AA	S	S	O	S	O	S	OEt	OH
1451a-l	Y*AA	O	O	O	O	O	O	OH	OMe
1452a-l	Y*AA	O	O	O	O	O	O	OMe	OMe
1453a-l	Y*AA	O	O	O	O	O	O	H	OMe
1454a-l	Y*AA	O	O	O	O	O	O	F	OMe
1455a-l	Y*AA	O	O	O	O	O	O	OEt	OMe
1456a-l	Y*AA	S	O	O	O	O	O	OH	OMe
1457a-l	Y*AA	S	O	O	O	O	O	OMe	OMe
1458a-l	Y*AA	S	O	O	O	O	O	H	OMe
1459a-l	Y*AA	S	O	O	O	O	O	F	OMe
1460a-l	Y*AA	S	O	O	O	O	O	OEt	OMe
1461a-l	Y*AA	S	S	O	O	O	O	OH	OMe
1462a-l	Y*AA	S	S	O	O	O	O	OMe	OMe
1463a-l	Y*AA	S	S	O	O	O	O	H	OMe
1464a-l	Y*AA	S	S	O	O	O	O	F	OMe
1465a-l	Y*AA	S	S	O	O	O	O	OEt	OMe
1466a-l	Y*AA	O	O	S	O	O	O	OH	OMe
1467a-l	Y*AA	O	O	S	O	O	O	OMe	OMe
1468a-l	Y*AA	O	O	S	O	O	O	H	OMe
1469a-l	Y*AA	O	O	S	O	O	O	F	OMe
1470a-l	Y*AA	O	O	S	O	O	O	OEt	OMe
1471a-l	Y*AA	S	O	S	O	O	O	OH	OMe
1472a-l	Y*AA	S	O	S	O	O	O	OMe	OMe
1473a-l	Y*AA	S	O	S	O	O	O	H	OMe
1474a-l	Y*AA	S	O	S	O	O	O	F	OMe
1475a-l	Y*AA	S	O	S	O	O	O	OEt	OMe
1476a-l	Y*AA	S	S	S	O	O	O	OH	OMe
1477a-l	Y*AA	S	S	S	O	O	O	OMe	OMe
1478a-l	Y*AA	S	S	S	O	O	O	H	OMe
1479a-l	Y*AA	S	S	S	O	O	O	F	OMe
1480a-l	Y*AA	S	S	S	O	O	O	OEt	OMe
1481a-l	Y*AA	O	O	S	S	O	O	OH	OMe
1482a-l	Y*AA	O	O	S	S	O	O	OMe	OMe
1483a-l	Y*AA	O	O	S	S	O	O	H	OMe
1484a-l	Y*AA	O	O	S	S	O	O	F	OMe
1485a-l	Y*AA	O	O	S	S	O	O	OEt	OMe
1486a-l	Y*AA	S	O	S	S	O	O	OH	OMe
1487a-l	Y*AA	S	O	S	S	O	O	OMe	OMe
1488a-l	Y*AA	S	O	S	S	O	O	H	OMe
1489a-l	Y*AA	S	O	S	S	O	O	F	OMe
1490a-l	Y*AA	S	O	S	S	O	O	OEt	OMe
1491a-l	Y*AA	S	S	S	S	O	O	OH	OMe
1492a-l	Y*AA	S	S	S	S	O	O	OMe	OMe
1493a-l	Y*AA	S	S	S	S	O	O	H	OMe
1494a-l	Y*AA	S	S	S	S	O	O	F	OMe
1495a-l	Y*AA	S	S	S	S	O	O	OEt	OMe

1496a-l	Y*AA	O	O	S	S	S	O	OH	OMe
1497a-l	Y*AA	O	O	S	S	S	O	OMe	OMe
1498a-l	Y*AA	O	O	S	S	S	O	H	OMe
1499a-l	Y*AA	O	O	S	S	S	O	F	OMe
1500a-l	Y*AA	O	O	S	S	S	O	OEt	OMe
1501a-l	Y*AA	S	O	S	S	S	O	OH	OMe
1502a-l	Y*AA	S	O	S	S	S	O	OMe	OMe
1503a-l	Y*AA	S	O	S	S	S	O	H	OMe
1504a-l	Y*AA	S	O	S	S	S	O	F	OMe
1505a-l	Y*AA	S	O	S	S	S	O	OEt	OMe
1506a-l	Y*AA	S	S	S	S	S	O	OH	OMe
1507a-l	Y*AA	S	S	S	S	S	O	OMe	OMe
1508a-l	Y*AA	S	S	S	S	S	O	H	OMe
1509a-l	Y*AA	S	S	S	S	S	O	F	OMe
1510a-l	Y*AA	S	S	S	S	S	O	OEt	OMe
1511a-l	Y*AA	O	O	S	S	S	S	OH	OMe
1512a-l	Y*AA	O	O	S	S	S	S	OMe	OMe
1513a-l	Y*AA	O	O	S	S	S	S	H	OMe
1514a-l	Y*AA	O	O	S	S	S	S	F	OMe
1515a-l	Y*AA	O	O	S	S	S	S	OEt	OMe
1516a-l	Y*AA	S	O	S	S	S	S	OH	OMe
1517a-l	Y*AA	S	O	S	S	S	S	OMe	OMe
1518a-l	Y*AA	S	O	S	S	S	S	H	OMe
1519a-l	Y*AA	S	O	S	S	S	S	F	OMe
1520a-l	Y*AA	S	O	S	S	S	S	OEt	OMe
1521a-l	Y*AA	S	S	S	S	S	S	OH	OMe
1522a-l	Y*AA	S	S	S	S	S	S	OMe	OMe
1523a-l	Y*AA	S	S	S	S	S	S	H	OMe
1524a-l	Y*AA	S	S	S	S	S	S	F	OMe
1525a-l	Y*AA	S	S	S	S	S	S	OEt	OMe
1526a-l	Y*AA	O	O	O	S	S	S	OH	OMe
1527a-l	Y*AA	O	O	O	S	S	S	OMe	OMe
1528a-l	Y*AA	O	O	O	S	S	S	H	OMe
1529a-l	Y*AA	O	O	O	S	S	S	F	OMe
1530a-l	Y*AA	O	O	O	S	S	S	OEt	OMe
1531a-l	Y*AA	S	O	O	S	S	S	OH	OMe
1532a-l	Y*AA	S	O	O	S	S	S	OMe	OMe
1533a-l	Y*AA	S	O	O	S	S	S	H	OMe
1534a-l	Y*AA	S	O	O	S	S	S	F	OMe
1535a-l	Y*AA	S	O	O	S	S	S	OEt	OMe
1536a-l	Y*AA	S	S	O	S	S	S	OH	OMe
1537a-l	Y*AA	S	S	O	S	S	S	OMe	OMe
1538a-l	Y*AA	S	S	O	S	S	S	H	OMe
1539a-l	Y*AA	S	S	O	S	S	S	F	OMe
1540a-l	Y*AA	S	S	O	S	S	S	OEt	OMe
1541a-l	Y*AA	O	O	O	O	S	S	OH	OMe
1542a-l	Y*AA	O	O	O	O	S	S	OMe	OMe
1543a-l	Y*AA	O	O	O	O	S	S	H	OMe
1544a-l	Y*AA	O	O	O	O	S	S	F	OMe

1545a-l	Y*AA	O	O	O	O	S	S	OEt	OMe
1546a-l	Y*AA	S	O	O	O	S	S	OH	OMe
1547a-l	Y*AA	S	O	O	O	S	S	OMe	OMe
1548a-l	Y*AA	S	O	O	O	S	S	H	OMe
1549a-l	Y*AA	S	O	O	O	S	S	F	OMe
1550a-l	Y*AA	S	O	O	O	S	S	OEt	OMe
1551a-l	Y*AA	S	S	O	O	S	S	OH	OMe
1552a-l	Y*AA	S	S	O	O	S	S	OMe	OMe
1553a-l	Y*AA	S	S	O	O	S	S	H	OMe
1554a-l	Y*AA	S	S	O	O	S	S	F	OMe
1555a-l	Y*AA	S	S	O	O	S	S	OEt	OMe
1556a-l	Y*AA	O	O	O	O	O	S	OH	OMe
1557a-l	Y*AA	O	O	O	O	O	S	OMe	OMe
1558a-l	Y*AA	O	O	O	O	O	S	H	OMe
1559a-l	Y*AA	O	O	O	O	O	S	F	OMe
1560a-l	Y*AA	O	O	O	O	O	S	OEt	OMe
1561a-l	Y*AA	S	O	O	O	O	S	OH	OMe
1562a-l	Y*AA	S	O	O	O	O	S	OMe	OMe
1563a-l	Y*AA	S	O	O	O	O	S	H	OMe
1564a-l	Y*AA	S	O	O	O	O	S	F	OMe
1565a-l	Y*AA	S	O	O	O	O	S	OEt	OMe
1566a-l	Y*AA	S	S	O	O	O	S	OH	OMe
1567a-l	Y*AA	S	S	O	O	O	S	OMe	OMe
1568a-l	Y*AA	S	S	O	O	O	S	H	OMe
1569a-l	Y*AA	S	S	O	O	O	S	F	OMe
1570a-l	Y*AA	S	S	O	O	O	S	OEt	OMe
1571a-l	Y*AA	O	O	S	O	S	O	OH	OMe
1572a-l	Y*AA	O	O	S	O	S	O	OMe	OMe
1573a-l	Y*AA	O	O	S	O	S	O	H	OMe
1574a-l	Y*AA	O	O	S	O	S	O	F	OMe
1575a-l	Y*AA	O	O	S	O	S	O	OEt	OMe
1576a-l	Y*AA	S	O	S	O	S	O	OH	OMe
1577a-l	Y*AA	S	O	S	O	S	O	OMe	OMe
1578a-l	Y*AA	S	O	S	O	S	O	H	OMe
1579a-l	Y*AA	S	O	S	O	S	O	F	OMe
1580a-l	Y*AA	S	O	S	O	S	O	OEt	OMe
1581a-l	Y*AA	S	S	S	O	S	O	OH	OMe
1582a-l	Y*AA	S	S	S	O	S	O	OMe	OMe
1583a-l	Y*AA	S	S	S	O	S	O	H	OMe
1584a-l	Y*AA	S	S	S	O	S	O	F	OMe
1585a-l	Y*AA	S	S	S	O	S	O	OEt	OMe
1586a-l	Y*AA	O	O	O	S	O	S	OH	OMe
1587a-l	Y*AA	O	O	O	S	O	S	OMe	OMe
1588a-l	Y*AA	O	O	O	S	O	S	H	OMe
1589a-l	Y*AA	O	O	O	S	O	S	F	OMe
1590a-l	Y*AA	O	O	O	S	O	S	OEt	OMe
1591a-l	Y*AA	S	O	O	S	O	S	OH	OMe
1592a-l	Y*AA	S	O	O	S	O	S	OMe	OMe
1593a-l	Y*AA	S	O	O	S	O	S	H	OMe

1594a-l	Y*AA	S	O	O	S	O	S	F	OMe
1595a-l	Y*AA	S	O	O	S	O	S	OEt	OMe
1596a-l	Y*AA	S	S	O	S	O	S	OH	OMe
1597a-l	Y*AA	S	S	O	S	O	S	OMe	OMe
1598a-l	Y*AA	S	S	O	S	O	S	H	OMe
1599a-l	Y*AA	S	S	O	S	O	S	F	OMe
1600a-l	Y*AA	S	S	O	S	O	S	OEt	OMe
1601a-l	Y*AC	O	O	O	O	O	O	OH	OH
1602a-l	Y*AC	O	O	O	O	O	O	OMe	OH
1603a-l	Y*AC	O	O	O	O	O	O	H	OH
1604a-l	Y*AC	O	O	O	O	O	O	F	OH
1605a-l	Y*AC	O	O	O	O	O	O	OEt	OH
1606a-l	Y*AC	S	O	O	O	O	O	OH	OH
1607a-l	Y*AC	S	O	O	O	O	O	OMe	OH
1608a-l	Y*AC	S	O	O	O	O	O	H	OH
1609a-l	Y*AC	S	O	O	O	O	O	F	OH
1610a-l	Y*AC	S	O	O	O	O	O	OEt	OH
1611a-l	Y*AC	S	S	O	O	O	O	OH	OH
1612a-l	Y*AC	S	S	O	O	O	O	OMe	OH
1613a-l	Y*AC	S	S	O	O	O	O	H	OH
1614a-l	Y*AC	S	S	O	O	O	O	F	OH
1615a-l	Y*AC	S	S	O	O	O	O	OEt	OH
1616a-l	Y*AC	O	O	S	O	O	O	OH	OH
1617a-l	Y*AC	O	O	S	O	O	O	OMe	OH
1618a-l	Y*AC	O	O	S	O	O	O	H	OH
1619a-l	Y*AC	O	O	S	O	O	O	F	OH
1620a-l	Y*AC	O	O	S	O	O	O	OEt	OH
1621a-l	Y*AC	S	O	S	O	O	O	OH	OH
1622a-l	Y*AC	S	O	S	O	O	O	OMe	OH
1623a-l	Y*AC	S	O	S	O	O	O	H	OH
1624a-l	Y*AC	S	O	S	O	O	O	F	OH
1625a-l	Y*AC	S	O	S	O	O	O	OEt	OH
1626a-l	Y*AC	S	S	S	O	O	O	OH	OH
1627a-l	Y*AC	S	S	S	O	O	O	OMe	OH
1628a-l	Y*AC	S	S	S	O	O	O	H	OH
1629a-l	Y*AC	S	S	S	O	O	O	F	OH
1630a-l	Y*AC	S	S	S	O	O	O	OEt	OH
1631a-l	Y*AC	O	O	S	S	O	O	OH	OH
1632a-l	Y*AC	O	O	S	S	O	O	OMe	OH
1633a-l	Y*AC	O	O	S	S	O	O	H	OH
1634a-l	Y*AC	O	O	S	S	O	O	F	OH
1635a-l	Y*AC	O	O	S	S	O	O	OEt	OH
1636a-l	Y*AC	S	O	S	S	O	O	OH	OH
1637a-l	Y*AC	S	O	S	S	O	O	OMe	OH
1638a-l	Y*AC	S	O	S	S	O	O	H	OH
1639a-l	Y*AC	S	O	S	S	O	O	F	OH
1640a-l	Y*AC	S	O	S	S	O	O	OEt	OH
1641a-l	Y*AC	S	S	S	S	O	O	OH	OH
1642a-l	Y*AC	S	S	S	S	O	O	OMe	OH

1643a-l	Y*AC	S	S	S	S	O	O	H	OH
1644a-l	Y*AC	S	S	S	S	O	O	F	OH
1645a-l	Y*AC	S	S	S	S	O	O	OEt	OH
1646a-l	Y*AC	O	O	S	S	S	O	OH	OH
1647a-l	Y*AC	O	O	S	S	S	O	OMe	OH
1648a-l	Y*AC	O	O	S	S	S	O	H	OH
1649a-l	Y*AC	O	O	S	S	S	O	F	OH
1650a-l	Y*AC	O	O	S	S	S	O	OEt	OH
1651a-l	Y*AC	S	O	S	S	S	O	OH	OH
1652a-l	Y*AC	S	O	S	S	S	O	OMe	OH
1653a-l	Y*AC	S	O	S	S	S	O	H	OH
1654a-l	Y*AC	S	O	S	S	S	O	F	OH
1655a-l	Y*AC	S	O	S	S	S	O	OEt	OH
1656a-l	Y*AC	S	S	S	S	S	O	OH	OH
1657a-l	Y*AC	S	S	S	S	S	O	OMe	OH
1658a-l	Y*AC	S	S	S	S	S	O	H	OH
1659a-l	Y*AC	S	S	S	S	S	O	F	OH
1660a-l	Y*AC	S	S	S	S	S	O	OEt	OH
1661a-l	Y*AC	O	O	S	S	S	S	OH	OH
1662a-l	Y*AC	O	O	S	S	S	S	OMe	OH
1663a-l	Y*AC	O	O	S	S	S	S	H	OH
1664a-l	Y*AC	O	O	S	S	S	S	F	OH
1665a-l	Y*AC	O	O	S	S	S	S	OEt	OH
1666a-l	Y*AC	S	O	S	S	S	S	OH	OH
1667a-l	Y*AC	S	O	S	S	S	S	OMe	OH
1668a-l	Y*AC	S	O	S	S	S	S	H	OH
1669a-l	Y*AC	S	O	S	S	S	S	F	OH
1670a-l	Y*AC	S	O	S	S	S	S	OEt	OH
1671a-l	Y*AC	S	S	S	S	S	S	OH	OH
1672a-l	Y*AC	S	S	S	S	S	S	OMe	OH
1673a-l	Y*AC	S	S	S	S	S	S	H	OH
1674a-l	Y*AC	S	S	S	S	S	S	F	OH
1675a-l	Y*AC	S	S	S	S	S	S	OEt	OH
1676a-l	Y*AC	O	O	O	S	S	S	OH	OH
1677a-l	Y*AC	O	O	O	S	S	S	OMe	OH
1678a-l	Y*AC	O	O	O	S	S	S	H	OH
1679a-l	Y*AC	O	O	O	S	S	S	F	OH
1680a-l	Y*AC	O	O	O	S	S	S	OEt	OH
1681a-l	Y*AC	S	O	O	S	S	S	OH	OH
1682a-l	Y*AC	S	O	O	S	S	S	OMe	OH
1683a-l	Y*AC	S	O	O	S	S	S	H	OH
1684a-l	Y*AC	S	O	O	S	S	S	F	OH
1685a-l	Y*AC	S	O	O	S	S	S	OEt	OH
1686a-l	Y*AC	S	S	O	S	S	S	OH	OH
1687a-l	Y*AC	S	S	O	S	S	S	OMe	OH
1688a-l	Y*AC	S	S	O	S	S	S	H	OH
1689a-l	Y*AC	S	S	O	S	S	S	F	OH
1690a-l	Y*AC	S	S	O	S	S	S	OEt	OH
1691a-l	Y*AC	O	O	O	O	S	S	OH	OH

1692a-l	Y*AC	O	O	O	O	S	S	OMe	OH
1693a-l	Y*AC	O	O	O	O	S	S	H	OH
1694a-l	Y*AC	O	O	O	O	S	S	F	OH
1695a-l	Y*AC	O	O	O	O	S	S	OEt	OH
1696a-l	Y*AC	S	O	O	O	S	S	OH	OH
1697a-l	Y*AC	S	O	O	O	S	S	OMe	OH
1698a-l	Y*AC	S	O	O	O	S	S	H	OH
1699a-l	Y*AC	S	O	O	O	S	S	F	OH
1700a-l	Y*AC	S	O	O	O	S	S	OEt	OH
1701a-l	Y*AC	S	S	O	O	S	S	OH	OH
1702a-l	Y*AC	S	S	O	O	S	S	OMe	OH
1703a-l	Y*AC	S	S	O	O	S	S	H	OH
1704a-l	Y*AC	S	S	O	O	S	S	F	OH
1705a-l	Y*AC	S	S	O	O	S	S	OEt	OH
1706a-l	Y*AC	O	O	O	O	O	S	OH	OH
1707a-l	Y*AC	O	O	O	O	O	S	OMe	OH
1708a-l	Y*AC	O	O	O	O	O	S	H	OH
1709a-l	Y*AC	O	O	O	O	O	S	F	OH
1710a-l	Y*AC	O	O	O	O	O	S	OEt	OH
1711a-l	Y*AC	S	O	O	O	O	S	OH	OH
1712a-l	Y*AC	S	O	O	O	O	S	OMe	OH
1713a-l	Y*AC	S	O	O	O	O	S	H	OH
1714a-l	Y*AC	S	O	O	O	O	S	F	OH
1715a-l	Y*AC	S	O	O	O	O	S	OEt	OH
1716a-l	Y*AC	S	S	O	O	O	S	OH	OH
1717a-l	Y*AC	S	S	O	O	O	S	OMe	OH
1718a-l	Y*AC	S	S	O	O	O	S	H	OH
1719a-l	Y*AC	S	S	O	O	O	S	F	OH
1720a-l	Y*AC	S	S	O	O	O	S	OEt	OH
1721a-l	Y*AC	O	O	S	O	S	O	OH	OH
1722a-l	Y*AC	O	O	S	O	S	O	OMe	OH
1723a-l	Y*AC	O	O	S	O	S	O	H	OH
1724a-l	Y*AC	O	O	S	O	S	O	F	OH
1725a-l	Y*AC	O	O	S	O	S	O	OEt	OH
1726a-l	Y*AC	S	O	S	O	S	O	OH	OH
1727a-l	Y*AC	S	O	S	O	S	O	OMe	OH
1728a-l	Y*AC	S	O	S	O	S	O	H	OH
1729a-l	Y*AC	S	O	S	O	S	O	F	OH
1730a-l	Y*AC	S	O	S	O	S	O	OEt	OH
1731a-l	Y*AC	S	S	S	O	S	O	OH	OH
1732a-l	Y*AC	S	S	S	O	S	O	OMe	OH
1733a-l	Y*AC	S	S	S	O	S	O	H	OH
1734a-l	Y*AC	S	S	S	O	S	O	F	OH
1735a-l	Y*AC	S	S	S	O	S	O	OEt	OH
1736a-l	Y*AC	O	O	O	S	O	S	OH	OH
1737a-l	Y*AC	O	O	O	S	O	S	OMe	OH
1738a-l	Y*AC	O	O	O	S	O	S	H	OH
1739a-l	Y*AC	O	O	O	S	O	S	F	OH
1740a-l	Y*AC	O	O	O	S	O	S	OEt	OH

1741a-l	Y*AC	S	O	O	S	O	S	OH	OH
1742a-l	Y*AC	S	O	O	S	O	S	OMe	OH
1743a-l	Y*AC	S	O	O	S	O	S	H	OH
1744a-l	Y*AC	S	O	O	S	O	S	F	OH
1745a-l	Y*AC	S	O	O	S	O	S	OEt	OH
1746a-l	Y*AC	S	S	O	S	O	S	OH	OH
1747a-l	Y*AC	S	S	O	S	O	S	OMe	OH
1748a-l	Y*AC	S	S	O	S	O	S	H	OH
1749a-l	Y*AC	S	S	O	S	O	S	F	OH
1750a-l	Y*AC	S	S	O	S	O	S	OEt	OH
1751a-l	Y*AC	O	O	O	O	O	O	OH	OMe
1752a-l	Y*AC	O	O	O	O	O	O	OMe	OMe
1753a-l	Y*AC	O	O	O	O	O	O	H	OMe
1754a-l	Y*AC	O	O	O	O	O	O	F	OMe
1755a-l	Y*AC	O	O	O	O	O	O	OEt	OMe
1756a-l	Y*AC	S	O	O	O	O	O	OH	OMe
1757a-l	Y*AC	S	O	O	O	O	O	OMe	OMe
1758a-l	Y*AC	S	O	O	O	O	O	H	OMe
1759a-l	Y*AC	S	O	O	O	O	O	F	OMe
1760a-l	Y*AC	S	O	O	O	O	O	OEt	OMe
1761a-l	Y*AC	S	S	O	O	O	O	OH	OMe
1762a-l	Y*AC	S	S	O	O	O	O	OMe	OMe
1763a-l	Y*AC	S	S	O	O	O	O	H	OMe
1764a-l	Y*AC	S	S	O	O	O	O	F	OMe
1765a-l	Y*AC	S	S	O	O	O	O	OEt	OMe
1766a-l	Y*AC	O	O	S	O	O	O	OH	OMe
1767a-l	Y*AC	O	O	S	O	O	O	OMe	OMe
1768a-l	Y*AC	O	O	S	O	O	O	H	OMe
1769a-l	Y*AC	O	O	S	O	O	O	F	OMe
1770a-l	Y*AC	O	O	S	O	O	O	OEt	OMe
1771a-l	Y*AC	S	O	S	O	O	O	OH	OMe
1772a-l	Y*AC	S	O	S	O	O	O	OMe	OMe
1773a-l	Y*AC	S	O	S	O	O	O	H	OMe
1774a-l	Y*AC	S	O	S	O	O	O	F	OMe
1775a-l	Y*AC	S	O	S	O	O	O	OEt	OMe
1776a-l	Y*AC	S	S	S	O	O	O	OH	OMe
1777a-l	Y*AC	S	S	S	O	O	O	OMe	OMe
1778a-l	Y*AC	S	S	S	O	O	O	H	OMe
1779a-l	Y*AC	S	S	S	O	O	O	F	OMe
1780a-l	Y*AC	S	S	S	O	O	O	OEt	OMe
1781a-l	Y*AC	O	O	S	S	O	O	OH	OMe
1782a-l	Y*AC	O	O	S	S	O	O	OMe	OMe
1783a-l	Y*AC	O	O	S	S	O	O	H	OMe
1784a-l	Y*AC	O	O	S	S	O	O	F	OMe
1785a-l	Y*AC	O	O	S	S	O	O	OEt	OMe
1786a-l	Y*AC	S	O	S	S	O	O	OH	OMe
1787a-l	Y*AC	S	O	S	S	O	O	OMe	OMe
1788a-l	Y*AC	S	O	S	S	O	O	H	OMe
1789a-l	Y*AC	S	O	S	S	O	O	F	OMe

1790a-l	Y*AC	S	O	S	S	O	O	OEt	OMe
1791a-l	Y*AC	S	S	S	S	O	O	OH	OMe
1792a-l	Y*AC	S	S	S	S	O	O	OMe	OMe
1793a-l	Y*AC	S	S	S	S	O	O	H	OMe
1794a-l	Y*AC	S	S	S	S	O	O	F	OMe
1795a-l	Y*AC	S	S	S	S	O	O	OEt	OMe
1796a-l	Y*AC	O	O	S	S	S	O	OH	OMe
1797a-l	Y*AC	O	O	S	S	S	O	OMe	OMe
1798a-l	Y*AC	O	O	S	S	S	O	H	OMe
1799a-l	Y*AC	O	O	S	S	S	O	F	OMe
1800a-l	Y*AC	O	O	S	S	S	O	OEt	OMe
1801a-l	Y*AC	S	O	S	S	S	O	OH	OMe
1802a-l	Y*AC	S	O	S	S	S	O	OMe	OMe
1803a-l	Y*AC	S	O	S	S	S	O	H	OMe
1804a-l	Y*AC	S	O	S	S	S	O	F	OMe
1805a-l	Y*AC	S	O	S	S	S	O	OEt	OMe
1806a-l	Y*AC	S	S	S	S	S	O	OH	OMe
1807a-l	Y*AC	S	S	S	S	S	O	OMe	OMe
1808a-l	Y*AC	S	S	S	S	S	O	H	OMe
1809a-l	Y*AC	S	S	S	S	S	O	F	OMe
1810a-l	Y*AC	S	S	S	S	S	O	OEt	OMe
1811a-l	Y*AC	O	O	S	S	S	S	OH	OMe
1812a-l	Y*AC	O	O	S	S	S	S	OMe	OMe
1813a-l	Y*AC	O	O	S	S	S	S	H	OMe
1814a-l	Y*AC	O	O	S	S	S	S	F	OMe
1815a-l	Y*AC	O	O	S	S	S	S	OEt	OMe
1816a-l	Y*AC	S	O	S	S	S	S	OH	OMe
1817a-l	Y*AC	S	O	S	S	S	S	OMe	OMe
1818a-l	Y*AC	S	O	S	S	S	S	H	OMe
1819a-l	Y*AC	S	O	S	S	S	S	F	OMe
1820a-l	Y*AC	S	O	S	S	S	S	OEt	OMe
1821a-l	Y*AC	S	S	S	S	S	S	OH	OMe
1822a-l	Y*AC	S	S	S	S	S	S	OMe	OMe
1823a-l	Y*AC	S	S	S	S	S	S	H	OMe
1824a-l	Y*AC	S	S	S	S	S	S	F	OMe
1825a-l	Y*AC	S	S	S	S	S	S	OEt	OMe
1826a-l	Y*AC	O	O	O	S	S	S	OH	OMe
1827a-l	Y*AC	O	O	O	S	S	S	OMe	OMe
1828a-l	Y*AC	O	O	O	S	S	S	H	OMe
1829a-l	Y*AC	O	O	O	S	S	S	F	OMe
1830a-l	Y*AC	O	O	O	S	S	S	OEt	OMe
1831a-l	Y*AC	S	O	O	S	S	S	OH	OMe
1832a-l	Y*AC	S	O	O	S	S	S	OMe	OMe
1833a-l	Y*AC	S	O	O	S	S	S	H	OMe
1834a-l	Y*AC	S	O	O	S	S	S	F	OMe
1835a-l	Y*AC	S	O	O	S	S	S	OEt	OMe
1836a-l	Y*AC	S	S	O	S	S	S	OH	OMe
1837a-l	Y*AC	S	S	O	S	S	S	OMe	OMe
1838a-l	Y*AC	S	S	O	S	S	S	H	OMe

1839a-l	Y*AC	S	S	O	S	S	S	F	OMe
1840a-l	Y*AC	S	S	O	S	S	S	OEt	OMe
1841a-l	Y*AC	O	O	O	O	S	S	OH	OMe
1842a-l	Y*AC	O	O	O	O	S	S	OMe	OMe
1843a-l	Y*AC	O	O	O	O	S	S	H	OMe
1844a-l	Y*AC	O	O	O	O	S	S	F	OMe
1845a-l	Y*AC	O	O	O	O	S	S	OEt	OMe
1846a-l	Y*AC	S	O	O	O	S	S	OH	OMe
1847a-l	Y*AC	S	O	O	O	S	S	OMe	OMe
1848a-l	Y*AC	S	O	O	O	S	S	H	OMe
1849a-l	Y*AC	S	O	O	O	S	S	F	OMe
1850a-l	Y*AC	S	O	O	O	S	S	OEt	OMe
1851a-l	Y*AC	S	S	O	O	S	S	OH	OMe
1852a-l	Y*AC	S	S	O	O	S	S	OMe	OMe
1853a-l	Y*AC	S	S	O	O	S	S	H	OMe
1854a-l	Y*AC	S	S	O	O	S	S	F	OMe
1855a-l	Y*AC	S	S	O	O	S	S	OEt	OMe
1856a-l	Y*AC	O	O	O	O	O	S	OH	OMe
1857a-l	Y*AC	O	O	O	O	O	S	OMe	OMe
1858a-l	Y*AC	O	O	O	O	O	S	H	OMe
1859a-l	Y*AC	O	O	O	O	O	S	F	OMe
1860a-l	Y*AC	O	O	O	O	O	S	OEt	OMe
1861a-l	Y*AC	S	O	O	O	O	S	OH	OMe
1862a-l	Y*AC	S	O	O	O	O	S	OMe	OMe
1863a-l	Y*AC	S	O	O	O	O	S	H	OMe
1864a-l	Y*AC	S	O	O	O	O	S	F	OMe
1865a-l	Y*AC	S	O	O	O	O	S	OEt	OMe
1866a-l	Y*AC	S	S	O	O	O	S	OH	OMe
1867a-l	Y*AC	S	S	O	O	O	S	OMe	OMe
1868a-l	Y*AC	S	S	O	O	O	S	H	OMe
1869a-l	Y*AC	S	S	O	O	O	S	F	OMe
1870a-l	Y*AC	S	S	O	O	O	S	OEt	OMe
1871a-l	Y*AC	O	O	S	O	S	O	OH	OMe
1872a-l	Y*AC	O	O	S	O	S	O	OMe	OMe
1873a-l	Y*AC	O	O	S	O	S	O	H	OMe
1874a-l	Y*AC	O	O	S	O	S	O	F	OMe
1875a-l	Y*AC	O	O	S	O	S	O	OEt	OMe
1876a-l	Y*AC	S	O	S	O	S	O	OH	OMe
1877a-l	Y*AC	S	O	S	O	S	O	OMe	OMe
1878a-l	Y*AC	S	O	S	O	S	O	H	OMe
1879a-l	Y*AC	S	O	S	O	S	O	F	OMe
1880a-l	Y*AC	S	O	S	O	S	O	OEt	OMe
1881a-l	Y*AC	S	S	S	O	S	O	OH	OMe
1882a-l	Y*AC	S	S	S	O	S	O	OMe	OMe
1883a-l	Y*AC	S	S	S	O	S	O	H	OMe
1884a-l	Y*AC	S	S	S	O	S	O	F	OMe
1885a-l	Y*AC	S	S	S	O	S	O	OEt	OMe
1886a-l	Y*AC	O	O	O	S	O	S	OH	OMe
1887a-l	Y*AC	O	O	O	S	O	S	OMe	OMe

1888a-l	Y*AC	O	O	O	S	O	S	H	OMe
1889a-l	Y*AC	O	O	O	S	O	S	F	OMe
1890a-l	Y*AC	O	O	O	S	O	S	OEt	OMe
1891a-l	Y*AC	S	O	O	S	O	S	OH	OMe
1892a-l	Y*AC	S	O	O	S	O	S	OMe	OMe
1893a-l	Y*AC	S	O	O	S	O	S	H	OMe
1894a-l	Y*AC	S	O	O	S	O	S	F	OMe
1895a-l	Y*AC	S	O	O	S	O	S	OEt	OMe
1896a-l	Y*AC	S	S	O	S	O	S	OH	OMe
1897a-l	Y*AC	S	S	O	S	O	S	OMe	OMe
1898a-l	Y*AC	S	S	O	S	O	S	H	OMe
1899a-l	Y*AC	S	S	O	S	O	S	F	OMe
1900a-l	Y*AC	S	S	O	S	O	S	OEt	OMe
1901a-l	Y*AU	O	O	O	O	O	O	OH	OH
1902a-l	Y*AU	O	O	O	O	O	O	OMe	OH
1903a-l	Y*AU	O	O	O	O	O	O	H	OH
1904a-l	Y*AU	O	O	O	O	O	O	F	OH
1905a-l	Y*AU	O	O	O	O	O	O	OEt	OH
1906a-l	Y*AU	S	O	O	O	O	O	OH	OH
1907a-l	Y*AU	S	O	O	O	O	O	OMe	OH
1908a-l	Y*AU	S	O	O	O	O	O	H	OH
1909a-l	Y*AU	S	O	O	O	O	O	F	OH
1910a-l	Y*AU	S	O	O	O	O	O	OEt	OH
1911a-l	Y*AU	S	S	O	O	O	O	OH	OH
1912a-l	Y*AU	S	S	O	O	O	O	OMe	OH
1913a-l	Y*AU	S	S	O	O	O	O	H	OH
1914a-l	Y*AU	S	S	O	O	O	O	F	OH
1915a-l	Y*AU	S	S	O	O	O	O	OEt	OH
1916a-l	Y*AU	O	O	S	O	O	O	OH	OH
1917a-l	Y*AU	O	O	S	O	O	O	OMe	OH
1918a-l	Y*AU	O	O	S	O	O	O	H	OH
1919a-l	Y*AU	O	O	S	O	O	O	F	OH
1920a-l	Y*AU	O	O	S	O	O	O	OEt	OH
1921a-l	Y*AU	S	O	S	O	O	O	OH	OH
1922a-l	Y*AU	S	O	S	O	O	O	OMe	OH
1923a-l	Y*AU	S	O	S	O	O	O	H	OH
1924a-l	Y*AU	S	O	S	O	O	O	F	OH
1925a-l	Y*AU	S	O	S	O	O	O	OEt	OH
1926a-l	Y*AU	S	S	S	O	O	O	OH	OH
1927a-l	Y*AU	S	S	S	O	O	O	OMe	OH
1928a-l	Y*AU	S	S	S	O	O	O	H	OH
1929a-l	Y*AU	S	S	S	O	O	O	F	OH
1930a-l	Y*AU	S	S	S	O	O	O	OEt	OH
1931a-l	Y*AU	O	O	S	S	O	O	OH	OH
1932a-l	Y*AU	O	O	S	S	O	O	OMe	OH
1933a-l	Y*AU	O	O	S	S	O	O	H	OH
1934a-l	Y*AU	O	O	S	S	O	O	F	OH
1935a-l	Y*AU	O	O	S	S	O	O	OEt	OH
1936a-l	Y*AU	S	O	S	S	O	O	OH	OH

1937a-l	Y*AU	S	O	S	S	O	O	OMe	OH
1938a-l	Y*AU	S	O	S	S	O	O	H	OH
1939a-l	Y*AU	S	O	S	S	O	O	F	OH
1940a-l	Y*AU	S	O	S	S	O	O	OEt	OH
1941a-l	Y*AU	S	S	S	S	O	O	OH	OH
1942a-l	Y*AU	S	S	S	S	O	O	OMe	OH
1943a-l	Y*AU	S	S	S	S	O	O	H	OH
1944a-l	Y*AU	S	S	S	S	O	O	F	OH
1945a-l	Y*AU	S	S	S	S	O	O	OEt	OH
1946a-l	Y*AU	O	O	S	S	S	O	OH	OH
1947a-l	Y*AU	O	O	S	S	S	O	OMe	OH
1948a-l	Y*AU	O	O	S	S	S	O	H	OH
1949a-l	Y*AU	O	O	S	S	S	O	F	OH
1950a-l	Y*AU	O	O	S	S	S	O	OEt	OH
1951a-l	Y*AU	S	O	S	S	S	O	OH	OH
1952a-l	Y*AU	S	O	S	S	S	O	OMe	OH
1953a-l	Y*AU	S	O	S	S	S	O	H	OH
1954a-l	Y*AU	S	O	S	S	S	O	F	OH
1955a-l	Y*AU	S	O	S	S	S	O	OEt	OH
1956a-l	Y*AU	S	S	S	S	S	O	OH	OH
1957a-l	Y*AU	S	S	S	S	S	O	OMe	OH
1958a-l	Y*AU	S	S	S	S	S	O	H	OH
1959a-l	Y*AU	S	S	S	S	S	O	F	OH
1960a-l	Y*AU	S	S	S	S	S	O	OEt	OH
1961a-l	Y*AU	O	O	S	S	S	S	OH	OH
1962a-l	Y*AU	O	O	S	S	S	S	OMe	OH
1963a-l	Y*AU	O	O	S	S	S	S	H	OH
1964a-l	Y*AU	O	O	S	S	S	S	F	OH
1965a-l	Y*AU	O	O	S	S	S	S	OEt	OH
1966a-l	Y*AU	S	O	S	S	S	S	OH	OH
1967a-l	Y*AU	S	O	S	S	S	S	OMe	OH
1968a-l	Y*AU	S	O	S	S	S	S	H	OH
1969a-l	Y*AU	S	O	S	S	S	S	F	OH
1970a-l	Y*AU	S	O	S	S	S	S	OEt	OH
1971a-l	Y*AU	S	S	S	S	S	S	OH	OH
1972a-l	Y*AU	S	S	S	S	S	S	OMe	OH
1973a-l	Y*AU	S	S	S	S	S	S	H	OH
1974a-l	Y*AU	S	S	S	S	S	S	F	OH
1975a-l	Y*AU	S	S	S	S	S	S	OEt	OH
1976a-l	Y*AU	O	O	O	S	S	S	OH	OH
1977a-l	Y*AU	O	O	O	S	S	S	OMe	OH
1978a-l	Y*AU	O	O	O	S	S	S	H	OH
1979a-l	Y*AU	O	O	O	S	S	S	F	OH
1980a-l	Y*AU	O	O	O	S	S	S	OEt	OH
1981a-l	Y*AU	S	O	O	S	S	S	OH	OH
1982a-l	Y*AU	S	O	O	S	S	S	OMe	OH
1983a-l	Y*AU	S	O	O	S	S	S	H	OH
1984a-l	Y*AU	S	O	O	S	S	S	F	OH
1985a-l	Y*AU	S	O	O	S	S	S	OEt	OH

1986a-l	Y*AU	S	S	O	S	S	S	OH	OH
1987a-l	Y*AU	S	S	O	S	S	S	OMe	OH
1988a-l	Y*AU	S	S	O	S	S	S	H	OH
1989a-l	Y*AU	S	S	O	S	S	S	F	OH
1990a-l	Y*AU	S	S	O	S	S	S	OEt	OH
1991a-l	Y*AU	O	O	O	O	S	S	OH	OH
1992a-l	Y*AU	O	O	O	O	S	S	OMe	OH
1993a-l	Y*AU	O	O	O	O	S	S	H	OH
1994a-l	Y*AU	O	O	O	O	S	S	F	OH
1995a-l	Y*AU	O	O	O	O	S	S	OEt	OH
1996a-l	Y*AU	S	O	O	O	S	S	OH	OH
1997a-l	Y*AU	S	O	O	O	S	S	OMe	OH
1998a-l	Y*AU	S	O	O	O	S	S	H	OH
1999a-l	Y*AU	S	O	O	O	S	S	F	OH
2000a-l	Y*AU	S	O	O	O	S	S	OEt	OH
2001a-l	Y*AU	S	S	O	O	S	S	OH	OH
2002a-l	Y*AU	S	S	O	O	S	S	OMe	OH
2003a-l	Y*AU	S	S	O	O	S	S	H	OH
2004a-l	Y*AU	S	S	O	O	S	S	F	OH
2005a-l	Y*AU	S	S	O	O	S	S	OEt	OH
2006a-l	Y*AU	O	O	O	O	O	S	OH	OH
2007a-l	Y*AU	O	O	O	O	O	S	OMe	OH
2008a-l	Y*AU	O	O	O	O	O	S	H	OH
2009a-l	Y*AU	O	O	O	O	O	S	F	OH
2010a-l	Y*AU	O	O	O	O	O	S	OEt	OH
2011a-l	Y*AU	S	O	O	O	O	S	OH	OH
2012a-l	Y*AU	S	O	O	O	O	S	OMe	OH
2013a-l	Y*AU	S	O	O	O	O	S	H	OH
2014a-l	Y*AU	S	O	O	O	O	S	F	OH
2015a-l	Y*AU	S	O	O	O	O	S	OEt	OH
2016a-l	Y*AU	S	S	O	O	O	S	OH	OH
2017a-l	Y*AU	S	S	O	O	O	S	OMe	OH
2018a-l	Y*AU	S	S	O	O	O	S	H	OH
2019a-l	Y*AU	S	S	O	O	O	S	F	OH
2020a-l	Y*AU	S	S	O	O	O	S	OEt	OH
2021a-l	Y*AU	O	O	S	O	S	O	OH	OH
2022a-l	Y*AU	O	O	S	O	S	O	OMe	OH
2023a-l	Y*AU	O	O	S	O	S	O	H	OH
2024a-l	Y*AU	O	O	S	O	S	O	F	OH
2025a-l	Y*AU	O	O	S	O	S	O	OEt	OH
2026a-l	Y*AU	S	O	S	O	S	O	OH	OH
2027a-l	Y*AU	S	O	S	O	S	O	OMe	OH
2028a-l	Y*AU	S	O	S	O	S	O	H	OH
2029a-l	Y*AU	S	O	S	O	S	O	F	OH
2030a-l	Y*AU	S	O	S	O	S	O	OEt	OH
2031a-l	Y*AU	S	S	S	O	S	O	OH	OH
2032a-l	Y*AU	S	S	S	O	S	O	OMe	OH
2033a-l	Y*AU	S	S	S	O	S	O	H	OH
2034a-l	Y*AU	S	S	S	O	S	O	F	OH

2035a-l	Y*AU	S	S	S	O	S	O	OEt	OH
2036a-l	Y*AU	O	O	O	S	O	S	OH	OH
2037a-l	Y*AU	O	O	O	S	O	S	OMe	OH
2038a-l	Y*AU	O	O	O	S	O	S	H	OH
2039a-l	Y*AU	O	O	O	S	O	S	F	OH
2040a-l	Y*AU	O	O	O	S	O	S	OEt	OH
2041a-l	Y*AU	S	O	O	S	O	S	OH	OH
2042a-l	Y*AU	S	O	O	S	O	S	OMe	OH
2043a-l	Y*AU	S	O	O	S	O	S	H	OH
2044a-l	Y*AU	S	O	O	S	O	S	F	OH
2045a-l	Y*AU	S	O	O	S	O	S	OEt	OH
2046a-l	Y*AU	S	S	O	S	O	S	OH	OH
2047a-l	Y*AU	S	S	O	S	O	S	OMe	OH
2048a-l	Y*AU	S	S	O	S	O	S	H	OH
2049a-l	Y*AU	S	S	O	S	O	S	F	OH
2050a-l	Y*AU	S	S	O	S	O	S	OEt	OH
2051a-l	Y*AU	O	O	O	O	O	O	OH	OMe
2052a-l	Y*AU	O	O	O	O	O	O	OMe	OMe
2053a-l	Y*AU	O	O	O	O	O	O	H	OMe
2054a-l	Y*AU	O	O	O	O	O	O	F	OMe
2055a-l	Y*AU	O	O	O	O	O	O	OEt	OMe
2056a-l	Y*AU	S	O	O	O	O	O	OH	OMe
2057a-l	Y*AU	S	O	O	O	O	O	OMe	OMe
2058a-l	Y*AU	S	O	O	O	O	O	H	OMe
2059a-l	Y*AU	S	O	O	O	O	O	F	OMe
2060a-l	Y*AU	S	O	O	O	O	O	OEt	OMe
2061a-l	Y*AU	S	S	O	O	O	O	OH	OMe
2062a-l	Y*AU	S	S	O	O	O	O	OMe	OMe
2063a-l	Y*AU	S	S	O	O	O	O	H	OMe
2064a-l	Y*AU	S	S	O	O	O	O	F	OMe
2065a-l	Y*AU	S	S	O	O	O	O	OEt	OMe
2066a-l	Y*AU	O	O	S	O	O	O	OH	OMe
2067a-l	Y*AU	O	O	S	O	O	O	OMe	OMe
2068a-l	Y*AU	O	O	S	O	O	O	H	OMe
2069a-l	Y*AU	O	O	S	O	O	O	F	OMe
2070a-l	Y*AU	O	O	S	O	O	O	OEt	OMe
2071a-l	Y*AU	S	O	S	O	O	O	OH	OMe
2072a-l	Y*AU	S	O	S	O	O	O	OMe	OMe
2073a-l	Y*AU	S	O	S	O	O	O	H	OMe
2074a-l	Y*AU	S	O	S	O	O	O	F	OMe
2075a-l	Y*AU	S	O	S	O	O	O	OEt	OMe
2076a-l	Y*AU	S	S	S	O	O	O	OH	OMe
2077a-l	Y*AU	S	S	S	O	O	O	OMe	OMe
2078a-l	Y*AU	S	S	S	O	O	O	H	OMe
2079a-l	Y*AU	S	S	S	O	O	O	F	OMe
2080a-l	Y*AU	S	S	S	O	O	O	OEt	OMe
2081a-l	Y*AU	O	O	S	S	O	O	OH	OMe
2082a-l	Y*AU	O	O	S	S	O	O	OMe	OMe
2083a-l	Y*AU	O	O	S	S	O	O	H	OMe

2084a-l	Y*AU	O	O	S	S	O	O	F	OMe
2085a-l	Y*AU	O	O	S	S	O	O	OEt	OMe
2086a-l	Y*AU	S	O	S	S	O	O	OH	OMe
2087a-l	Y*AU	S	O	S	S	O	O	OMe	OMe
2088a-l	Y*AU	S	O	S	S	O	O	H	OMe
2089a-l	Y*AU	S	O	S	S	O	O	F	OMe
2090a-l	Y*AU	S	O	S	S	O	O	OEt	OMe
2091a-l	Y*AU	S	S	S	S	O	O	OH	OMe
2092a-l	Y*AU	S	S	S	S	O	O	OMe	OMe
2093a-l	Y*AU	S	S	S	S	O	O	H	OMe
2094a-l	Y*AU	S	S	S	S	O	O	F	OMe
2095a-l	Y*AU	S	S	S	S	O	O	OEt	OMe
2096a-l	Y*AU	O	O	S	S	S	O	OH	OMe
2097a-l	Y*AU	O	O	S	S	S	O	OMe	OMe
2098a-l	Y*AU	O	O	S	S	S	O	H	OMe
2099a-l	Y*AU	O	O	S	S	S	O	F	OMe
2100a-l	Y*AU	O	O	S	S	S	O	OEt	OMe
2101a-l	Y*AU	S	O	S	S	S	O	OH	OMe
2102a-l	Y*AU	S	O	S	S	S	O	OMe	OMe
2103a-l	Y*AU	S	O	S	S	S	O	H	OMe
2104a-l	Y*AU	S	O	S	S	S	O	F	OMe
2105a-l	Y*AU	S	O	S	S	S	O	OEt	OMe
2106a-l	Y*AU	S	S	S	S	S	O	OH	OMe
2107a-l	Y*AU	S	S	S	S	S	O	OMe	OMe
2108a-l	Y*AU	S	S	S	S	S	O	H	OMe
2109a-l	Y*AU	S	S	S	S	S	O	F	OMe
2110a-l	Y*AU	S	S	S	S	S	O	OEt	OMe
2111a-l	Y*AU	O	O	S	S	S	S	OH	OMe
2112a-l	Y*AU	O	O	S	S	S	S	OMe	OMe
2113a-l	Y*AU	O	O	S	S	S	S	H	OMe
2114a-l	Y*AU	O	O	S	S	S	S	F	OMe
2115a-l	Y*AU	O	O	S	S	S	S	OEt	OMe
2116a-l	Y*AU	S	O	S	S	S	S	OH	OMe
2117a-l	Y*AU	S	O	S	S	S	S	OMe	OMe
2118a-l	Y*AU	S	O	S	S	S	S	H	OMe
2119a-l	Y*AU	S	O	S	S	S	S	F	OMe
2120a-l	Y*AU	S	O	S	S	S	S	OEt	OMe
2121a-l	Y*AU	S	S	S	S	S	S	OH	OMe
2122a-l	Y*AU	S	S	S	S	S	S	OMe	OMe
2123a-l	Y*AU	S	S	S	S	S	S	H	OMe
2124a-l	Y*AU	S	S	S	S	S	S	F	OMe
2125a-l	Y*AU	S	S	S	S	S	S	OEt	OMe
2126a-l	Y*AU	O	O	O	S	S	S	OH	OMe
2127a-l	Y*AU	O	O	O	S	S	S	OMe	OMe
2128a-l	Y*AU	O	O	O	S	S	S	H	OMe
2129a-l	Y*AU	O	O	O	S	S	S	F	OMe
2130a-l	Y*AU	O	O	O	S	S	S	OEt	OMe
2131a-l	Y*AU	S	O	O	S	S	S	OH	OMe
2132a-l	Y*AU	S	O	O	S	S	S	OMe	OMe

2133a-l	Y*AU	S	O	O	S	S	S	H	OMe
2134a-l	Y*AU	S	O	O	S	S	S	F	OMe
2135a-l	Y*AU	S	O	O	S	S	S	OEt	OMe
2136a-l	Y*AU	S	S	O	S	S	S	OH	OMe
2137a-l	Y*AU	S	S	O	S	S	S	OMe	OMe
2138a-l	Y*AU	S	S	O	S	S	S	H	OMe
2139a-l	Y*AU	S	S	O	S	S	S	F	OMe
2140a-l	Y*AU	S	S	O	S	S	S	OEt	OMe
2141a-l	Y*AU	O	O	O	O	S	S	OH	OMe
2142a-l	Y*AU	O	O	O	O	S	S	OMe	OMe
2143a-l	Y*AU	O	O	O	O	S	S	H	OMe
2144a-l	Y*AU	O	O	O	O	S	S	F	OMe
2145a-l	Y*AU	O	O	O	O	S	S	OEt	OMe
2146a-l	Y*AU	S	O	O	O	S	S	OH	OMe
2147a-l	Y*AU	S	O	O	O	S	S	OMe	OMe
2148a-l	Y*AU	S	O	O	O	S	S	H	OMe
2149a-l	Y*AU	S	O	O	O	S	S	F	OMe
2150a-l	Y*AU	S	O	O	O	S	S	OEt	OMe
2151a-l	Y*AU	S	S	O	O	S	S	OH	OMe
2152a-l	Y*AU	S	S	O	O	S	S	OMe	OMe
2153a-l	Y*AU	S	S	O	O	S	S	H	OMe
2154a-l	Y*AU	S	S	O	O	S	S	F	OMe
2155a-l	Y*AU	S	S	O	O	S	S	OEt	OMe
2156a-l	Y*AU	O	O	O	O	O	S	OH	OMe
2157a-l	Y*AU	O	O	O	O	O	S	OMe	OMe
2158a-l	Y*AU	O	O	O	O	O	S	H	OMe
2159a-l	Y*AU	O	O	O	O	O	S	F	OMe
2160a-l	Y*AU	O	O	O	O	O	S	OEt	OMe
2161a-l	Y*AU	S	O	O	O	O	S	OH	OMe
2162a-l	Y*AU	S	O	O	O	O	S	OMe	OMe
2163a-l	Y*AU	S	O	O	O	O	S	H	OMe
2164a-l	Y*AU	S	O	O	O	O	S	F	OMe
2165a-l	Y*AU	S	O	O	O	O	S	OEt	OMe
2166a-l	Y*AU	S	S	O	O	O	S	OH	OMe
2167a-l	Y*AU	S	S	O	O	O	S	OMe	OMe
2168a-l	Y*AU	S	S	O	O	O	S	H	OMe
2169a-l	Y*AU	S	S	O	O	O	S	F	OMe
2170a-l	Y*AU	S	S	O	O	O	S	OEt	OMe
2171a-l	Y*AU	O	O	S	O	S	O	OH	OMe
2172a-l	Y*AU	O	O	S	O	S	O	OMe	OMe
2173a-l	Y*AU	O	O	S	O	S	O	H	OMe
2174a-l	Y*AU	O	O	S	O	S	O	F	OMe
2175a-l	Y*AU	O	O	S	O	S	O	OEt	OMe
2176a-l	Y*AU	S	O	S	O	S	O	OH	OMe
2177a-l	Y*AU	S	O	S	O	S	O	OMe	OMe
2178a-l	Y*AU	S	O	S	O	S	O	H	OMe
2179a-l	Y*AU	S	O	S	O	S	O	F	OMe
2180a-l	Y*AU	S	O	S	O	S	O	OEt	OMe
2181a-l	Y*AU	S	S	S	O	S	O	OH	OMe

2182a-l	Y*AU	S	S	S	O	S	O	OMe	OMe
2183a-l	Y*AU	S	S	S	O	S	O	H	OMe
2184a-l	Y*AU	S	S	S	O	S	O	F	OMe
2185a-l	Y*AU	S	S	S	O	S	O	OEt	OMe
2186a-l	Y*AU	O	O	O	S	O	S	OH	OMe
2187a-l	Y*AU	O	O	O	S	O	S	OMe	OMe
2188a-l	Y*AU	O	O	O	S	O	S	H	OMe
2189a-l	Y*AU	O	O	O	S	O	S	F	OMe
2190a-l	Y*AU	O	O	O	S	O	S	OEt	OMe
2191a-l	Y*AU	S	O	O	S	O	S	OH	OMe
2192a-l	Y*AU	S	O	O	S	O	S	OMe	OMe
2193a-l	Y*AU	S	O	O	S	O	S	H	OMe
2194a-l	Y*AU	S	O	O	S	O	S	F	OMe
2195a-l	Y*AU	S	O	O	S	O	S	OEt	OMe
2196a-l	Y*AU	S	S	O	S	O	S	OH	OMe
2197a-l	Y*AU	S	S	O	S	O	S	OMe	OMe
2198a-l	Y*AU	S	S	O	S	O	S	H	OMe
2199a-l	Y*AU	S	S	O	S	O	S	F	OMe
2200a-l	Y*AU	S	S	O	S	O	S	OEt	OMe
2201a-l	Y*AI	O	O	O	O	O	O	OH	OH
2202a-l	Y*AI	O	O	O	O	O	O	OMe	OH
2203a-l	Y*AI	O	O	O	O	O	O	H	OH
2204a-l	Y*AI	O	O	O	O	O	O	F	OH
2205a-l	Y*AI	O	O	O	O	O	O	OEt	OH
2206a-l	Y*AI	S	O	O	O	O	O	OH	OH
2207a-l	Y*AI	S	O	O	O	O	O	OMe	OH
2208a-l	Y*AI	S	O	O	O	O	O	H	OH
2209a-l	Y*AI	S	O	O	O	O	O	F	OH
2210a-l	Y*AI	S	O	O	O	O	O	OEt	OH
2211a-l	Y*AI	S	S	O	O	O	O	OH	OH
2212a-l	Y*AI	S	S	O	O	O	O	OMe	OH
2213a-l	Y*AI	S	S	O	O	O	O	H	OH
2214a-l	Y*AI	S	S	O	O	O	O	F	OH
2215a-l	Y*AI	S	S	O	O	O	O	OEt	OH
2216a-l	Y*AI	O	O	S	O	O	O	OH	OH
2217a-l	Y*AI	O	O	S	O	O	O	OMe	OH
2218a-l	Y*AI	O	O	S	O	O	O	H	OH
2219a-l	Y*AI	O	O	S	O	O	O	F	OH
2220a-l	Y*AI	O	O	S	O	O	O	OEt	OH
2221a-l	Y*AI	S	O	S	O	O	O	OH	OH
2222a-l	Y*AI	S	O	S	O	O	O	OMe	OH
2223a-l	Y*AI	S	O	S	O	O	O	H	OH
2224a-l	Y*AI	S	O	S	O	O	O	F	OH
2225a-l	Y*AI	S	O	S	O	O	O	OEt	OH
2226a-l	Y*AI	S	S	S	O	O	O	OH	OH
2227a-l	Y*AI	S	S	S	O	O	O	OMe	OH
2228a-l	Y*AI	S	S	S	O	O	O	H	OH
2229a-l	Y*AI	S	S	S	O	O	O	F	OH
2230a-l	Y*AI	S	S	S	O	O	O	OEt	OH

2231a-l	Y*AI	O	O	S	S	O	O	OH	OH
2232a-l	Y*AI	O	O	S	S	O	O	OMe	OH
2233a-l	Y*AI	O	O	S	S	O	O	H	OH
2234a-l	Y*AI	O	O	S	S	O	O	F	OH
2235a-l	Y*AI	O	O	S	S	O	O	OEt	OH
2236a-l	Y*AI	S	O	S	S	O	O	OH	OH
2237a-l	Y*AI	S	O	S	S	O	O	OMe	OH
2238a-l	Y*AI	S	O	S	S	O	O	H	OH
2239a-l	Y*AI	S	O	S	S	O	O	F	OH
2240a-l	Y*AI	S	O	S	S	O	O	OEt	OH
2241a-l	Y*AI	S	S	S	S	O	O	OH	OH
2242a-l	Y*AI	S	S	S	S	O	O	OMe	OH
2243a-l	Y*AI	S	S	S	S	O	O	H	OH
2244a-l	Y*AI	S	S	S	S	O	O	F	OH
2245a-l	Y*AI	S	S	S	S	O	O	OEt	OH
2246a-l	Y*AI	O	O	S	S	S	O	OH	OH
2247a-l	Y*AI	O	O	S	S	S	O	OMe	OH
2248a-l	Y*AI	O	O	S	S	S	O	H	OH
2249a-l	Y*AI	O	O	S	S	S	O	F	OH
2250a-l	Y*AI	O	O	S	S	S	O	OEt	OH
2251a-l	Y*AI	S	O	S	S	S	O	OH	OH
2252a-l	Y*AI	S	O	S	S	S	O	OMe	OH
2253a-l	Y*AI	S	O	S	S	S	O	H	OH
2254a-l	Y*AI	S	O	S	S	S	O	F	OH
2255a-l	Y*AI	S	O	S	S	S	O	OEt	OH
2256a-l	Y*AI	S	S	S	S	S	O	OH	OH
2257a-l	Y*AI	S	S	S	S	S	O	OMe	OH
2258a-l	Y*AI	S	S	S	S	S	O	H	OH
2259a-l	Y*AI	S	S	S	S	S	O	F	OH
2260a-l	Y*AI	S	S	S	S	S	O	OEt	OH
2261a-l	Y*AI	O	O	S	S	S	S	OH	OH
2262a-l	Y*AI	O	O	S	S	S	S	OMe	OH
2263a-l	Y*AI	O	O	S	S	S	S	H	OH
2264a-l	Y*AI	O	O	S	S	S	S	F	OH
2265a-l	Y*AI	O	O	S	S	S	S	OEt	OH
2266a-l	Y*AI	S	O	S	S	S	S	OH	OH
2267a-l	Y*AI	S	O	S	S	S	S	OMe	OH
2268a-l	Y*AI	S	O	S	S	S	S	H	OH
2269a-l	Y*AI	S	O	S	S	S	S	F	OH
2270a-l	Y*AI	S	O	S	S	S	S	OEt	OH
2271a-l	Y*AI	S	S	S	S	S	S	OH	OH
2272a-l	Y*AI	S	S	S	S	S	S	OMe	OH
2273a-l	Y*AI	S	S	S	S	S	S	H	OH
2274a-l	Y*AI	S	S	S	S	S	S	F	OH
2275a-l	Y*AI	S	S	S	S	S	S	OEt	OH
2276a-l	Y*AI	O	O	O	S	S	S	OH	OH
2277a-l	Y*AI	O	O	O	S	S	S	OMe	OH
2278a-l	Y*AI	O	O	O	S	S	S	H	OH
2279a-l	Y*AI	O	O	O	S	S	S	F	OH

2280a-l	Y*AI	O	O	O	S	S	S	OEt	OH
2281a-l	Y*AI	S	O	O	S	S	S	OH	OH
2282a-l	Y*AI	S	O	O	S	S	S	OMe	OH
2283a-l	Y*AI	S	O	O	S	S	S	H	OH
2284a-l	Y*AI	S	O	O	S	S	S	F	OH
2285a-l	Y*AI	S	O	O	S	S	S	OEt	OH
2286a-l	Y*AI	S	S	O	S	S	S	OH	OH
2287a-l	Y*AI	S	S	O	S	S	S	OMe	OH
2288a-l	Y*AI	S	S	O	S	S	S	H	OH
2289a-l	Y*AI	S	S	O	S	S	S	F	OH
2290a-l	Y*AI	S	S	O	S	S	S	OEt	OH
2291a-l	Y*AI	O	O	O	O	S	S	OH	OH
2292a-l	Y*AI	O	O	O	O	S	S	OMe	OH
2293a-l	Y*AI	O	O	O	O	S	S	H	OH
2294a-l	Y*AI	O	O	O	O	S	S	F	OH
2295a-l	Y*AI	O	O	O	O	S	S	OEt	OH
2296a-l	Y*AI	S	O	O	O	S	S	OH	OH
2297a-l	Y*AI	S	O	O	O	S	S	OMe	OH
2298a-l	Y*AI	S	O	O	O	S	S	H	OH
2299a-l	Y*AI	S	O	O	O	S	S	F	OH
2300a-l	Y*AI	S	O	O	O	S	S	OEt	OH
2301a-l	Y*AI	S	S	O	O	S	S	OH	OH
2302a-l	Y*AI	S	S	O	O	S	S	OMe	OH
2303a-l	Y*AI	S	S	O	O	S	S	H	OH
2304a-l	Y*AI	S	S	O	O	S	S	F	OH
2305a-l	Y*AI	S	S	O	O	S	S	OEt	OH
2306a-l	Y*AI	O	O	O	O	O	S	OH	OH
2307a-l	Y*AI	O	O	O	O	O	S	OMe	OH
2308a-l	Y*AI	O	O	O	O	O	S	H	OH
2309a-l	Y*AI	O	O	O	O	O	S	F	OH
2310a-l	Y*AI	O	O	O	O	O	S	OEt	OH
2311a-l	Y*AI	S	O	O	O	O	S	OH	OH
2312a-l	Y*AI	S	O	O	O	O	S	OMe	OH
2313a-l	Y*AI	S	O	O	O	O	S	H	OH
2314a-l	Y*AI	S	O	O	O	O	S	F	OH
2315a-l	Y*AI	S	O	O	O	O	S	OEt	OH
2316a-l	Y*AI	S	S	O	O	O	S	OH	OH
2317a-l	Y*AI	S	S	O	O	O	S	OMe	OH
2318a-l	Y*AI	S	S	O	O	O	S	H	OH
2319a-l	Y*AI	S	S	O	O	O	S	F	OH
2320a-l	Y*AI	S	S	O	O	O	S	OEt	OH
2321a-l	Y*AI	O	O	S	O	S	O	OH	OH
2322a-l	Y*AI	O	O	S	O	S	O	OMe	OH
2323a-l	Y*AI	O	O	S	O	S	O	H	OH
2324a-l	Y*AI	O	O	S	O	S	O	F	OH
2325a-l	Y*AI	O	O	S	O	S	O	OEt	OH
2326a-l	Y*AI	S	O	S	O	S	O	OH	OH
2327a-l	Y*AI	S	O	S	O	S	O	OMe	OH
2328a-l	Y*AI	S	O	S	O	S	O	H	OH

2329a-l	Y*AI	S	O	S	O	S	O	F	OH
2330a-l	Y*AI	S	O	S	O	S	O	OEt	OH
2331a-l	Y*AI	S	S	S	O	S	O	OH	OH
2332a-l	Y*AI	S	S	S	O	S	O	OMe	OH
2333a-l	Y*AI	S	S	S	O	S	O	H	OH
2334a-l	Y*AI	S	S	S	O	S	O	F	OH
2335a-l	Y*AI	S	S	S	O	S	O	OEt	OH
2336a-l	Y*AI	O	O	O	S	O	S	OH	OH
2337a-l	Y*AI	O	O	O	S	O	S	OMe	OH
2338a-l	Y*AI	O	O	O	S	O	S	H	OH
2339a-l	Y*AI	O	O	O	S	O	S	F	OH
2340a-l	Y*AI	O	O	O	S	O	S	OEt	OH
2341a-l	Y*AI	S	O	O	S	O	S	OH	OH
2342a-l	Y*AI	S	O	O	S	O	S	OMe	OH
2343a-l	Y*AI	S	O	O	S	O	S	H	OH
2344a-l	Y*AI	S	O	O	S	O	S	F	OH
2345a-l	Y*AI	S	O	O	S	O	S	OEt	OH
2346a-l	Y*AI	S	S	O	S	O	S	OH	OH
2347a-l	Y*AI	S	S	O	S	O	S	OMe	OH
2348a-l	Y*AI	S	S	O	S	O	S	H	OH
2349a-l	Y*AI	S	S	O	S	O	S	F	OH
2350a-l	Y*AI	S	S	O	S	O	S	OEt	OH
2351a-l	Y*AI	O	O	O	O	O	O	OH	OMe
2352a-l	Y*AI	O	O	O	O	O	O	OMe	OMe
2353a-l	Y*AI	O	O	O	O	O	O	H	OMe
2354a-l	Y*AI	O	O	O	O	O	O	F	OMe
2355a-l	Y*AI	O	O	O	O	O	O	OEt	OMe
2356a-l	Y*AI	S	O	O	O	O	O	OH	OMe
2357a-l	Y*AI	S	O	O	O	O	O	OMe	OMe
2358a-l	Y*AI	S	O	O	O	O	O	H	OMe
2359a-l	Y*AI	S	O	O	O	O	O	F	OMe
2360a-l	Y*AI	S	O	O	O	O	O	OEt	OMe
2361a-l	Y*AI	S	S	O	O	O	O	OH	OMe
2362a-l	Y*AI	S	S	O	O	O	O	OMe	OMe
2363a-l	Y*AI	S	S	O	O	O	O	H	OMe
2364a-l	Y*AI	S	S	O	O	O	O	F	OMe
2365a-l	Y*AI	S	S	O	O	O	O	OEt	OMe
2366a-l	Y*AI	O	O	S	O	O	O	OH	OMe
2367a-l	Y*AI	O	O	S	O	O	O	OMe	OMe
2368a-l	Y*AI	O	O	S	O	O	O	H	OMe
2369a-l	Y*AI	O	O	S	O	O	O	F	OMe
2370a-l	Y*AI	O	O	S	O	O	O	OEt	OMe
2371a-l	Y*AI	S	O	S	O	O	O	OH	OMe
2372a-l	Y*AI	S	O	S	O	O	O	OMe	OMe
2373a-l	Y*AI	S	O	S	O	O	O	H	OMe
2374a-l	Y*AI	S	O	S	O	O	O	F	OMe
2375a-l	Y*AI	S	O	S	O	O	O	OEt	OMe
2376a-l	Y*AI	S	S	S	O	O	O	OH	OMe
2377a-l	Y*AI	S	S	S	O	O	O	OMe	OMe

2378a-l	Y*AI	S	S	S	O	O	O	H	OMe
2379a-l	Y*AI	S	S	S	O	O	O	F	OMe
2380a-l	Y*AI	S	S	S	O	O	O	OEt	OMe
2381a-l	Y*AI	O	O	S	S	O	O	OH	OMe
2382a-l	Y*AI	O	O	S	S	O	O	OMe	OMe
2383a-l	Y*AI	O	O	S	S	O	O	H	OMe
2384a-l	Y*AI	O	O	S	S	O	O	F	OMe
2385a-l	Y*AI	O	O	S	S	O	O	OEt	OMe
2386a-l	Y*AI	S	O	S	S	O	O	OH	OMe
2387a-l	Y*AI	S	O	S	S	O	O	OMe	OMe
2388a-l	Y*AI	S	O	S	S	O	O	H	OMe
2389a-l	Y*AI	S	O	S	S	O	O	F	OMe
2390a-l	Y*AI	S	O	S	S	O	O	OEt	OMe
2391a-l	Y*AI	S	S	S	S	O	O	OH	OMe
2392a-l	Y*AI	S	S	S	S	O	O	OMe	OMe
2393a-l	Y*AI	S	S	S	S	O	O	H	OMe
2394a-l	Y*AI	S	S	S	S	O	O	F	OMe
2395a-l	Y*AI	S	S	S	S	O	O	OEt	OMe
2396a-l	Y*AI	O	O	S	S	S	O	OH	OMe
2397a-l	Y*AI	O	O	S	S	S	O	OMe	OMe
2398a-l	Y*AI	O	O	S	S	S	O	H	OMe
2399a-l	Y*AI	O	O	S	S	S	O	F	OMe
2400a-l	Y*AI	O	O	S	S	S	O	OEt	OMe
2401a-l	Y*AI	S	O	S	S	S	O	OH	OMe
2402a-l	Y*AI	S	O	S	S	S	O	OMe	OMe
2403a-l	Y*AI	S	O	S	S	S	O	H	OMe
2404a-l	Y*AI	S	O	S	S	S	O	F	OMe
2405a-l	Y*AI	S	O	S	S	S	O	OEt	OMe
2406a-l	Y*AI	S	S	S	S	S	O	OH	OMe
2407a-l	Y*AI	S	S	S	S	S	O	OMe	OMe
2408a-l	Y*AI	S	S	S	S	S	O	H	OMe
2409a-l	Y*AI	S	S	S	S	S	O	F	OMe
2410a-l	Y*AI	S	S	S	S	S	O	OEt	OMe
2411a-l	Y*AI	O	O	S	S	S	S	OH	OMe
2412a-l	Y*AI	O	O	S	S	S	S	OMe	OMe
2413a-l	Y*AI	O	O	S	S	S	S	H	OMe
2414a-l	Y*AI	O	O	S	S	S	S	F	OMe
2415a-l	Y*AI	O	O	S	S	S	S	OEt	OMe
2416a-l	Y*AI	S	O	S	S	S	S	OH	OMe
2417a-l	Y*AI	S	O	S	S	S	S	OMe	OMe
2418a-l	Y*AI	S	O	S	S	S	S	H	OMe
2419a-l	Y*AI	S	O	S	S	S	S	F	OMe
2420a-l	Y*AI	S	O	S	S	S	S	OEt	OMe
2421a-l	Y*AI	S	S	S	S	S	S	OH	OMe
2422a-l	Y*AI	S	S	S	S	S	S	OMe	OMe
2423a-l	Y*AI	S	S	S	S	S	S	H	OMe
2424a-l	Y*AI	S	S	S	S	S	S	F	OMe
2425a-l	Y*AI	S	S	S	S	S	S	OEt	OMe
2426a-l	Y*AI	O	O	O	S	S	S	OH	OMe

2427a-l	Y*AI	O	O	O	S	S	S	OMe	OMe
2428a-l	Y*AI	O	O	O	S	S	S	H	OMe
2429a-l	Y*AI	O	O	O	S	S	S	F	OMe
2430a-l	Y*AI	O	O	O	S	S	S	OEt	OMe
2431a-l	Y*AI	S	O	O	S	S	S	OH	OMe
2432a-l	Y*AI	S	O	O	S	S	S	OMe	OMe
2433a-l	Y*AI	S	O	O	S	S	S	H	OMe
2434a-l	Y*AI	S	O	O	S	S	S	F	OMe
2435a-l	Y*AI	S	O	O	S	S	S	OEt	OMe
2436a-l	Y*AI	S	S	O	S	S	S	OH	OMe
2437a-l	Y*AI	S	S	O	S	S	S	OMe	OMe
2438a-l	Y*AI	S	S	O	S	S	S	H	OMe
2439a-l	Y*AI	S	S	O	S	S	S	F	OMe
2440a-l	Y*AI	S	S	O	S	S	S	OEt	OMe
2441a-l	Y*AI	O	O	O	O	S	S	OH	OMe
2442a-l	Y*AI	O	O	O	O	S	S	OMe	OMe
2443a-l	Y*AI	O	O	O	O	S	S	H	OMe
2444a-l	Y*AI	O	O	O	O	S	S	F	OMe
2445a-l	Y*AI	O	O	O	O	S	S	OEt	OMe
2446a-l	Y*AI	S	O	O	O	S	S	OH	OMe
2447a-l	Y*AI	S	O	O	O	S	S	OMe	OMe
2448a-l	Y*AI	S	O	O	O	S	S	H	OMe
2449a-l	Y*AI	S	O	O	O	S	S	F	OMe
2450a-l	Y*AI	S	O	O	O	S	S	OEt	OMe
2451a-l	Y*AI	S	S	O	O	S	S	OH	OMe
2452a-l	Y*AI	S	S	O	O	S	S	OMe	OMe
2453a-l	Y*AI	S	S	O	O	S	S	H	OMe
2454a-l	Y*AI	S	S	O	O	S	S	F	OMe
2455a-l	Y*AI	S	S	O	O	S	S	OEt	OMe
2456a-l	Y*AI	O	O	O	O	O	S	OH	OMe
2457a-l	Y*AI	O	O	O	O	O	S	OMe	OMe
2458a-l	Y*AI	O	O	O	O	O	S	H	OMe
2459a-l	Y*AI	O	O	O	O	O	S	F	OMe
2460a-l	Y*AI	O	O	O	O	O	S	OEt	OMe
2461a-l	Y*AI	S	O	O	O	O	S	OH	OMe
2462a-l	Y*AI	S	O	O	O	O	S	OMe	OMe
2463a-l	Y*AI	S	O	O	O	O	S	H	OMe
2464a-l	Y*AI	S	O	O	O	O	S	F	OMe
2465a-l	Y*AI	S	O	O	O	O	S	OEt	OMe
2466a-l	Y*AI	S	S	O	O	O	S	OH	OMe
2467a-l	Y*AI	S	S	O	O	O	S	OMe	OMe
2468a-l	Y*AI	S	S	O	O	O	S	H	OMe
2469a-l	Y*AI	S	S	O	O	O	S	F	OMe
2470a-l	Y*AI	S	S	O	O	O	S	OEt	OMe
2471a-l	Y*AI	O	O	S	O	S	O	OH	OMe
2472a-l	Y*AI	O	O	S	O	S	O	OMe	OMe
2473a-l	Y*AI	O	O	S	O	S	O	H	OMe
2474a-l	Y*AI	O	O	S	O	S	O	F	OMe
2475a-l	Y*AI	O	O	S	O	S	O	OEt	OMe

2476a-l	Y*AI	S	O	S	O	S	O	OH	OMe
2477a-l	Y*AI	S	O	S	O	S	O	OMe	OMe
2478a-l	Y*AI	S	O	S	O	S	O	H	OMe
2479a-l	Y*AI	S	O	S	O	S	O	F	OMe
2480a-l	Y*AI	S	O	S	O	S	O	OEt	OMe
2481a-l	Y*AI	S	S	S	O	S	O	OH	OMe
2482a-l	Y*AI	S	S	S	O	S	O	OMe	OMe
2483a-l	Y*AI	S	S	S	O	S	O	H	OMe
2484a-l	Y*AI	S	S	S	O	S	O	F	OMe
2485a-l	Y*AI	S	S	S	O	S	O	OEt	OMe
2486a-l	Y*AI	O	O	O	S	O	S	OH	OMe
2487a-l	Y*AI	O	O	O	S	O	S	OMe	OMe
2488a-l	Y*AI	O	O	O	S	O	S	H	OMe
2489a-l	Y*AI	O	O	O	S	O	S	F	OMe
2490a-l	Y*AI	O	O	O	S	O	S	OEt	OMe
2491a-l	Y*AI	S	O	O	S	O	S	OH	OMe
2492a-l	Y*AI	S	O	O	S	O	S	OMe	OMe
2493a-l	Y*AI	S	O	O	S	O	S	H	OMe
2494a-l	Y*AI	S	O	O	S	O	S	F	OMe
2495a-l	Y*AI	S	O	O	S	O	S	OEt	OMe
2496a-l	Y*AI	S	S	O	S	O	S	OH	OMe
2497a-l	Y*AI	S	S	O	S	O	S	OMe	OMe
2498a-l	Y*AI	S	S	O	S	O	S	H	OMe
2499a-l	Y*AI	S	S	O	S	O	S	F	OMe
2500a-l	Y*AI	S	S	O	S	O	S	OEt	OMe
2501a-l	Y*AT	O	O	O	O	O	O	OH	OH
2502a-l	Y*AT	O	O	O	O	O	O	OMe	OH
2503a-l	Y*AT	O	O	O	O	O	O	H	OH
2504a-l	Y*AT	O	O	O	O	O	O	F	OH
2505a-l	Y*AT	O	O	O	O	O	O	OEt	OH
2506a-l	Y*AT	S	O	O	O	O	O	OH	OH
2507a-l	Y*AT	S	O	O	O	O	O	OMe	OH
2508a-l	Y*AT	S	O	O	O	O	O	H	OH
2509a-l	Y*AT	S	O	O	O	O	O	F	OH
2510a-l	Y*AT	S	O	O	O	O	O	OEt	OH
2511a-l	Y*AT	S	S	O	O	O	O	OH	OH
2512a-l	Y*AT	S	S	O	O	O	O	OMe	OH
2513a-l	Y*AT	S	S	O	O	O	O	H	OH
2514a-l	Y*AT	S	S	O	O	O	O	F	OH
2515a-l	Y*AT	S	S	O	O	O	O	OEt	OH
2516a-l	Y*AT	O	O	S	O	O	O	OH	OH
2517a-l	Y*AT	O	O	S	O	O	O	OMe	OH
2518a-l	Y*AT	O	O	S	O	O	O	H	OH
2519a-l	Y*AT	O	O	S	O	O	O	F	OH
2520a-l	Y*AT	O	O	S	O	O	O	OEt	OH
2521a-l	Y*AT	S	O	S	O	O	O	OH	OH
2522a-l	Y*AT	S	O	S	O	O	O	OMe	OH
2523a-l	Y*AT	S	O	S	O	O	O	H	OH
2524a-l	Y*AT	S	O	S	O	O	O	F	OH

2525a-l	Y*AT	S	O	S	O	O	O	OEt	OH
2526a-l	Y*AT	S	S	S	O	O	O	OH	OH
2527a-l	Y*AT	S	S	S	O	O	O	OMe	OH
2528a-l	Y*AT	S	S	S	O	O	O	H	OH
2529a-l	Y*AT	S	S	S	O	O	O	F	OH
2530a-l	Y*AT	S	S	S	O	O	O	OEt	OH
2531a-l	Y*AT	O	O	S	S	O	O	OH	OH
2532a-l	Y*AT	O	O	S	S	O	O	OMe	OH
2533a-l	Y*AT	O	O	S	S	O	O	H	OH
2534a-l	Y*AT	O	O	S	S	O	O	F	OH
2535a-l	Y*AT	O	O	S	S	O	O	OEt	OH
2536a-l	Y*AT	S	O	S	S	O	O	OH	OH
2537a-l	Y*AT	S	O	S	S	O	O	OMe	OH
2538a-l	Y*AT	S	O	S	S	O	O	H	OH
2539a-l	Y*AT	S	O	S	S	O	O	F	OH
2540a-l	Y*AT	S	O	S	S	O	O	OEt	OH
2541a-l	Y*AT	S	S	S	S	O	O	OH	OH
2542a-l	Y*AT	S	S	S	S	O	O	OMe	OH
2543a-l	Y*AT	S	S	S	S	O	O	H	OH
2544a-l	Y*AT	S	S	S	S	O	O	F	OH
2545a-l	Y*AT	S	S	S	S	O	O	OEt	OH
2546a-l	Y*AT	O	O	S	S	S	O	OH	OH
2547a-l	Y*AT	O	O	S	S	S	O	OMe	OH
2548a-l	Y*AT	O	O	S	S	S	O	H	OH
2549a-l	Y*AT	O	O	S	S	S	O	F	OH
2550a-l	Y*AT	O	O	S	S	S	O	OEt	OH
2551a-l	Y*AT	S	O	S	S	S	O	OH	OH
2552a-l	Y*AT	S	O	S	S	S	O	OMe	OH
2553a-l	Y*AT	S	O	S	S	S	O	H	OH
2554a-l	Y*AT	S	O	S	S	S	O	F	OH
2555a-l	Y*AT	S	O	S	S	S	O	OEt	OH
2556a-l	Y*AT	S	S	S	S	S	O	OH	OH
2557a-l	Y*AT	S	S	S	S	S	O	OMe	OH
2558a-l	Y*AT	S	S	S	S	S	O	H	OH
2559a-l	Y*AT	S	S	S	S	S	O	F	OH
2560a-l	Y*AT	S	S	S	S	S	O	OEt	OH
2561a-l	Y*AT	O	O	S	S	S	S	OH	OH
2562a-l	Y*AT	O	O	S	S	S	S	OMe	OH
2563a-l	Y*AT	O	O	S	S	S	S	H	OH
2564a-l	Y*AT	O	O	S	S	S	S	F	OH
2565a-l	Y*AT	O	O	S	S	S	S	OEt	OH
2566a-l	Y*AT	S	O	S	S	S	S	OH	OH
2567a-l	Y*AT	S	O	S	S	S	S	OMe	OH
2568a-l	Y*AT	S	O	S	S	S	S	H	OH
2569a-l	Y*AT	S	O	S	S	S	S	F	OH
2570a-l	Y*AT	S	O	S	S	S	S	OEt	OH
2571a-l	Y*AT	S	S	S	S	S	S	OH	OH
2572a-l	Y*AT	S	S	S	S	S	S	OMe	OH
2573a-l	Y*AT	S	S	S	S	S	S	H	OH

2574a-l	Y*AT	S	S	S	S	S	S	F	OH
2575a-l	Y*AT	S	S	S	S	S	S	OEt	OH
2576a-l	Y*AT	O	O	O	S	S	S	OH	OH
2577a-l	Y*AT	O	O	O	S	S	S	OMe	OH
2578a-l	Y*AT	O	O	O	S	S	S	H	OH
2579a-l	Y*AT	O	O	O	S	S	S	F	OH
2580a-l	Y*AT	O	O	O	S	S	S	OEt	OH
2581a-l	Y*AT	S	O	O	S	S	S	OH	OH
2582a-l	Y*AT	S	O	O	S	S	S	OMe	OH
2583a-l	Y*AT	S	O	O	S	S	S	H	OH
2584a-l	Y*AT	S	O	O	S	S	S	F	OH
2585a-l	Y*AT	S	O	O	S	S	S	OEt	OH
2586a-l	Y*AT	S	S	O	S	S	S	OH	OH
2587a-l	Y*AT	S	S	O	S	S	S	OMe	OH
2588a-l	Y*AT	S	S	O	S	S	S	H	OH
2589a-l	Y*AT	S	S	O	S	S	S	F	OH
2590a-l	Y*AT	S	S	O	S	S	S	OEt	OH
2591a-l	Y*AT	O	O	O	O	S	S	OH	OH
2592a-l	Y*AT	O	O	O	O	S	S	OMe	OH
2593a-l	Y*AT	O	O	O	O	S	S	H	OH
2594a-l	Y*AT	O	O	O	O	S	S	F	OH
2595a-l	Y*AT	O	O	O	O	S	S	OEt	OH
2596a-l	Y*AT	S	O	O	O	S	S	OH	OH
2597a-l	Y*AT	S	O	O	O	S	S	OMe	OH
2598a-l	Y*AT	S	O	O	O	S	S	H	OH
2599a-l	Y*AT	S	O	O	O	S	S	F	OH
2600a-l	Y*AT	S	O	O	O	S	S	OEt	OH
2601a-l	Y*AT	S	S	O	O	S	S	OH	OH
2602a-l	Y*AT	S	S	O	O	S	S	OMe	OH
2603a-l	Y*AT	S	S	O	O	S	S	H	OH
2604a-l	Y*AT	S	S	O	O	S	S	F	OH
2605a-l	Y*AT	S	S	O	O	S	S	OEt	OH
2606a-l	Y*AT	O	O	O	O	O	S	OH	OH
2607a-l	Y*AT	O	O	O	O	O	S	OMe	OH
2608a-l	Y*AT	O	O	O	O	O	S	H	OH
2609a-l	Y*AT	O	O	O	O	O	S	F	OH
2610a-l	Y*AT	O	O	O	O	O	S	OEt	OH
2611a-l	Y*AT	S	O	O	O	O	S	OH	OH
2612a-l	Y*AT	S	O	O	O	O	S	OMe	OH
2613a-l	Y*AT	S	O	O	O	O	S	H	OH
2614a-l	Y*AT	S	O	O	O	O	S	F	OH
2615a-l	Y*AT	S	O	O	O	O	S	OEt	OH
2616a-l	Y*AT	S	S	O	O	O	S	OH	OH
2617a-l	Y*AT	S	S	O	O	O	S	OMe	OH
2618a-l	Y*AT	S	S	O	O	O	S	H	OH
2619a-l	Y*AT	S	S	O	O	O	S	F	OH
2620a-l	Y*AT	S	S	O	O	O	S	OEt	OH
2621a-l	Y*AT	O	O	S	O	S	O	OH	OH
2622a-l	Y*AT	O	O	S	O	S	O	OMe	OH

2623a-l	Y*AT	O	O	S	O	S	O	H	OH
2624a-l	Y*AT	O	O	S	O	S	O	F	OH
2625a-l	Y*AT	O	O	S	O	S	O	OEt	OH
2626a-l	Y*AT	S	O	S	O	S	O	OH	OH
2627a-l	Y*AT	S	O	S	O	S	O	OMe	OH
2628a-l	Y*AT	S	O	S	O	S	O	H	OH
2629a-l	Y*AT	S	O	S	O	S	O	F	OH
2630a-l	Y*AT	S	O	S	O	S	O	OEt	OH
2631a-l	Y*AT	S	S	S	O	S	O	OH	OH
2632a-l	Y*AT	S	S	S	O	S	O	OMe	OH
2633a-l	Y*AT	S	S	S	O	S	O	H	OH
2634a-l	Y*AT	S	S	S	O	S	O	F	OH
2635a-l	Y*AT	S	S	S	O	S	O	OEt	OH
2636a-l	Y*AT	O	O	O	S	O	S	OH	OH
2637a-l	Y*AT	O	O	O	S	O	S	OMe	OH
2638a-l	Y*AT	O	O	O	S	O	S	H	OH
2639a-l	Y*AT	O	O	O	S	O	S	F	OH
2640a-l	Y*AT	O	O	O	S	O	S	OEt	OH
2641a-l	Y*AT	S	O	O	S	O	S	OH	OH
2642a-l	Y*AT	S	O	O	S	O	S	OMe	OH
2643a-l	Y*AT	S	O	O	S	O	S	H	OH
2644a-l	Y*AT	S	O	O	S	O	S	F	OH
2645a-l	Y*AT	S	O	O	S	O	S	OEt	OH
2646a-l	Y*AT	S	S	O	S	O	S	OH	OH
2647a-l	Y*AT	S	S	O	S	O	S	OMe	OH
2648a-l	Y*AT	S	S	O	S	O	S	H	OH
2649a-l	Y*AT	S	S	O	S	O	S	F	OH
2650a-l	Y*AT	S	S	O	S	O	S	OEt	OH
2651a-l	Y*AT	O	O	O	O	O	O	OH	OMe
2652a-l	Y*AT	O	O	O	O	O	O	OMe	OMe
2653a-l	Y*AT	O	O	O	O	O	O	H	OMe
2654a-l	Y*AT	O	O	O	O	O	O	F	OMe
2655a-l	Y*AT	O	O	O	O	O	O	OEt	OMe
2656a-l	Y*AT	S	O	O	O	O	O	OH	OMe
2657a-l	Y*AT	S	O	O	O	O	O	OMe	OMe
2658a-l	Y*AT	S	O	O	O	O	O	H	OMe
2659a-l	Y*AT	S	O	O	O	O	O	F	OMe
2660a-l	Y*AT	S	O	O	O	O	O	OEt	OMe
2661a-l	Y*AT	S	S	O	O	O	O	OH	OMe
2662a-l	Y*AT	S	S	O	O	O	O	OMe	OMe
2663a-l	Y*AT	S	S	O	O	O	O	H	OMe
2664a-l	Y*AT	S	S	O	O	O	O	F	OMe
2665a-l	Y*AT	S	S	O	O	O	O	OEt	OMe
2666a-l	Y*AT	O	O	S	O	O	O	OH	OMe
2667a-l	Y*AT	O	O	S	O	O	O	OMe	OMe
2668a-l	Y*AT	O	O	S	O	O	O	H	OMe
2669a-l	Y*AT	O	O	S	O	O	O	F	OMe
2670a-l	Y*AT	O	O	S	O	O	O	OEt	OMe
2671a-l	Y*AT	S	O	S	O	O	O	OH	OMe

2672a-l	Y*AT	S	O	S	O	O	O	OMe	OMe
2673a-l	Y*AT	S	O	S	O	O	O	H	OMe
2674a-l	Y*AT	S	O	S	O	O	O	F	OMe
2675a-l	Y*AT	S	O	S	O	O	O	OEt	OMe
2676a-l	Y*AT	S	S	S	O	O	O	OH	OMe
2677a-l	Y*AT	S	S	S	O	O	O	OMe	OMe
2678a-l	Y*AT	S	S	S	O	O	O	H	OMe
2679a-l	Y*AT	S	S	S	O	O	O	F	OMe
2680a-l	Y*AT	S	S	S	O	O	O	OEt	OMe
2681a-l	Y*AT	O	O	S	S	O	O	OH	OMe
2682a-l	Y*AT	O	O	S	S	O	O	OMe	OMe
2683a-l	Y*AT	O	O	S	S	O	O	H	OMe
2684a-l	Y*AT	O	O	S	S	O	O	F	OMe
2685a-l	Y*AT	O	O	S	S	O	O	OEt	OMe
2686a-l	Y*AT	S	O	S	S	O	O	OH	OMe
2687a-l	Y*AT	S	O	S	S	O	O	OMe	OMe
2688a-l	Y*AT	S	O	S	S	O	O	H	OMe
2689a-l	Y*AT	S	O	S	S	O	O	F	OMe
2690a-l	Y*AT	S	O	S	S	O	O	OEt	OMe
2691a-l	Y*AT	S	S	S	S	O	O	OH	OMe
2692a-l	Y*AT	S	S	S	S	O	O	OMe	OMe
2693a-l	Y*AT	S	S	S	S	O	O	H	OMe
2694a-l	Y*AT	S	S	S	S	O	O	F	OMe
2695a-l	Y*AT	S	S	S	S	O	O	OEt	OMe
2696a-l	Y*AT	O	O	S	S	S	O	OH	OMe
2697a-l	Y*AT	O	O	S	S	S	O	OMe	OMe
2698a-l	Y*AT	O	O	S	S	S	O	H	OMe
2699a-l	Y*AT	O	O	S	S	S	O	F	OMe
2700a-l	Y*AT	O	O	S	S	S	O	OEt	OMe
2701a-l	Y*AT	S	O	S	S	S	O	OH	OMe
2702a-l	Y*AT	S	O	S	S	S	O	OMe	OMe
2703a-l	Y*AT	S	O	S	S	S	O	H	OMe
2704a-l	Y*AT	S	O	S	S	S	O	F	OMe
2705a-l	Y*AT	S	O	S	S	S	O	OEt	OMe
2706a-l	Y*AT	S	S	S	S	S	O	OH	OMe
2707a-l	Y*AT	S	S	S	S	S	O	OMe	OMe
2708a-l	Y*AT	S	S	S	S	S	O	H	OMe
2709a-l	Y*AT	S	S	S	S	S	O	F	OMe
2710a-l	Y*AT	S	S	S	S	S	O	OEt	OMe
2711a-l	Y*AT	O	O	S	S	S	S	OH	OMe
2712a-l	Y*AT	O	O	S	S	S	S	OMe	OMe
2713a-l	Y*AT	O	O	S	S	S	S	H	OMe
2714a-l	Y*AT	O	O	S	S	S	S	F	OMe
2715a-l	Y*AT	O	O	S	S	S	S	OEt	OMe
2716a-l	Y*AT	S	O	S	S	S	S	OH	OMe
2717a-l	Y*AT	S	O	S	S	S	S	OMe	OMe
2718a-l	Y*AT	S	O	S	S	S	S	H	OMe
2719a-l	Y*AT	S	O	S	S	S	S	F	OMe
2720a-l	Y*AT	S	O	S	S	S	S	OEt	OMe

2721a-l	Y*AT	S	S	S	S	S	S	OH	OMe
2722a-l	Y*AT	S	S	S	S	S	S	OMe	OMe
2723a-l	Y*AT	S	S	S	S	S	S	H	OMe
2724a-l	Y*AT	S	S	S	S	S	S	F	OMe
2725a-l	Y*AT	S	S	S	S	S	S	OEt	OMe
2726a-l	Y*AT	O	O	O	S	S	S	OH	OMe
2727a-l	Y*AT	O	O	O	S	S	S	OMe	OMe
2728a-l	Y*AT	O	O	O	S	S	S	H	OMe
2729a-l	Y*AT	O	O	O	S	S	S	F	OMe
2730a-l	Y*AT	O	O	O	S	S	S	OEt	OMe
2731a-l	Y*AT	S	O	O	S	S	S	OH	OMe
2732a-l	Y*AT	S	O	O	S	S	S	OMe	OMe
2733a-l	Y*AT	S	O	O	S	S	S	H	OMe
2734a-l	Y*AT	S	O	O	S	S	S	F	OMe
2735a-l	Y*AT	S	O	O	S	S	S	OEt	OMe
2736a-l	Y*AT	S	S	O	S	S	S	OH	OMe
2737a-l	Y*AT	S	S	O	S	S	S	OMe	OMe
2738a-l	Y*AT	S	S	O	S	S	S	H	OMe
2739a-l	Y*AT	S	S	O	S	S	S	F	OMe
2740a-l	Y*AT	S	S	O	S	S	S	OEt	OMe
2741a-l	Y*AT	O	O	O	O	S	S	OH	OMe
2742a-l	Y*AT	O	O	O	O	S	S	OMe	OMe
2743a-l	Y*AT	O	O	O	O	S	S	H	OMe
2744a-l	Y*AT	O	O	O	O	S	S	F	OMe
2745a-l	Y*AT	O	O	O	O	S	S	OEt	OMe
2746a-l	Y*AT	S	O	O	O	S	S	OH	OMe
2747a-l	Y*AT	S	O	O	O	S	S	OMe	OMe
2748a-l	Y*AT	S	O	O	O	S	S	H	OMe
2749a-l	Y*AT	S	O	O	O	S	S	F	OMe
2750a-l	Y*AT	S	O	O	O	S	S	OEt	OMe
2751a-l	Y*AT	S	S	O	O	S	S	OH	OMe
2752a-l	Y*AT	S	S	O	O	S	S	OMe	OMe
2753a-l	Y*AT	S	S	O	O	S	S	H	OMe
2754a-l	Y*AT	S	S	O	O	S	S	F	OMe
2755a-l	Y*AT	S	S	O	O	S	S	OEt	OMe
2756a-l	Y*AT	O	O	O	O	O	S	OH	OMe
2757a-l	Y*AT	O	O	O	O	O	S	OMe	OMe
2758a-l	Y*AT	O	O	O	O	O	S	H	OMe
2759a-l	Y*AT	O	O	O	O	O	S	F	OMe
2760a-l	Y*AT	O	O	O	O	O	S	OEt	OMe
2761a-l	Y*AT	S	O	O	O	O	S	OH	OMe
2762a-l	Y*AT	S	O	O	O	O	S	OMe	OMe
2763a-l	Y*AT	S	O	O	O	O	S	H	OMe
2764a-l	Y*AT	S	O	O	O	O	S	F	OMe
2765a-l	Y*AT	S	O	O	O	O	S	OEt	OMe
2766a-l	Y*AT	S	S	O	O	O	S	OH	OMe
2767a-l	Y*AT	S	S	O	O	O	S	OMe	OMe
2768a-l	Y*AT	S	S	O	O	O	S	H	OMe
2769a-l	Y*AT	S	S	O	O	O	S	F	OMe

2770a-l	Y*AT	S	S	O	O	O	S	OEt	OMe
2771a-l	Y*AT	O	O	S	O	S	O	OH	OMe
2772a-l	Y*AT	O	O	S	O	S	O	OMe	OMe
2773a-l	Y*AT	O	O	S	O	S	O	H	OMe
2774a-l	Y*AT	O	O	S	O	S	O	F	OMe
2775a-l	Y*AT	O	O	S	O	S	O	OEt	OMe
2776a-l	Y*AT	S	O	S	O	S	O	OH	OMe
2777a-l	Y*AT	S	O	S	O	S	O	OMe	OMe
2778a-l	Y*AT	S	O	S	O	S	O	H	OMe
2779a-l	Y*AT	S	O	S	O	S	O	F	OMe
2780a-l	Y*AT	S	O	S	O	S	O	OEt	OMe
2781a-l	Y*AT	S	S	S	O	S	O	OH	OMe
2782a-l	Y*AT	S	S	S	O	S	O	OMe	OMe
2783a-l	Y*AT	S	S	S	O	S	O	H	OMe
2784a-l	Y*AT	S	S	S	O	S	O	F	OMe
2785a-l	Y*AT	S	S	S	O	S	O	OEt	OMe
2786a-l	Y*AT	O	O	O	S	O	S	OH	OMe
2787a-l	Y*AT	O	O	O	S	O	S	OMe	OMe
2788a-l	Y*AT	O	O	O	S	O	S	H	OMe
2789a-l	Y*AT	O	O	O	S	O	S	F	OMe
2790a-l	Y*AT	O	O	O	S	O	S	OEt	OMe
2791a-l	Y*AT	S	O	O	S	O	S	OH	OMe
2792a-l	Y*AT	S	O	O	S	O	S	OMe	OMe
2793a-l	Y*AT	S	O	O	S	O	S	H	OMe
2794a-l	Y*AT	S	O	O	S	O	S	F	OMe
2795a-l	Y*AT	S	O	O	S	O	S	OEt	OMe
2796a-l	Y*AT	S	S	O	S	O	S	OH	OMe
2797a-l	Y*AT	S	S	O	S	O	S	OMe	OMe
2798a-l	Y*AT	S	S	O	S	O	S	H	OMe
2799a-l	Y*AT	S	S	O	S	O	S	F	OMe
2800a-l	Y*AT	S	S	O	S	O	S	OEt	OMe
2801a-l	Y*AE	O	O	O	O	O	O	OH	OH
2802a-l	Y*AE	O	O	O	O	O	O	OMe	OH
2803a-l	Y*AE	O	O	O	O	O	O	H	OH
2804a-l	Y*AE	O	O	O	O	O	O	F	OH
2805a-l	Y*AE	O	O	O	O	O	O	OEt	OH
2806a-l	Y*AE	S	O	O	O	O	O	OH	OH
2807a-l	Y*AE	S	O	O	O	O	O	OMe	OH
2808a-l	Y*AE	S	O	O	O	O	O	H	OH
2809a-l	Y*AE	S	O	O	O	O	O	F	OH
2810a-l	Y*AE	S	O	O	O	O	O	OEt	OH
2811a-l	Y*AE	S	S	O	O	O	O	OH	OH
2812a-l	Y*AE	S	S	O	O	O	O	OMe	OH
2813a-l	Y*AE	S	S	O	O	O	O	H	OH
2814a-l	Y*AE	S	S	O	O	O	O	F	OH
2815a-l	Y*AE	S	S	O	O	O	O	OEt	OH
2816a-l	Y*AE	O	O	S	O	O	O	OH	OH
2817a-l	Y*AE	O	O	S	O	O	O	OMe	OH
2818a-l	Y*AE	O	O	S	O	O	O	H	OH

2819a-l	Y*AE	O	O	S	O	O	O	F	OH
2820a-l	Y*AE	O	O	S	O	O	O	OEt	OH
2821a-l	Y*AE	S	O	S	O	O	O	OH	OH
2822a-l	Y*AE	S	O	S	O	O	O	OMe	OH
2823a-l	Y*AE	S	O	S	O	O	O	H	OH
2824a-l	Y*AE	S	O	S	O	O	O	F	OH
2825a-l	Y*AE	S	O	S	O	O	O	OEt	OH
2826a-l	Y*AE	S	S	S	O	O	O	OH	OH
2827a-l	Y*AE	S	S	S	O	O	O	OMe	OH
2828a-l	Y*AE	S	S	S	O	O	O	H	OH
2829a-l	Y*AE	S	S	S	O	O	O	F	OH
2830a-l	Y*AE	S	S	S	O	O	O	OEt	OH
2831a-l	Y*AE	O	O	S	S	O	O	OH	OH
2832a-l	Y*AE	O	O	S	S	O	O	OMe	OH
2833a-l	Y*AE	O	O	S	S	O	O	H	OH
2834a-l	Y*AE	O	O	S	S	O	O	F	OH
2835a-l	Y*AE	O	O	S	S	O	O	OEt	OH
2836a-l	Y*AE	S	O	S	S	O	O	OH	OH
2837a-l	Y*AE	S	O	S	S	O	O	OMe	OH
2838a-l	Y*AE	S	O	S	S	O	O	H	OH
2839a-l	Y*AE	S	O	S	S	O	O	F	OH
2840a-l	Y*AE	S	O	S	S	O	O	OEt	OH
2841a-l	Y*AE	S	S	S	S	O	O	OH	OH
2842a-l	Y*AE	S	S	S	S	O	O	OMe	OH
2843a-l	Y*AE	S	S	S	S	O	O	H	OH
2844a-l	Y*AE	S	S	S	S	O	O	F	OH
2845a-l	Y*AE	S	S	S	S	O	O	OEt	OH
2846a-l	Y*AE	O	O	S	S	S	O	OH	OH
2847a-l	Y*AE	O	O	S	S	S	O	OMe	OH
2848a-l	Y*AE	O	O	S	S	S	O	H	OH
2849a-l	Y*AE	O	O	S	S	S	O	F	OH
2850a-l	Y*AE	O	O	S	S	S	O	OEt	OH
2851a-l	Y*AE	S	O	S	S	S	O	OH	OH
2852a-l	Y*AE	S	O	S	S	S	O	OMe	OH
2853a-l	Y*AE	S	O	S	S	S	O	H	OH
2854a-l	Y*AE	S	O	S	S	S	O	F	OH
2855a-l	Y*AE	S	O	S	S	S	O	OEt	OH
2856a-l	Y*AE	S	S	S	S	S	O	OH	OH
2857a-l	Y*AE	S	S	S	S	S	O	OMe	OH
2858a-l	Y*AE	S	S	S	S	S	O	H	OH
2859a-l	Y*AE	S	S	S	S	S	O	F	OH
2860a-l	Y*AE	S	S	S	S	S	O	OEt	OH
2861a-l	Y*AE	O	O	S	S	S	S	OH	OH
2862a-l	Y*AE	O	O	S	S	S	S	OMe	OH
2863a-l	Y*AE	O	O	S	S	S	S	H	OH
2864a-l	Y*AE	O	O	S	S	S	S	F	OH
2865a-l	Y*AE	O	O	S	S	S	S	OEt	OH
2866a-l	Y*AE	S	O	S	S	S	S	OH	OH
2867a-l	Y*AE	S	O	S	S	S	S	OMe	OH

2868a-l	Y*AE	S	O	S	S	S	S	H	OH
2869a-l	Y*AE	S	O	S	S	S	S	F	OH
2870a-l	Y*AE	S	O	S	S	S	S	OEt	OH
2871a-l	Y*AE	S	S	S	S	S	S	OH	OH
2872a-l	Y*AE	S	S	S	S	S	S	OMe	OH
2873a-l	Y*AE	S	S	S	S	S	S	H	OH
2874a-l	Y*AE	S	S	S	S	S	S	F	OH
2875a-l	Y*AE	S	S	S	S	S	S	OEt	OH
2876a-l	Y*AE	O	O	O	S	S	S	OH	OH
2877a-l	Y*AE	O	O	O	S	S	S	OMe	OH
2878a-l	Y*AE	O	O	O	S	S	S	H	OH
2879a-l	Y*AE	O	O	O	S	S	S	F	OH
2880a-l	Y*AE	O	O	O	S	S	S	OEt	OH
2881a-l	Y*AE	S	O	O	S	S	S	OH	OH
2882a-l	Y*AE	S	O	O	S	S	S	OMe	OH
2883a-l	Y*AE	S	O	O	S	S	S	H	OH
2884a-l	Y*AE	S	O	O	S	S	S	F	OH
2885a-l	Y*AE	S	O	O	S	S	S	OEt	OH
2886a-l	Y*AE	S	S	O	S	S	S	OH	OH
2887a-l	Y*AE	S	S	O	S	S	S	OMe	OH
2888a-l	Y*AE	S	S	O	S	S	S	H	OH
2889a-l	Y*AE	S	S	O	S	S	S	F	OH
2890a-l	Y*AE	S	S	O	S	S	S	OEt	OH
2891a-l	Y*AE	O	O	O	O	S	S	OH	OH
2892a-l	Y*AE	O	O	O	O	S	S	OMe	OH
2893a-l	Y*AE	O	O	O	O	S	S	H	OH
2894a-l	Y*AE	O	O	O	O	S	S	F	OH
2895a-l	Y*AE	O	O	O	O	S	S	OEt	OH
2896a-l	Y*AE	S	O	O	O	S	S	OH	OH
2897a-l	Y*AE	S	O	O	O	S	S	OMe	OH
2898a-l	Y*AE	S	O	O	O	S	S	H	OH
2899a-l	Y*AE	S	O	O	O	S	S	F	OH
2900a-l	Y*AE	S	O	O	O	S	S	OEt	OH
2901a-l	Y*AE	S	S	O	O	S	S	OH	OH
2902a-l	Y*AE	S	S	O	O	S	S	OMe	OH
2903a-l	Y*AE	S	S	O	O	S	S	H	OH
2904a-l	Y*AE	S	S	O	O	S	S	F	OH
2905a-l	Y*AE	S	S	O	O	S	S	OEt	OH
2906a-l	Y*AE	O	O	O	O	O	S	OH	OH
2907a-l	Y*AE	O	O	O	O	O	S	OMe	OH
2908a-l	Y*AE	O	O	O	O	O	S	H	OH
2909a-l	Y*AE	O	O	O	O	O	S	F	OH
2910a-l	Y*AE	O	O	O	O	O	S	OEt	OH
2911a-l	Y*AE	S	O	O	O	O	S	OH	OH
2912a-l	Y*AE	S	O	O	O	O	S	OMe	OH
2913a-l	Y*AE	S	O	O	O	O	S	H	OH
2914a-l	Y*AE	S	O	O	O	O	S	F	OH
2915a-l	Y*AE	S	O	O	O	O	S	OEt	OH
2916a-l	Y*AE	S	S	O	O	O	S	OH	OH

2917a-l	Y*AE	S	S	O	O	O	S	OMe	OH
2918a-l	Y*AE	S	S	O	O	O	S	H	OH
2919a-l	Y*AE	S	S	O	O	O	S	F	OH
2920a-l	Y*AE	S	S	O	O	O	S	OEt	OH
2921a-l	Y*AE	O	O	S	O	S	O	OH	OH
2922a-l	Y*AE	O	O	S	O	S	O	OMe	OH
2923a-l	Y*AE	O	O	S	O	S	O	H	OH
2924a-l	Y*AE	O	O	S	O	S	O	F	OH
2925a-l	Y*AE	O	O	S	O	S	O	OEt	OH
2926a-l	Y*AE	S	O	S	O	S	O	OH	OH
2927a-l	Y*AE	S	O	S	O	S	O	OMe	OH
2928a-l	Y*AE	S	O	S	O	S	O	H	OH
2929a-l	Y*AE	S	O	S	O	S	O	F	OH
2930a-l	Y*AE	S	O	S	O	S	O	OEt	OH
2931a-l	Y*AE	S	S	S	O	S	O	OH	OH
2932a-l	Y*AE	S	S	S	O	S	O	OMe	OH
2933a-l	Y*AE	S	S	S	O	S	O	H	OH
2934a-l	Y*AE	S	S	S	O	S	O	F	OH
2935a-l	Y*AE	S	S	S	O	S	O	OEt	OH
2936a-l	Y*AE	O	O	O	S	O	S	OH	OH
2937a-l	Y*AE	O	O	O	S	O	S	OMe	OH
2938a-l	Y*AE	O	O	O	S	O	S	H	OH
2939a-l	Y*AE	O	O	O	S	O	S	F	OH
2940a-l	Y*AE	O	O	O	S	O	S	OEt	OH
2941a-l	Y*AE	S	O	O	S	O	S	OH	OH
2942a-l	Y*AE	S	O	O	S	O	S	OMe	OH
2943a-l	Y*AE	S	O	O	S	O	S	H	OH
2944a-l	Y*AE	S	O	O	S	O	S	F	OH
2945a-l	Y*AE	S	O	O	S	O	S	OEt	OH
2946a-l	Y*AE	S	S	O	S	O	S	OH	OH
2947a-l	Y*AE	S	S	O	S	O	S	OMe	OH
2948a-l	Y*AE	S	S	O	S	O	S	H	OH
2949a-l	Y*AE	S	S	O	S	O	S	F	OH
2950a-l	Y*AE	S	S	O	S	O	S	OEt	OH
2951a-l	Y*AE	O	O	O	O	O	O	OH	OMe
2952a-l	Y*AE	O	O	O	O	O	O	OMe	OMe
2953a-l	Y*AE	O	O	O	O	O	O	H	OMe
2954a-l	Y*AE	O	O	O	O	O	O	F	OMe
2955a-l	Y*AE	O	O	O	O	O	O	OEt	OMe
2956a-l	Y*AE	S	O	O	O	O	O	OH	OMe
2957a-l	Y*AE	S	O	O	O	O	O	OMe	OMe
2958a-l	Y*AE	S	O	O	O	O	O	H	OMe
2959a-l	Y*AE	S	O	O	O	O	O	F	OMe
2960a-l	Y*AE	S	O	O	O	O	O	OEt	OMe
2961a-l	Y*AE	S	S	O	O	O	O	OH	OMe
2962a-l	Y*AE	S	S	O	O	O	O	OMe	OMe
2963a-l	Y*AE	S	S	O	O	O	O	H	OMe
2964a-l	Y*AE	S	S	O	O	O	O	F	OMe
2965a-l	Y*AE	S	S	O	O	O	O	OEt	OMe

2966a-l	Y*AE	O	O	S	O	O	O	OH	OMe
2967a-l	Y*AE	O	O	S	O	O	O	OMe	OMe
2968a-l	Y*AE	O	O	S	O	O	O	H	OMe
2969a-l	Y*AE	O	O	S	O	O	O	F	OMe
2970a-l	Y*AE	O	O	S	O	O	O	OEt	OMe
2971a-l	Y*AE	S	O	S	O	O	O	OH	OMe
2972a-l	Y*AE	S	O	S	O	O	O	OMe	OMe
2973a-l	Y*AE	S	O	S	O	O	O	H	OMe
2974a-l	Y*AE	S	O	S	O	O	O	F	OMe
2975a-l	Y*AE	S	O	S	O	O	O	OEt	OMe
2976a-l	Y*AE	S	S	S	O	O	O	OH	OMe
2977a-l	Y*AE	S	S	S	O	O	O	OMe	OMe
2978a-l	Y*AE	S	S	S	O	O	O	H	OMe
2979a-l	Y*AE	S	S	S	O	O	O	F	OMe
2980a-l	Y*AE	S	S	S	O	O	O	OEt	OMe
2981a-l	Y*AE	O	O	S	S	O	O	OH	OMe
2982a-l	Y*AE	O	O	S	S	O	O	OMe	OMe
2983a-l	Y*AE	O	O	S	S	O	O	H	OMe
2984a-l	Y*AE	O	O	S	S	O	O	F	OMe
2985a-l	Y*AE	O	O	S	S	O	O	OEt	OMe
2986a-l	Y*AE	S	O	S	S	O	O	OH	OMe
2987a-l	Y*AE	S	O	S	S	O	O	OMe	OMe
2988a-l	Y*AE	S	O	S	S	O	O	H	OMe
2989a-l	Y*AE	S	O	S	S	O	O	F	OMe
2990a-l	Y*AE	S	O	S	S	O	O	OEt	OMe
2991a-l	Y*AE	S	S	S	S	O	O	OH	OMe
2992a-l	Y*AE	S	S	S	S	O	O	OMe	OMe
2993a-l	Y*AE	S	S	S	S	O	O	H	OMe
2994a-l	Y*AE	S	S	S	S	O	O	F	OMe
2995a-l	Y*AE	S	S	S	S	O	O	OEt	OMe
2996a-l	Y*AE	O	O	S	S	S	O	OH	OMe
2997a-l	Y*AE	O	O	S	S	S	O	OMe	OMe
2998a-l	Y*AE	O	O	S	S	S	O	H	OMe
2999a-l	Y*AE	O	O	S	S	S	O	F	OMe
3000a-l	Y*AE	O	O	S	S	S	O	OEt	OMe
3001a-l	Y*AE	S	O	S	S	S	O	OH	OMe
3002a-l	Y*AE	S	O	S	S	S	O	OMe	OMe
3003a-l	Y*AE	S	O	S	S	S	O	H	OMe
3004a-l	Y*AE	S	O	S	S	S	O	F	OMe
3005a-l	Y*AE	S	O	S	S	S	O	OEt	OMe
3006a-l	Y*AE	S	S	S	S	S	O	OH	OMe
3007a-l	Y*AE	S	S	S	S	S	O	OMe	OMe
3008a-l	Y*AE	S	S	S	S	S	O	H	OMe
3009a-l	Y*AE	S	S	S	S	S	O	F	OMe
3010a-l	Y*AE	S	S	S	S	S	O	OEt	OMe
3011a-l	Y*AE	O	O	S	S	S	S	OH	OMe
3012a-l	Y*AE	O	O	S	S	S	S	OMe	OMe
3013a-l	Y*AE	O	O	S	S	S	S	H	OMe
3014a-l	Y*AE	O	O	S	S	S	S	F	OMe

3015a-l	Y*AE	O	O	S	S	S	S	OEt	OMe
3016a-l	Y*AE	S	O	S	S	S	S	OH	OMe
3017a-l	Y*AE	S	O	S	S	S	S	OMe	OMe
3018a-l	Y*AE	S	O	S	S	S	S	H	OMe
3019a-l	Y*AE	S	O	S	S	S	S	F	OMe
3020a-l	Y*AE	S	O	S	S	S	S	OEt	OMe
3021a-l	Y*AE	S	S	S	S	S	S	OH	OMe
3022a-l	Y*AE	S	S	S	S	S	S	OMe	OMe
3023a-l	Y*AE	S	S	S	S	S	S	H	OMe
3024a-l	Y*AE	S	S	S	S	S	S	F	OMe
3025a-l	Y*AE	S	S	S	S	S	S	OEt	OMe
3026a-l	Y*AE	O	O	O	S	S	S	OH	OMe
3027a-l	Y*AE	O	O	O	S	S	S	OMe	OMe
3028a-l	Y*AE	O	O	O	S	S	S	H	OMe
3029a-l	Y*AE	O	O	O	S	S	S	F	OMe
3030a-l	Y*AE	O	O	O	S	S	S	OEt	OMe
3031a-l	Y*AE	S	O	O	S	S	S	OH	OMe
3032a-l	Y*AE	S	O	O	S	S	S	OMe	OMe
3033a-l	Y*AE	S	O	O	S	S	S	H	OMe
3034a-l	Y*AE	S	O	O	S	S	S	F	OMe
3035a-l	Y*AE	S	O	O	S	S	S	OEt	OMe
3036a-l	Y*AE	S	S	O	S	S	S	OH	OMe
3037a-l	Y*AE	S	S	O	S	S	S	OMe	OMe
3038a-l	Y*AE	S	S	O	S	S	S	H	OMe
3039a-l	Y*AE	S	S	O	S	S	S	F	OMe
3040a-l	Y*AE	S	S	O	S	S	S	OEt	OMe
3041a-l	Y*AE	O	O	O	O	S	S	OH	OMe
3042a-l	Y*AE	O	O	O	O	S	S	OMe	OMe
3043a-l	Y*AE	O	O	O	O	S	S	H	OMe
3044a-l	Y*AE	O	O	O	O	S	S	F	OMe
3045a-l	Y*AE	O	O	O	O	S	S	OEt	OMe
3046a-l	Y*AE	S	O	O	O	S	S	OH	OMe
3047a-l	Y*AE	S	O	O	O	S	S	OMe	OMe
3048a-l	Y*AE	S	O	O	O	S	S	H	OMe
3049a-l	Y*AE	S	O	O	O	S	S	F	OMe
3050a-l	Y*AE	S	O	O	O	S	S	OEt	OMe
3051a-l	Y*AE	S	S	O	O	S	S	OH	OMe
3052a-l	Y*AE	S	S	O	O	S	S	OMe	OMe
3053a-l	Y*AE	S	S	O	O	S	S	H	OMe
3054a-l	Y*AE	S	S	O	O	S	S	F	OMe
3055a-l	Y*AE	S	S	O	O	S	S	OEt	OMe
3056a-l	Y*AE	O	O	O	O	O	S	OH	OMe
3057a-l	Y*AE	O	O	O	O	O	S	OMe	OMe
3058a-l	Y*AE	O	O	O	O	O	S	H	OMe
3059a-l	Y*AE	O	O	O	O	O	S	F	OMe
3060a-l	Y*AE	O	O	O	O	O	S	OEt	OMe
3061a-l	Y*AE	S	O	O	O	O	S	OH	OMe
3062a-l	Y*AE	S	O	O	O	O	S	OMe	OMe
3063a-l	Y*AE	S	O	O	O	O	S	H	OMe

3064a-l	Y*AE	S	O	O	O	O	S	F	OMe
3065a-l	Y*AE	S	O	O	O	O	S	OEt	OMe
3066a-l	Y*AE	S	S	O	O	O	S	OH	OMe
3067a-l	Y*AE	S	S	O	O	O	S	OMe	OMe
3068a-l	Y*AE	S	S	O	O	O	S	H	OMe
3069a-l	Y*AE	S	S	O	O	O	S	F	OMe
3070a-l	Y*AE	S	S	O	O	O	S	OEt	OMe
3071a-l	Y*AE	O	O	S	O	S	O	OH	OMe
3072a-l	Y*AE	O	O	S	O	S	O	OMe	OMe
3073a-l	Y*AE	O	O	S	O	S	O	H	OMe
3074a-l	Y*AE	O	O	S	O	S	O	F	OMe
3075a-l	Y*AE	O	O	S	O	S	O	OEt	OMe
3076a-l	Y*AE	S	O	S	O	S	O	OH	OMe
3077a-l	Y*AE	S	O	S	O	S	O	OMe	OMe
3078a-l	Y*AE	S	O	S	O	S	O	H	OMe
3079a-l	Y*AE	S	O	S	O	S	O	F	OMe
3080a-l	Y*AE	S	O	S	O	S	O	OEt	OMe
3081a-l	Y*AE	S	S	S	O	S	O	OH	OMe
3082a-l	Y*AE	S	S	S	O	S	O	OMe	OMe
3083a-l	Y*AE	S	S	S	O	S	O	H	OMe
3084a-l	Y*AE	S	S	S	O	S	O	F	OMe
3085a-l	Y*AE	S	S	S	O	S	O	OEt	OMe
3086a-l	Y*AE	O	O	O	S	O	S	OH	OMe
3087a-l	Y*AE	O	O	O	S	O	S	OMe	OMe
3088a-l	Y*AE	O	O	O	S	O	S	H	OMe
3089a-l	Y*AE	O	O	O	S	O	S	F	OMe
3090a-l	Y*AE	O	O	O	S	O	S	OEt	OMe
3091a-l	Y*AE	S	O	O	S	O	S	OH	OMe
3092a-l	Y*AE	S	O	O	S	O	S	OMe	OMe
3093a-l	Y*AE	S	O	O	S	O	S	H	OMe
3094a-l	Y*AE	S	O	O	S	O	S	F	OMe
3095a-l	Y*AE	S	O	O	S	O	S	OEt	OMe
3096a-l	Y*AE	S	S	O	S	O	S	OH	OMe
3097a-l	Y*AE	S	S	O	S	O	S	OMe	OMe
3098a-l	Y*AE	S	S	O	S	O	S	H	OMe
3099a-l	Y*AE	S	S	O	S	O	S	F	OMe
3100a-l	Y*AE	S	S	O	S	O	S	OEt	OMe
3101a-l	Y*EG	O	O	O	O	O	O	OH	OH
3102a-l	Y*EG	O	O	O	O	O	O	OMe	OH
3103a-l	Y*EG	O	O	O	O	O	O	H	OH
3104a-l	Y*EG	O	O	O	O	O	O	F	OH
3105a-l	Y*EG	O	O	O	O	O	O	OEt	OH
3106a-l	Y*EG	S	O	O	O	O	O	OH	OH
3107a-l	Y*EG	S	O	O	O	O	O	OMe	OH
3108a-l	Y*EG	S	O	O	O	O	O	H	OH
3109a-l	Y*EG	S	O	O	O	O	O	F	OH
3110a-l	Y*EG	S	O	O	O	O	O	OEt	OH
3111a-l	Y*EG	S	S	O	O	O	O	OH	OH
3112a-l	Y*EG	S	S	O	O	O	O	OMe	OH

3113a-l	Y*EG	S	S	O	O	O	O	H	OH
3114a-l	Y*EG	S	S	O	O	O	O	F	OH
3115a-l	Y*EG	S	S	O	O	O	O	OEt	OH
3116a-l	Y*EG	O	O	S	O	O	O	OH	OH
3117a-l	Y*EG	O	O	S	O	O	O	OMe	OH
3118a-l	Y*EG	O	O	S	O	O	O	H	OH
3119a-l	Y*EG	O	O	S	O	O	O	F	OH
3120a-l	Y*EG	O	O	S	O	O	O	OEt	OH
3121a-l	Y*EG	S	O	S	O	O	O	OH	OH
3122a-l	Y*EG	S	O	S	O	O	O	OMe	OH
3123a-l	Y*EG	S	O	S	O	O	O	H	OH
3124a-l	Y*EG	S	O	S	O	O	O	F	OH
3125a-l	Y*EG	S	O	S	O	O	O	OEt	OH
3126a-l	Y*EG	S	S	S	O	O	O	OH	OH
3127a-l	Y*EG	S	S	S	O	O	O	OMe	OH
3128a-l	Y*EG	S	S	S	O	O	O	H	OH
3129a-l	Y*EG	S	S	S	O	O	O	F	OH
3130a-l	Y*EG	S	S	S	O	O	O	OEt	OH
3131a-l	Y*EG	O	O	S	S	O	O	OH	OH
3132a-l	Y*EG	O	O	S	S	O	O	OMe	OH
3133a-l	Y*EG	O	O	S	S	O	O	H	OH
3134a-l	Y*EG	O	O	S	S	O	O	F	OH
3135a-l	Y*EG	O	O	S	S	O	O	OEt	OH
3136a-l	Y*EG	S	O	S	S	O	O	OH	OH
3137a-l	Y*EG	S	O	S	S	O	O	OMe	OH
3138a-l	Y*EG	S	O	S	S	O	O	H	OH
3139a-l	Y*EG	S	O	S	S	O	O	F	OH
3140a-l	Y*EG	S	O	S	S	O	O	OEt	OH
3141a-l	Y*EG	S	S	S	S	O	O	OH	OH
3142a-l	Y*EG	S	S	S	S	O	O	OMe	OH
3143a-l	Y*EG	S	S	S	S	O	O	H	OH
3144a-l	Y*EG	S	S	S	S	O	O	F	OH
3145a-l	Y*EG	S	S	S	S	O	O	OEt	OH
3146a-l	Y*EG	O	O	S	S	S	O	OH	OH
3147a-l	Y*EG	O	O	S	S	S	O	OMe	OH
3148a-l	Y*EG	O	O	S	S	S	O	H	OH
3149a-l	Y*EG	O	O	S	S	S	O	F	OH
3150a-l	Y*EG	O	O	S	S	S	O	OEt	OH
3151a-l	Y*EG	S	O	S	S	S	O	OH	OH
3152a-l	Y*EG	S	O	S	S	S	O	OMe	OH
3153a-l	Y*EG	S	O	S	S	S	O	H	OH
3154a-l	Y*EG	S	O	S	S	S	O	F	OH
3155a-l	Y*EG	S	O	S	S	S	O	OEt	OH
3156a-l	Y*EG	S	S	S	S	S	O	OH	OH
3157a-l	Y*EG	S	S	S	S	S	O	OMe	OH
3158a-l	Y*EG	S	S	S	S	S	O	H	OH
3159a-l	Y*EG	S	S	S	S	S	O	F	OH
3160a-l	Y*EG	S	S	S	S	S	O	OEt	OH
3161a-l	Y*EG	O	O	S	S	S	S	OH	OH

3162a-l	Y*EG	O	O	S	S	S	S	OMe	OH
3163a-l	Y*EG	O	O	S	S	S	S	H	OH
3164a-l	Y*EG	O	O	S	S	S	S	F	OH
3165a-l	Y*EG	O	O	S	S	S	S	OEt	OH
3166a-l	Y*EG	S	O	S	S	S	S	OH	OH
3167a-l	Y*EG	S	O	S	S	S	S	OMe	OH
3168a-l	Y*EG	S	O	S	S	S	S	H	OH
3169a-l	Y*EG	S	O	S	S	S	S	F	OH
3170a-l	Y*EG	S	O	S	S	S	S	OEt	OH
3171a-l	Y*EG	S	S	S	S	S	S	OH	OH
3172a-l	Y*EG	S	S	S	S	S	S	OMe	OH
3173a-l	Y*EG	S	S	S	S	S	S	H	OH
3174a-l	Y*EG	S	S	S	S	S	S	F	OH
3175a-l	Y*EG	S	S	S	S	S	S	OEt	OH
3176a-l	Y*EG	O	O	O	S	S	S	OH	OH
3177a-l	Y*EG	O	O	O	S	S	S	OMe	OH
3178a-l	Y*EG	O	O	O	S	S	S	H	OH
3179a-l	Y*EG	O	O	O	S	S	S	F	OH
3180a-l	Y*EG	O	O	O	S	S	S	OEt	OH
3181a-l	Y*EG	S	O	O	S	S	S	OH	OH
3182a-l	Y*EG	S	O	O	S	S	S	OMe	OH
3183a-l	Y*EG	S	O	O	S	S	S	H	OH
3184a-l	Y*EG	S	O	O	S	S	S	F	OH
3185a-l	Y*EG	S	O	O	S	S	S	OEt	OH
3186a-l	Y*EG	S	S	O	S	S	S	OH	OH
3187a-l	Y*EG	S	S	O	S	S	S	OMe	OH
3188a-l	Y*EG	S	S	O	S	S	S	H	OH
3189a-l	Y*EG	S	S	O	S	S	S	F	OH
3190a-l	Y*EG	S	S	O	S	S	S	OEt	OH
3191a-l	Y*EG	O	O	O	O	S	S	OH	OH
3192a-l	Y*EG	O	O	O	O	S	S	OMe	OH
3193a-l	Y*EG	O	O	O	O	S	S	H	OH
3194a-l	Y*EG	O	O	O	O	S	S	F	OH
3195a-l	Y*EG	O	O	O	O	S	S	OEt	OH
3196a-l	Y*EG	S	O	O	O	S	S	OH	OH
3197a-l	Y*EG	S	O	O	O	S	S	OMe	OH
3198a-l	Y*EG	S	O	O	O	S	S	H	OH
3199a-l	Y*EG	S	O	O	O	S	S	F	OH
3200a-l	Y*EG	S	O	O	O	S	S	OEt	OH
3201a-l	Y*EG	S	S	O	O	S	S	OH	OH
3202a-l	Y*EG	S	S	O	O	S	S	OMe	OH
3203a-l	Y*EG	S	S	O	O	S	S	H	OH
3204a-l	Y*EG	S	S	O	O	S	S	F	OH
3205a-l	Y*EG	S	S	O	O	S	S	OEt	OH
3206a-l	Y*EG	O	O	O	O	O	S	OH	OH
3207a-l	Y*EG	O	O	O	O	O	S	OMe	OH
3208a-l	Y*EG	O	O	O	O	O	S	H	OH
3209a-l	Y*EG	O	O	O	O	O	S	F	OH
3210a-l	Y*EG	O	O	O	O	O	S	OEt	OH

3211a-l	Y*EG	S	O	O	O	O	S	OH	OH
3212a-l	Y*EG	S	O	O	O	O	S	OMe	OH
3213a-l	Y*EG	S	O	O	O	O	S	H	OH
3214a-l	Y*EG	S	O	O	O	O	S	F	OH
3215a-l	Y*EG	S	O	O	O	O	S	OEt	OH
3216a-l	Y*EG	S	S	O	O	O	S	OH	OH
3217a-l	Y*EG	S	S	O	O	O	S	OMe	OH
3218a-l	Y*EG	S	S	O	O	O	S	H	OH
3219a-l	Y*EG	S	S	O	O	O	S	F	OH
3220a-l	Y*EG	S	S	O	O	O	S	OEt	OH
3221a-l	Y*EG	O	O	S	O	S	O	OH	OH
3222a-l	Y*EG	O	O	S	O	S	O	OMe	OH
3223a-l	Y*EG	O	O	S	O	S	O	H	OH
3224a-l	Y*EG	O	O	S	O	S	O	F	OH
3225a-l	Y*EG	O	O	S	O	S	O	OEt	OH
3226a-l	Y*EG	S	O	S	O	S	O	OH	OH
3227a-l	Y*EG	S	O	S	O	S	O	OMe	OH
3228a-l	Y*EG	S	O	S	O	S	O	H	OH
3229a-l	Y*EG	S	O	S	O	S	O	F	OH
3230a-l	Y*EG	S	O	S	O	S	O	OEt	OH
3231a-l	Y*EG	S	S	S	O	S	O	OH	OH
3232a-l	Y*EG	S	S	S	O	S	O	OMe	OH
3233a-l	Y*EG	S	S	S	O	S	O	H	OH
3234a-l	Y*EG	S	S	S	O	S	O	F	OH
3235a-l	Y*EG	S	S	S	O	S	O	OEt	OH
3236a-l	Y*EG	O	O	O	S	O	S	OH	OH
3237a-l	Y*EG	O	O	O	S	O	S	OMe	OH
3238a-l	Y*EG	O	O	O	S	O	S	H	OH
3239a-l	Y*EG	O	O	O	S	O	S	F	OH
3240a-l	Y*EG	O	O	O	S	O	S	OEt	OH
3241a-l	Y*EG	S	O	O	S	O	S	OH	OH
3242a-l	Y*EG	S	O	O	S	O	S	OMe	OH
3243a-l	Y*EG	S	O	O	S	O	S	H	OH
3244a-l	Y*EG	S	O	O	S	O	S	F	OH
3245a-l	Y*EG	S	O	O	S	O	S	OEt	OH
3246a-l	Y*EG	S	S	O	S	O	S	OH	OH
3247a-l	Y*EG	S	S	O	S	O	S	OMe	OH
3248a-l	Y*EG	S	S	O	S	O	S	H	OH
3249a-l	Y*EG	S	S	O	S	O	S	F	OH
3250a-l	Y*EG	S	S	O	S	O	S	OEt	OH
3251a-l	Y*EG	O	O	O	O	O	O	OH	OMe
3252a-l	Y*EG	O	O	O	O	O	O	OMe	OMe
3253a-l	Y*EG	O	O	O	O	O	O	H	OMe
3254a-l	Y*EG	O	O	O	O	O	O	F	OMe
3255a-l	Y*EG	O	O	O	O	O	O	OEt	OMe
3256a-l	Y*EG	S	O	O	O	O	O	OH	OMe
3257a-l	Y*EG	S	O	O	O	O	O	OMe	OMe
3258a-l	Y*EG	S	O	O	O	O	O	H	OMe
3259a-l	Y*EG	S	O	O	O	O	O	F	OMe

3260a-l	Y*EG	S	O	O	O	O	O	OEt	OMe
3261a-l	Y*EG	S	S	O	O	O	O	OH	OMe
3262a-l	Y*EG	S	S	O	O	O	O	OMe	OMe
3263a-l	Y*EG	S	S	O	O	O	O	H	OMe
3264a-l	Y*EG	S	S	O	O	O	O	F	OMe
3265a-l	Y*EG	S	S	O	O	O	O	OEt	OMe
3266a-l	Y*EG	O	O	S	O	O	O	OH	OMe
3267a-l	Y*EG	O	O	S	O	O	O	OMe	OMe
3268a-l	Y*EG	O	O	S	O	O	O	H	OMe
3269a-l	Y*EG	O	O	S	O	O	O	F	OMe
3270a-l	Y*EG	O	O	S	O	O	O	OEt	OMe
3271a-l	Y*EG	S	O	S	O	O	O	OH	OMe
3272a-l	Y*EG	S	O	S	O	O	O	OMe	OMe
3273a-l	Y*EG	S	O	S	O	O	O	H	OMe
3274a-l	Y*EG	S	O	S	O	O	O	F	OMe
3275a-l	Y*EG	S	O	S	O	O	O	OEt	OMe
3276a-l	Y*EG	S	S	S	O	O	O	OH	OMe
3277a-l	Y*EG	S	S	S	O	O	O	OMe	OMe
3278a-l	Y*EG	S	S	S	O	O	O	H	OMe
3279a-l	Y*EG	S	S	S	O	O	O	F	OMe
3280a-l	Y*EG	S	S	S	O	O	O	OEt	OMe
3281a-l	Y*EG	O	O	S	S	O	O	OH	OMe
3282a-l	Y*EG	O	O	S	S	O	O	OMe	OMe
3283a-l	Y*EG	O	O	S	S	O	O	H	OMe
3284a-l	Y*EG	O	O	S	S	O	O	F	OMe
3285a-l	Y*EG	O	O	S	S	O	O	OEt	OMe
3286a-l	Y*EG	S	O	S	S	O	O	OH	OMe
3287a-l	Y*EG	S	O	S	S	O	O	OMe	OMe
3288a-l	Y*EG	S	O	S	S	O	O	H	OMe
3289a-l	Y*EG	S	O	S	S	O	O	F	OMe
3290a-l	Y*EG	S	O	S	S	O	O	OEt	OMe
3291a-l	Y*EG	S	S	S	S	O	O	OH	OMe
3292a-l	Y*EG	S	S	S	S	O	O	OMe	OMe
3293a-l	Y*EG	S	S	S	S	O	O	H	OMe
3294a-l	Y*EG	S	S	S	S	O	O	F	OMe
3295a-l	Y*EG	S	S	S	S	O	O	OEt	OMe
3296a-l	Y*EG	O	O	S	S	S	O	OH	OMe
3297a-l	Y*EG	O	O	S	S	S	O	OMe	OMe
3298a-l	Y*EG	O	O	S	S	S	O	H	OMe
3299a-l	Y*EG	O	O	S	S	S	O	F	OMe
3300a-l	Y*EG	O	O	S	S	S	O	OEt	OMe
3301a-l	Y*EG	S	O	S	S	S	O	OH	OMe
3302a-l	Y*EG	S	O	S	S	S	O	OMe	OMe
3303a-l	Y*EG	S	O	S	S	S	O	H	OMe
3304a-l	Y*EG	S	O	S	S	S	O	F	OMe
3305a-l	Y*EG	S	O	S	S	S	O	OEt	OMe
3306a-l	Y*EG	S	S	S	S	S	O	OH	OMe
3307a-l	Y*EG	S	S	S	S	S	O	OMe	OMe
3308a-l	Y*EG	S	S	S	S	S	O	H	OMe

3309a-l	Y*EG	S	S	S	S	S	O	F	OMe
3310a-l	Y*EG	S	S	S	S	S	O	OEt	OMe
3311a-l	Y*EG	O	O	S	S	S	S	OH	OMe
3312a-l	Y*EG	O	O	S	S	S	S	OMe	OMe
3313a-l	Y*EG	O	O	S	S	S	S	H	OMe
3314a-l	Y*EG	O	O	S	S	S	S	F	OMe
3315a-l	Y*EG	O	O	S	S	S	S	OEt	OMe
3316a-l	Y*EG	S	O	S	S	S	S	OH	OMe
3317a-l	Y*EG	S	O	S	S	S	S	OMe	OMe
3318a-l	Y*EG	S	O	S	S	S	S	H	OMe
3319a-l	Y*EG	S	O	S	S	S	S	F	OMe
3320a-l	Y*EG	S	O	S	S	S	S	OEt	OMe
3321a-l	Y*EG	S	S	S	S	S	S	OH	OMe
3322a-l	Y*EG	S	S	S	S	S	S	OMe	OMe
3323a-l	Y*EG	S	S	S	S	S	S	H	OMe
3324a-l	Y*EG	S	S	S	S	S	S	F	OMe
3325a-l	Y*EG	S	S	S	S	S	S	OEt	OMe
3326a-l	Y*EG	O	O	O	S	S	S	OH	OMe
3327a-l	Y*EG	O	O	O	S	S	S	OMe	OMe
3328a-l	Y*EG	O	O	O	S	S	S	H	OMe
3329a-l	Y*EG	O	O	O	S	S	S	F	OMe
3330a-l	Y*EG	O	O	O	S	S	S	OEt	OMe
3331a-l	Y*EG	S	O	O	S	S	S	OH	OMe
3332a-l	Y*EG	S	O	O	S	S	S	OMe	OMe
3333a-l	Y*EG	S	O	O	S	S	S	H	OMe
3334a-l	Y*EG	S	O	O	S	S	S	F	OMe
3335a-l	Y*EG	S	O	O	S	S	S	OEt	OMe
3336a-l	Y*EG	S	S	O	S	S	S	OH	OMe
3337a-l	Y*EG	S	S	O	S	S	S	OMe	OMe
3338a-l	Y*EG	S	S	O	S	S	S	H	OMe
3339a-l	Y*EG	S	S	O	S	S	S	F	OMe
3340a-l	Y*EG	S	S	O	S	S	S	OEt	OMe
3341a-l	Y*EG	O	O	O	O	S	S	OH	OMe
3342a-l	Y*EG	O	O	O	O	S	S	OMe	OMe
3343a-l	Y*EG	O	O	O	O	S	S	H	OMe
3344a-l	Y*EG	O	O	O	O	S	S	F	OMe
3345a-l	Y*EG	O	O	O	O	S	S	OEt	OMe
3346a-l	Y*EG	S	O	O	O	S	S	OH	OMe
3347a-l	Y*EG	S	O	O	O	S	S	OMe	OMe
3348a-l	Y*EG	S	O	O	O	S	S	H	OMe
3349a-l	Y*EG	S	O	O	O	S	S	F	OMe
3350a-l	Y*EG	S	O	O	O	S	S	OEt	OMe
3351a-l	Y*EG	S	S	O	O	S	S	OH	OMe
3352a-l	Y*EG	S	S	O	O	S	S	OMe	OMe
3353a-l	Y*EG	S	S	O	O	S	S	H	OMe
3354a-l	Y*EG	S	S	O	O	S	S	F	OMe
3355a-l	Y*EG	S	S	O	O	S	S	OEt	OMe
3356a-l	Y*EG	O	O	O	O	O	S	OH	OMe
3357a-l	Y*EG	O	O	O	O	O	S	OMe	OMe

3358a-l	Y*EG	O	O	O	O	O	S	H	OMe
3359a-l	Y*EG	O	O	O	O	O	S	F	OMe
3360a-l	Y*EG	O	O	O	O	O	S	OEt	OMe
3361a-l	Y*EG	S	O	O	O	O	S	OH	OMe
3362a-l	Y*EG	S	O	O	O	O	S	OMe	OMe
3363a-l	Y*EG	S	O	O	O	O	S	H	OMe
3364a-l	Y*EG	S	O	O	O	O	S	F	OMe
3365a-l	Y*EG	S	O	O	O	O	S	OEt	OMe
3366a-l	Y*EG	S	S	O	O	O	S	OH	OMe
3367a-l	Y*EG	S	S	O	O	O	S	OMe	OMe
3368a-l	Y*EG	S	S	O	O	O	S	H	OMe
3369a-l	Y*EG	S	S	O	O	O	S	F	OMe
3370a-l	Y*EG	S	S	O	O	O	S	OEt	OMe
3371a-l	Y*EG	O	O	S	O	S	O	OH	OMe
3372a-l	Y*EG	O	O	S	O	S	O	OMe	OMe
3373a-l	Y*EG	O	O	S	O	S	O	H	OMe
3374a-l	Y*EG	O	O	S	O	S	O	F	OMe
3375a-l	Y*EG	O	O	S	O	S	O	OEt	OMe
3376a-l	Y*EG	S	O	S	O	S	O	OH	OMe
3377a-l	Y*EG	S	O	S	O	S	O	OMe	OMe
3378a-l	Y*EG	S	O	S	O	S	O	H	OMe
3379a-l	Y*EG	S	O	S	O	S	O	F	OMe
3380a-l	Y*EG	S	O	S	O	S	O	OEt	OMe
3381a-l	Y*EG	S	S	S	O	S	O	OH	OMe
3382a-l	Y*EG	S	S	S	O	S	O	OMe	OMe
3383a-l	Y*EG	S	S	S	O	S	O	H	OMe
3384a-l	Y*EG	S	S	S	O	S	O	F	OMe
3385a-l	Y*EG	S	S	S	O	S	O	OEt	OMe
3386a-l	Y*EG	O	O	O	S	O	S	OH	OMe
3387a-l	Y*EG	O	O	O	S	O	S	OMe	OMe
3388a-l	Y*EG	O	O	O	S	O	S	H	OMe
3389a-l	Y*EG	O	O	O	S	O	S	F	OMe
3390a-l	Y*EG	O	O	O	S	O	S	OEt	OMe
3391a-l	Y*EG	S	O	O	S	O	S	OH	OMe
3392a-l	Y*EG	S	O	O	S	O	S	OMe	OMe
3393a-l	Y*EG	S	O	O	S	O	S	H	OMe
3394a-l	Y*EG	S	O	O	S	O	S	F	OMe
3395a-l	Y*EG	S	O	O	S	O	S	OEt	OMe
3396a-l	Y*EG	S	S	O	S	O	S	OH	OMe
3397a-l	Y*EG	S	S	O	S	O	S	OMe	OMe
3398a-l	Y*EG	S	S	O	S	O	S	H	OMe
3399a-l	Y*EG	S	S	O	S	O	S	F	OMe
3400a-l	Y*EG	S	S	O	S	O	S	OEt	OMe
3401a-l	Y*EA	O	O	O	O	O	O	OH	OH
3402a-l	Y*EA	O	O	O	O	O	O	OMe	OH
3403a-l	Y*EA	O	O	O	O	O	O	H	OH
3404a-l	Y*EA	O	O	O	O	O	O	F	OH
3405a-l	Y*EA	O	O	O	O	O	O	OEt	OH
3406a-l	Y*EA	S	O	O	O	O	O	OH	OH

3407a-l	Y*EA	S	O	O	O	O	O	OMe	OH
3408a-l	Y*EA	S	O	O	O	O	O	H	OH
3409a-l	Y*EA	S	O	O	O	O	O	F	OH
3410a-l	Y*EA	S	O	O	O	O	O	OEt	OH
3411a-l	Y*EA	S	S	O	O	O	O	OH	OH
3412a-l	Y*EA	S	S	O	O	O	O	OMe	OH
3413a-l	Y*EA	S	S	O	O	O	O	H	OH
3414a-l	Y*EA	S	S	O	O	O	O	F	OH
3415a-l	Y*EA	S	S	O	O	O	O	OEt	OH
3416a-l	Y*EA	O	O	S	O	O	O	OH	OH
3417a-l	Y*EA	O	O	S	O	O	O	OMe	OH
3418a-l	Y*EA	O	O	S	O	O	O	H	OH
3419a-l	Y*EA	O	O	S	O	O	O	F	OH
3420a-l	Y*EA	O	O	S	O	O	O	OEt	OH
3421a-l	Y*EA	S	O	S	O	O	O	OH	OH
3422a-l	Y*EA	S	O	S	O	O	O	OMe	OH
3423a-l	Y*EA	S	O	S	O	O	O	H	OH
3424a-l	Y*EA	S	O	S	O	O	O	F	OH
3425a-l	Y*EA	S	O	S	O	O	O	OEt	OH
3426a-l	Y*EA	S	S	S	O	O	O	OH	OH
3427a-l	Y*EA	S	S	S	O	O	O	OMe	OH
3428a-l	Y*EA	S	S	S	O	O	O	H	OH
3429a-l	Y*EA	S	S	S	O	O	O	F	OH
3430a-l	Y*EA	S	S	S	O	O	O	OEt	OH
3431a-l	Y*EA	O	O	S	S	O	O	OH	OH
3432a-l	Y*EA	O	O	S	S	O	O	OMe	OH
3433a-l	Y*EA	O	O	S	S	O	O	H	OH
3434a-l	Y*EA	O	O	S	S	O	O	F	OH
3435a-l	Y*EA	O	O	S	S	O	O	OEt	OH
3436a-l	Y*EA	S	O	S	S	O	O	OH	OH
3437a-l	Y*EA	S	O	S	S	O	O	OMe	OH
3438a-l	Y*EA	S	O	S	S	O	O	H	OH
3439a-l	Y*EA	S	O	S	S	O	O	F	OH
3440a-l	Y*EA	S	O	S	S	O	O	OEt	OH
3441a-l	Y*EA	S	S	S	S	O	O	OH	OH
3442a-l	Y*EA	S	S	S	S	O	O	OMe	OH
3443a-l	Y*EA	S	S	S	S	O	O	H	OH
3444a-l	Y*EA	S	S	S	S	O	O	F	OH
3445a-l	Y*EA	S	S	S	S	O	O	OEt	OH
3446a-l	Y*EA	O	O	S	S	S	O	OH	OH
3447a-l	Y*EA	O	O	S	S	S	O	OMe	OH
3448a-l	Y*EA	O	O	S	S	S	O	H	OH
3449a-l	Y*EA	O	O	S	S	S	O	F	OH
3450a-l	Y*EA	O	O	S	S	S	O	OEt	OH
3451a-l	Y*EA	S	O	S	S	S	O	OH	OH
3452a-l	Y*EA	S	O	S	S	S	O	OMe	OH
3453a-l	Y*EA	S	O	S	S	S	O	H	OH
3454a-l	Y*EA	S	O	S	S	S	O	F	OH
3455a-l	Y*EA	S	O	S	S	S	O	OEt	OH

3456a-l	Y*EA	S	S	S	S	S	O	OH	OH
3457a-l	Y*EA	S	S	S	S	S	O	OMe	OH
3458a-l	Y*EA	S	S	S	S	S	O	H	OH
3459a-l	Y*EA	S	S	S	S	S	O	F	OH
3460a-l	Y*EA	S	S	S	S	S	O	OEt	OH
3461a-l	Y*EA	O	O	S	S	S	S	OH	OH
3462a-l	Y*EA	O	O	S	S	S	S	OMe	OH
3463a-l	Y*EA	O	O	S	S	S	S	H	OH
3464a-l	Y*EA	O	O	S	S	S	S	F	OH
3465a-l	Y*EA	O	O	S	S	S	S	OEt	OH
3466a-l	Y*EA	S	O	S	S	S	S	OH	OH
3467a-l	Y*EA	S	O	S	S	S	S	OMe	OH
3468a-l	Y*EA	S	O	S	S	S	S	H	OH
3469a-l	Y*EA	S	O	S	S	S	S	F	OH
3470a-l	Y*EA	S	O	S	S	S	S	OEt	OH
3471a-l	Y*EA	S	S	S	S	S	S	OH	OH
3472a-l	Y*EA	S	S	S	S	S	S	OMe	OH
3473a-l	Y*EA	S	S	S	S	S	S	H	OH
3474a-l	Y*EA	S	S	S	S	S	S	F	OH
3475a-l	Y*EA	S	S	S	S	S	S	OEt	OH
3476a-l	Y*EA	O	O	O	S	S	S	OH	OH
3477a-l	Y*EA	O	O	O	S	S	S	OMe	OH
3478a-l	Y*EA	O	O	O	S	S	S	H	OH
3479a-l	Y*EA	O	O	O	S	S	S	F	OH
3480a-l	Y*EA	O	O	O	S	S	S	OEt	OH
3481a-l	Y*EA	S	O	O	S	S	S	OH	OH
3482a-l	Y*EA	S	O	O	S	S	S	OMe	OH
3483a-l	Y*EA	S	O	O	S	S	S	H	OH
3484a-l	Y*EA	S	O	O	S	S	S	F	OH
3485a-l	Y*EA	S	O	O	S	S	S	OEt	OH
3486a-l	Y*EA	S	S	O	S	S	S	OH	OH
3487a-l	Y*EA	S	S	O	S	S	S	OMe	OH
3488a-l	Y*EA	S	S	O	S	S	S	H	OH
3489a-l	Y*EA	S	S	O	S	S	S	F	OH
3490a-l	Y*EA	S	S	O	S	S	S	OEt	OH
3491a-l	Y*EA	O	O	O	O	S	S	OH	OH
3492a-l	Y*EA	O	O	O	O	S	S	OMe	OH
3493a-l	Y*EA	O	O	O	O	S	S	H	OH
3494a-l	Y*EA	O	O	O	O	S	S	F	OH
3495a-l	Y*EA	O	O	O	O	S	S	OEt	OH
3496a-l	Y*EA	S	O	O	O	S	S	OH	OH
3497a-l	Y*EA	S	O	O	O	S	S	OMe	OH
3498a-l	Y*EA	S	O	O	O	S	S	H	OH
3499a-l	Y*EA	S	O	O	O	S	S	F	OH
3500a-l	Y*EA	S	O	O	O	S	S	OEt	OH
3501a-l	Y*EA	S	S	O	O	S	S	OH	OH
3502a-l	Y*EA	S	S	O	O	S	S	OMe	OH
3503a-l	Y*EA	S	S	O	O	S	S	H	OH
3504a-l	Y*EA	S	S	O	O	S	S	F	OH

3505a-l	Y*EA	S	S	O	O	S	S	OEt	OH
3506a-l	Y*EA	O	O	O	O	O	S	OH	OH
3507a-l	Y*EA	O	O	O	O	O	S	OMe	OH
3508a-l	Y*EA	O	O	O	O	O	S	H	OH
3509a-l	Y*EA	O	O	O	O	O	S	F	OH
3510a-l	Y*EA	O	O	O	O	O	S	OEt	OH
3511a-l	Y*EA	S	O	O	O	O	S	OH	OH
3512a-l	Y*EA	S	O	O	O	O	S	OMe	OH
3513a-l	Y*EA	S	O	O	O	O	S	H	OH
3514a-l	Y*EA	S	O	O	O	O	S	F	OH
3515a-l	Y*EA	S	O	O	O	O	S	OEt	OH
3516a-l	Y*EA	S	S	O	O	O	S	OH	OH
3517a-l	Y*EA	S	S	O	O	O	S	OMe	OH
3518a-l	Y*EA	S	S	O	O	O	S	H	OH
3519a-l	Y*EA	S	S	O	O	O	S	F	OH
3520a-l	Y*EA	S	S	O	O	O	S	OEt	OH
3521a-l	Y*EA	O	O	S	O	S	O	OH	OH
3522a-l	Y*EA	O	O	S	O	S	O	OMe	OH
3523a-l	Y*EA	O	O	S	O	S	O	H	OH
3524a-l	Y*EA	O	O	S	O	S	O	F	OH
3525a-l	Y*EA	O	O	S	O	S	O	OEt	OH
3526a-l	Y*EA	S	O	S	O	S	O	OH	OH
3527a-l	Y*EA	S	O	S	O	S	O	OMe	OH
3528a-l	Y*EA	S	O	S	O	S	O	H	OH
3529a-l	Y*EA	S	O	S	O	S	O	F	OH
3530a-l	Y*EA	S	O	S	O	S	O	OEt	OH
3531a-l	Y*EA	S	S	S	O	S	O	OH	OH
3532a-l	Y*EA	S	S	S	O	S	O	OMe	OH
3533a-l	Y*EA	S	S	S	O	S	O	H	OH
3534a-l	Y*EA	S	S	S	O	S	O	F	OH
3535a-l	Y*EA	S	S	S	O	S	O	OEt	OH
3536a-l	Y*EA	O	O	O	S	O	S	OH	OH
3537a-l	Y*EA	O	O	O	S	O	S	OMe	OH
3538a-l	Y*EA	O	O	O	S	O	S	H	OH
3539a-l	Y*EA	O	O	O	S	O	S	F	OH
3540a-l	Y*EA	O	O	O	S	O	S	OEt	OH
3541a-l	Y*EA	S	O	O	S	O	S	OH	OH
3542a-l	Y*EA	S	O	O	S	O	S	OMe	OH
3543a-l	Y*EA	S	O	O	S	O	S	H	OH
3544a-l	Y*EA	S	O	O	S	O	S	F	OH
3545a-l	Y*EA	S	O	O	S	O	S	OEt	OH
3546a-l	Y*EA	S	S	O	S	O	S	OH	OH
3547a-l	Y*EA	S	S	O	S	O	S	OMe	OH
3548a-l	Y*EA	S	S	O	S	O	S	H	OH
3549a-l	Y*EA	S	S	O	S	O	S	F	OH
3550a-l	Y*EA	S	S	O	S	O	S	OEt	OH
3551a-l	Y*EA	O	O	O	O	O	O	OH	OMe
3552a-l	Y*EA	O	O	O	O	O	O	OMe	OMe
3553a-l	Y*EA	O	O	O	O	O	O	H	OMe

3554a-l	Y*EA	O	O	O	O	O	O	F	OMe
3555a-l	Y*EA	O	O	O	O	O	O	OEt	OMe
3556a-l	Y*EA	S	O	O	O	O	O	OH	OMe
3557a-l	Y*EA	S	O	O	O	O	O	OMe	OMe
3558a-l	Y*EA	S	O	O	O	O	O	H	OMe
3559a-l	Y*EA	S	O	O	O	O	O	F	OMe
3560a-l	Y*EA	S	O	O	O	O	O	OEt	OMe
3561a-l	Y*EA	S	S	O	O	O	O	OH	OMe
3562a-l	Y*EA	S	S	O	O	O	O	OMe	OMe
3563a-l	Y*EA	S	S	O	O	O	O	H	OMe
3564a-l	Y*EA	S	S	O	O	O	O	F	OMe
3565a-l	Y*EA	S	S	O	O	O	O	OEt	OMe
3566a-l	Y*EA	O	O	S	O	O	O	OH	OMe
3567a-l	Y*EA	O	O	S	O	O	O	OMe	OMe
3568a-l	Y*EA	O	O	S	O	O	O	H	OMe
3569a-l	Y*EA	O	O	S	O	O	O	F	OMe
3570a-l	Y*EA	O	O	S	O	O	O	OEt	OMe
3571a-l	Y*EA	S	O	S	O	O	O	OH	OMe
3572a-l	Y*EA	S	O	S	O	O	O	OMe	OMe
3573a-l	Y*EA	S	O	S	O	O	O	H	OMe
3574a-l	Y*EA	S	O	S	O	O	O	F	OMe
3575a-l	Y*EA	S	O	S	O	O	O	OEt	OMe
3576a-l	Y*EA	S	S	S	O	O	O	OH	OMe
3577a-l	Y*EA	S	S	S	O	O	O	OMe	OMe
3578a-l	Y*EA	S	S	S	O	O	O	H	OMe
3579a-l	Y*EA	S	S	S	O	O	O	F	OMe
3580a-l	Y*EA	S	S	S	O	O	O	OEt	OMe
3581a-l	Y*EA	O	O	S	S	O	O	OH	OMe
3582a-l	Y*EA	O	O	S	S	O	O	OMe	OMe
3583a-l	Y*EA	O	O	S	S	O	O	H	OMe
3584a-l	Y*EA	O	O	S	S	O	O	F	OMe
3585a-l	Y*EA	O	O	S	S	O	O	OEt	OMe
3586a-l	Y*EA	S	O	S	S	O	O	OH	OMe
3587a-l	Y*EA	S	O	S	S	O	O	OMe	OMe
3588a-l	Y*EA	S	O	S	S	O	O	H	OMe
3589a-l	Y*EA	S	O	S	S	O	O	F	OMe
3590a-l	Y*EA	S	O	S	S	O	O	OEt	OMe
3591a-l	Y*EA	S	S	S	S	O	O	OH	OMe
3592a-l	Y*EA	S	S	S	S	O	O	OMe	OMe
3593a-l	Y*EA	S	S	S	S	O	O	H	OMe
3594a-l	Y*EA	S	S	S	S	O	O	F	OMe
3595a-l	Y*EA	S	S	S	S	O	O	OEt	OMe
3596a-l	Y*EA	O	O	S	S	S	O	OH	OMe
3597a-l	Y*EA	O	O	S	S	S	O	OMe	OMe
3598a-l	Y*EA	O	O	S	S	S	O	H	OMe
3599a-l	Y*EA	O	O	S	S	S	O	F	OMe
3600a-l	Y*EA	O	O	S	S	S	O	OEt	OMe
3601a-l	Y*EA	S	O	S	S	S	O	OH	OMe
3602a-l	Y*EA	S	O	S	S	S	O	OMe	OMe

3603a-l	Y*EA	S	O	S	S	S	O	H	OMe
3604a-l	Y*EA	S	O	S	S	S	O	F	OMe
3605a-l	Y*EA	S	O	S	S	S	O	OEt	OMe
3606a-l	Y*EA	S	S	S	S	S	O	OH	OMe
3607a-l	Y*EA	S	S	S	S	S	O	OMe	OMe
3608a-l	Y*EA	S	S	S	S	S	O	H	OMe
3609a-l	Y*EA	S	S	S	S	S	O	F	OMe
3610a-l	Y*EA	S	S	S	S	S	O	OEt	OMe
3611a-l	Y*EA	O	O	S	S	S	S	OH	OMe
3612a-l	Y*EA	O	O	S	S	S	S	OMe	OMe
3613a-l	Y*EA	O	O	S	S	S	S	H	OMe
3614a-l	Y*EA	O	O	S	S	S	S	F	OMe
3615a-l	Y*EA	O	O	S	S	S	S	OEt	OMe
3616a-l	Y*EA	S	O	S	S	S	S	OH	OMe
3617a-l	Y*EA	S	O	S	S	S	S	OMe	OMe
3618a-l	Y*EA	S	O	S	S	S	S	H	OMe
3619a-l	Y*EA	S	O	S	S	S	S	F	OMe
3620a-l	Y*EA	S	O	S	S	S	S	OEt	OMe
3621a-l	Y*EA	S	S	S	S	S	S	OH	OMe
3622a-l	Y*EA	S	S	S	S	S	S	OMe	OMe
3623a-l	Y*EA	S	S	S	S	S	S	H	OMe
3624a-l	Y*EA	S	S	S	S	S	S	F	OMe
3625a-l	Y*EA	S	S	S	S	S	S	OEt	OMe
3626a-l	Y*EA	O	O	O	S	S	S	OH	OMe
3627a-l	Y*EA	O	O	O	S	S	S	OMe	OMe
3628a-l	Y*EA	O	O	O	S	S	S	H	OMe
3629a-l	Y*EA	O	O	O	S	S	S	F	OMe
3630a-l	Y*EA	O	O	O	S	S	S	OEt	OMe
3631a-l	Y*EA	S	O	O	S	S	S	OH	OMe
3632a-l	Y*EA	S	O	O	S	S	S	OMe	OMe
3633a-l	Y*EA	S	O	O	S	S	S	H	OMe
3634a-l	Y*EA	S	O	O	S	S	S	F	OMe
3635a-l	Y*EA	S	O	O	S	S	S	OEt	OMe
3636a-l	Y*EA	S	S	O	S	S	S	OH	OMe
3637a-l	Y*EA	S	S	O	S	S	S	OMe	OMe
3638a-l	Y*EA	S	S	O	S	S	S	H	OMe
3639a-l	Y*EA	S	S	O	S	S	S	F	OMe
3640a-l	Y*EA	S	S	O	S	S	S	OEt	OMe
3641a-l	Y*EA	O	O	O	O	S	S	OH	OMe
3642a-l	Y*EA	O	O	O	O	S	S	OMe	OMe
3643a-l	Y*EA	O	O	O	O	S	S	H	OMe
3644a-l	Y*EA	O	O	O	O	S	S	F	OMe
3645a-l	Y*EA	O	O	O	O	S	S	OEt	OMe
3646a-l	Y*EA	S	O	O	O	S	S	OH	OMe
3647a-l	Y*EA	S	O	O	O	S	S	OMe	OMe
3648a-l	Y*EA	S	O	O	O	S	S	H	OMe
3649a-l	Y*EA	S	O	O	O	S	S	F	OMe
3650a-l	Y*EA	S	O	O	O	S	S	OEt	OMe
3651a-l	Y*EA	S	S	O	O	S	S	OH	OMe

3652a-l	Y*EA	S	S	O	O	S	S	OMe	OMe
3653a-l	Y*EA	S	S	O	O	S	S	H	OMe
3654a-l	Y*EA	S	S	O	O	S	S	F	OMe
3655a-l	Y*EA	S	S	O	O	S	S	OEt	OMe
3656a-l	Y*EA	O	O	O	O	O	S	OH	OMe
3657a-l	Y*EA	O	O	O	O	O	S	OMe	OMe
3658a-l	Y*EA	O	O	O	O	O	S	H	OMe
3659a-l	Y*EA	O	O	O	O	O	S	F	OMe
3660a-l	Y*EA	O	O	O	O	O	S	OEt	OMe
3661a-l	Y*EA	S	O	O	O	O	S	OH	OMe
3662a-l	Y*EA	S	O	O	O	O	S	OMe	OMe
3663a-l	Y*EA	S	O	O	O	O	S	H	OMe
3664a-l	Y*EA	S	O	O	O	O	S	F	OMe
3665a-l	Y*EA	S	O	O	O	O	S	OEt	OMe
3666a-l	Y*EA	S	S	O	O	O	S	OH	OMe
3667a-l	Y*EA	S	S	O	O	O	S	OMe	OMe
3668a-l	Y*EA	S	S	O	O	O	S	H	OMe
3669a-l	Y*EA	S	S	O	O	O	S	F	OMe
3670a-l	Y*EA	S	S	O	O	O	S	OEt	OMe
3671a-l	Y*EA	O	O	S	O	S	O	OH	OMe
3672a-l	Y*EA	O	O	S	O	S	O	OMe	OMe
3673a-l	Y*EA	O	O	S	O	S	O	H	OMe
3674a-l	Y*EA	O	O	S	O	S	O	F	OMe
3675a-l	Y*EA	O	O	S	O	S	O	OEt	OMe
3676a-l	Y*EA	S	O	S	O	S	O	OH	OMe
3677a-l	Y*EA	S	O	S	O	S	O	OMe	OMe
3678a-l	Y*EA	S	O	S	O	S	O	H	OMe
3679a-l	Y*EA	S	O	S	O	S	O	F	OMe
3680a-l	Y*EA	S	O	S	O	S	O	OEt	OMe
3681a-l	Y*EA	S	S	S	O	S	O	OH	OMe
3682a-l	Y*EA	S	S	S	O	S	O	OMe	OMe
3683a-l	Y*EA	S	S	S	O	S	O	H	OMe
3684a-l	Y*EA	S	S	S	O	S	O	F	OMe
3685a-l	Y*EA	S	S	S	O	S	O	OEt	OMe
3686a-l	Y*EA	O	O	O	S	O	S	OH	OMe
3687a-l	Y*EA	O	O	O	S	O	S	OMe	OMe
3688a-l	Y*EA	O	O	O	S	O	S	H	OMe
3689a-l	Y*EA	O	O	O	S	O	S	F	OMe
3690a-l	Y*EA	O	O	O	S	O	S	OEt	OMe
3691a-l	Y*EA	S	O	O	S	O	S	OH	OMe
3692a-l	Y*EA	S	O	O	S	O	S	OMe	OMe
3693a-l	Y*EA	S	O	O	S	O	S	H	OMe
3694a-l	Y*EA	S	O	O	S	O	S	F	OMe
3695a-l	Y*EA	S	O	O	S	O	S	OEt	OMe
3696a-l	Y*EA	S	S	O	S	O	S	OH	OMe
3697a-l	Y*EA	S	S	O	S	O	S	OMe	OMe
3698a-l	Y*EA	S	S	O	S	O	S	H	OMe
3699a-l	Y*EA	S	S	O	S	O	S	F	OMe
3700a-l	Y*EA	S	S	O	S	O	S	OEt	OMe

3701a-l	Y*EC	O	O	O	O	O	O	OH	OH
3702a-l	Y*EC	O	O	O	O	O	O	OMe	OH
3703a-l	Y*EC	O	O	O	O	O	O	H	OH
3704a-l	Y*EC	O	O	O	O	O	O	F	OH
3705a-l	Y*EC	O	O	O	O	O	O	OEt	OH
3706a-l	Y*EC	S	O	O	O	O	O	OH	OH
3707a-l	Y*EC	S	O	O	O	O	O	OMe	OH
3708a-l	Y*EC	S	O	O	O	O	O	H	OH
3709a-l	Y*EC	S	O	O	O	O	O	F	OH
3710a-l	Y*EC	S	O	O	O	O	O	OEt	OH
3711a-l	Y*EC	S	S	O	O	O	O	OH	OH
3712a-l	Y*EC	S	S	O	O	O	O	OMe	OH
3713a-l	Y*EC	S	S	O	O	O	O	H	OH
3714a-l	Y*EC	S	S	O	O	O	O	F	OH
3715a-l	Y*EC	S	S	O	O	O	O	OEt	OH
3716a-l	Y*EC	O	O	S	O	O	O	OH	OH
3717a-l	Y*EC	O	O	S	O	O	O	OMe	OH
3718a-l	Y*EC	O	O	S	O	O	O	H	OH
3719a-l	Y*EC	O	O	S	O	O	O	F	OH
3720a-l	Y*EC	O	O	S	O	O	O	OEt	OH
3721a-l	Y*EC	S	O	S	O	O	O	OH	OH
3722a-l	Y*EC	S	O	S	O	O	O	OMe	OH
3723a-l	Y*EC	S	O	S	O	O	O	H	OH
3724a-l	Y*EC	S	O	S	O	O	O	F	OH
3725a-l	Y*EC	S	O	S	O	O	O	OEt	OH
3726a-l	Y*EC	S	S	S	O	O	O	OH	OH
3727a-l	Y*EC	S	S	S	O	O	O	OMe	OH
3728a-l	Y*EC	S	S	S	O	O	O	H	OH
3729a-l	Y*EC	S	S	S	O	O	O	F	OH
3730a-l	Y*EC	S	S	S	O	O	O	OEt	OH
3731a-l	Y*EC	O	O	S	S	O	O	OH	OH
3732a-l	Y*EC	O	O	S	S	O	O	OMe	OH
3733a-l	Y*EC	O	O	S	S	O	O	H	OH
3734a-l	Y*EC	O	O	S	S	O	O	F	OH
3735a-l	Y*EC	O	O	S	S	O	O	OEt	OH
3736a-l	Y*EC	S	O	S	S	O	O	OH	OH
3737a-l	Y*EC	S	O	S	S	O	O	OMe	OH
3738a-l	Y*EC	S	O	S	S	O	O	H	OH
3739a-l	Y*EC	S	O	S	S	O	O	F	OH
3740a-l	Y*EC	S	O	S	S	O	O	OEt	OH
3741a-l	Y*EC	S	S	S	S	O	O	OH	OH
3742a-l	Y*EC	S	S	S	S	O	O	OMe	OH
3743a-l	Y*EC	S	S	S	S	O	O	H	OH
3744a-l	Y*EC	S	S	S	S	O	O	F	OH
3745a-l	Y*EC	S	S	S	S	O	O	OEt	OH
3746a-l	Y*EC	O	O	S	S	S	O	OH	OH
3747a-l	Y*EC	O	O	S	S	S	O	OMe	OH
3748a-l	Y*EC	O	O	S	S	S	O	H	OH
3749a-l	Y*EC	O	O	S	S	S	O	F	OH

3750a-l	Y*EC	O	O	S	S	S	O	OEt	OH
3751a-l	Y*EC	S	O	S	S	S	O	OH	OH
3752a-l	Y*EC	S	O	S	S	S	O	OMe	OH
3753a-l	Y*EC	S	O	S	S	S	O	H	OH
3754a-l	Y*EC	S	O	S	S	S	O	F	OH
3755a-l	Y*EC	S	O	S	S	S	O	OEt	OH
3756a-l	Y*EC	S	S	S	S	S	O	OH	OH
3757a-l	Y*EC	S	S	S	S	S	O	OMe	OH
3758a-l	Y*EC	S	S	S	S	S	O	H	OH
3759a-l	Y*EC	S	S	S	S	S	O	F	OH
3760a-l	Y*EC	S	S	S	S	S	O	OEt	OH
3761a-l	Y*EC	O	O	S	S	S	S	OH	OH
3762a-l	Y*EC	O	O	S	S	S	S	OMe	OH
3763a-l	Y*EC	O	O	S	S	S	S	H	OH
3764a-l	Y*EC	O	O	S	S	S	S	F	OH
3765a-l	Y*EC	O	O	S	S	S	S	OEt	OH
3766a-l	Y*EC	S	O	S	S	S	S	OH	OH
3767a-l	Y*EC	S	O	S	S	S	S	OMe	OH
3768a-l	Y*EC	S	O	S	S	S	S	H	OH
3769a-l	Y*EC	S	O	S	S	S	S	F	OH
3770a-l	Y*EC	S	O	S	S	S	S	OEt	OH
3771a-l	Y*EC	S	S	S	S	S	S	OH	OH
3772a-l	Y*EC	S	S	S	S	S	S	OMe	OH
3773a-l	Y*EC	S	S	S	S	S	S	H	OH
3774a-l	Y*EC	S	S	S	S	S	S	F	OH
3775a-l	Y*EC	S	S	S	S	S	S	OEt	OH
3776a-l	Y*EC	O	O	O	S	S	S	OH	OH
3777a-l	Y*EC	O	O	O	S	S	S	OMe	OH
3778a-l	Y*EC	O	O	O	S	S	S	H	OH
3779a-l	Y*EC	O	O	O	S	S	S	F	OH
3780a-l	Y*EC	O	O	O	S	S	S	OEt	OH
3781a-l	Y*EC	S	O	O	S	S	S	OH	OH
3782a-l	Y*EC	S	O	O	S	S	S	OMe	OH
3783a-l	Y*EC	S	O	O	S	S	S	H	OH
3784a-l	Y*EC	S	O	O	S	S	S	F	OH
3785a-l	Y*EC	S	O	O	S	S	S	OEt	OH
3786a-l	Y*EC	S	S	O	S	S	S	OH	OH
3787a-l	Y*EC	S	S	O	S	S	S	OMe	OH
3788a-l	Y*EC	S	S	O	S	S	S	H	OH
3789a-l	Y*EC	S	S	O	S	S	S	F	OH
3790a-l	Y*EC	S	S	O	S	S	S	OEt	OH
3791a-l	Y*EC	O	O	O	O	S	S	OH	OH
3792a-l	Y*EC	O	O	O	O	S	S	OMe	OH
3793a-l	Y*EC	O	O	O	O	S	S	H	OH
3794a-l	Y*EC	O	O	O	O	S	S	F	OH
3795a-l	Y*EC	O	O	O	O	S	S	OEt	OH
3796a-l	Y*EC	S	O	O	O	S	S	OH	OH
3797a-l	Y*EC	S	O	O	O	S	S	OMe	OH
3798a-l	Y*EC	S	O	O	O	S	S	H	OH

3799a-l	Y*EC	S	O	O	O	S	S	F	OH
3800a-l	Y*EC	S	O	O	O	S	S	OEt	OH
3801a-l	Y*EC	S	S	O	O	S	S	OH	OH
3802a-l	Y*EC	S	S	O	O	S	S	OMe	OH
3803a-l	Y*EC	S	S	O	O	S	S	H	OH
3804a-l	Y*EC	S	S	O	O	S	S	F	OH
3805a-l	Y*EC	S	S	O	O	S	S	OEt	OH
3806a-l	Y*EC	O	O	O	O	O	S	OH	OH
3807a-l	Y*EC	O	O	O	O	O	S	OMe	OH
3808a-l	Y*EC	O	O	O	O	O	S	H	OH
3809a-l	Y*EC	O	O	O	O	O	S	F	OH
3810a-l	Y*EC	O	O	O	O	O	S	OEt	OH
3811a-l	Y*EC	S	O	O	O	O	S	OH	OH
3812a-l	Y*EC	S	O	O	O	O	S	OMe	OH
3813a-l	Y*EC	S	O	O	O	O	S	H	OH
3814a-l	Y*EC	S	O	O	O	O	S	F	OH
3815a-l	Y*EC	S	O	O	O	O	S	OEt	OH
3816a-l	Y*EC	S	S	O	O	O	S	OH	OH
3817a-l	Y*EC	S	S	O	O	O	S	OMe	OH
3818a-l	Y*EC	S	S	O	O	O	S	H	OH
3819a-l	Y*EC	S	S	O	O	O	S	F	OH
3820a-l	Y*EC	S	S	O	O	O	S	OEt	OH
3821a-l	Y*EC	O	O	S	O	S	O	OH	OH
3822a-l	Y*EC	O	O	S	O	S	O	OMe	OH
3823a-l	Y*EC	O	O	S	O	S	O	H	OH
3824a-l	Y*EC	O	O	S	O	S	O	F	OH
3825a-l	Y*EC	O	O	S	O	S	O	OEt	OH
3826a-l	Y*EC	S	O	S	O	S	O	OH	OH
3827a-l	Y*EC	S	O	S	O	S	O	OMe	OH
3828a-l	Y*EC	S	O	S	O	S	O	H	OH
3829a-l	Y*EC	S	O	S	O	S	O	F	OH
3830a-l	Y*EC	S	O	S	O	S	O	OEt	OH
3831a-l	Y*EC	S	S	S	O	S	O	OH	OH
3832a-l	Y*EC	S	S	S	O	S	O	OMe	OH
3833a-l	Y*EC	S	S	S	O	S	O	H	OH
3834a-l	Y*EC	S	S	S	O	S	O	F	OH
3835a-l	Y*EC	S	S	S	O	S	O	OEt	OH
3836a-l	Y*EC	O	O	O	S	O	S	OH	OH
3837a-l	Y*EC	O	O	O	S	O	S	OMe	OH
3838a-l	Y*EC	O	O	O	S	O	S	H	OH
3839a-l	Y*EC	O	O	O	S	O	S	F	OH
3840a-l	Y*EC	O	O	O	S	O	S	OEt	OH
3841a-l	Y*EC	S	O	O	S	O	S	OH	OH
3842a-l	Y*EC	S	O	O	S	O	S	OMe	OH
3843a-l	Y*EC	S	O	O	S	O	S	H	OH
3844a-l	Y*EC	S	O	O	S	O	S	F	OH
3845a-l	Y*EC	S	O	O	S	O	S	OEt	OH
3846a-l	Y*EC	S	S	O	S	O	S	OH	OH
3847a-l	Y*EC	S	S	O	S	O	S	OMe	OH

3848a-l	Y*EC	S	S	O	S	O	S	H	OH
3849a-l	Y*EC	S	S	O	S	O	S	F	OH
3850a-l	Y*EC	S	S	O	S	O	S	OEt	OH
3851a-l	Y*EC	O	O	O	O	O	O	OH	OMe
3852a-l	Y*EC	O	O	O	O	O	O	OMe	OMe
3853a-l	Y*EC	O	O	O	O	O	O	H	OMe
3854a-l	Y*EC	O	O	O	O	O	O	F	OMe
3855a-l	Y*EC	O	O	O	O	O	O	OEt	OMe
3856a-l	Y*EC	S	O	O	O	O	O	OH	OMe
3857a-l	Y*EC	S	O	O	O	O	O	OMe	OMe
3858a-l	Y*EC	S	O	O	O	O	O	H	OMe
3859a-l	Y*EC	S	O	O	O	O	O	F	OMe
3860a-l	Y*EC	S	O	O	O	O	O	OEt	OMe
3861a-l	Y*EC	S	S	O	O	O	O	OH	OMe
3862a-l	Y*EC	S	S	O	O	O	O	OMe	OMe
3863a-l	Y*EC	S	S	O	O	O	O	H	OMe
3864a-l	Y*EC	S	S	O	O	O	O	F	OMe
3865a-l	Y*EC	S	S	O	O	O	O	OEt	OMe
3866a-l	Y*EC	O	O	S	O	O	O	OH	OMe
3867a-l	Y*EC	O	O	S	O	O	O	OMe	OMe
3868a-l	Y*EC	O	O	S	O	O	O	H	OMe
3869a-l	Y*EC	O	O	S	O	O	O	F	OMe
3870a-l	Y*EC	O	O	S	O	O	O	OEt	OMe
3871a-l	Y*EC	S	O	S	O	O	O	OH	OMe
3872a-l	Y*EC	S	O	S	O	O	O	OMe	OMe
3873a-l	Y*EC	S	O	S	O	O	O	H	OMe
3874a-l	Y*EC	S	O	S	O	O	O	F	OMe
3875a-l	Y*EC	S	O	S	O	O	O	OEt	OMe
3876a-l	Y*EC	S	S	S	O	O	O	OH	OMe
3877a-l	Y*EC	S	S	S	O	O	O	OMe	OMe
3878a-l	Y*EC	S	S	S	O	O	O	H	OMe
3879a-l	Y*EC	S	S	S	O	O	O	F	OMe
3880a-l	Y*EC	S	S	S	O	O	O	OEt	OMe
3881a-l	Y*EC	O	O	S	S	O	O	OH	OMe
3882a-l	Y*EC	O	O	S	S	O	O	OMe	OMe
3883a-l	Y*EC	O	O	S	S	O	O	H	OMe
3884a-l	Y*EC	O	O	S	S	O	O	F	OMe
3885a-l	Y*EC	O	O	S	S	O	O	OEt	OMe
3886a-l	Y*EC	S	O	S	S	O	O	OH	OMe
3887a-l	Y*EC	S	O	S	S	O	O	OMe	OMe
3888a-l	Y*EC	S	O	S	S	O	O	H	OMe
3889a-l	Y*EC	S	O	S	S	O	O	F	OMe
3890a-l	Y*EC	S	O	S	S	O	O	OEt	OMe
3891a-l	Y*EC	S	S	S	S	O	O	OH	OMe
3892a-l	Y*EC	S	S	S	S	O	O	OMe	OMe
3893a-l	Y*EC	S	S	S	S	O	O	H	OMe
3894a-l	Y*EC	S	S	S	S	O	O	F	OMe
3895a-l	Y*EC	S	S	S	S	O	O	OEt	OMe
3896a-l	Y*EC	O	O	S	S	S	O	OH	OMe

3897a-l	Y*EC	O	O	S	S	S	O	OMe	OMe
3898a-l	Y*EC	O	O	S	S	S	O	H	OMe
3899a-l	Y*EC	O	O	S	S	S	O	F	OMe
3900a-l	Y*EC	O	O	S	S	S	O	OEt	OMe
3901a-l	Y*EC	S	O	S	S	S	O	OH	OMe
3902a-l	Y*EC	S	O	S	S	S	O	OMe	OMe
3903a-l	Y*EC	S	O	S	S	S	O	H	OMe
3904a-l	Y*EC	S	O	S	S	S	O	F	OMe
3905a-l	Y*EC	S	O	S	S	S	O	OEt	OMe
3906a-l	Y*EC	S	S	S	S	S	O	OH	OMe
3907a-l	Y*EC	S	S	S	S	S	O	OMe	OMe
3908a-l	Y*EC	S	S	S	S	S	O	H	OMe
3909a-l	Y*EC	S	S	S	S	S	O	F	OMe
3910a-l	Y*EC	S	S	S	S	S	O	OEt	OMe
3911a-l	Y*EC	O	O	S	S	S	S	OH	OMe
3912a-l	Y*EC	O	O	S	S	S	S	OMe	OMe
3913a-l	Y*EC	O	O	S	S	S	S	H	OMe
3914a-l	Y*EC	O	O	S	S	S	S	F	OMe
3915a-l	Y*EC	O	O	S	S	S	S	OEt	OMe
3916a-l	Y*EC	S	O	S	S	S	S	OH	OMe
3917a-l	Y*EC	S	O	S	S	S	S	OMe	OMe
3918a-l	Y*EC	S	O	S	S	S	S	H	OMe
3919a-l	Y*EC	S	O	S	S	S	S	F	OMe
3920a-l	Y*EC	S	O	S	S	S	S	OEt	OMe
3921a-l	Y*EC	S	S	S	S	S	S	OH	OMe
3922a-l	Y*EC	S	S	S	S	S	S	OMe	OMe
3923a-l	Y*EC	S	S	S	S	S	S	H	OMe
3924a-l	Y*EC	S	S	S	S	S	S	F	OMe
3925a-l	Y*EC	S	S	S	S	S	S	OEt	OMe
3926a-l	Y*EC	O	O	O	S	S	S	OH	OMe
3927a-l	Y*EC	O	O	O	S	S	S	OMe	OMe
3928a-l	Y*EC	O	O	O	S	S	S	H	OMe
3929a-l	Y*EC	O	O	O	S	S	S	F	OMe
3930a-l	Y*EC	O	O	O	S	S	S	OEt	OMe
3931a-l	Y*EC	S	O	O	S	S	S	OH	OMe
3932a-l	Y*EC	S	O	O	S	S	S	OMe	OMe
3933a-l	Y*EC	S	O	O	S	S	S	H	OMe
3934a-l	Y*EC	S	O	O	S	S	S	F	OMe
3935a-l	Y*EC	S	O	O	S	S	S	OEt	OMe
3936a-l	Y*EC	S	S	O	S	S	S	OH	OMe
3937a-l	Y*EC	S	S	O	S	S	S	OMe	OMe
3938a-l	Y*EC	S	S	O	S	S	S	H	OMe
3939a-l	Y*EC	S	S	O	S	S	S	F	OMe
3940a-l	Y*EC	S	S	O	S	S	S	OEt	OMe
3941a-l	Y*EC	O	O	O	O	S	S	OH	OMe
3942a-l	Y*EC	O	O	O	O	S	S	OMe	OMe
3943a-l	Y*EC	O	O	O	O	S	S	H	OMe
3944a-l	Y*EC	O	O	O	O	S	S	F	OMe
3945a-l	Y*EC	O	O	O	O	S	S	OEt	OMe

3946a-l	Y*EC	S	O	O	O	S	S	OH	OMe
3947a-l	Y*EC	S	O	O	O	S	S	OMe	OMe
3948a-l	Y*EC	S	O	O	O	S	S	H	OMe
3949a-l	Y*EC	S	O	O	O	S	S	F	OMe
3950a-l	Y*EC	S	O	O	O	S	S	OEt	OMe
3951a-l	Y*EC	S	S	O	O	S	S	OH	OMe
3952a-l	Y*EC	S	S	O	O	S	S	OMe	OMe
3953a-l	Y*EC	S	S	O	O	S	S	H	OMe
3954a-l	Y*EC	S	S	O	O	S	S	F	OMe
3955a-l	Y*EC	S	S	O	O	S	S	OEt	OMe
3956a-l	Y*EC	O	O	O	O	O	S	OH	OMe
3957a-l	Y*EC	O	O	O	O	O	S	OMe	OMe
3958a-l	Y*EC	O	O	O	O	O	S	H	OMe
3959a-l	Y*EC	O	O	O	O	O	S	F	OMe
3960a-l	Y*EC	O	O	O	O	O	S	OEt	OMe
3961a-l	Y*EC	S	O	O	O	O	S	OH	OMe
3962a-l	Y*EC	S	O	O	O	O	S	OMe	OMe
3963a-l	Y*EC	S	O	O	O	O	S	H	OMe
3964a-l	Y*EC	S	O	O	O	O	S	F	OMe
3965a-l	Y*EC	S	O	O	O	O	S	OEt	OMe
3966a-l	Y*EC	S	S	O	O	O	S	OH	OMe
3967a-l	Y*EC	S	S	O	O	O	S	OMe	OMe
3968a-l	Y*EC	S	S	O	O	O	S	H	OMe
3969a-l	Y*EC	S	S	O	O	O	S	F	OMe
3970a-l	Y*EC	S	S	O	O	O	S	OEt	OMe
3971a-l	Y*EC	O	O	S	O	S	O	OH	OMe
3972a-l	Y*EC	O	O	S	O	S	O	OMe	OMe
3973a-l	Y*EC	O	O	S	O	S	O	H	OMe
3974a-l	Y*EC	O	O	S	O	S	O	F	OMe
3975a-l	Y*EC	O	O	S	O	S	O	OEt	OMe
3976a-l	Y*EC	S	O	S	O	S	O	OH	OMe
3977a-l	Y*EC	S	O	S	O	S	O	OMe	OMe
3978a-l	Y*EC	S	O	S	O	S	O	H	OMe
3979a-l	Y*EC	S	O	S	O	S	O	F	OMe
3980a-l	Y*EC	S	O	S	O	S	O	OEt	OMe
3981a-l	Y*EC	S	S	S	O	S	O	OH	OMe
3982a-l	Y*EC	S	S	S	O	S	O	OMe	OMe
3983a-l	Y*EC	S	S	S	O	S	O	H	OMe
3984a-l	Y*EC	S	S	S	O	S	O	F	OMe
3985a-l	Y*EC	S	S	S	O	S	O	OEt	OMe
3986a-l	Y*EC	O	O	O	S	O	S	OH	OMe
3987a-l	Y*EC	O	O	O	S	O	S	OMe	OMe
3988a-l	Y*EC	O	O	O	S	O	S	H	OMe
3989a-l	Y*EC	O	O	O	S	O	S	F	OMe
3990a-l	Y*EC	O	O	O	S	O	S	OEt	OMe
3991a-l	Y*EC	S	O	O	S	O	S	OH	OMe
3992a-l	Y*EC	S	O	O	S	O	S	OMe	OMe
3993a-l	Y*EC	S	O	O	S	O	S	H	OMe
3994a-l	Y*EC	S	O	O	S	O	S	F	OMe

3995a-l	Y*EC	S	O	O	S	O	S	OEt	OMe
3996a-l	Y*EC	S	S	O	S	O	S	OH	OMe
3997a-l	Y*EC	S	S	O	S	O	S	OMe	OMe
3998a-l	Y*EC	S	S	O	S	O	S	H	OMe
3999a-l	Y*EC	S	S	O	S	O	S	F	OMe
4000a-l	Y*EC	S	S	O	S	O	S	OEt	OMe
4001a-l	Y*EU	O	O	O	O	O	O	OH	OH
4002a-l	Y*EU	O	O	O	O	O	O	OMe	OH
4003a-l	Y*EU	O	O	O	O	O	O	H	OH
4004a-l	Y*EU	O	O	O	O	O	O	F	OH
4005a-l	Y*EU	O	O	O	O	O	O	OEt	OH
4006a-l	Y*EU	S	O	O	O	O	O	OH	OH
4007a-l	Y*EU	S	O	O	O	O	O	OMe	OH
4008a-l	Y*EU	S	O	O	O	O	O	H	OH
4009a-l	Y*EU	S	O	O	O	O	O	F	OH
4010a-l	Y*EU	S	O	O	O	O	O	OEt	OH
4011a-l	Y*EU	S	S	O	O	O	O	OH	OH
4012a-l	Y*EU	S	S	O	O	O	O	OMe	OH
4013a-l	Y*EU	S	S	O	O	O	O	H	OH
4014a-l	Y*EU	S	S	O	O	O	O	F	OH
4015a-l	Y*EU	S	S	O	O	O	O	OEt	OH
4016a-l	Y*EU	O	O	S	O	O	O	OH	OH
4017a-l	Y*EU	O	O	S	O	O	O	OMe	OH
4018a-l	Y*EU	O	O	S	O	O	O	H	OH
4019a-l	Y*EU	O	O	S	O	O	O	F	OH
4020a-l	Y*EU	O	O	S	O	O	O	OEt	OH
4021a-l	Y*EU	S	O	S	O	O	O	OH	OH
4022a-l	Y*EU	S	O	S	O	O	O	OMe	OH
4023a-l	Y*EU	S	O	S	O	O	O	H	OH
4024a-l	Y*EU	S	O	S	O	O	O	F	OH
4025a-l	Y*EU	S	O	S	O	O	O	OEt	OH
4026a-l	Y*EU	S	S	S	O	O	O	OH	OH
4027a-l	Y*EU	S	S	S	O	O	O	OMe	OH
4028a-l	Y*EU	S	S	S	O	O	O	H	OH
4029a-l	Y*EU	S	S	S	O	O	O	F	OH
4030a-l	Y*EU	S	S	S	O	O	O	OEt	OH
4031a-l	Y*EU	O	O	S	S	O	O	OH	OH
4032a-l	Y*EU	O	O	S	S	O	O	OMe	OH
4033a-l	Y*EU	O	O	S	S	O	O	H	OH
4034a-l	Y*EU	O	O	S	S	O	O	F	OH
4035a-l	Y*EU	O	O	S	S	O	O	OEt	OH
4036a-l	Y*EU	S	O	S	S	O	O	OH	OH
4037a-l	Y*EU	S	O	S	S	O	O	OMe	OH
4038a-l	Y*EU	S	O	S	S	O	O	H	OH
4039a-l	Y*EU	S	O	S	S	O	O	F	OH
4040a-l	Y*EU	S	O	S	S	O	O	OEt	OH
4041a-l	Y*EU	S	S	S	S	O	O	OH	OH
4042a-l	Y*EU	S	S	S	S	O	O	OMe	OH
4043a-l	Y*EU	S	S	S	S	O	O	H	OH

4044a-l	Y*EU	S	S	S	S	O	O	F	OH
4045a-l	Y*EU	S	S	S	S	O	O	OEt	OH
4046a-l	Y*EU	O	O	S	S	S	O	OH	OH
4047a-l	Y*EU	O	O	S	S	S	O	OMe	OH
4048a-l	Y*EU	O	O	S	S	S	O	H	OH
4049a-l	Y*EU	O	O	S	S	S	O	F	OH
4050a-l	Y*EU	O	O	S	S	S	O	OEt	OH
4051a-l	Y*EU	S	O	S	S	S	O	OH	OH
4052a-l	Y*EU	S	O	S	S	S	O	OMe	OH
4053a-l	Y*EU	S	O	S	S	S	O	H	OH
4054a-l	Y*EU	S	O	S	S	S	O	F	OH
4055a-l	Y*EU	S	O	S	S	S	O	OEt	OH
4056a-l	Y*EU	S	S	S	S	S	O	OH	OH
4057a-l	Y*EU	S	S	S	S	S	O	OMe	OH
4058a-l	Y*EU	S	S	S	S	S	O	H	OH
4059a-l	Y*EU	S	S	S	S	S	O	F	OH
4060a-l	Y*EU	S	S	S	S	S	O	OEt	OH
4061a-l	Y*EU	O	O	S	S	S	S	OH	OH
4062a-l	Y*EU	O	O	S	S	S	S	OMe	OH
4063a-l	Y*EU	O	O	S	S	S	S	H	OH
4064a-l	Y*EU	O	O	S	S	S	S	F	OH
4065a-l	Y*EU	O	O	S	S	S	S	OEt	OH
4066a-l	Y*EU	S	O	S	S	S	S	OH	OH
4067a-l	Y*EU	S	O	S	S	S	S	OMe	OH
4068a-l	Y*EU	S	O	S	S	S	S	H	OH
4069a-l	Y*EU	S	O	S	S	S	S	F	OH
4070a-l	Y*EU	S	O	S	S	S	S	OEt	OH
4071a-l	Y*EU	S	S	S	S	S	S	OH	OH
4072a-l	Y*EU	S	S	S	S	S	S	OMe	OH
4073a-l	Y*EU	S	S	S	S	S	S	H	OH
4074a-l	Y*EU	S	S	S	S	S	S	F	OH
4075a-l	Y*EU	S	S	S	S	S	S	OEt	OH
4076a-l	Y*EU	O	O	O	S	S	S	OH	OH
4077a-l	Y*EU	O	O	O	S	S	S	OMe	OH
4078a-l	Y*EU	O	O	O	S	S	S	H	OH
4079a-l	Y*EU	O	O	O	S	S	S	F	OH
4080a-l	Y*EU	O	O	O	S	S	S	OEt	OH
4081a-l	Y*EU	S	O	O	S	S	S	OH	OH
4082a-l	Y*EU	S	O	O	S	S	S	OMe	OH
4083a-l	Y*EU	S	O	O	S	S	S	H	OH
4084a-l	Y*EU	S	O	O	S	S	S	F	OH
4085a-l	Y*EU	S	O	O	S	S	S	OEt	OH
4086a-l	Y*EU	S	S	O	S	S	S	OH	OH
4087a-l	Y*EU	S	S	O	S	S	S	OMe	OH
4088a-l	Y*EU	S	S	O	S	S	S	H	OH
4089a-l	Y*EU	S	S	O	S	S	S	F	OH
4090a-l	Y*EU	S	S	O	S	S	S	OEt	OH
4091a-l	Y*EU	O	O	O	O	S	S	OH	OH
4092a-l	Y*EU	O	O	O	O	S	S	OMe	OH

4093a-l	Y*EU	O	O	O	O	S	S	H	OH
4094a-l	Y*EU	O	O	O	O	S	S	F	OH
4095a-l	Y*EU	O	O	O	O	S	S	OEt	OH
4096a-l	Y*EU	S	O	O	O	S	S	OH	OH
4097a-l	Y*EU	S	O	O	O	S	S	OMe	OH
4098a-l	Y*EU	S	O	O	O	S	S	H	OH
4099a-l	Y*EU	S	O	O	O	S	S	F	OH
4100a-l	Y*EU	S	O	O	O	S	S	OEt	OH
4101a-l	Y*EU	S	S	O	O	S	S	OH	OH
4102a-l	Y*EU	S	S	O	O	S	S	OMe	OH
4103a-l	Y*EU	S	S	O	O	S	S	H	OH
4104a-l	Y*EU	S	S	O	O	S	S	F	OH
4105a-l	Y*EU	S	S	O	O	S	S	OEt	OH
4106a-l	Y*EU	O	O	O	O	O	S	OH	OH
4107a-l	Y*EU	O	O	O	O	O	S	OMe	OH
4108a-l	Y*EU	O	O	O	O	O	S	H	OH
4109a-l	Y*EU	O	O	O	O	O	S	F	OH
4110a-l	Y*EU	O	O	O	O	O	S	OEt	OH
4111a-l	Y*EU	S	O	O	O	O	S	OH	OH
4112a-l	Y*EU	S	O	O	O	O	S	OMe	OH
4113a-l	Y*EU	S	O	O	O	O	S	H	OH
4114a-l	Y*EU	S	O	O	O	O	S	F	OH
4115a-l	Y*EU	S	O	O	O	O	S	OEt	OH
4116a-l	Y*EU	S	S	O	O	O	S	OH	OH
4117a-l	Y*EU	S	S	O	O	O	S	OMe	OH
4118a-l	Y*EU	S	S	O	O	O	S	H	OH
4119a-l	Y*EU	S	S	O	O	O	S	F	OH
4120a-l	Y*EU	S	S	O	O	O	S	OEt	OH
4121a-l	Y*EU	O	O	S	O	S	O	OH	OH
4122a-l	Y*EU	O	O	S	O	S	O	OMe	OH
4123a-l	Y*EU	O	O	S	O	S	O	H	OH
4124a-l	Y*EU	O	O	S	O	S	O	F	OH
4125a-l	Y*EU	O	O	S	O	S	O	OEt	OH
4126a-l	Y*EU	S	O	S	O	S	O	OH	OH
4127a-l	Y*EU	S	O	S	O	S	O	OMe	OH
4128a-l	Y*EU	S	O	S	O	S	O	H	OH
4129a-l	Y*EU	S	O	S	O	S	O	F	OH
4130a-l	Y*EU	S	O	S	O	S	O	OEt	OH
4131a-l	Y*EU	S	S	S	O	S	O	OH	OH
4132a-l	Y*EU	S	S	S	O	S	O	OMe	OH
4133a-l	Y*EU	S	S	S	O	S	O	H	OH
4134a-l	Y*EU	S	S	S	O	S	O	F	OH
4135a-l	Y*EU	S	S	S	O	S	O	OEt	OH
4136a-l	Y*EU	O	O	O	S	O	S	OH	OH
4137a-l	Y*EU	O	O	O	S	O	S	OMe	OH
4138a-l	Y*EU	O	O	O	S	O	S	H	OH
4139a-l	Y*EU	O	O	O	S	O	S	F	OH
4140a-l	Y*EU	O	O	O	S	O	S	OEt	OH
4141a-l	Y*EU	S	O	O	S	O	S	OH	OH

4142a-l	Y*EU	S	O	O	S	O	S	OMe	OH
4143a-l	Y*EU	S	O	O	S	O	S	H	OH
4144a-l	Y*EU	S	O	O	S	O	S	F	OH
4145a-l	Y*EU	S	O	O	S	O	S	OEt	OH
4146a-l	Y*EU	S	S	O	S	O	S	OH	OH
4147a-l	Y*EU	S	S	O	S	O	S	OMe	OH
4148a-l	Y*EU	S	S	O	S	O	S	H	OH
4149a-l	Y*EU	S	S	O	S	O	S	F	OH
4150a-l	Y*EU	S	S	O	S	O	S	OEt	OH
4151a-l	Y*EU	O	O	O	O	O	O	OH	OMe
4152a-l	Y*EU	O	O	O	O	O	O	OMe	OMe
4153a-l	Y*EU	O	O	O	O	O	O	H	OMe
4154a-l	Y*EU	O	O	O	O	O	O	F	OMe
4155a-l	Y*EU	O	O	O	O	O	O	OEt	OMe
4156a-l	Y*EU	S	O	O	O	O	O	OH	OMe
4157a-l	Y*EU	S	O	O	O	O	O	OMe	OMe
4158a-l	Y*EU	S	O	O	O	O	O	H	OMe
4159a-l	Y*EU	S	O	O	O	O	O	F	OMe
4160a-l	Y*EU	S	O	O	O	O	O	OEt	OMe
4161a-l	Y*EU	S	S	O	O	O	O	OH	OMe
4162a-l	Y*EU	S	S	O	O	O	O	OMe	OMe
4163a-l	Y*EU	S	S	O	O	O	O	H	OMe
4164a-l	Y*EU	S	S	O	O	O	O	F	OMe
4165a-l	Y*EU	S	S	O	O	O	O	OEt	OMe
4166a-l	Y*EU	O	O	S	O	O	O	OH	OMe
4167a-l	Y*EU	O	O	S	O	O	O	OMe	OMe
4168a-l	Y*EU	O	O	S	O	O	O	H	OMe
4169a-l	Y*EU	O	O	S	O	O	O	F	OMe
4170a-l	Y*EU	O	O	S	O	O	O	OEt	OMe
4171a-l	Y*EU	S	O	S	O	O	O	OH	OMe
4172a-l	Y*EU	S	O	S	O	O	O	OMe	OMe
4173a-l	Y*EU	S	O	S	O	O	O	H	OMe
4174a-l	Y*EU	S	O	S	O	O	O	F	OMe
4175a-l	Y*EU	S	O	S	O	O	O	OEt	OMe
4176a-l	Y*EU	S	S	S	O	O	O	OH	OMe
4177a-l	Y*EU	S	S	S	O	O	O	OMe	OMe
4178a-l	Y*EU	S	S	S	O	O	O	H	OMe
4179a-l	Y*EU	S	S	S	O	O	O	F	OMe
4180a-l	Y*EU	S	S	S	O	O	O	OEt	OMe
4181a-l	Y*EU	O	O	S	S	O	O	OH	OMe
4182a-l	Y*EU	O	O	S	S	O	O	OMe	OMe
4183a-l	Y*EU	O	O	S	S	O	O	H	OMe
4184a-l	Y*EU	O	O	S	S	O	O	F	OMe
4185a-l	Y*EU	O	O	S	S	O	O	OEt	OMe
4186a-l	Y*EU	S	O	S	S	O	O	OH	OMe
4187a-l	Y*EU	S	O	S	S	O	O	OMe	OMe
4188a-l	Y*EU	S	O	S	S	O	O	H	OMe
4189a-l	Y*EU	S	O	S	S	O	O	F	OMe
4190a-l	Y*EU	S	O	S	S	O	O	OEt	OMe

4191a-l	Y*EU	S	S	S	S	O	O	OH	OMe
4192a-l	Y*EU	S	S	S	S	O	O	OMe	OMe
4193a-l	Y*EU	S	S	S	S	O	O	H	OMe
4194a-l	Y*EU	S	S	S	S	O	O	F	OMe
4195a-l	Y*EU	S	S	S	S	O	O	OEt	OMe
4196a-l	Y*EU	O	O	S	S	S	O	OH	OMe
4197a-l	Y*EU	O	O	S	S	S	O	OMe	OMe
4198a-l	Y*EU	O	O	S	S	S	O	H	OMe
4199a-l	Y*EU	O	O	S	S	S	O	F	OMe
4200a-l	Y*EU	O	O	S	S	S	O	OEt	OMe
4201a-l	Y*EU	S	O	S	S	S	O	OH	OMe
4202a-l	Y*EU	S	O	S	S	S	O	OMe	OMe
4203a-l	Y*EU	S	O	S	S	S	O	H	OMe
4204a-l	Y*EU	S	O	S	S	S	O	F	OMe
4205a-l	Y*EU	S	O	S	S	S	O	OEt	OMe
4206a-l	Y*EU	S	S	S	S	S	O	OH	OMe
4207a-l	Y*EU	S	S	S	S	S	O	OMe	OMe
4208a-l	Y*EU	S	S	S	S	S	O	H	OMe
4209a-l	Y*EU	S	S	S	S	S	O	F	OMe
4210a-l	Y*EU	S	S	S	S	S	O	OEt	OMe
4211a-l	Y*EU	O	O	S	S	S	S	OH	OMe
4212a-l	Y*EU	O	O	S	S	S	S	OMe	OMe
4213a-l	Y*EU	O	O	S	S	S	S	H	OMe
4214a-l	Y*EU	O	O	S	S	S	S	F	OMe
4215a-l	Y*EU	O	O	S	S	S	S	OEt	OMe
4216a-l	Y*EU	S	O	S	S	S	S	OH	OMe
4217a-l	Y*EU	S	O	S	S	S	S	OMe	OMe
4218a-l	Y*EU	S	O	S	S	S	S	H	OMe
4219a-l	Y*EU	S	O	S	S	S	S	F	OMe
4220a-l	Y*EU	S	O	S	S	S	S	OEt	OMe
4221a-l	Y*EU	S	S	S	S	S	S	OH	OMe
4222a-l	Y*EU	S	S	S	S	S	S	OMe	OMe
4223a-l	Y*EU	S	S	S	S	S	S	H	OMe
4224a-l	Y*EU	S	S	S	S	S	S	F	OMe
4225a-l	Y*EU	S	S	S	S	S	S	OEt	OMe
4226a-l	Y*EU	O	O	O	S	S	S	OH	OMe
4227a-l	Y*EU	O	O	O	S	S	S	OMe	OMe
4228a-l	Y*EU	O	O	O	S	S	S	H	OMe
4229a-l	Y*EU	O	O	O	S	S	S	F	OMe
4230a-l	Y*EU	O	O	O	S	S	S	OEt	OMe
4231a-l	Y*EU	S	O	O	S	S	S	OH	OMe
4232a-l	Y*EU	S	O	O	S	S	S	OMe	OMe
4233a-l	Y*EU	S	O	O	S	S	S	H	OMe
4234a-l	Y*EU	S	O	O	S	S	S	F	OMe
4235a-l	Y*EU	S	O	O	S	S	S	OEt	OMe
4236a-l	Y*EU	S	S	O	S	S	S	OH	OMe
4237a-l	Y*EU	S	S	O	S	S	S	OMe	OMe
4238a-l	Y*EU	S	S	O	S	S	S	H	OMe
4239a-l	Y*EU	S	S	O	S	S	S	F	OMe

4240a-l	Y*EU	S	S	O	S	S	S	OEt	OMe
4241a-l	Y*EU	O	O	O	O	S	S	OH	OMe
4242a-l	Y*EU	O	O	O	O	S	S	OMe	OMe
4243a-l	Y*EU	O	O	O	O	S	S	H	OMe
4244a-l	Y*EU	O	O	O	O	S	S	F	OMe
4245a-l	Y*EU	O	O	O	O	S	S	OEt	OMe
4246a-l	Y*EU	S	O	O	O	S	S	OH	OMe
4247a-l	Y*EU	S	O	O	O	S	S	OMe	OMe
4248a-l	Y*EU	S	O	O	O	S	S	H	OMe
4249a-l	Y*EU	S	O	O	O	S	S	F	OMe
4250a-l	Y*EU	S	O	O	O	S	S	OEt	OMe
4251a-l	Y*EU	S	S	O	O	S	S	OH	OMe
4252a-l	Y*EU	S	S	O	O	S	S	OMe	OMe
4253a-l	Y*EU	S	S	O	O	S	S	H	OMe
4254a-l	Y*EU	S	S	O	O	S	S	F	OMe
4255a-l	Y*EU	S	S	O	O	S	S	OEt	OMe
4256a-l	Y*EU	O	O	O	O	O	S	OH	OMe
4257a-l	Y*EU	O	O	O	O	O	S	OMe	OMe
4258a-l	Y*EU	O	O	O	O	O	S	H	OMe
4259a-l	Y*EU	O	O	O	O	O	S	F	OMe
4260a-l	Y*EU	O	O	O	O	O	S	OEt	OMe
4261a-l	Y*EU	S	O	O	O	O	S	OH	OMe
4262a-l	Y*EU	S	O	O	O	O	S	OMe	OMe
4263a-l	Y*EU	S	O	O	O	O	S	H	OMe
4264a-l	Y*EU	S	O	O	O	O	S	F	OMe
4265a-l	Y*EU	S	O	O	O	O	S	OEt	OMe
4266a-l	Y*EU	S	S	O	O	O	S	OH	OMe
4267a-l	Y*EU	S	S	O	O	O	S	OMe	OMe
4268a-l	Y*EU	S	S	O	O	O	S	H	OMe
4269a-l	Y*EU	S	S	O	O	O	S	F	OMe
4270a-l	Y*EU	S	S	O	O	O	S	OEt	OMe
4271a-l	Y*EU	O	O	S	O	S	O	OH	OMe
4272a-l	Y*EU	O	O	S	O	S	O	OMe	OMe
4273a-l	Y*EU	O	O	S	O	S	O	H	OMe
4274a-l	Y*EU	O	O	S	O	S	O	F	OMe
4275a-l	Y*EU	O	O	S	O	S	O	OEt	OMe
4276a-l	Y*EU	S	O	S	O	S	O	OH	OMe
4277a-l	Y*EU	S	O	S	O	S	O	OMe	OMe
4278a-l	Y*EU	S	O	S	O	S	O	H	OMe
4279a-l	Y*EU	S	O	S	O	S	O	F	OMe
4280a-l	Y*EU	S	O	S	O	S	O	OEt	OMe
4281a-l	Y*EU	S	S	S	O	S	O	OH	OMe
4282a-l	Y*EU	S	S	S	O	S	O	OMe	OMe
4283a-l	Y*EU	S	S	S	O	S	O	H	OMe
4284a-l	Y*EU	S	S	S	O	S	O	F	OMe
4285a-l	Y*EU	S	S	S	O	S	O	OEt	OMe
4286a-l	Y*EU	O	O	O	S	O	S	OH	OMe
4287a-l	Y*EU	O	O	O	S	O	S	OMe	OMe
4288a-l	Y*EU	O	O	O	S	O	S	H	OMe

4289a-l	Y*EU	O	O	O	S	O	S	F	OMe
4290a-l	Y*EU	O	O	O	S	O	S	OEt	OMe
4291a-l	Y*EU	S	O	O	S	O	S	OH	OMe
4292a-l	Y*EU	S	O	O	S	O	S	OMe	OMe
4293a-l	Y*EU	S	O	O	S	O	S	H	OMe
4294a-l	Y*EU	S	O	O	S	O	S	F	OMe
4295a-l	Y*EU	S	O	O	S	O	S	OEt	OMe
4296a-l	Y*EU	S	S	O	S	O	S	OH	OMe
4297a-l	Y*EU	S	S	O	S	O	S	OMe	OMe
4298a-l	Y*EU	S	S	O	S	O	S	H	OMe
4299a-l	Y*EU	S	S	O	S	O	S	F	OMe
4300a-l	Y*EU	S	S	O	S	O	S	OEt	OMe
4301a-l	Y*EI	O	O	O	O	O	O	OH	OH
4302a-l	Y*EI	O	O	O	O	O	O	OMe	OH
4303a-l	Y*EI	O	O	O	O	O	O	H	OH
4304a-l	Y*EI	O	O	O	O	O	O	F	OH
4305a-l	Y*EI	O	O	O	O	O	O	OEt	OH
4306a-l	Y*EI	S	O	O	O	O	O	OH	OH
4307a-l	Y*EI	S	O	O	O	O	O	OMe	OH
4308a-l	Y*EI	S	O	O	O	O	O	H	OH
4309a-l	Y*EI	S	O	O	O	O	O	F	OH
4310a-l	Y*EI	S	O	O	O	O	O	OEt	OH
4311a-l	Y*EI	S	S	O	O	O	O	OH	OH
4312a-l	Y*EI	S	S	O	O	O	O	OMe	OH
4313a-l	Y*EI	S	S	O	O	O	O	H	OH
4314a-l	Y*EI	S	S	O	O	O	O	F	OH
4315a-l	Y*EI	S	S	O	O	O	O	OEt	OH
4316a-l	Y*EI	O	O	S	O	O	O	OH	OH
4317a-l	Y*EI	O	O	S	O	O	O	OMe	OH
4318a-l	Y*EI	O	O	S	O	O	O	H	OH
4319a-l	Y*EI	O	O	S	O	O	O	F	OH
4320a-l	Y*EI	O	O	S	O	O	O	OEt	OH
4321a-l	Y*EI	S	O	S	O	O	O	OH	OH
4322a-l	Y*EI	S	O	S	O	O	O	OMe	OH
4323a-l	Y*EI	S	O	S	O	O	O	H	OH
4324a-l	Y*EI	S	O	S	O	O	O	F	OH
4325a-l	Y*EI	S	O	S	O	O	O	OEt	OH
4326a-l	Y*EI	S	S	S	O	O	O	OH	OH
4327a-l	Y*EI	S	S	S	O	O	O	OMe	OH
4328a-l	Y*EI	S	S	S	O	O	O	H	OH
4329a-l	Y*EI	S	S	S	O	O	O	F	OH
4330a-l	Y*EI	S	S	S	O	O	O	OEt	OH
4331a-l	Y*EI	O	O	S	S	O	O	OH	OH
4332a-l	Y*EI	O	O	S	S	O	O	OMe	OH
4333a-l	Y*EI	O	O	S	S	O	O	H	OH
4334a-l	Y*EI	O	O	S	S	O	O	F	OH
4335a-l	Y*EI	O	O	S	S	O	O	OEt	OH
4336a-l	Y*EI	S	O	S	S	O	O	OH	OH
4337a-l	Y*EI	S	O	S	S	O	O	OMe	OH

4338a-l	Y*EI	S	O	S	S	O	O	H	OH
4339a-l	Y*EI	S	O	S	S	O	O	F	OH
4340a-l	Y*EI	S	O	S	S	O	O	OEt	OH
4341a-l	Y*EI	S	S	S	S	O	O	OH	OH
4342a-l	Y*EI	S	S	S	S	O	O	OMe	OH
4343a-l	Y*EI	S	S	S	S	O	O	H	OH
4344a-l	Y*EI	S	S	S	S	O	O	F	OH
4345a-l	Y*EI	S	S	S	S	O	O	OEt	OH
4346a-l	Y*EI	O	O	S	S	S	O	OH	OH
4347a-l	Y*EI	O	O	S	S	S	O	OMe	OH
4348a-l	Y*EI	O	O	S	S	S	O	H	OH
4349a-l	Y*EI	O	O	S	S	S	O	F	OH
4350a-l	Y*EI	O	O	S	S	S	O	OEt	OH
4351a-l	Y*EI	S	O	S	S	S	O	OH	OH
4352a-l	Y*EI	S	O	S	S	S	O	OMe	OH
4353a-l	Y*EI	S	O	S	S	S	O	H	OH
4354a-l	Y*EI	S	O	S	S	S	O	F	OH
4355a-l	Y*EI	S	O	S	S	S	O	OEt	OH
4356a-l	Y*EI	S	S	S	S	S	O	OH	OH
4357a-l	Y*EI	S	S	S	S	S	O	OMe	OH
4358a-l	Y*EI	S	S	S	S	S	O	H	OH
4359a-l	Y*EI	S	S	S	S	S	O	F	OH
4360a-l	Y*EI	S	S	S	S	S	O	OEt	OH
4361a-l	Y*EI	O	O	S	S	S	S	OH	OH
4362a-l	Y*EI	O	O	S	S	S	S	OMe	OH
4363a-l	Y*EI	O	O	S	S	S	S	H	OH
4364a-l	Y*EI	O	O	S	S	S	S	F	OH
4365a-l	Y*EI	O	O	S	S	S	S	OEt	OH
4366a-l	Y*EI	S	O	S	S	S	S	OH	OH
4367a-l	Y*EI	S	O	S	S	S	S	OMe	OH
4368a-l	Y*EI	S	O	S	S	S	S	H	OH
4369a-l	Y*EI	S	O	S	S	S	S	F	OH
4370a-l	Y*EI	S	O	S	S	S	S	OEt	OH
4371a-l	Y*EI	S	S	S	S	S	S	OH	OH
4372a-l	Y*EI	S	S	S	S	S	S	OMe	OH
4373a-l	Y*EI	S	S	S	S	S	S	H	OH
4374a-l	Y*EI	S	S	S	S	S	S	F	OH
4375a-l	Y*EI	S	S	S	S	S	S	OEt	OH
4376a-l	Y*EI	O	O	O	S	S	S	OH	OH
4377a-l	Y*EI	O	O	O	S	S	S	OMe	OH
4378a-l	Y*EI	O	O	O	S	S	S	H	OH
4379a-l	Y*EI	O	O	O	S	S	S	F	OH
4380a-l	Y*EI	O	O	O	S	S	S	OEt	OH
4381a-l	Y*EI	S	O	O	S	S	S	OH	OH
4382a-l	Y*EI	S	O	O	S	S	S	OMe	OH
4383a-l	Y*EI	S	O	O	S	S	S	H	OH
4384a-l	Y*EI	S	O	O	S	S	S	F	OH
4385a-l	Y*EI	S	O	O	S	S	S	OEt	OH
4386a-l	Y*EI	S	S	O	S	S	S	OH	OH

4387a-l	Y*EI	S	S	O	S	S	S	OMe	OH
4388a-l	Y*EI	S	S	O	S	S	S	H	OH
4389a-l	Y*EI	S	S	O	S	S	S	F	OH
4390a-l	Y*EI	S	S	O	S	S	S	OEt	OH
4391a-l	Y*EI	O	O	O	O	S	S	OH	OH
4392a-l	Y*EI	O	O	O	O	S	S	OMe	OH
4393a-l	Y*EI	O	O	O	O	S	S	H	OH
4394a-l	Y*EI	O	O	O	O	S	S	F	OH
4395a-l	Y*EI	O	O	O	O	S	S	OEt	OH
4396a-l	Y*EI	S	O	O	O	S	S	OH	OH
4397a-l	Y*EI	S	O	O	O	S	S	OMe	OH
4398a-l	Y*EI	S	O	O	O	S	S	H	OH
4399a-l	Y*EI	S	O	O	O	S	S	F	OH
4400a-l	Y*EI	S	O	O	O	S	S	OEt	OH
4401a-l	Y*EI	S	S	O	O	S	S	OH	OH
4402a-l	Y*EI	S	S	O	O	S	S	OMe	OH
4403a-l	Y*EI	S	S	O	O	S	S	H	OH
4404a-l	Y*EI	S	S	O	O	S	S	F	OH
4405a-l	Y*EI	S	S	O	O	S	S	OEt	OH
4406a-l	Y*EI	O	O	O	O	O	S	OH	OH
4407a-l	Y*EI	O	O	O	O	O	S	OMe	OH
4408a-l	Y*EI	O	O	O	O	O	S	H	OH
4409a-l	Y*EI	O	O	O	O	O	S	F	OH
4410a-l	Y*EI	O	O	O	O	O	S	OEt	OH
4411a-l	Y*EI	S	O	O	O	O	S	OH	OH
4412a-l	Y*EI	S	O	O	O	O	S	OMe	OH
4413a-l	Y*EI	S	O	O	O	O	S	H	OH
4414a-l	Y*EI	S	O	O	O	O	S	F	OH
4415a-l	Y*EI	S	O	O	O	O	S	OEt	OH
4416a-l	Y*EI	S	S	O	O	O	S	OH	OH
4417a-l	Y*EI	S	S	O	O	O	S	OMe	OH
4418a-l	Y*EI	S	S	O	O	O	S	H	OH
4419a-l	Y*EI	S	S	O	O	O	S	F	OH
4420a-l	Y*EI	S	S	O	O	O	S	OEt	OH
4421a-l	Y*EI	O	O	S	O	S	O	OH	OH
4422a-l	Y*EI	O	O	S	O	S	O	OMe	OH
4423a-l	Y*EI	O	O	S	O	S	O	H	OH
4424a-l	Y*EI	O	O	S	O	S	O	F	OH
4425a-l	Y*EI	O	O	S	O	S	O	OEt	OH
4426a-l	Y*EI	S	O	S	O	S	O	OH	OH
4427a-l	Y*EI	S	O	S	O	S	O	OMe	OH
4428a-l	Y*EI	S	O	S	O	S	O	H	OH
4429a-l	Y*EI	S	O	S	O	S	O	F	OH
4430a-l	Y*EI	S	O	S	O	S	O	OEt	OH
4431a-l	Y*EI	S	S	S	O	S	O	OH	OH
4432a-l	Y*EI	S	S	S	O	S	O	OMe	OH
4433a-l	Y*EI	S	S	S	O	S	O	H	OH
4434a-l	Y*EI	S	S	S	O	S	O	F	OH
4435a-l	Y*EI	S	S	S	O	S	O	OEt	OH

4436a-l	Y*EI	O	O	O	S	O	S	OH	OH
4437a-l	Y*EI	O	O	O	S	O	S	OMe	OH
4438a-l	Y*EI	O	O	O	S	O	S	H	OH
4439a-l	Y*EI	O	O	O	S	O	S	F	OH
4440a-l	Y*EI	O	O	O	S	O	S	OEt	OH
4441a-l	Y*EI	S	O	O	S	O	S	OH	OH
4442a-l	Y*EI	S	O	O	S	O	S	OMe	OH
4443a-l	Y*EI	S	O	O	S	O	S	H	OH
4444a-l	Y*EI	S	O	O	S	O	S	F	OH
4445a-l	Y*EI	S	O	O	S	O	S	OEt	OH
4446a-l	Y*EI	S	S	O	S	O	S	OH	OH
4447a-l	Y*EI	S	S	O	S	O	S	OMe	OH
4448a-l	Y*EI	S	S	O	S	O	S	H	OH
4449a-l	Y*EI	S	S	O	S	O	S	F	OH
4450a-l	Y*EI	S	S	O	S	O	S	OEt	OH
4451a-l	Y*EI	O	O	O	O	O	O	OH	OMe
4452a-l	Y*EI	O	O	O	O	O	O	OMe	OMe
4453a-l	Y*EI	O	O	O	O	O	O	H	OMe
4454a-l	Y*EI	O	O	O	O	O	O	F	OMe
4455a-l	Y*EI	O	O	O	O	O	O	OEt	OMe
4456a-l	Y*EI	S	O	O	O	O	O	OH	OMe
4457a-l	Y*EI	S	O	O	O	O	O	OMe	OMe
4458a-l	Y*EI	S	O	O	O	O	O	H	OMe
4459a-l	Y*EI	S	O	O	O	O	O	F	OMe
4460a-l	Y*EI	S	O	O	O	O	O	OEt	OMe
4461a-l	Y*EI	S	S	O	O	O	O	OH	OMe
4462a-l	Y*EI	S	S	O	O	O	O	OMe	OMe
4463a-l	Y*EI	S	S	O	O	O	O	H	OMe
4464a-l	Y*EI	S	S	O	O	O	O	F	OMe
4465a-l	Y*EI	S	S	O	O	O	O	OEt	OMe
4466a-l	Y*EI	O	O	S	O	O	O	OH	OMe
4467a-l	Y*EI	O	O	S	O	O	O	OMe	OMe
4468a-l	Y*EI	O	O	S	O	O	O	H	OMe
4469a-l	Y*EI	O	O	S	O	O	O	F	OMe
4470a-l	Y*EI	O	O	S	O	O	O	OEt	OMe
4471a-l	Y*EI	S	O	S	O	O	O	OH	OMe
4472a-l	Y*EI	S	O	S	O	O	O	OMe	OMe
4473a-l	Y*EI	S	O	S	O	O	O	H	OMe
4474a-l	Y*EI	S	O	S	O	O	O	F	OMe
4475a-l	Y*EI	S	O	S	O	O	O	OEt	OMe
4476a-l	Y*EI	S	S	S	O	O	O	OH	OMe
4477a-l	Y*EI	S	S	S	O	O	O	OMe	OMe
4478a-l	Y*EI	S	S	S	O	O	O	H	OMe
4479a-l	Y*EI	S	S	S	O	O	O	F	OMe
4480a-l	Y*EI	S	S	S	O	O	O	OEt	OMe
4481a-l	Y*EI	O	O	S	S	O	O	OH	OMe
4482a-l	Y*EI	O	O	S	S	O	O	OMe	OMe
4483a-l	Y*EI	O	O	S	S	O	O	H	OMe
4484a-l	Y*EI	O	O	S	S	O	O	F	OMe

4485a-l	Y*EI	O	O	S	S	O	O	OEt	OMe
4486a-l	Y*EI	S	O	S	S	O	O	OH	OMe
4487a-l	Y*EI	S	O	S	S	O	O	OMe	OMe
4488a-l	Y*EI	S	O	S	S	O	O	H	OMe
4489a-l	Y*EI	S	O	S	S	O	O	F	OMe
4490a-l	Y*EI	S	O	S	S	O	O	OEt	OMe
4491a-l	Y*EI	S	S	S	S	O	O	OH	OMe
4492a-l	Y*EI	S	S	S	S	O	O	OMe	OMe
4493a-l	Y*EI	S	S	S	S	O	O	H	OMe
4494a-l	Y*EI	S	S	S	S	O	O	F	OMe
4495a-l	Y*EI	S	S	S	S	O	O	OEt	OMe
4496a-l	Y*EI	O	O	S	S	S	O	OH	OMe
4497a-l	Y*EI	O	O	S	S	S	O	OMe	OMe
4498a-l	Y*EI	O	O	S	S	S	O	H	OMe
4499a-l	Y*EI	O	O	S	S	S	O	F	OMe
4500a-l	Y*EI	O	O	S	S	S	O	OEt	OMe
4501a-l	Y*EI	S	O	S	S	S	O	OH	OMe
4502a-l	Y*EI	S	O	S	S	S	O	OMe	OMe
4503a-l	Y*EI	S	O	S	S	S	O	H	OMe
4504a-l	Y*EI	S	O	S	S	S	O	F	OMe
4505a-l	Y*EI	S	O	S	S	S	O	OEt	OMe
4506a-l	Y*EI	S	S	S	S	S	O	OH	OMe
4507a-l	Y*EI	S	S	S	S	S	O	OMe	OMe
4508a-l	Y*EI	S	S	S	S	S	O	H	OMe
4509a-l	Y*EI	S	S	S	S	S	O	F	OMe
4510a-l	Y*EI	S	S	S	S	S	O	OEt	OMe
4511a-l	Y*EI	O	O	S	S	S	S	OH	OMe
4512a-l	Y*EI	O	O	S	S	S	S	OMe	OMe
4513a-l	Y*EI	O	O	S	S	S	S	H	OMe
4514a-l	Y*EI	O	O	S	S	S	S	F	OMe
4515a-l	Y*EI	O	O	S	S	S	S	OEt	OMe
4516a-l	Y*EI	S	O	S	S	S	S	OH	OMe
4517a-l	Y*EI	S	O	S	S	S	S	OMe	OMe
4518a-l	Y*EI	S	O	S	S	S	S	H	OMe
4519a-l	Y*EI	S	O	S	S	S	S	F	OMe
4520a-l	Y*EI	S	O	S	S	S	S	OEt	OMe
4521a-l	Y*EI	S	S	S	S	S	S	OH	OMe
4522a-l	Y*EI	S	S	S	S	S	S	OMe	OMe
4523a-l	Y*EI	S	S	S	S	S	S	H	OMe
4524a-l	Y*EI	S	S	S	S	S	S	F	OMe
4525a-l	Y*EI	S	S	S	S	S	S	OEt	OMe
4526a-l	Y*EI	O	O	O	S	S	S	OH	OMe
4527a-l	Y*EI	O	O	O	S	S	S	OMe	OMe
4528a-l	Y*EI	O	O	O	S	S	S	H	OMe
4529a-l	Y*EI	O	O	O	S	S	S	F	OMe
4530a-l	Y*EI	O	O	O	S	S	S	OEt	OMe
4531a-l	Y*EI	S	O	O	S	S	S	OH	OMe
4532a-l	Y*EI	S	O	O	S	S	S	OMe	OMe
4533a-l	Y*EI	S	O	O	S	S	S	H	OMe

4534a-l	Y*EI	S	O	O	S	S	S	F	OMe
4535a-l	Y*EI	S	O	O	S	S	S	OEt	OMe
4536a-l	Y*EI	S	S	O	S	S	S	OH	OMe
4537a-l	Y*EI	S	S	O	S	S	S	OMe	OMe
4538a-l	Y*EI	S	S	O	S	S	S	H	OMe
4539a-l	Y*EI	S	S	O	S	S	S	F	OMe
4540a-l	Y*EI	S	S	O	S	S	S	OEt	OMe
4541a-l	Y*EI	O	O	O	O	S	S	OH	OMe
4542a-l	Y*EI	O	O	O	O	S	S	OMe	OMe
4543a-l	Y*EI	O	O	O	O	S	S	H	OMe
4544a-l	Y*EI	O	O	O	O	S	S	F	OMe
4545a-l	Y*EI	O	O	O	O	S	S	OEt	OMe
4546a-l	Y*EI	S	O	O	O	S	S	OH	OMe
4547a-l	Y*EI	S	O	O	O	S	S	OMe	OMe
4548a-l	Y*EI	S	O	O	O	S	S	H	OMe
4549a-l	Y*EI	S	O	O	O	S	S	F	OMe
4550a-l	Y*EI	S	O	O	O	S	S	OEt	OMe
4551a-l	Y*EI	S	S	O	O	S	S	OH	OMe
4552a-l	Y*EI	S	S	O	O	S	S	OMe	OMe
4553a-l	Y*EI	S	S	O	O	S	S	H	OMe
4554a-l	Y*EI	S	S	O	O	S	S	F	OMe
4555a-l	Y*EI	S	S	O	O	S	S	OEt	OMe
4556a-l	Y*EI	O	O	O	O	O	S	OH	OMe
4557a-l	Y*EI	O	O	O	O	O	S	OMe	OMe
4558a-l	Y*EI	O	O	O	O	O	S	H	OMe
4559a-l	Y*EI	O	O	O	O	O	S	F	OMe
4560a-l	Y*EI	O	O	O	O	O	S	OEt	OMe
4561a-l	Y*EI	S	O	O	O	O	S	OH	OMe
4562a-l	Y*EI	S	O	O	O	O	S	OMe	OMe
4563a-l	Y*EI	S	O	O	O	O	S	H	OMe
4564a-l	Y*EI	S	O	O	O	O	S	F	OMe
4565a-l	Y*EI	S	O	O	O	O	S	OEt	OMe
4566a-l	Y*EI	S	S	O	O	O	S	OH	OMe
4567a-l	Y*EI	S	S	O	O	O	S	OMe	OMe
4568a-l	Y*EI	S	S	O	O	O	S	H	OMe
4569a-l	Y*EI	S	S	O	O	O	S	F	OMe
4570a-l	Y*EI	S	S	O	O	O	S	OEt	OMe
4571a-l	Y*EI	O	O	S	O	S	O	OH	OMe
4572a-l	Y*EI	O	O	S	O	S	O	OMe	OMe
4573a-l	Y*EI	O	O	S	O	S	O	H	OMe
4574a-l	Y*EI	O	O	S	O	S	O	F	OMe
4575a-l	Y*EI	O	O	S	O	S	O	OEt	OMe
4576a-l	Y*EI	S	O	S	O	S	O	OH	OMe
4577a-l	Y*EI	S	O	S	O	S	O	OMe	OMe
4578a-l	Y*EI	S	O	S	O	S	O	H	OMe
4579a-l	Y*EI	S	O	S	O	S	O	F	OMe
4580a-l	Y*EI	S	O	S	O	S	O	OEt	OMe
4581a-l	Y*EI	S	S	S	O	S	O	OH	OMe
4582a-l	Y*EI	S	S	S	O	S	O	OMe	OMe

4583a-l	Y*EI	S	S	S	O	S	O	H	OMe
4584a-l	Y*EI	S	S	S	O	S	O	F	OMe
4585a-l	Y*EI	S	S	S	O	S	O	OEt	OMe
4586a-l	Y*EI	O	O	O	S	O	S	OH	OMe
4587a-l	Y*EI	O	O	O	S	O	S	OMe	OMe
4588a-l	Y*EI	O	O	O	S	O	S	H	OMe
4589a-l	Y*EI	O	O	O	S	O	S	F	OMe
4590a-l	Y*EI	O	O	O	S	O	S	OEt	OMe
4591a-l	Y*EI	S	O	O	S	O	S	OH	OMe
4592a-l	Y*EI	S	O	O	S	O	S	OMe	OMe
4593a-l	Y*EI	S	O	O	S	O	S	H	OMe
4594a-l	Y*EI	S	O	O	S	O	S	F	OMe
4595a-l	Y*EI	S	O	O	S	O	S	OEt	OMe
4596a-l	Y*EI	S	S	O	S	O	S	OH	OMe
4597a-l	Y*EI	S	S	O	S	O	S	OMe	OMe
4598a-l	Y*EI	S	S	O	S	O	S	H	OMe
4599a-l	Y*EI	S	S	O	S	O	S	F	OMe
4600a-l	Y*EI	S	S	O	S	O	S	OEt	OMe
4601a-l	Y*ET	O	O	O	O	O	O	OH	OH
4602a-l	Y*ET	O	O	O	O	O	O	OMe	OH
4603a-l	Y*ET	O	O	O	O	O	O	H	OH
4604a-l	Y*ET	O	O	O	O	O	O	F	OH
4605a-l	Y*ET	O	O	O	O	O	O	OEt	OH
4606a-l	Y*ET	S	O	O	O	O	O	OH	OH
4607a-l	Y*ET	S	O	O	O	O	O	OMe	OH
4608a-l	Y*ET	S	O	O	O	O	O	H	OH
4609a-l	Y*ET	S	O	O	O	O	O	F	OH
4610a-l	Y*ET	S	O	O	O	O	O	OEt	OH
4611a-l	Y*ET	S	S	O	O	O	O	OH	OH
4612a-l	Y*ET	S	S	O	O	O	O	OMe	OH
4613a-l	Y*ET	S	S	O	O	O	O	H	OH
4614a-l	Y*ET	S	S	O	O	O	O	F	OH
4615a-l	Y*ET	S	S	O	O	O	O	OEt	OH
4616a-l	Y*ET	O	O	S	O	O	O	OH	OH
4617a-l	Y*ET	O	O	S	O	O	O	OMe	OH
4618a-l	Y*ET	O	O	S	O	O	O	H	OH
4619a-l	Y*ET	O	O	S	O	O	O	F	OH
4620a-l	Y*ET	O	O	S	O	O	O	OEt	OH
4621a-l	Y*ET	S	O	S	O	O	O	OH	OH
4622a-l	Y*ET	S	O	S	O	O	O	OMe	OH
4623a-l	Y*ET	S	O	S	O	O	O	H	OH
4624a-l	Y*ET	S	O	S	O	O	O	F	OH
4625a-l	Y*ET	S	O	S	O	O	O	OEt	OH
4626a-l	Y*ET	S	S	S	O	O	O	OH	OH
4627a-l	Y*ET	S	S	S	O	O	O	OMe	OH
4628a-l	Y*ET	S	S	S	O	O	O	H	OH
4629a-l	Y*ET	S	S	S	O	O	O	F	OH
4630a-l	Y*ET	S	S	S	O	O	O	OEt	OH
4631a-l	Y*ET	O	O	S	S	O	O	OH	OH

4632a-l	Y*ET	O	O	S	S	O	O	OMe	OH
4633a-l	Y*ET	O	O	S	S	O	O	H	OH
4634a-l	Y*ET	O	O	S	S	O	O	F	OH
4635a-l	Y*ET	O	O	S	S	O	O	OEt	OH
4636a-l	Y*ET	S	O	S	S	O	O	OH	OH
4637a-l	Y*ET	S	O	S	S	O	O	OMe	OH
4638a-l	Y*ET	S	O	S	S	O	O	H	OH
4639a-l	Y*ET	S	O	S	S	O	O	F	OH
4640a-l	Y*ET	S	O	S	S	O	O	OEt	OH
4641a-l	Y*ET	S	S	S	S	O	O	OH	OH
4642a-l	Y*ET	S	S	S	S	O	O	OMe	OH
4643a-l	Y*ET	S	S	S	S	O	O	H	OH
4644a-l	Y*ET	S	S	S	S	O	O	F	OH
4645a-l	Y*ET	S	S	S	S	O	O	OEt	OH
4646a-l	Y*ET	O	O	S	S	S	O	OH	OH
4647a-l	Y*ET	O	O	S	S	S	O	OMe	OH
4648a-l	Y*ET	O	O	S	S	S	O	H	OH
4649a-l	Y*ET	O	O	S	S	S	O	F	OH
4650a-l	Y*ET	O	O	S	S	S	O	OEt	OH
4651a-l	Y*ET	S	O	S	S	S	O	OH	OH
4652a-l	Y*ET	S	O	S	S	S	O	OMe	OH
4653a-l	Y*ET	S	O	S	S	S	O	H	OH
4654a-l	Y*ET	S	O	S	S	S	O	F	OH
4655a-l	Y*ET	S	O	S	S	S	O	OEt	OH
4656a-l	Y*ET	S	S	S	S	S	O	OH	OH
4657a-l	Y*ET	S	S	S	S	S	O	OMe	OH
4658a-l	Y*ET	S	S	S	S	S	O	H	OH
4659a-l	Y*ET	S	S	S	S	S	O	F	OH
4660a-l	Y*ET	S	S	S	S	S	O	OEt	OH
4661a-l	Y*ET	O	O	S	S	S	S	OH	OH
4662a-l	Y*ET	O	O	S	S	S	S	OMe	OH
4663a-l	Y*ET	O	O	S	S	S	S	H	OH
4664a-l	Y*ET	O	O	S	S	S	S	F	OH
4665a-l	Y*ET	O	O	S	S	S	S	OEt	OH
4666a-l	Y*ET	S	O	S	S	S	S	OH	OH
4667a-l	Y*ET	S	O	S	S	S	S	OMe	OH
4668a-l	Y*ET	S	O	S	S	S	S	H	OH
4669a-l	Y*ET	S	O	S	S	S	S	F	OH
4670a-l	Y*ET	S	O	S	S	S	S	OEt	OH
4671a-l	Y*ET	S	S	S	S	S	S	OH	OH
4672a-l	Y*ET	S	S	S	S	S	S	OMe	OH
4673a-l	Y*ET	S	S	S	S	S	S	H	OH
4674a-l	Y*ET	S	S	S	S	S	S	F	OH
4675a-l	Y*ET	S	S	S	S	S	S	OEt	OH
4676a-l	Y*ET	O	O	O	S	S	S	OH	OH
4677a-l	Y*ET	O	O	O	S	S	S	OMe	OH
4678a-l	Y*ET	O	O	O	S	S	S	H	OH
4679a-l	Y*ET	O	O	O	S	S	S	F	OH
4680a-l	Y*ET	O	O	O	S	S	S	OEt	OH

4681a-l	Y*ET	S	O	O	S	S	S	OH	OH
4682a-l	Y*ET	S	O	O	S	S	S	OMe	OH
4683a-l	Y*ET	S	O	O	S	S	S	H	OH
4684a-l	Y*ET	S	O	O	S	S	S	F	OH
4685a-l	Y*ET	S	O	O	S	S	S	OEt	OH
4686a-l	Y*ET	S	S	O	S	S	S	OH	OH
4687a-l	Y*ET	S	S	O	S	S	S	OMe	OH
4688a-l	Y*ET	S	S	O	S	S	S	H	OH
4689a-l	Y*ET	S	S	O	S	S	S	F	OH
4690a-l	Y*ET	S	S	O	S	S	S	OEt	OH
4691a-l	Y*ET	O	O	O	O	S	S	OH	OH
4692a-l	Y*ET	O	O	O	O	S	S	OMe	OH
4693a-l	Y*ET	O	O	O	O	S	S	H	OH
4694a-l	Y*ET	O	O	O	O	S	S	F	OH
4695a-l	Y*ET	O	O	O	O	S	S	OEt	OH
4696a-l	Y*ET	S	O	O	O	S	S	OH	OH
4697a-l	Y*ET	S	O	O	O	S	S	OMe	OH
4698a-l	Y*ET	S	O	O	O	S	S	H	OH
4699a-l	Y*ET	S	O	O	O	S	S	F	OH
4700a-l	Y*ET	S	O	O	O	S	S	OEt	OH
4701a-l	Y*ET	S	S	O	O	S	S	OH	OH
4702a-l	Y*ET	S	S	O	O	S	S	OMe	OH
4703a-l	Y*ET	S	S	O	O	S	S	H	OH
4704a-l	Y*ET	S	S	O	O	S	S	F	OH
4705a-l	Y*ET	S	S	O	O	S	S	OEt	OH
4706a-l	Y*ET	O	O	O	O	O	S	OH	OH
4707a-l	Y*ET	O	O	O	O	O	S	OMe	OH
4708a-l	Y*ET	O	O	O	O	O	S	H	OH
4709a-l	Y*ET	O	O	O	O	O	S	F	OH
4710a-l	Y*ET	O	O	O	O	O	S	OEt	OH
4711a-l	Y*ET	S	O	O	O	O	S	OH	OH
4712a-l	Y*ET	S	O	O	O	O	S	OMe	OH
4713a-l	Y*ET	S	O	O	O	O	S	H	OH
4714a-l	Y*ET	S	O	O	O	O	S	F	OH
4715a-l	Y*ET	S	O	O	O	O	S	OEt	OH
4716a-l	Y*ET	S	S	O	O	O	S	OH	OH
4717a-l	Y*ET	S	S	O	O	O	S	OMe	OH
4718a-l	Y*ET	S	S	O	O	O	S	H	OH
4719a-l	Y*ET	S	S	O	O	O	S	F	OH
4720a-l	Y*ET	S	S	O	O	O	S	OEt	OH
4721a-l	Y*ET	O	O	S	O	S	O	OH	OH
4722a-l	Y*ET	O	O	S	O	S	O	OMe	OH
4723a-l	Y*ET	O	O	S	O	S	O	H	OH
4724a-l	Y*ET	O	O	S	O	S	O	F	OH
4725a-l	Y*ET	O	O	S	O	S	O	OEt	OH
4726a-l	Y*ET	S	O	S	O	S	O	OH	OH
4727a-l	Y*ET	S	O	S	O	S	O	OMe	OH
4728a-l	Y*ET	S	O	S	O	S	O	H	OH
4729a-l	Y*ET	S	O	S	O	S	O	F	OH

4730a-l	Y*ET	S	O	S	O	S	O	OEt	OH
4731a-l	Y*ET	S	S	S	O	S	O	OH	OH
4732a-l	Y*ET	S	S	S	O	S	O	OMe	OH
4733a-l	Y*ET	S	S	S	O	S	O	H	OH
4734a-l	Y*ET	S	S	S	O	S	O	F	OH
4735a-l	Y*ET	S	S	S	O	S	O	OEt	OH
4736a-l	Y*ET	O	O	O	S	O	S	OH	OH
4737a-l	Y*ET	O	O	O	S	O	S	OMe	OH
4738a-l	Y*ET	O	O	O	S	O	S	H	OH
4739a-l	Y*ET	O	O	O	S	O	S	F	OH
4740a-l	Y*ET	O	O	O	S	O	S	OEt	OH
4741a-l	Y*ET	S	O	O	S	O	S	OH	OH
4742a-l	Y*ET	S	O	O	S	O	S	OMe	OH
4743a-l	Y*ET	S	O	O	S	O	S	H	OH
4744a-l	Y*ET	S	O	O	S	O	S	F	OH
4745a-l	Y*ET	S	O	O	S	O	S	OEt	OH
4746a-l	Y*ET	S	S	O	S	O	S	OH	OH
4747a-l	Y*ET	S	S	O	S	O	S	OMe	OH
4748a-l	Y*ET	S	S	O	S	O	S	H	OH
4749a-l	Y*ET	S	S	O	S	O	S	F	OH
4750a-l	Y*ET	S	S	O	S	O	S	OEt	OH
4751a-l	Y*ET	O	O	O	O	O	O	OH	OMe
4752a-l	Y*ET	O	O	O	O	O	O	OMe	OMe
4753a-l	Y*ET	O	O	O	O	O	O	H	OMe
4754a-l	Y*ET	O	O	O	O	O	O	F	OMe
4755a-l	Y*ET	O	O	O	O	O	O	OEt	OMe
4756a-l	Y*ET	S	O	O	O	O	O	OH	OMe
4757a-l	Y*ET	S	O	O	O	O	O	OMe	OMe
4758a-l	Y*ET	S	O	O	O	O	O	H	OMe
4759a-l	Y*ET	S	O	O	O	O	O	F	OMe
4760a-l	Y*ET	S	O	O	O	O	O	OEt	OMe
4761a-l	Y*ET	S	S	O	O	O	O	OH	OMe
4762a-l	Y*ET	S	S	O	O	O	O	OMe	OMe
4763a-l	Y*ET	S	S	O	O	O	O	H	OMe
4764a-l	Y*ET	S	S	O	O	O	O	F	OMe
4765a-l	Y*ET	S	S	O	O	O	O	OEt	OMe
4766a-l	Y*ET	O	O	S	O	O	O	OH	OMe
4767a-l	Y*ET	O	O	S	O	O	O	OMe	OMe
4768a-l	Y*ET	O	O	S	O	O	O	H	OMe
4769a-l	Y*ET	O	O	S	O	O	O	F	OMe
4770a-l	Y*ET	O	O	S	O	O	O	OEt	OMe
4771a-l	Y*ET	S	O	S	O	O	O	OH	OMe
4772a-l	Y*ET	S	O	S	O	O	O	OMe	OMe
4773a-l	Y*ET	S	O	S	O	O	O	H	OMe
4774a-l	Y*ET	S	O	S	O	O	O	F	OMe
4775a-l	Y*ET	S	O	S	O	O	O	OEt	OMe
4776a-l	Y*ET	S	S	S	O	O	O	OH	OMe
4777a-l	Y*ET	S	S	S	O	O	O	OMe	OMe
4778a-l	Y*ET	S	S	S	O	O	O	H	OMe

4779a-l	Y*ET	S	S	S	O	O	O	F	OMe
4780a-l	Y*ET	S	S	S	O	O	O	OEt	OMe
4781a-l	Y*ET	O	O	S	S	O	O	OH	OMe
4782a-l	Y*ET	O	O	S	S	O	O	OMe	OMe
4783a-l	Y*ET	O	O	S	S	O	O	H	OMe
4784a-l	Y*ET	O	O	S	S	O	O	F	OMe
4785a-l	Y*ET	O	O	S	S	O	O	OEt	OMe
4786a-l	Y*ET	S	O	S	S	O	O	OH	OMe
4787a-l	Y*ET	S	O	S	S	O	O	OMe	OMe
4788a-l	Y*ET	S	O	S	S	O	O	H	OMe
4789a-l	Y*ET	S	O	S	S	O	O	F	OMe
4790a-l	Y*ET	S	O	S	S	O	O	OEt	OMe
4791a-l	Y*ET	S	S	S	S	O	O	OH	OMe
4792a-l	Y*ET	S	S	S	S	O	O	OMe	OMe
4793a-l	Y*ET	S	S	S	S	O	O	H	OMe
4794a-l	Y*ET	S	S	S	S	O	O	F	OMe
4795a-l	Y*ET	S	S	S	S	O	O	OEt	OMe
4796a-l	Y*ET	O	O	S	S	S	O	OH	OMe
4797a-l	Y*ET	O	O	S	S	S	O	OMe	OMe
4798a-l	Y*ET	O	O	S	S	S	O	H	OMe
4799a-l	Y*ET	O	O	S	S	S	O	F	OMe
4800a-l	Y*ET	O	O	S	S	S	O	OEt	OMe
4801a-l	Y*ET	S	O	S	S	S	O	OH	OMe
4802a-l	Y*ET	S	O	S	S	S	O	OMe	OMe
4803a-l	Y*ET	S	O	S	S	S	O	H	OMe
4804a-l	Y*ET	S	O	S	S	S	O	F	OMe
4805a-l	Y*ET	S	O	S	S	S	O	OEt	OMe
4806a-l	Y*ET	S	S	S	S	S	O	OH	OMe
4807a-l	Y*ET	S	S	S	S	S	O	OMe	OMe
4808a-l	Y*ET	S	S	S	S	S	O	H	OMe
4809a-l	Y*ET	S	S	S	S	S	O	F	OMe
4810a-l	Y*ET	S	S	S	S	S	O	OEt	OMe
4811a-l	Y*ET	O	O	S	S	S	S	OH	OMe
4812a-l	Y*ET	O	O	S	S	S	S	OMe	OMe
4813a-l	Y*ET	O	O	S	S	S	S	H	OMe
4814a-l	Y*ET	O	O	S	S	S	S	F	OMe
4815a-l	Y*ET	O	O	S	S	S	S	OEt	OMe
4816a-l	Y*ET	S	O	S	S	S	S	OH	OMe
4817a-l	Y*ET	S	O	S	S	S	S	OMe	OMe
4818a-l	Y*ET	S	O	S	S	S	S	H	OMe
4819a-l	Y*ET	S	O	S	S	S	S	F	OMe
4820a-l	Y*ET	S	O	S	S	S	S	OEt	OMe
4821a-l	Y*ET	S	S	S	S	S	S	OH	OMe
4822a-l	Y*ET	S	S	S	S	S	S	OMe	OMe
4823a-l	Y*ET	S	S	S	S	S	S	H	OMe
4824a-l	Y*ET	S	S	S	S	S	S	F	OMe
4825a-l	Y*ET	S	S	S	S	S	S	OEt	OMe
4826a-l	Y*ET	O	O	O	S	S	S	OH	OMe
4827a-l	Y*ET	O	O	O	S	S	S	OMe	OMe

4828a-l	Y*ET	O	O	O	S	S	S	H	OMe
4829a-l	Y*ET	O	O	O	S	S	S	F	OMe
4830a-l	Y*ET	O	O	O	S	S	S	OEt	OMe
4831a-l	Y*ET	S	O	O	S	S	S	OH	OMe
4832a-l	Y*ET	S	O	O	S	S	S	OMe	OMe
4833a-l	Y*ET	S	O	O	S	S	S	H	OMe
4834a-l	Y*ET	S	O	O	S	S	S	F	OMe
4835a-l	Y*ET	S	O	O	S	S	S	OEt	OMe
4836a-l	Y*ET	S	S	O	S	S	S	OH	OMe
4837a-l	Y*ET	S	S	O	S	S	S	OMe	OMe
4838a-l	Y*ET	S	S	O	S	S	S	H	OMe
4839a-l	Y*ET	S	S	O	S	S	S	F	OMe
4840a-l	Y*ET	S	S	O	S	S	S	OEt	OMe
4841a-l	Y*ET	O	O	O	O	S	S	OH	OMe
4842a-l	Y*ET	O	O	O	O	S	S	OMe	OMe
4843a-l	Y*ET	O	O	O	O	S	S	H	OMe
4844a-l	Y*ET	O	O	O	O	S	S	F	OMe
4845a-l	Y*ET	O	O	O	O	S	S	OEt	OMe
4846a-l	Y*ET	S	O	O	O	S	S	OH	OMe
4847a-l	Y*ET	S	O	O	O	S	S	OMe	OMe
4848a-l	Y*ET	S	O	O	O	S	S	H	OMe
4849a-l	Y*ET	S	O	O	O	S	S	F	OMe
4850a-l	Y*ET	S	O	O	O	S	S	OEt	OMe
4851a-l	Y*ET	S	S	O	O	S	S	OH	OMe
4852a-l	Y*ET	S	S	O	O	S	S	OMe	OMe
4853a-l	Y*ET	S	S	O	O	S	S	H	OMe
4854a-l	Y*ET	S	S	O	O	S	S	F	OMe
4855a-l	Y*ET	S	S	O	O	S	S	OEt	OMe
4856a-l	Y*ET	O	O	O	O	O	S	OH	OMe
4857a-l	Y*ET	O	O	O	O	O	S	OMe	OMe
4858a-l	Y*ET	O	O	O	O	O	S	H	OMe
4859a-l	Y*ET	O	O	O	O	O	S	F	OMe
4860a-l	Y*ET	O	O	O	O	O	S	OEt	OMe
4861a-l	Y*ET	S	O	O	O	O	S	OH	OMe
4862a-l	Y*ET	S	O	O	O	O	S	OMe	OMe
4863a-l	Y*ET	S	O	O	O	O	S	H	OMe
4864a-l	Y*ET	S	O	O	O	O	S	F	OMe
4865a-l	Y*ET	S	O	O	O	O	S	OEt	OMe
4866a-l	Y*ET	S	S	O	O	O	S	OH	OMe
4867a-l	Y*ET	S	S	O	O	O	S	OMe	OMe
4868a-l	Y*ET	S	S	O	O	O	S	H	OMe
4869a-l	Y*ET	S	S	O	O	O	S	F	OMe
4870a-l	Y*ET	S	S	O	O	O	S	OEt	OMe
4871a-l	Y*ET	O	O	S	O	S	O	OH	OMe
4872a-l	Y*ET	O	O	S	O	S	O	OMe	OMe
4873a-l	Y*ET	O	O	S	O	S	O	H	OMe
4874a-l	Y*ET	O	O	S	O	S	O	F	OMe
4875a-l	Y*ET	O	O	S	O	S	O	OEt	OMe
4876a-l	Y*ET	S	O	S	O	S	O	OH	OMe

4877a-l	Y*ET	S	O	S	O	S	O	OMe	OMe
4878a-l	Y*ET	S	O	S	O	S	O	H	OMe
4879a-l	Y*ET	S	O	S	O	S	O	F	OMe
4880a-l	Y*ET	S	O	S	O	S	O	OEt	OMe
4881a-l	Y*ET	S	S	S	O	S	O	OH	OMe
4882a-l	Y*ET	S	S	S	O	S	O	OMe	OMe
4883a-l	Y*ET	S	S	S	O	S	O	H	OMe
4884a-l	Y*ET	S	S	S	O	S	O	F	OMe
4885a-l	Y*ET	S	S	S	O	S	O	OEt	OMe
4886a-l	Y*ET	O	O	O	S	O	S	OH	OMe
4887a-l	Y*ET	O	O	O	S	O	S	OMe	OMe
4888a-l	Y*ET	O	O	O	S	O	S	H	OMe
4889a-l	Y*ET	O	O	O	S	O	S	F	OMe
4890a-l	Y*ET	O	O	O	S	O	S	OEt	OMe
4891a-l	Y*ET	S	O	O	S	O	S	OH	OMe
4892a-l	Y*ET	S	O	O	S	O	S	OMe	OMe
4893a-l	Y*ET	S	O	O	S	O	S	H	OMe
4894a-l	Y*ET	S	O	O	S	O	S	F	OMe
4895a-l	Y*ET	S	O	O	S	O	S	OEt	OMe
4896a-l	Y*ET	S	S	O	S	O	S	OH	OMe
4897a-l	Y*ET	S	S	O	S	O	S	OMe	OMe
4898a-l	Y*ET	S	S	O	S	O	S	H	OMe
4899a-l	Y*ET	S	S	O	S	O	S	F	OMe
4900a-l	Y*ET	S	S	O	S	O	S	OEt	OMe
4901a-l	Y*EE	O	O	O	O	O	O	OH	OH
4902a-l	Y*EE	O	O	O	O	O	O	OMe	OH
4903a-l	Y*EE	O	O	O	O	O	O	H	OH
4904a-l	Y*EE	O	O	O	O	O	O	F	OH
4905a-l	Y*EE	O	O	O	O	O	O	OEt	OH
4906a-l	Y*EE	S	O	O	O	O	O	OH	OH
4907a-l	Y*EE	S	O	O	O	O	O	OMe	OH
4908a-l	Y*EE	S	O	O	O	O	O	H	OH
4909a-l	Y*EE	S	O	O	O	O	O	F	OH
4910a-l	Y*EE	S	O	O	O	O	O	OEt	OH
4911a-l	Y*EE	S	S	O	O	O	O	OH	OH
4912a-l	Y*EE	S	S	O	O	O	O	OMe	OH
4913a-l	Y*EE	S	S	O	O	O	O	H	OH
4914a-l	Y*EE	S	S	O	O	O	O	F	OH
4915a-l	Y*EE	S	S	O	O	O	O	OEt	OH
4916a-l	Y*EE	O	O	S	O	O	O	OH	OH
4917a-l	Y*EE	O	O	S	O	O	O	OMe	OH
4918a-l	Y*EE	O	O	S	O	O	O	H	OH
4919a-l	Y*EE	O	O	S	O	O	O	F	OH
4920a-l	Y*EE	O	O	S	O	O	O	OEt	OH
4921a-l	Y*EE	S	O	S	O	O	O	OH	OH
4922a-l	Y*EE	S	O	S	O	O	O	OMe	OH
4923a-l	Y*EE	S	O	S	O	O	O	H	OH
4924a-l	Y*EE	S	O	S	O	O	O	F	OH
4925a-l	Y*EE	S	O	S	O	O	O	OEt	OH

4926a-l	Y*EE	S	S	S	O	O	O	OH	OH
4927a-l	Y*EE	S	S	S	O	O	O	OMe	OH
4928a-l	Y*EE	S	S	S	O	O	O	H	OH
4929a-l	Y*EE	S	S	S	O	O	O	F	OH
4930a-l	Y*EE	S	S	S	O	O	O	OEt	OH
4931a-l	Y*EE	O	O	S	S	O	O	OH	OH
4932a-l	Y*EE	O	O	S	S	O	O	OMe	OH
4933a-l	Y*EE	O	O	S	S	O	O	H	OH
4934a-l	Y*EE	O	O	S	S	O	O	F	OH
4935a-l	Y*EE	O	O	S	S	O	O	OEt	OH
4936a-l	Y*EE	S	O	S	S	O	O	OH	OH
4937a-l	Y*EE	S	O	S	S	O	O	OMe	OH
4938a-l	Y*EE	S	O	S	S	O	O	H	OH
4939a-l	Y*EE	S	O	S	S	O	O	F	OH
4940a-l	Y*EE	S	O	S	S	O	O	OEt	OH
4941a-l	Y*EE	S	S	S	S	O	O	OH	OH
4942a-l	Y*EE	S	S	S	S	O	O	OMe	OH
4943a-l	Y*EE	S	S	S	S	O	O	H	OH
4944a-l	Y*EE	S	S	S	S	O	O	F	OH
4945a-l	Y*EE	S	S	S	S	O	O	OEt	OH
4946a-l	Y*EE	O	O	S	S	S	O	OH	OH
4947a-l	Y*EE	O	O	S	S	S	O	OMe	OH
4948a-l	Y*EE	O	O	S	S	S	O	H	OH
4949a-l	Y*EE	O	O	S	S	S	O	F	OH
4950a-l	Y*EE	O	O	S	S	S	O	OEt	OH
4951a-l	Y*EE	S	O	S	S	S	O	OH	OH
4952a-l	Y*EE	S	O	S	S	S	O	OMe	OH
4953a-l	Y*EE	S	O	S	S	S	O	H	OH
4954a-l	Y*EE	S	O	S	S	S	O	F	OH
4955a-l	Y*EE	S	O	S	S	S	O	OEt	OH
4956a-l	Y*EE	S	S	S	S	S	O	OH	OH
4957a-l	Y*EE	S	S	S	S	S	O	OMe	OH
4958a-l	Y*EE	S	S	S	S	S	O	H	OH
4959a-l	Y*EE	S	S	S	S	S	O	F	OH
4960a-l	Y*EE	S	S	S	S	S	O	OEt	OH
4961a-l	Y*EE	O	O	S	S	S	S	OH	OH
4962a-l	Y*EE	O	O	S	S	S	S	OMe	OH
4963a-l	Y*EE	O	O	S	S	S	S	H	OH
4964a-l	Y*EE	O	O	S	S	S	S	F	OH
4965a-l	Y*EE	O	O	S	S	S	S	OEt	OH
4966a-l	Y*EE	S	O	S	S	S	S	OH	OH
4967a-l	Y*EE	S	O	S	S	S	S	OMe	OH
4968a-l	Y*EE	S	O	S	S	S	S	H	OH
4969a-l	Y*EE	S	O	S	S	S	S	F	OH
4970a-l	Y*EE	S	O	S	S	S	S	OEt	OH
4971a-l	Y*EE	S	S	S	S	S	S	OH	OH
4972a-l	Y*EE	S	S	S	S	S	S	OMe	OH
4973a-l	Y*EE	S	S	S	S	S	S	H	OH
4974a-l	Y*EE	S	S	S	S	S	S	F	OH

4975a-l	Y*EE	S	S	S	S	S	S	OEt	OH
4976a-l	Y*EE	O	O	O	S	S	S	OH	OH
4977a-l	Y*EE	O	O	O	S	S	S	OMe	OH
4978a-l	Y*EE	O	O	O	S	S	S	H	OH
4979a-l	Y*EE	O	O	O	S	S	S	F	OH
4980a-l	Y*EE	O	O	O	S	S	S	OEt	OH
4981a-l	Y*EE	S	O	O	S	S	S	OH	OH
4982a-l	Y*EE	S	O	O	S	S	S	OMe	OH
4983a-l	Y*EE	S	O	O	S	S	S	H	OH
4984a-l	Y*EE	S	O	O	S	S	S	F	OH
4985a-l	Y*EE	S	O	O	S	S	S	OEt	OH
4986a-l	Y*EE	S	S	O	S	S	S	OH	OH
4987a-l	Y*EE	S	S	O	S	S	S	OMe	OH
4988a-l	Y*EE	S	S	O	S	S	S	H	OH
4989a-l	Y*EE	S	S	O	S	S	S	F	OH
4990a-l	Y*EE	S	S	O	S	S	S	OEt	OH
4991a-l	Y*EE	O	O	O	O	S	S	OH	OH
4992a-l	Y*EE	O	O	O	O	S	S	OMe	OH
4993a-l	Y*EE	O	O	O	O	S	S	H	OH
4994a-l	Y*EE	O	O	O	O	S	S	F	OH
4995a-l	Y*EE	O	O	O	O	S	S	OEt	OH
4996a-l	Y*EE	S	O	O	O	S	S	OH	OH
4997a-l	Y*EE	S	O	O	O	S	S	OMe	OH
4998a-l	Y*EE	S	O	O	O	S	S	H	OH
4999a-l	Y*EE	S	O	O	O	S	S	F	OH
5000a-l	Y*EE	S	O	O	O	S	S	OEt	OH
5001a-l	Y*EE	S	S	O	O	S	S	OH	OH
5002a-l	Y*EE	S	S	O	O	S	S	OMe	OH
5003a-l	Y*EE	S	S	O	O	S	S	H	OH
5004a-l	Y*EE	S	S	O	O	S	S	F	OH
5005a-l	Y*EE	S	S	O	O	S	S	OEt	OH
5006a-l	Y*EE	O	O	O	O	O	S	OH	OH
5007a-l	Y*EE	O	O	O	O	O	S	OMe	OH
5008a-l	Y*EE	O	O	O	O	O	S	H	OH
5009a-l	Y*EE	O	O	O	O	O	S	F	OH
5010a-l	Y*EE	O	O	O	O	O	S	OEt	OH
5011a-l	Y*EE	S	O	O	O	O	S	OH	OH
5012a-l	Y*EE	S	O	O	O	O	S	OMe	OH
5013a-l	Y*EE	S	O	O	O	O	S	H	OH
5014a-l	Y*EE	S	O	O	O	O	S	F	OH
5015a-l	Y*EE	S	O	O	O	O	S	OEt	OH
5016a-l	Y*EE	S	S	O	O	O	S	OH	OH
5017a-l	Y*EE	S	S	O	O	O	S	OMe	OH
5018a-l	Y*EE	S	S	O	O	O	S	H	OH
5019a-l	Y*EE	S	S	O	O	O	S	F	OH
5020a-l	Y*EE	S	S	O	O	O	S	OEt	OH
5021a-l	Y*EE	O	O	S	O	S	O	OH	OH
5022a-l	Y*EE	O	O	S	O	S	O	OMe	OH
5023a-l	Y*EE	O	O	S	O	S	O	H	OH

5024a-l	Y*EE	O	O	S	O	S	O	F	OH
5025a-l	Y*EE	O	O	S	O	S	O	OEt	OH
5026a-l	Y*EE	S	O	S	O	S	O	OH	OH
5027a-l	Y*EE	S	O	S	O	S	O	OMe	OH
5028a-l	Y*EE	S	O	S	O	S	O	H	OH
5029a-l	Y*EE	S	O	S	O	S	O	F	OH
5030a-l	Y*EE	S	O	S	O	S	O	OEt	OH
5031a-l	Y*EE	S	S	S	O	S	O	OH	OH
5032a-l	Y*EE	S	S	S	O	S	O	OMe	OH
5033a-l	Y*EE	S	S	S	O	S	O	H	OH
5034a-l	Y*EE	S	S	S	O	S	O	F	OH
5035a-l	Y*EE	S	S	S	O	S	O	OEt	OH
5036a-l	Y*EE	O	O	O	S	O	S	OH	OH
5037a-l	Y*EE	O	O	O	S	O	S	OMe	OH
5038a-l	Y*EE	O	O	O	S	O	S	H	OH
5039a-l	Y*EE	O	O	O	S	O	S	F	OH
5040a-l	Y*EE	O	O	O	S	O	S	OEt	OH
5041a-l	Y*EE	S	O	O	S	O	S	OH	OH
5042a-l	Y*EE	S	O	O	S	O	S	OMe	OH
5043a-l	Y*EE	S	O	O	S	O	S	H	OH
5044a-l	Y*EE	S	O	O	S	O	S	F	OH
5045a-l	Y*EE	S	O	O	S	O	S	OEt	OH
5046a-l	Y*EE	S	S	O	S	O	S	OH	OH
5047a-l	Y*EE	S	S	O	S	O	S	OMe	OH
5048a-l	Y*EE	S	S	O	S	O	S	H	OH
5049a-l	Y*EE	S	S	O	S	O	S	F	OH
5050a-l	Y*EE	S	S	O	S	O	S	OEt	OH
5051a-l	Y*EE	O	O	O	O	O	O	OH	OMe
5052a-l	Y*EE	O	O	O	O	O	O	OMe	OMe
5053a-l	Y*EE	O	O	O	O	O	O	H	OMe
5054a-l	Y*EE	O	O	O	O	O	O	F	OMe
5055a-l	Y*EE	O	O	O	O	O	O	OEt	OMe
5056a-l	Y*EE	S	O	O	O	O	O	OH	OMe
5057a-l	Y*EE	S	O	O	O	O	O	OMe	OMe
5058a-l	Y*EE	S	O	O	O	O	O	H	OMe
5059a-l	Y*EE	S	O	O	O	O	O	F	OMe
5060a-l	Y*EE	S	O	O	O	O	O	OEt	OMe
5061a-l	Y*EE	S	S	O	O	O	O	OH	OMe
5062a-l	Y*EE	S	S	O	O	O	O	OMe	OMe
5063a-l	Y*EE	S	S	O	O	O	O	H	OMe
5064a-l	Y*EE	S	S	O	O	O	O	F	OMe
5065a-l	Y*EE	S	S	O	O	O	O	OEt	OMe
5066a-l	Y*EE	O	O	S	O	O	O	OH	OMe
5067a-l	Y*EE	O	O	S	O	O	O	OMe	OMe
5068a-l	Y*EE	O	O	S	O	O	O	H	OMe
5069a-l	Y*EE	O	O	S	O	O	O	F	OMe
5070a-l	Y*EE	O	O	S	O	O	O	OEt	OMe
5071a-l	Y*EE	S	O	S	O	O	O	OH	OMe
5072a-l	Y*EE	S	O	S	O	O	O	OMe	OMe

5073a-l	Y*EE	S	O	S	O	O	O	H	OMe
5074a-l	Y*EE	S	O	S	O	O	O	F	OMe
5075a-l	Y*EE	S	O	S	O	O	O	OEt	OMe
5076a-l	Y*EE	S	S	S	O	O	O	OH	OMe
5077a-l	Y*EE	S	S	S	O	O	O	OMe	OMe
5078a-l	Y*EE	S	S	S	O	O	O	H	OMe
5079a-l	Y*EE	S	S	S	O	O	O	F	OMe
5080a-l	Y*EE	S	S	S	O	O	O	OEt	OMe
5081a-l	Y*EE	O	O	S	S	O	O	OH	OMe
5082a-l	Y*EE	O	O	S	S	O	O	OMe	OMe
5083a-l	Y*EE	O	O	S	S	O	O	H	OMe
5084a-l	Y*EE	O	O	S	S	O	O	F	OMe
5085a-l	Y*EE	O	O	S	S	O	O	OEt	OMe
5086a-l	Y*EE	S	O	S	S	O	O	OH	OMe
5087a-l	Y*EE	S	O	S	S	O	O	OMe	OMe
5088a-l	Y*EE	S	O	S	S	O	O	H	OMe
5089a-l	Y*EE	S	O	S	S	O	O	F	OMe
5090a-l	Y*EE	S	O	S	S	O	O	OEt	OMe
5091a-l	Y*EE	S	S	S	S	O	O	OH	OMe
5092a-l	Y*EE	S	S	S	S	O	O	OMe	OMe
5093a-l	Y*EE	S	S	S	S	O	O	H	OMe
5094a-l	Y*EE	S	S	S	S	O	O	F	OMe
5095a-l	Y*EE	S	S	S	S	O	O	OEt	OMe
5096a-l	Y*EE	O	O	S	S	S	O	OH	OMe
5097a-l	Y*EE	O	O	S	S	S	O	OMe	OMe
5098a-l	Y*EE	O	O	S	S	S	O	H	OMe
5099a-l	Y*EE	O	O	S	S	S	O	F	OMe
5100a-l	Y*EE	O	O	S	S	S	O	OEt	OMe
5101a-l	Y*EE	S	O	S	S	S	O	OH	OMe
5102a-l	Y*EE	S	O	S	S	S	O	OMe	OMe
5103a-l	Y*EE	S	O	S	S	S	O	H	OMe
5104a-l	Y*EE	S	O	S	S	S	O	F	OMe
5105a-l	Y*EE	S	O	S	S	S	O	OEt	OMe
5106a-l	Y*EE	S	S	S	S	S	O	OH	OMe
5107a-l	Y*EE	S	S	S	S	S	O	OMe	OMe
5108a-l	Y*EE	S	S	S	S	S	O	H	OMe
5109a-l	Y*EE	S	S	S	S	S	O	F	OMe
5110a-l	Y*EE	S	S	S	S	S	O	OEt	OMe
5111a-l	Y*EE	O	O	S	S	S	S	OH	OMe
5112a-l	Y*EE	O	O	S	S	S	S	OMe	OMe
5113a-l	Y*EE	O	O	S	S	S	S	H	OMe
5114a-l	Y*EE	O	O	S	S	S	S	F	OMe
5115a-l	Y*EE	O	O	S	S	S	S	OEt	OMe
5116a-l	Y*EE	S	O	S	S	S	S	OH	OMe
5117a-l	Y*EE	S	O	S	S	S	S	OMe	OMe
5118a-l	Y*EE	S	O	S	S	S	S	H	OMe
5119a-l	Y*EE	S	O	S	S	S	S	F	OMe
5120a-l	Y*EE	S	O	S	S	S	S	OEt	OMe
5121a-l	Y*EE	S	S	S	S	S	S	OH	OMe

5122a-l	Y*EE	S	S	S	S	S	S	OMe	OMe
5123a-l	Y*EE	S	S	S	S	S	S	H	OMe
5124a-l	Y*EE	S	S	S	S	S	S	F	OMe
5125a-l	Y*EE	S	S	S	S	S	S	OEt	OMe
5126a-l	Y*EE	O	O	O	S	S	S	OH	OMe
5127a-l	Y*EE	O	O	O	S	S	S	OMe	OMe
5128a-l	Y*EE	O	O	O	S	S	S	H	OMe
5129a-l	Y*EE	O	O	O	S	S	S	F	OMe
5130a-l	Y*EE	O	O	O	S	S	S	OEt	OMe
5131a-l	Y*EE	S	O	O	S	S	S	OH	OMe
5132a-l	Y*EE	S	O	O	S	S	S	OMe	OMe
5133a-l	Y*EE	S	O	O	S	S	S	H	OMe
5134a-l	Y*EE	S	O	O	S	S	S	F	OMe
5135a-l	Y*EE	S	O	O	S	S	S	OEt	OMe
5136a-l	Y*EE	S	S	O	S	S	S	OH	OMe
5137a-l	Y*EE	S	S	O	S	S	S	OMe	OMe
5138a-l	Y*EE	S	S	O	S	S	S	H	OMe
5139a-l	Y*EE	S	S	O	S	S	S	F	OMe
5140a-l	Y*EE	S	S	O	S	S	S	OEt	OMe
5141a-l	Y*EE	O	O	O	O	S	S	OH	OMe
5142a-l	Y*EE	O	O	O	O	S	S	OMe	OMe
5143a-l	Y*EE	O	O	O	O	S	S	H	OMe
5144a-l	Y*EE	O	O	O	O	S	S	F	OMe
5145a-l	Y*EE	O	O	O	O	S	S	OEt	OMe
5146a-l	Y*EE	S	O	O	O	S	S	OH	OMe
5147a-l	Y*EE	S	O	O	O	S	S	OMe	OMe
5148a-l	Y*EE	S	O	O	O	S	S	H	OMe
5149a-l	Y*EE	S	O	O	O	S	S	F	OMe
5150a-l	Y*EE	S	O	O	O	S	S	OEt	OMe
5151a-l	Y*EE	S	S	O	O	S	S	OH	OMe
5152a-l	Y*EE	S	S	O	O	S	S	OMe	OMe
5153a-l	Y*EE	S	S	O	O	S	S	H	OMe
5154a-l	Y*EE	S	S	O	O	S	S	F	OMe
5155a-l	Y*EE	S	S	O	O	S	S	OEt	OMe
5156a-l	Y*EE	O	O	O	O	O	S	OH	OMe
5157a-l	Y*EE	O	O	O	O	O	S	OMe	OMe
5158a-l	Y*EE	O	O	O	O	O	S	H	OMe
5159a-l	Y*EE	O	O	O	O	O	S	F	OMe
5160a-l	Y*EE	O	O	O	O	O	S	OEt	OMe
5161a-l	Y*EE	S	O	O	O	O	S	OH	OMe
5162a-l	Y*EE	S	O	O	O	O	S	OMe	OMe
5163a-l	Y*EE	S	O	O	O	O	S	H	OMe
5164a-l	Y*EE	S	O	O	O	O	S	F	OMe
5165a-l	Y*EE	S	O	O	O	O	S	OEt	OMe
5166a-l	Y*EE	S	S	O	O	O	S	OH	OMe
5167a-l	Y*EE	S	S	O	O	O	S	OMe	OMe
5168a-l	Y*EE	S	S	O	O	O	S	H	OMe
5169a-l	Y*EE	S	S	O	O	O	S	F	OMe
5170a-l	Y*EE	S	S	O	O	O	S	OEt	OMe

5171a-l	Y*EE	O	O	S	O	S	O	OH	OMe
5172a-l	Y*EE	O	O	S	O	S	O	OMe	OMe
5173a-l	Y*EE	O	O	S	O	S	O	H	OMe
5174a-l	Y*EE	O	O	S	O	S	O	F	OMe
5175a-l	Y*EE	O	O	S	O	S	O	OEt	OMe
5176a-l	Y*EE	S	O	S	O	S	O	OH	OMe
5177a-l	Y*EE	S	O	S	O	S	O	OMe	OMe
5178a-l	Y*EE	S	O	S	O	S	O	H	OMe
5179a-l	Y*EE	S	O	S	O	S	O	F	OMe
5180a-l	Y*EE	S	O	S	O	S	O	OEt	OMe
5181a-l	Y*EE	S	S	S	O	S	O	OH	OMe
5182a-l	Y*EE	S	S	S	O	S	O	OMe	OMe
5183a-l	Y*EE	S	S	S	O	S	O	H	OMe
5184a-l	Y*EE	S	S	S	O	S	O	F	OMe
5185a-l	Y*EE	S	S	S	O	S	O	OEt	OMe
5186a-l	Y*EE	O	O	O	S	O	S	OH	OMe
5187a-l	Y*EE	O	O	O	S	O	S	OMe	OMe
5188a-l	Y*EE	O	O	O	S	O	S	H	OMe
5189a-l	Y*EE	O	O	O	S	O	S	F	OMe
5190a-l	Y*EE	O	O	O	S	O	S	OEt	OMe
5191a-l	Y*EE	S	O	O	S	O	S	OH	OMe
5192a-l	Y*EE	S	O	O	S	O	S	OMe	OMe
5193a-l	Y*EE	S	O	O	S	O	S	H	OMe
5194a-l	Y*EE	S	O	O	S	O	S	F	OMe
5195a-l	Y*EE	S	O	O	S	O	S	OEt	OMe
5196a-l	Y*EE	S	S	O	S	O	S	OH	OMe
5197a-l	Y*EE	S	S	O	S	O	S	OMe	OMe
5198a-l	Y*EE	S	S	O	S	O	S	H	OMe
5199a-l	Y*EE	S	S	O	S	O	S	F	OMe
5200a-l	Y*EE	S	S	O	S	O	S	OEt	OMe

[0540] In some embodiments, disclosed herein is a pharmaceutically acceptable salt or pharmaceutically acceptable solvate or a pharmaceutical composition comprising one or more mRNA(s) which is/are produced/manufactured from one or more sequence initiator compound selected from Table 3.

[0541] In another aspect, described herein is a complex comprising an IVT mRNA sequence initiator and a DNA template, wherein the IVT mRNA sequence initiator comprises a compound described herein, wherein (a) the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1, a second nucleotide at nucleotide position +2, and a third nucleotide at nucleotide position +3; and (b) wherein the IVT mRNA sequence initiator is hybridized to the DNA template at least at nucleotide positions +1, +2, and +3.

[0542] In another aspect, described herein is a complex comprising an IVT mRNA sequence

initiator and a DNA template, wherein the IVT mRNA sequence initiator comprises a compound described herein, wherein (a) the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1 and a second nucleotide at nucleotide position +2; and (b) wherein the IVT mRNA sequence initiator is hybridized to the DNA template at least at nucleotide positions +1 and +2.

Pharmaceutical Compositions

[0543] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[0544] A pharmaceutical composition can be a mixture of a sequence initiator compound described herein with one or more other chemical components (i.e. pharmaceutically acceptable ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to an organism.

[0545] The compositions described herein can be administered to the subject in a variety of ways, including parenterally, intravenously, intradermally, intramuscularly, colonically, rectally or intraperitoneally. In some embodiments, the sequence initiator compound described herein or a pharmaceutically acceptable salt thereof is administered by intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject. In some embodiments, the pharmaceutical compositions can be administered parenterally, intravenously, intramuscularly or orally. The oral agents comprising a sequence initiator compound described herein can be in any suitable form for oral administration, such as liquid, tablets, capsules, or the like. The oral

formulations can be further coated or treated to prevent or reduce dissolution in stomach. The compositions of the present disclosure can be administered to a subject using any suitable methods known in the art. Suitable formulations for use in the present disclosure and methods of delivery are generally well known in the art. For example, the sequence initiator compound described herein can be formulated as pharmaceutical compositions with a pharmaceutically acceptable diluent, carrier or excipient. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions including pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, such as, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

[0546] Pharmaceutical formulations described herein can be administrable to a subject in a variety of ways by multiple administration routes, including but not limited to, oral, parenteral (*e.g.*, intravenous, subcutaneous, intramuscular, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intralymphatic, intranasal injections), intranasal, buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[0547] In some embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulations containing a sequence initiator compound described herein are in the form of a capsule. In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions or solutions selected from the group including, but not limited to, aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups.

[0548] For administration by inhalation, a sequence initiator compound described herein can be formulated for use as an aerosol, a mist or a powder. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner. In some embodiments, a sequence initiator compound described herein can be prepared as transdermal dosage forms. In some embodiments, a sequence initiator compound described herein can be formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection. In some embodiments, a sequence initiator compound described herein can be administered topically and can be formulated into a variety of topically administrable

compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. In some embodiments, a sequence initiator compound described herein can be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas.

[0549] In one aspect, described herein is a pharmaceutical composition comprising an RNA molecule comprising the IVT mRNA sequence initiator disclosed herein and one or more of pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises lipid nanoparticles. In some embodiments, the RNA is encapsulated in an lipid nanoparticle.

Transcription

[0550] In Eukaryotes, transcription of messenger RNAs (mRNAs) is done by RNA polymerase II. This is a complicated multi-subunit enzyme with complex regulation. To carry out large scale transcription in vitro, researches commonly use single subunit phage polymerases derived from T7, T3, SP6, K1-5, K1E, K1F or K11 bacteriophages. This family of polymerases has simple, minimal promoter sequences of ~17 nucleotides which require no accessory proteins and have minimal constraints of the initiating nucleotide sequence. While this application focuses on T7 RNA Polymerase (T7 RNAP), one skilled in the art would understand that this disclosure could be practiced with other RNA polymerases.

[0551] T7 RNAP exists in at least two protein states. The first is referred to as the “abortive complex” and is associated with transcriptional initiation. The second is a very processive conformation called the “elongation complex”. In vitro transcription can be broken into six steps: 1) binding of the RNA polymerase to the promoter sequence, 2) initiation of transcription, 3) non-processive elongation termed abortive transcription during which the polymerase frequently releases the DNA template and short abortive transcripts 4) conversion of the open complex to the closed complex, 5) processive elongation and 6) transcriptional termination. A significant amount of RNA produced during transcription consists of short abortive fragments of ~2-8 nucleotides in length (Biochemistry 19:3245-3253 (1980); Nucleic Acids Res. 9:31-45 (1981); Nucleic Acids Res. 15:8783-8798 (1987); Biochemistry 27:3966-3974 (1988)). After synthesis of about 10-14 bases, RNA polymerases escape from abortive cycling, at the same time losing sequence-specific contacts with the promoter DNA, and forming a processive elongation complex, in which the RNA chain is extended in a sequence-independent manner (*J. Mol. Biol.* 183:165-177 (1985); *Proc. Natl. Acad. Sci. U.S.A.* 83:3614-3618 (1986); *Mol. Cell Biol.* 7:3371-3379 (1987)).

[0552] The consensus sequence for the most active Class III T7 promoters encompasses 17 bp

of sequence upstream, and 6 bp downstream, of the transcription start site (*Cell* 16:815-25. (1979)). The position of the first transcribed nucleotide is commonly referred to as the +1 transcript nucleotide of the RNA, the second transcribed nucleotide as +2 transcript nucleotide and so on (Table 2). During transcription, the two strands are melted to form a transcription bubble and the bottom strand of the duplex (shown 3' to 5' in Table 4) is the template for transcription. For transcript nucleotides +3 and beyond, the template strand defines the identity of the transcribed nucleotides primarily through Watson-Crick base pairing interactions. Here the nucleotide encoding the first RNA transcript nucleotide is defined as the +1 nucleotide of the template. In the example shown in Table 4, the +1 transcript nucleotide is G and the +1 template nucleotide is C. Likewise the +4 transcript nucleotide is A and the +4 template nucleotide is T.

Table 4

Position in transcript		+1+2+3+4+5+6	
Transcript sequence		pppGGGAGA	
Promoter top strand	5'--TAATACGACTCACTATAGGGAGA.		..-3' SEQ ID NO.1
Promoter bottom strand	3'--ATTATGCTGAGTGATATCCCTCT.		..-5' SEQ ID NO.2
Position in template		+1+2+3+4+5+6	

[0553] Unlike DNA polymerases, T7 RNAP initiates RNA synthesis in the absence of a primer. The first step in initiation is called de novo RNA synthesis, in which RNA polymerase recognizes a specific sequence on the DNA template, selects the first pair of nucleotide triphosphates complementary to template residues at positions +1 and +2, and catalyzes the formation of a phosphodiester bond to form a dinucleotide. The initiating nucleotides have lower affinities for the polymerase than those used during elongation. The K_d value is 2 mM for the first initiating NTP and 80 μM for the second, whereas the K_d is approximately 5 μM for NTPs during elongation (*J. Mol. Biol.* (2007) 370, 256-268). It has been found that de novo synthesis is the rate-limiting step during transcription. T7 RNAP exhibits a strong bias for GTP as the initiating nucleotide (*J. Biol. Chem.* 248: 2235-2244 (1973)). Among the 17 T7 promoters in the genome, 15 initiate with GTP (and 13 with pppGpG), whereas there is no obvious NTP preference during transcription elongation (*J. Mol. Biol.* 370:256-268 (2007)). T7 RNA polymerase initiates poorly on promoters encoding A at position +1; transcription instead initiates predominantly with an encoded G at position +2 (*J. Biol. Chem.* 278:2819-2823 (2003)).

[0554] During de novo RNA synthesis, binding of the initiating nucleotides is achieved primarily by the free energy created from base stacking, specific interactions between the polymerase residues, the guanine moieties of the initiating nucleotides and base complementarity interactions (*J. Mol. Biol.* 370:256-268 (2007)).

[0555] It is known that T7 RNAP can also initiate with short oligonucleotide primers. For example, it is known that 13 promoters in the T7 genome initiate with pppGpG (*J. Mol. Biol.* 370:256-268 (2007)). Several groups showed that T7 RNAP can initiate from dinucleotide primers (*Biochemistry* 24:5716-5723 (1985)). Axelrod et al. showed that an uncapped GpA dinucleotide could initiate from +1 and +2 template nucleotides that were 2'-deoxycytidine and 2'-deoxythymidine, respectively ("CT" template). Their reaction conditions were 200 micromolar (μ M) dimer and 100 μ M ATP, CTP, GTP and UTP. Their reaction mixture also contained 100 μ M 3' dATP, 3' dCTP 3' dUTP or 50 μ M 3' dGTP. They observe only GpA initiated RNAs and not a mixture of GpA initiated RNAs and 5' triphosphate RNAs from GTP initiation. This is likely due to the reaction conditions employed. 100 μ M GTP is well below the 2 mM K_d of T7 polymerase for the first initiating guanosine (*J. Mol. Biol.* (2007) 370, 256-268). Since GTP competes for initiation with the initiating oligonucleotide, using a low GTP concentration favors GpA initiation but results in low transcription yield (maximum calculated yield estimated to be <150 μ g/mL of reaction). When initiating transcription on "CT" template with ApG, CpG, UpG or GpG, they observed formation of RNA transcripts with an additional untemplated 5' nucleotide (A, C, U or G, respectively).

[0556] The methods and compositions provided herein for preparation of 5'-capped RNA include, but are not limited to, mRNA, small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), small cajal body-specific RNA (scaRNA). These methods involve the use of a mRNA sequence initiator, for example, Cap containing oligonucleotide primers, along with nucleoside 5'-triphosphates (NTPs) and RNA polymerase for DNA-templated and promoter controlled synthesis of RNA. In certain aspects, the methods use an initiating capped oligonucleotide primer that provides utility in RNA synthesis, in particular synthesis of capped mRNAs. The exemplary initiating oligonucleotide primer has a structure that resembles Cap 0, Cap 1, Cap 2 or TMG-Cap of natural RNA molecules, which include 2'-O-methylated nucleoside units at, penultimate Cap 1 and next to penultimate Cap 2 5'-positions of RNA. The natural Cap 0 structure does not have 2'-O-methylated nucleoside units.

[0557] The methods and compositions for preparation of RNA including, but not limited to, mRNA, snRNA, snoRNA, scaRNA, transfer RNA (tRNA), ribosomal RNA (rRNA), and transfer-messenger RNA (tmRNA) that carry modifications at or near 5'-end of the molecule. These methods involve the use of initiators, e.g. initiating oligonucleotide primers with or without Cap, nucleoside 5'-triphosphates (NTPs) and RNA polymerase for DNA-templated and promoter controlled synthesis of RNA. In certain aspects, the methods use a modified initiating oligonucleotide primer carrying structural modifications that provide utility in RNA synthesis; in

particular synthesis of 5'-modified RNAs.

[0558] An exemplary initiating capped oligonucleotide primer has an open 3'-OH group that allows for initiation of RNA polymerase mediated synthesis of RNA on a DNA template by adding nucleotide units to the 3'-end of the primer. The initiating capped oligonucleotide primer is substantially complementary to template DNA sequence at the transcription initiation site (i.e., the initiation site is located closer to 3'-terminus of a promoter sequence and may overlap with promoter sequence). In certain embodiments, the initiating capped oligonucleotide primer directs synthesis of RNA predominantly in one direction ("forward") starting from the 3'-end of the primer. In certain aspects and embodiments, the initiating capped oligonucleotide primer outcompetes any nucleoside 5'-triphosphate for initiation of RNA synthesis, thereby maximizing the production of the RNA that starts with initiating capped oligonucleotide primer and minimizing a production of RNA that starts with 5'-triphosphate-nucleoside (typically GTP).

[0559] The manufacture of mRNA by in vitro transcription utilizes highly active phage RNA polymerases (T3, T7, SP6 and others). RNA polymerase works under control of specific promoter which is incorporated in DNA plasmid construct in front of a template nucleotide sequence. Transcription process usually starts with purine nucleoside 5'-triphosphate (typically GTP) and continues until the RNA polymerase encounters a terminating sequence or completes the DNA template.

[0560] As discussed above, mCAP dinucleotide analogs, $^7\text{mG}(5')\text{ppp}(5')\text{N}$, that contain Cap 0 have been used for initiation in vitro transcription (e.g., RNA 1: 957-967 (1995)). The capped RNA molecules produced using these dinucleotide analogs contain Cap 0. However only about 50% of synthesized capped RNA molecules have the correct "forward" orientation of Cap 0. To convert RNA with Cap 0 to RNA with Cap 1 an additional enzymatic reaction must be preformed using (nucleoside-2'-O) methyltransferase. However this conversion may be not quantitative; it is not easy to control and it is difficult to separate the remaining Cap 0 RNAs from Cap 1 RNAs. In addition, the competition from NTPs (specifically GTP) for initiation transcription further reduces the quantity of active capped RNA molecules produced.

[0561] In addition, modified dinucleotide analogs, such as $^7\text{mG}_{3'\text{Ome}}(5')\text{ppp}(5')\text{N}$ and other related ARCA analogs, that carry modified ^7mG residue with blocked 3' and/or 2' position on ribose, have been used for initiation of in vitro transcription (e.g., RNA 7:1486-1495 (2001)). These ARCA cap analogs direct RNA synthesis only in the "forward" orientation and therefore produce a RNA molecule with (natural) Cap 0 on the 5'-terminus (having 2' and/or 3' modifications to ^7mG residue). Such RNAs are more active in translation systems compared to RNAs prepared using standard dinucleotide analogs, $^7\text{mG}(5')\text{ppp}(5')\text{N}$. To convert RNA with ARCA Cap 0 to RNA with

ARCA Cap 1 an additional enzymatic reaction must be performed with (nucleoside-2'-O) methyltransferase similar to that required for the dinucleotide analogs previously discussed. This method has the same disadvantages as that elaborated for the mCAP dinucleotide analogs; the conversion of RNA with Cap 0 to RNA with ARCA Cap 1 may be not quantitative; the reaction is not easy to control, it is difficult to separate remaining Cap 0 RNAs from Cap 1 RNAs and competition from NTPs (specifically GTP) for initiation of transcription further reduces the quantity of active capped RNA molecules produced.

[0562] Short oligonucleotide primers (2 to 6-mer) with 3'-terminal guanosine residue have been used for initiation of in vitro transcription (Pitulle, C. et al., *Gene*, 112:101-105 (1992)). These oligonucleotide primers contained modified and unmodified ribonucleoside residues (e.g., modified ribonucleoside residues included 2'-O-methylated nucleoside residues and 2'-deoxyribonucleoside residues). The shorter oligonucleotide primers (dimers to tetramer) substantially out-compete GTP for initiation of transcription while longer primers (pentamer to hexamer) are much less efficient in initiation of transcription compared to GTP. It may be because these longer primers (as they are designed) have a low percent of complementarity with DNA template at initiation site. In contrast, dimer, AG (as designed), was complementary to the DNA template at initiation site. The RNA molecules produced using oligonucleotide primers, discussed in this section, had internal 2'-O-methylated nucleoside but did not contain 5'-Cap 0, Cap 1, Cap 2 or TMG-cap. To convert RNA without cap structure to RNA with Cap 1, Cap 2 or TMG-cap structure an additional enzymatic reactions using capping enzymes would have to be performed. However such conversion has the same disadvantages as those stated above.

[0563] Other short RNA oligonucleotides containing cap structures and internal 2'-O-methylated nucleoside residues have been chemically prepared (Ohkubo et al., *Org. Letters* 15:4386-4389 (2013)). These short capped oligonucleotides were ligated with a "decapitated" (without 5'-cap structure) fragment of long RNA using T4 DNA ligase and a complementary DNA splinter oligonucleotide. The final RNA synthesized using this chemical-enzymatic method had both internal 2'-O-methylated nucleoside residues and 5'-TMG-cap structure. However only short capped RNAs (<200-mer) were prepared using this ligation approach. Moreover, the yields were low (15-30%). It is not easy to control and optimize the T4 DNA ligation reaction and it requires a laborious separation process using PolyAcrylamide Gel Electrophoresis and isolation of capped RNAs from remaining uncapped RNAs. Separation of long (500-10000 bases) capped mRNAs from remaining uncapped mRNAs by PAGE method is not feasible.

[0564] Finally, 5'-modified nucleoside or 5'-modified mononucleotide or 5'-modified

dinucleotide, typically a derivative of guanosine, have been used for initiating in vitro transcription of RNA (*Gene*, 112:101-105 (1992) and *Bioconjug. Chem.*, 10371-378 (1999)). These initiator nucleosides and nucleotides may carry labels or affinity groups (e.g. biotin) and, when incorporated on the 5'-end of RNA, would allow for easy detection, isolation and purification of synthesized RNA. This 5'-labeled or tagged RNAs may be necessary for some applications. However this strategy was not used for the preparation of mRNA with Cap 0, Cap 1, Cap 2 or TMG-cap structures.

[0565] In certain aspects of the present disclosure, compositions of the capped mRNA sequence initiators as described herein are provided. In related aspects, are methods in which RNA is synthesized using capped mRNA sequence initiators described herein.

mRNA Sequence Initiators

[0566] Provided herein are mRNA sequence initiators that may be used for RNA synthesis. mRNA sequence initiators may have a hybridization sequence which may be complementary to a sequence on DNA template at initiation site. In some embodiments, the length of the hybridization sequence of the initiators for use in the methods and compositions provided herein depends on several factors including the identity of template nucleotide sequence and the temperature at which this initiator is hybridized to DNA template or used during in vitro transcription. Determination of the desired length of a specific nucleotide sequence of a capped initiator for use in transcription can be easily determined by a person of ordinary skill in the art or by routine experimentation. For example, the length of a nucleic acid or oligonucleotide may be determined based on a desired hybridization specificity or selectivity.

[0567] mRNA sequence initiators may be capped oligonucleotide primers. In some embodiments, the nucleotide length of initiating capped oligonucleotide primer (including the inverted 5'-5' Cap nucleotide) is between 3 to about 9, in some embodiments the nucleotide length of initiating capped oligonucleotide primer (including Cap) is between 3 to about 7, in some embodiments the nucleotide length of initiating capped oligonucleotide primer (including Cap) is between 3 to about 5, and in some embodiments the nucleotide length of initiating capped oligonucleotide primer (including Cap) is about 3. The length of hybridization sequence within an initiator, e.g., an initiating capped oligonucleotide primer may be equal to or shorter than the total length of the initiating capped oligonucleotide primer.

[0568] The presence of hybridization sequence forces an initiator, e.g. an initiating capped oligonucleotide primer, to predominantly align with complementary sequence of the DNA template at the initiation site in only the desired orientation (i.e., the "forward" orientation). In some

embodiments, in the forward orientation, the RNA transcript begins with the inverted guanosine residue. The dominance of the forward orientation of primer alignment on DNA template over incorrect “reverse” orientation is maintained by the thermodynamics of the hybridization complex. The latter may be determined by the length of the hybridization sequence of initiating capped oligonucleotide primer and the identity of bases involved in hybridization with DNA template. Hybridization in the desired forward orientation may also depend on the temperature and reaction conditions at which DNA template and initiating capped oligonucleotide primer are hybridized or used during in vitro transcription.

[0569] An exemplary initiator, e.g., an initiating capped oligonucleotide primer of the present disclosure enhances efficacy of initiation of transcription compared to efficacy of initiation with standard GTP, ATP, CTP or UTP. In some embodiments, initiation of transcription is considered enhanced when synthesis of RNA starts predominantly from initiating capped oligonucleotide primer and not from any NTP in transcription mixture. The enhanced efficiency of initiation of transcription results in a higher yield of RNA transcript. The enhanced efficiency of initiation of transcription may be increased to about 10%, about 20%, about 40%, about 60%, about 80%, about 90%, about 100%, about 150%, about 200% or about 500% over synthesis of RNA with conventional methods without initiating capped primer. In certain embodiments, a capped mRNA sequence initiator, e.g. an initiating capped oligonucleotide primer, out-competes any NTP (including GTP) for initiation of transcription. One of ordinary skill in the art is able to readily determine the level of substrate activity and efficacy of initiating capped oligonucleotide primers. One example of a method of determining substrate efficacy is illustrated in Example 13). In certain embodiments, initiation takes place from a capped oligonucleotide primer rather than an NTP, which results in a higher level of capping of the transcribed mRNA.

[0570] In some aspects, methods are provided in which RNA is synthesized utilizing an initiating capped oligonucleotide primer that has substitutions or modifications. In some aspects, the substitutions and modifications of an initiating capped oligonucleotide primer do not substantially impair the synthesis of RNA. Routine test syntheses can be preformed to determine if desirable synthesis results can be obtained with the modified initiating capped oligonucleotide primers. Those skilled in the art can perform such routine experimentation to determine if desirable results can be obtained. The substitution or modification of initiating capped oligonucleotide primer include for example, one or more modified nucleoside bases, one or more modified sugars, one or more modified internucleotide linkage and/or one or more modified triphosphate bridges.

[0571] An initiator, for example, a modified initiating capped oligonucleotide primer, which may include one or more modification groups of the methods and compositions provided herein,

can be elongated by RNA polymerase on DNA template by incorporation of NTP onto open 3'-OH group. An initiating capped oligonucleotide primer may include natural RNA and DNA nucleosides, modified nucleosides or nucleoside analogs. The initiating capped oligonucleotide primer may contain natural internucleotide phosphodiester linkages or modifications thereof, or combination thereof.

[0572] In one embodiment the modification group may be a thermally labile group which dissociates from a modified initiating capped oligonucleotide primer at an increasing rate as the temperature of the enzyme reaction medium is raised. Examples of thermally labile groups for oligonucleotides and NTPs are described in *Nucleic Acids Res.*, 36:e131 (2008), *Collect. Symp. Ser.*, 10:259-263 (2008) and *Analytical Chemistry*, 81:4955-4962 (2009).

[0573] In some aspects, methods are provided in which RNA is synthesized where at least one or more NTP is added to a transcription reaction may have a modification as disclosed herein. In some aspects, the modification of the at least one NTP does not substantially impair RNA polymerase mediated synthesis of RNA. The modification of NTP may include for example, one or more modified nucleoside bases, one or more modified sugars, one or more modified 5'-triphosphate. The modified NTP may incorporate onto the 3'-end of an initiating capped oligonucleotide primer and it does not block transcription and supports further elongation of the primer.

[0574] In another embodiment, the modification group of an initiating capped oligonucleotide primer may be a detectable label or detectable marker. Thus, following transcription, the target RNA, containing the detectable label or marker, can be identified by size, mass, color and/or affinity capture. In some embodiments, the detectable label or marker is a fluorescent dye; and the affinity capture label is biotin. In certain embodiments, one or more components of a transcription reaction (initiating capped oligonucleotide primer and/or NTPs) may be labeled with a detectable label or marker. Thus, following transcription, the RNA molecule can be identified, for example, by size, mass, affinity capture or color. In some embodiments, the detectable label is a fluorescent dye; and the affinity capture label is biotin.

[0575] Standard chemical and enzymatic synthesis methods may be utilized to synthesize mRNA sequence initiators of the present disclosure and are disclosed herein in the Examples section.

Kits

[0576] Kits including mRNA sequence initiators for performing transcription are also contemplated. For example, kits may contain all transcription reagents for synthesis of common

RNAs (e.g., FLuc mRNA). More specifically, a kit may contain: a mRNA sequence initiator; a container marked for transcription; instructions for performing RNA synthesis; and one or more reagents selected from the group consisting of one or more modified or unmodified initiating capped oligonucleotide primers, one or more unmodified NTPs, one or more modified NTPs (e.g., pseudouridine 5'-triphosphate), an RNA polymerase, other enzymes, a reaction buffer, magnesium and a DNA template.

[0577] mRNA sequence initiators of the present disclosure have a significant advantage over current methods and compositions involving use of various initiating nucleosides, nucleotides and oligonucleotides or use of polyphosphate dinucleotide derivatives containing Cap 0 structure, such as mCAP and ARCA. A mRNA sequence initiator, e.g., an initiating capped oligonucleotide primer may be compatible with existing transcription systems and reagents and no additional enzymes or reagents are required. In addition, the use of initiating capped oligonucleotide primers makes several non-enzymatic and enzymatic steps (such as capping and 2'-O-methylation) unnecessary thus reducing complexity of the process and a cost of RNA synthesis.

[0578] While the exemplary methods described herein relate to T7 RNA polymerase mediated transcription reaction, a number of other RNA polymerases known in the art for use in transcription reactions may be utilized with the compositions and methods of the present disclosure. Other enzymes, including natural or mutated variants that may be utilized include, for example, SP6 and T3 RNA polymerases and RNA polymerases from other sources including thermostable RNA polymerases.

[0579] Some nucleic acid replication and amplification methods may include transcription as a part of the process. Among these methods are: transcription mediated amplification (TMA) and nucleic acid sequence-based amplification (NASBA), DNA and RNA sequencing and other nucleic acid extension reactions known in the art. The skilled artisan will understand that other methods may be used either in place of, or together with, transcription methods, including variants of transcription reactions developed in the future.

Therapeutic Uses

[0580] In one aspect, described herein is a method for reducing the risk of coronary disease in a subject in need thereof, comprising administering to the subject an effective amount of a pharmaceutical composition described herein.

[0581] In one aspect, described herein is the production of mRNAs containing a capped mRNA sequence initiator, e.g., an initiation capped oligonucleotide primer for use as therapeutic agents in a pharmaceutical composition, the introduction of RNAs containing the capped initiator into cells to

treat a medical condition of the cells or the introduction of RNAs containing the capped initiator into cells that utilize those RNAs to produce proteins that may have a therapeutic affect on the host cells.

[0582] One method for treating a condition utilizing an RNA containing capped initiator comprises the step of administering the RNA containing the capped initiator described herein or a composition comprising such RNA to a subject having, or suspected of having a condition whose symptoms/symptomologies may be reduced in severity or eliminated.

[0583] An RNA containing a capped initiator as described herein, when formulated in a pharmaceutically acceptable carrier and/or pharmaceutically acceptable salt at a concentration of 4 mg/ml or less, is effective to produce a reduction of the symptoms and/or symptomologies by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater than an untreated individual with the pharmaceutically acceptable carrier alone.

[0584] Pharmaceutical compositions may be formulated for administration by injection or other appropriate routes known to those skilled in the art for treating a particular condition. An injectable composition for parenteral administration typically contains the active compound in a suitable solution and/or pharmaceutical carrier such as sterile physiological saline. The composition may also be formulated as a suspension in a lipid or phospholipid, in a liposomal suspension, or in an aqueous emulsion.

[0585] Methods for preparing a variety of compositions and/or formulations are known to those skilled in the art see Remington's Pharmaceutical Sciences (19th Ed., Williams & Wilkins, 1995). The composition to be administered will contain a quantity of the selected compound in a pharmaceutically safe and effective amount for increasing expression of the desired protein in the target cells or tissue.

[0586] In some embodiments, the pharmaceutical composition contains at least 0.1% (w/v) of the compound, as described above, in some embodiments, the pharmaceutical composition contains greater than 0.1%, in some embodiments, the pharmaceutical composition contains up to about 10%, in some embodiments, the pharmaceutical composition contains up to about 5%, and in some embodiments, the pharmaceutical composition contains up to about 1% (w/v) of the compound. Choice of a suitable concentration depends on factors such as the desired dose, frequency and method of delivery of the active agent.

[0587] For treatment of a subject, such as a mammal or a human, dosages are determined based on factors such as the weight and overall health of the subject, the condition treated, severity of symptoms, etc. Dosages and concentrations are determined to produce the desired benefit while avoiding any undesirable side effects. Typical dosages of the subject compounds are in the range of

about 0.0005 to 500 mg/day for a human patient, and ranging in some embodiments between about 1-100 mg/day. For example, higher dose regimens include e.g. 50-100, 75-100, or 50-75 mg/day, and lower dose regimens include e.g. 1-50, 25-50, or 1-25 mg/day.

RNA Modification

[0588] Provided herein are RNA molecules modified with initiators, e.g. initiating capped oligonucleotide primers described herein suitable for targeted ex vivo and in vivo delivery systems. A modified RNA molecule may comprise two or more linked ribonucleic acid subunits. Non-limiting exemplary modified RNAs include CRISPR guide RNA, short interfering RNA (siRNA), microRNA (miRNA), short hairpin RNA (shRNA), small nuclear RNA (snRNA), messenger RNA (mRNA), precursor mRNA (pre-mRNA), antisense RNA (asRNA), and heteronuclear RNA (hnRNA). Modified RNAs as described herein encompass both the RNA sequence and any structural embodiment thereof, e.g. single stranded, double stranded, triple stranded, circular, helical, hairpin, stem loop, buldge, etc. A modified RNA may comprise a length of at least about 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 100, 200, 300, 400, or 500 bases. A modified RNA may comprise a length of at least about 1 kilobase (kb), 2kb, 3kb, 4 kb, 5 kb, 10 kb, 20kb, 50 kb, or more. In some embodiments, the modified RNA is a CRISPR guide RNA (gRNA). A gRNA may be a single guide RNA or a dual guide RNA. In some embodiments, the modified RNA is a mRNA. In some embodiments, a mRNA can be isolated from a cell or a tissue. In some embodiments, a mRNA can be transcribed from a DNA. In some embodiments, a mRNA can be chemically synthesized.

[0589] In certain embodiments, modified RNA molecules provided herein are resistant to degradation by RNases or other exonucleases. In certain embodiments, modified RNA molecules provided herein are stabilized to prevent degradation by endonucleases. In some embodiments, modified RNA molecules provided herein are suitable for in vivo delivery and induces less cellular immune receptor activation (e.g. TLR, RIG-I) as compared to unmodified RNA. RNA modifications as described in Diebold (2008) *Adv Drug Deliv Rev.* Apr 29;60(7):813-23) and Sorrentino (1998) *Cell Mol Life Sci.* Aug;54(8):785-94, the entirety of both are incorporated herein by reference.

[0590] The nucleotides as described herein can be synthetic or chemically modified. For example, guide RNAs provided herein can be synthetic or chemically modified guide RNAs. The nucleotides in the guide RNA that are modified may be those corresponding to one or more nucleotides in the binding region of the guide RNA with Cas9 and/or the nucleotides in the binding region of the guide RNA with the target DNA. Remaining unmodified nucleotides of the guide RNA may be those required to be identified for minimal binding of Cas9 to the 2' -OH location on

the bases. In some embodiments, the nucleotides may be modified at the 2' position of the sugar moiety of the nucleotide. In some embodiments, the 2'-OH group of the sugar moiety is replaced by a group selected from H, OR, R, halo, SH, SR, H₂, NHR, N(R)₂ or CN, wherein R is C₁-C₆ alkyl, alkenyl or alkynyl and halo is F, Cl, Br or I. Other modifications may include, inverted (deoxy) abasics, amino, fluoro, chloro, bromo, CN, CF, methoxy, imidazole, carboxylate, thioate, C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkaryl or aralkyl, heterozycloalkyl; heterozycloalkaryl; aminoalkylamino; polyalkylamino or substituted silyl. Methods for making RNAs with specific sequences and modifications are known by those skilled in the art, for example, in Dellinger et al. (2011), J. Am. Chem. Soc, 133, 11540; US 8,202,983; Kumar et al., (2007), J. Am. Chem. Soc, 129, 6859-64; WO2013176844, the entirety of which are incorporated herein by reference.

[0591] In some embodiments, polynucleotides or oligonucleotides as provided herein may be synthetic. For example, mRNAs maybe chemically synthesized mRNAs. Synthetic RNA production yield is based on sequences and modifications. 2' -O- methyl modifications have been shown to increase coupling efficacy or efficiency during RNA synthesis and therefore increase yield of chemically synthesized RNA. Furthermore, nucleotides may be modified by phosphorothioates. Phosphorothioate (phosphorothioate)(PS) bonds substitute a sulphur atom for a non-bridging oxygen in the phosphate backbone of an oligonucleotide. Accordingly, exemplary nucleotides of the disclosure include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β - D-ribo configuration, α -LNA having an α -L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 2'-amino- α -LNA having a 2'- amino functionalization) or hybrids thereof.

Conjugates for Targeted Delivery

[0592] Provided herein are conjugates suitable for targeted delivery of agents, such as mRNA, guide RNA, miRNA, siRNA, DNA, peptides, or other micro or macro molecules. A conjugate can contain one or more aptamers, ligands, or moieties for targeted delivery ex vivo or in vivo. In some embodiments, a conjugate comprises a targeting moiety (or ligand), a linker, and an active agent (or payload) that is connected to the targeting moiety. An active agent can be a therapeutic agent, a prophylactic agent, or a diagnostic /prognostic agent. An active agent may have a capability of manipulating a physiological function (e.g., gene expression) in a subject. An active agent maybe a guide RNA, a mRNA, a miRNA, a siRNA, a DNA, or a peptide. The active agent may be connected with the targeting moiety via a linker, via a non-covalent linkage, via nucleobase paring,

or any combination thereof. In some embodiments, the conjugate may be a conjugate between a single active agent and a single targeting moiety with the formula: X-Y-Z, wherein X is the targeting moiety; Y is a linker; and Z is the guide RNA. In certain embodiments, one targeting ligand can be conjugated to two or more active agents, wherein the conjugate has the formula: X-(Y-Z)_n. For example, the conjugate may comprise a guide RNA and a mRNA. In certain embodiments, one active agent can be linked to two or more targeting ligands wherein the conjugate has the formula: (X-Y)_n-Z. In other embodiments, one or more targeting moieties may be connected to one or more active pay loads wherein the conjugate formula may be (X-Y-Z)_n. In various combinations, the formula of the conjugates maybe, for example, X-Y-Z-Y-X, (X-Y-Z)_n-Y-Z, or X-Y-(X-Y-Z)_n, wherein X is a targeting moiety; Y is a linker; Z is an active agent, e.g. a guide RNA. The number of each moiety in the conjugate may vary dependent on types of agents, sizes of the conjugate, delivery targets, particles used to packaging the conjugate, other active agents (e.g., immunologic adjuvants) and routes of administration. Each occurrence of X, Y, and Z can be the same or different, e.g. the conjugate can contain more than one type of targeting moiety, more than one type of linker, and/or more than one type of active agent, n is an integer equal to or greater than 1. In some embodiments, n is an integer between 1 and 50, or between 2 and 20, or between 5 and 40. In some embodiments, n may be an integer of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 41, 43, 44, 45, 46, 47, 48, 49 or 50.

[0593] In some embodiments, an active agent, e.g., a guide RNA may be delivered to cells and tissues using viral, polymeric and liposomal formulations, cell-penetrating peptides, aptamers, ligands, or conjugates and antibody approaches. A moiety or ligand may direct guide RNAs to particular organ, tissue, or cell, for example, a liver hepatocyte, and may be referred to as a targeting moiety. In some embodiments, targeting moieties modify one or more properties of the attached molecule (e.g., a mRNA or a guide RNA), including but not limited to pharmacodynamic, pharmacokinetic, binding, absorption, cellular distribution, cellular uptake, charge and clearance.

[0594] Exemplary moieties that can be attached to a herein described active agent include, but are not limited to, intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, thioethers, polyethers, cholesterol, thiocholesterols, cholic acid moieties, folate, lipids, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, adamantane, acridine, fluoresceins, rhodamines, coumarins, dyes, lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553); cholic acid (Manoharan et al, Bioorg. Med. Chem. Lett., 1994, 4, 1053); a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al, Ann. NY. Acad. Sci., 1992, 660, 306; Manoharan et al, Bioorg. Med. Chem. Lett., 1993, 3, 2765); a thiocholesterol

(Oberhauser et al., Nucl. Acids Res., 1992, 20, 533); an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al, EMBO J., 1991, 10, 111; Kabanov et al, FEBS Lett., 1990, 259, 327; Svinarchuk et al, Biochimie, 1993, 75, 49); a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium-1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al, Tetrahedron Lett., 1995, 36, 3651; Shea et al, Nucl. Acids Res., 1990, 18, 3777); a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969); adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651); a palmityl moiety (Mishra et al, Biochim. Biophys. Acta, 1995, 1264, 229); or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al, J. Pharmacol. Exp. Ther., 1996, 277, 923), all references incorporated herein in their entirety. Targeting moieties may include naturally occurring molecules, or recombinant or synthetic molecules, including, but not limited to, polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolid) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG, e.g., PEG-2K, PEG-5K, PEG-10K, PEG-12K, PEG-15K, PEG-20K, PEG-40K), MPEG, [MPEG]₂, polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, polyphosphazine, polyethylenimine, cationic groups, spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, mucin, glycosylated polyaminoacids, transferrin, bisphosphonate, polyglutamate, polyaspartate, aptamer, asialofetuin, hyaluronan, procollagen, immunoglobulins (e.g., antibodies), insulin, transferrin, albumin, sugar-albumin conjugates, intercalating agents (e.g., acridines), cross-linkers (e.g. psoralen, mitomycin C), porphyrins (e.g., TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g., EDTA), lipophilic molecules (e.g, steroids, bile acids, cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3 -propanediol, heptadecyl group, palmitic acid, myristic acid, 03-(oleoyl)lithocholic acid, 03-(oleoyl)cholonic acid, dimethoxytrityl, or phenoxazine), peptides (e.g., an alpha helical peptide, amphipathic peptide, RGD peptide, cell permeation peptide, endosomolytic/fusogenic peptide), alkylating agents, phosphate, amino, mercapto, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g. biotin), transport/absorption facilitators (e.g., naproxen, aspirin, vitamin E, folic acid), synthetic ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu³⁺ complexes of

tetraazamacrocycles), dinitrophenyl, HRP, AP, antibodies, hormones and hormone receptors, lectins, carbohydrates, multivalent carbohydrates, vitamins (e.g., vitamin A, vitamin E, vitamin K, vitamin B, e.g., folic acid, B12, riboflavin, biotin and pyridoxal), vitamin cofactors, lipopolysaccharide, an activator of p38 MAP kinase, an activator of NF- κ B, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholid A, indanocine, myoservin, tumor necrosis factor alpha (TNF α), interleukin-1 beta, gamma interferon, natural or recombinant low density lipoprotein (LDL), natural or recombinant high-density lipoprotein (HDL), and a cell-permeation agent (e.g., a helical cell-permeation agent), peptide and peptidomimetic ligands, including those having naturally occurring or modified peptides, e.g., D or L peptides; α , β , or γ peptides; N-methyl peptides; azapeptides; peptides having one or more amide, i.e., peptide, linkages replaced with one or more urea, thiourea, carbamate, or sulfonyl urea linkages; or cyclic peptides; amphipathic peptides including, but not limited to, cecropins, lycotoxins, paradaxins, buforin, CPF, bombinin-like peptide (BLP), cathelicidins, ceratotoxins, *S. clava* peptides, hagfish intestinal antimicrobial peptides (HFIAPs), magainines, brevinins-2, dermaseptins, melittins, pleurocidin, H2A peptides, *Xenopus* peptides, esculentinis-1, and caerins. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The peptide or peptidomimetic ligand or moiety can be about 5-50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long. In some embodiments, the targeting moiety may be other peptides such as somatostatin, octeotide, LHRH (luteinizing hormone releasing hormone), epidermal growth factor receptor (EGFR) binding peptide, aptide or bipodal peptide, RGD-containing peptides, a protein scaffold such as a fibronectin domain, a single domain antibody, a stable scFv, or other homing peptides. As non-limiting examples, a protein or peptide based targeting moiety may be a protein such as thrombospondin, tumor necrosis factors (TNF), annexin V, an interferon, angiostatin, endostatin, cytokine, transferrin, GM-CSF (granulocyte-macrophage colony-stimulating factor), or growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), (platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF). In some embodiments, the targeting moiety maybe an antibody, an antibody fragment, RGD peptide, folic acid or prostate specific membrane antigen (PSMA). In some embodiments, the protein scaffold may be an antibody-derived protein scaffold. Non-limiting examples include single domain antibody (dAbs), nanobody, single-chain variable fragment (scFv), antigen-binding fragment (Fab), Avibody, minibody, CH2D domain, Fcab, and bispecific T-cell engager (BiTE) molecules. In some embodiments, scFv is a stable scFv, wherein the scFv has hyperstable properties. In some embodiments, the nanobody may be derived

from the single variable domain (VHH) of camelidae antibody.

[0595] In some embodiments, a targeting moiety recognizes or binds a target cell, a marker, or a molecule that is present exclusively or predominantly on the surface of particular cells. For example, a targeting moiety may bind a tumor antigen and direct the activating agent, e.g. a guide RNA-Cas complex to a malignant cell. In some embodiments, the targeting moiety recognizes an intra-cellular protein. In some embodiments, a targeting moiety directs a conjugate to specific tissues, cells, or locations in a cell (for e.g. trivalent N-acetylgalactosamine targets asialoglycoprotein receptor (ASGPR) on the surface of hepatocytes in mammals; Nair et al. J. Am. Chem. Soc. 2014, 136, 16958, see also US17/192,709). The targeting moiety can direct the conjugate in culture or in a whole organism, or both. In each case, the targeting moiety may bind to a receptor that is present on the surface of or within the targeted cell(s), wherein the targeting moiety binds to the receptor with an effective specificity, affinity and avidity. In other embodiments the targeting moiety targets the conjugate to a specific tissue such as the liver, kidney, lung or pancreas. In other cases, targeting moieties can direct the conjugate to cells of the reticular endothelial or lymphatic system, or to professional phagocytic cells such as macrophages or eosinophils. In some embodiments, the targeting moiety may recognize a RTK receptor, an EGF receptor, a serine or threonine kinase, G-protein coupled receptor, methyl CpG binding protein, cell surface glycoprotein, cancer stem cell antigen or marker, carbonic anhydrase, cytolytic T lymphocyte antigen, DNA methyltransferase, an ectoenzyme, a glycosylphosphatidylinositol-anchored co-receptor, a glypican-related integral membrane proteoglycan, a heat shock protein, a hypoxia induced protein, a multi drug resistant transporter, a Tumor-associated macrophage marker, a tumor associated carbohydrate antigen, a TNF receptor family member, a transmembrane protein, a tumor necrosis factor receptor superfamily member, a tumour differentiation antigen, a zinc dependent metallo-exopeptidase, a zinc transporter, a sodium-dependent transmembrane transport protein, a member of the SIGLEC family of lectins, or a matrix metalloproteinase.

[0596] Targeting moieties can be conjugated to nucleobases, sugar moieties, or internucleosidic linkages of a nucleic acid, e.g. a guide RNA or mRNA. Conjugation to purine nucleobases or derivatives thereof can occur at any position including, endocyclic and exocyclic atoms. In some embodiments, the 2-, 6-, 7-, or 8-positions of a purine nucleobase are attached to a moiety. Conjugation to pyrimidine nucleobases or derivatives thereof can also occur at any position. In some embodiments, the 2-, 5-, and 6-positions of a pyrimidine nucleobase can be substituted with a moiety. When a moiety is conjugated to a nucleobase, the preferred position is one that does not interfere with hybridization, i.e., does not interfere with the hydrogen bonding interactions needed for base pairing.

[0597] Conjugation to sugar moieties of nucleosides can occur at any carbon atom. Example carbon atoms of a sugar moiety that can be attached to a conjugate moiety include the 2', 3', and 5' carbon atoms. The gamma-position can also be attached to a conjugate moiety, such as in an abasic residue. Internucleosidic linkages can also bear conjugate moieties. For phosphorus-containing linkages (e.g., phosphodiester, phosphorothioate, phosphorodithiotate, phosphoroamidate, and the like), the conjugate moiety can be attached directly to the phosphorus atom or to an O, N, or S atom bound to the phosphorus atom. For amine- or amide-containing internucleosidic linkages (e.g., PNA), the conjugate moiety can be attached to the nitrogen atom of the amine or amide or to an adjacent carbon atom.

[0598] There are numerous methods for preparing conjugates of oligonucleotides. Generally, an oligonucleotide is attached to a conjugate moiety by contacting a reactive group (e.g., OH, SH, amine, carboxyl, aldehyde, and the like) on the oligonucleotide with a reactive group on the conjugate moiety. In some embodiments, one reactive group is electrophilic and the other is nucleophilic. For example, an electrophilic group can be a carbonyl-containing functionality and a nucleophilic group can be an amine or thiol. Methods for conjugation of nucleic acids and related oligomeric compounds with and without linking groups are well described in the literature such as, for example, in Manoharan in *Antisense Research and Applications*, Crooke and LeBleu, eds., CRC Press, Boca Raton, Fla., 1993, Chapter 17, which is incorporated herein by reference in its entirety.

[0599] A targeting moiety can be attached to an active agent or therapeutic nucleic acid described herein, such as a guide RNA, via RNA-RNA or RNA-DNA base pairing and hybridization. Not intended to be bound by any theories, a targeting moiety can comprise a coupling sequence that is capable of recognizing or binding an active agent, e.g., a guide RNA or a mRNA. In some embodiments, a targeting moiety comprises a coupling sequence capable of hybridizing to a 5' portion, a 3' portion, or a middle portion of a guide RNA. A guide RNA that hybridizes with a coupling sequence may comprise an extension. For example, the coupling sequence may be able to hybridize with the extension sequence of the guide RNA, thereby directing the guide RNA to desired in vivo, ex vivo, intercellular or intracellular locations, while the guide RNA functionality such as interaction with CRISPR enzyme or binding with target sequence(s) is not affected. In some embodiments, the guide RNA comprises an extension that includes a polynucleotide tail. In some embodiments, the guide nucleic acid comprises a poly(A) tail, a poly(U) tail, or a poly(T) tail capable of hybridizing with a poly(U) tail, a poly(A) tail, or a poly(A) tail of the coupling sequence respectively. In some embodiments, the guide nucleic acid may be a guide RNA that comprises the sequence of (A)_n or (U)_n. In some embodiments, the guide nucleic acid may comprise DNA and may comprise the sequence of (A)_n or (T)_n. In some embodiments,

the coupling sequence may comprise the sequence of (A)_n, (U)_n or (T)_n. As instantly used, n may be any integer between 1 and 200.

[0600] A coupling sequence may share sequence identity or complementarity with a nucleic acid active agent, or a portion thereof. In some embodiments, a coupling sequence may share at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% of identity with a guide RNA described herein, or a portion of such guide RNA. In some embodiments, a coupling sequence may share at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% of identity with the complementary sequence of a guide RNA described herein, or the complementary of a portion of such guide RNA. In some embodiments, the coupling sequence may comprise identity or complementarity with at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, or at least 100 contiguous nucleobases of the guide RNA or a complementary thereof.

[0601] In some embodiments, a targeting moiety may comprise or be associated with a coupling sequence that is chemically modified. In some embodiments, the coupling sequence comprises an extension that hybridizes with a therapeutic nucleic acid, e.g. a guide RNA, or a portion thereof. In some embodiments, the extension of the coupling sequence may be chemically modified. In some embodiments, the therapeutic nucleic acid, e.g. a guide RNA, may comprise an extension. In some embodiments, the extension of the guide RNA may be chemically modified.

[0602] A targeting moiety can be attached to a nucleic acid described herein via a carrier. The carriers may include (i) at least one "backbone attachment point," preferably two "backbone

attachment points" and (ii) at least one "tethering attachment point." A "backbone attachment point" as used herein refers to a functional group, e.g. a hydroxyl group, or generally, a bond available for, and that is suitable for incorporation of the carrier monomer into the backbone, e.g., the phosphate, or modified phosphate, e.g., sulfur containing, backbone, of an oligonucleotide. A "tethering attachment point" (TAP) in refers to an atom of the carrier monomer, e.g., a carbon atom or a heteroatom (distinct from an atom which provides a backbone attachment point), that connects a selected moiety. The selected moiety can be, e.g., a carbohydrate, e.g. monosaccharide, disaccharide, trisaccharide, tetrasaccharide, oligosaccharide and polysaccharide. Optionally, the selected moiety is connected by an intervening tether to the carrier monomer. Thus, the carrier will often include a functional group, e.g., an amino group, or generally, provide a bond, that is suitable for incorporation or tethering of another chemical entity, e.g., a ligand to the constituent atom. Representative U.S. patents that teach the preparation of conjugates of nucleic acids include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218, 105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578, 717; 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118, 802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578, 718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762, 779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904, 582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082, 830; 5,112,963; 5,149,782; 5,214,136; 5,245,022; 5,254, 469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317, 098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510, 475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574, 142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599, 923; 5,599,928; 5,672,662; 5,688,941; 5,714,166; 6,153, 737; 6,172,208; 6,300,319; 6,335,434; 6,335,437; 6,395, 437; 6,444,806; 6,486,308; 6,525,031; 6,528,631; 6,559, 279; contents of which are herein incorporated in their entireties by reference.

[0603] A targeting moiety can be attached to an active agent, e. g. a guide RNA, via a linker. A linker may be bound to one or more active agents and a targeting moiety ligand to form a conjugate, wherein the conjugate releases at least one active agent, e.g. a guide RNA or guide RNA-Cas complex, upon delivery to a target cell. The linker may be attached to the targeting moiety and the active agent by functional groups independently selected from an ester bond, disulfide, amide, acylhydrazone, ether, carbamate, carbonate, and urea. Alternatively the linker can be attached to either the targeting moiety or the active agent by a non-cleavable group such as provided by the conjugation between a thiol and a maleimide, an azide and an alkyne. In some embodiments, a targeting moiety comprises one or more linkers. In some embodiments, one or more linkers as described herein connect a portion of the targeting moiety to a different portion of the targeting moiety.

[0604] The linkers can each independently comprises one or more functional groups selected

from the group consisting of ethylene glycol, propylene glycol, amide, ester, ether, alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of the alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl groups optionally is substituted with one or more groups, each independently selected from halogen, cyano, nitro, hydroxyl, carboxyl, carbamoyl, ether, alkoxy, aryloxy, amino, amide, carbamate, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heterocyclyl, wherein each of the carboxyl, carbamoyl, ether, alkoxy, aryloxy, amino, amide, carbamate, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more groups, each independently selected from halogen, cyano, nitro, hydroxyl, carboxyl, carbamoyl, ether, alkoxy, aryloxy, amino, amide, carbamate, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heterocyclyl. In some embodiments, a linker independently comprises phosphate, phosphorothioate, amide, ether, oxime, hydrazine or carbamate.

[0605] In some embodiments, the linker can independently comprise a C₁-C₁₀ straight chain alkyl, C₁-C₁₀ straight chain O-alkyl, C₁-C₁₀ straight chain substituted alkyl, C₁-C₁₀ straight chain substituted O-alkyl, C₄-C₁₃ branched chain alkyl, C₄-C₁₃ branched chain O-alkyl, C₂-C₁₂ straight chain alkenyl, C₂-C₁₂ straight chain O-alkenyl, aralkyl, C₃-C₁₂ straight chain substituted alkenyl, C₃-C₁₂ straight chain substituted O-alkenyl, polyethylene glycol, polylactic acid, polyglycolic acid, poly(lactide-co-glycolide), polycaprolactone, polycyanoacrylate, ketone, aryl, heterocyclic, succinic ester, amino acid, aromatic group, ether, crown ether, urea, thiourea, amide, purine, pyrimidine, pyridine, indole derivative acting as a cross linker, chelator, aldehyde, ketone, bisamine, bis alcohol, heterocyclic ring structure, azirine, disulfide, thioether, hydrazone and combinations thereof. For example, the linker can be a C₃ straight chain alkyl or a ketone. The alkyl chain of the linker can be substituted with one or more substituents or heteroatoms. In some embodiments, the alkyl chain of the linker may optionally be interrupted by one or more atoms or groups selected from -O-, -C(=O)-, -NR-, -O-C(=O)-NR-, -S-, -S-S-.

[0606] In some embodiments, the linker may be cleavable and is cleaved to release the active agent. The cleavable functionality may be hydrolyzed in vivo or may be designed to be hydrolyzed enzymatically, for example by Cathepsin B. A "cleavable" linker, as used herein, refers to any linker which can be cleaved physically or chemically. Examples for physical cleavage may be cleavage by light, radioactive emission or heat, while examples for chemical cleavage include cleavage by re-do reactions, hydrolysis, pH-dependent cleavage.

[0607] Linkers may comprise a direct bond or an atom such as oxygen or sulfur, a unit such as NR¹, C(O), C(O)NH, SO, SO₂, SO₂NH or a chain of atoms, such as, but not limited to, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,

arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, aryl, heteroaryl, heterocycl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclalkyl, alkylheterocyclalkenyl, alkylheterocyclalkynyl, alkenylheterocyclalkyl, alkenylheterocyclalkenyl, alkenylheterocyclalkynyl, alkynylheterocyclalkyl, alkynylheterocyclalkenyl, alkynylheterocyclalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylheteroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), SO₂, N(R'), C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R' is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker is between 1-24 atoms, preferably 4-24 atoms, preferably 6-18 atoms, more preferably 8-18 atoms, and most preferably 8-16 atoms.

[0608] In one embodiment, the linker comprises at least one cleavable linking group. In certain embodiments, the linker is a branched linker. The branchpoint of the branched linker may be at least trivalent, but may be a tetravalent, pentavalent or hexavalent atom, or a group presenting such multiple valencies. In certain embodiments, the branchpoint is, —N, —N(O)—C, —O—C, —S—C, —SS—C, —C(O)N(O)—C, —OC(O)N(O)—C, —N(O)C(O)—C, or —N(O)C(O)O—C; wherein Q is independently for each occurrence H or optionally substituted alkyl. In other embodiment, the branchpoint is glycerol or glycerol derivative.

[0609] In one embodiment, a linker may be cleaved by an enzyme. As a non-limiting example, the linker may be a polypeptide moiety, e.g. AA in WO2010093395 to Govindan, the content of which is incorporated herein by reference in its entirety; that is cleavable by intracellular peptidase. Govindan teaches AA in the linker may be a di, tri, or tetrapeptide such as Ala-Leu, Leu- Ala-Leu, and Ala-Leu- Ala-Leu. In another example, the cleavable linker may be a branched peptide. The branched peptide linker may comprise two or more amino acid moieties that provide an enzyme cleavage site. Any branched peptide linker disclosed in WO 1998019705 to Dubowchik, the content of which is incorporated herein by reference in its entirety, may be used as a linker in the conjugate of the present disclosure. As another example, the linker may comprise a lysosomally cleavable polypeptide disclosed in US 8877901 to Govindan et al., the content of which is incorporated herein by reference in its entirety. As another example, the linker may comprise a

protein peptide sequence which is selectively enzymatically cleavable by tumor associated proteases, such as any Y and Z structures disclosed in US 6214345 to Firestone et al, the content of which is incorporated herein by reference in its entirety.

[0610] In some embodiments, a linker may comprise a cleavable linking group. A cleavable linking group is one which is sufficiently stable outside the cell, but which upon entry into a target cell is cleaved to release the two parts the linker is holding together. In a preferred embodiment, the cleavable linking group is cleaved at least 10 times or more, preferably at least 100 times faster in the target cell or under a first reference condition (which can, e.g., be selected to mimic or represent intracellular conditions) than in the blood of a subject, or under a second reference condition (which can, e.g., be selected to mimic or represent conditions found in the blood or serum). Cleavable linking groups may be susceptible to cleavage agents, e.g., pH, redox potential or the presence of degradative molecules. Generally, cleavage agents are more prevalent or found at higher levels or activities inside cells than in serum or blood. Examples of such degradative agents include: redox agents which are selected for particular substrates or which have no substrate specificity, including, e.g., oxidative or reductive enzymes or reductive agents such as mercaptans, present in cells, that can degrade a redox cleavable linking group by reduction; esterases; endosomes or agents that can create an acidic environment, e.g., those that result in a pH of five or lower; enzymes that can hydrolyze or degrade an acid cleavable linking group by acting as a general acid, peptidases (which can be substrate specific), and phosphatases.

[0611] A cleavable linkage group, such as a disulfide bond can be susceptible to pH. The pH of human serum is 7.4, while the average intracellular pH is slightly lower, ranging from about 7.1-7.3. Endosomes have a more acidic pH, in the range of 5.5-6.0, and lysosomes have an even more acidic pH at around 5.0. Some linkers will have a cleavable linking group that is cleaved at a preferred pH, thereby releasing the cationic lipid from the ligand inside the cell, or into the desired compartment of the cell.

[0612] A linker can include a cleavable linking group that is cleavable by a particular enzyme. The type of cleavable linking group incorporated into a linker can depend on the cell to be targeted. For example, liver targeting ligands can be linked to the cationic lipids through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker will be cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

[0613] One class of cleavable linking groups are redox cleavable linking groups that are cleaved upon reduction or oxidation. An example of reductively cleavable linking group is a disulphide linking group (—S—S—). To determine if a candidate cleavable linking group is a

suitable “reductively cleavable linking group,” or for example is suitable for use with a particular RNA moiety and particular targeting agent one can look to methods described herein. For example, a candidate can be evaluated by incubation with dithiothreitol (DTT), or other reducing agent using reagents known in the art, which mimic the rate of cleavage which would be observed in a cell, e.g., a target cell. The candidates can also be evaluated under conditions which are selected to mimic blood or serum conditions. In a preferred embodiment, candidate compounds are cleaved by at most 10% in the blood. In preferred embodiments, useful candidate compounds are degraded at least 2, 4, 10 or 100 times faster in the cell (or under in vitro conditions selected to mimic intracellular conditions) as compared to blood (or under in vitro conditions selected to mimic extracellular conditions). The rate of cleavage of candidate compounds can be determined using standard enzyme kinetics assays under conditions chosen to mimic intracellular media and compared to conditions chosen to mimic extracellular media.

[0614] In some embodiments, a linker may comprise a phosphate based cleavable linking group. Phosphate-based cleavable linking groups are cleaved by agents that degrade or hydrolyze the phosphate group. An example of an agent that cleaves phosphate groups in cells are enzymes such as phosphatases in cells. Examples of phosphate-based linking groups (i.e., phosphorus-containing linkages or phosphorus-containing linkers) are —P(O)(ORk)—O— , —O—P(S)(ORk)—O— , —O—P(S)(SRk)—O— , —S—P(O)(ORk)—O— , —O—P(O)(ORk)—S— , —S—P(O)(ORk)—S— , —O—P(S)(ORk)—S— , —S—P(S)(ORk)—O— , —O—P(O)(Rk)—O— , —O—P(S)(Rk)—O— , —S—P(O)(Rk)—O— , —S—P(S)(Rk)—O— , —S—P(O)(Rk)—S— , —O—P(S)(Rk)—S— . In some embodiments, phosphate-based linking groups are —O—P(O)(OH)—O— , —O—P(S)(OH)—O— , —O—P(S)(SH)—O— , —S—P(O)(OH)—O— , —O—P(O)(OH)—S— , —S—P(O)(OH)—S— , —O—P(S)(OH)—S— , —S—P(S)(OH)—O— , —O—P(O)(H)—O— , —O—P(S)(H)—O— , —S—P(O)(H)—O— , —S—P(S)(H)—O— , —S—P(O)(H)—S— , —O—P(S)(H)—S—S— . In some embodiments, a phosphate-based linker is —O—P(O)(OH)—O— .

[0615] In some embodiments, a linker may comprise an acid cleavable linking group. Acid cleavable linking groups are linking groups that are cleaved under acidic conditions. In preferred embodiments acid cleavable linking groups are cleaved in an acidic environment with a pH of about 6.5 or lower (e.g., about 6.0, 5.5, 5.0, or lower), or by agents such as enzymes that can act as a general acid. In a cell, specific low pH organelles, such as endosomes and lysosomes can provide a cleaving environment for acid cleavable linking groups. Examples of acid cleavable linking groups include but are not limited to hydrazones, esters, and esters of amino acids. Acid cleavable groups can have the general formula —C=NN— , C(O)O , or —OC(O) . A preferred embodiment is when the carbon attached to the oxygen of the ester (the alkoxy group) is an aryl group, substituted

alkyl group, or tertiary alkyl group such as dimethyl pentyl or t-butyl. These candidates can be evaluated using methods analogous to those described above.

[0616] In some embodiments, a linker may comprise an ester based linking group. Ester-based cleavable linking groups are cleaved by enzymes such as esterases and amidases in cells. Examples of ester-based cleavable linking groups include but are not limited to esters of alkylene, alkenylene and alkynylene groups. Ester cleavable linking groups have the general formula —C(O)O— , or —OC(O)— . These candidates can be evaluated using methods analogous to those described above.

[0617] In some embodiments, a linker may comprise a peptide based linking group. Peptide-based cleavable linking groups are cleaved by enzymes such as peptidases and proteases in cells. Peptide-based cleavable linking groups are peptide bonds formed between amino acids to yield oligopeptides (e.g., dipeptides, tripeptides etc.) and polypeptides. Peptide-based cleavable groups do not include the amide group (—C(O)NH—). The amide group can be formed between any alkylene, alkenylene or alkynylene. A peptide bond is a special type of amide bond formed between amino acids to yield peptides and proteins. The peptide based cleavage group is generally limited to the peptide bond (i.e., the amide bond) formed between amino acids yielding peptides and proteins and does not include the entire amide functional group. Peptide-based cleavable linking groups have the general formula $\text{—NHCHRAC(O)NHCHRBC(O)—}$, where RA and RB are the R groups of the two adjacent amino acids.

[0618] Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

[0619] In general, the suitability of a candidate cleavable linking group can be evaluated by testing the ability of a degradative agent (or condition) to cleave the candidate linking group. It will also be desirable to also test the candidate cleavable linking group for the ability to resist cleavage in the blood or when in contact with other non-target tissue. Thus one can determine the relative susceptibility to cleavage between a first and a second condition, where the first is selected to be indicative of cleavage in a target cell and the second is selected to be indicative of cleavage in other tissues or biological fluids, e.g., blood or serum. The evaluations can be carried out in cell free systems, in cells, in cell culture, in organ or tissue culture, or in whole animals. preferred embodiments, useful candidate compounds are cleaved at least 2, 4, 10 or 100 times faster in the cell (or under in vitro conditions selected to mimic intracellular conditions) as compared to blood or serum (or under in vitro conditions selected to mimic extracellular conditions).

[0620] In some embodiments, the MA004 mRNA comprises a mRNA sequence of Seq. ID. 0001 (Table 5). In some embodiments, the degree of similarity between a sequence of MA004 mRNA and another sequence may be at least 50% identical, 55% identical, 60% identical, 65% identical,

70% identical, 75% identical, 80% identical, 85% identical, 90% identical, 95% identical, 97% identical, 98% identical, 99% identical, or 100% identical. As used in Table 5, uppercase nucleotides, A, G, and C, indicate ribonucleotides adenine, guanine, and cytosine, respectively. As used in Table 5, lowercase u' indicates N¹-methylpseudouridine.

[0621] Percent sequence identity can be calculated using computer programs or direct sequence comparison. Preferred computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, FASTA, BLASTP, and TBLASTN (see, e.g., D. W. Mount, 2001, Bioinformatics: Sequence and Genome Analysis, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.). The BLASTP and TBLASTN programs are publicly available from NCBI and other sources. The Smith Waterman algorithm can also be used to determine percent identity. Exemplary parameters for amino acid sequence comparison include the following: 1) algorithm from Needleman and Wunsch (J. Mol. Biol., 48:443-453 (1970)); 2) BLOSSUM62 comparison matrix from Hentikoff and Hentikoff (Proc. Nat. Acad. Sci. USA., 89:10915-10919 (1992)) 3) gap penalty=12; and 4) gap length penalty=4. A program useful with these parameters can be publicly available as the “gap” program (Genetics Computer Group, Madison, Wis.). The aforementioned parameters are the default parameters for polypeptide comparisons (with no penalty for end gaps). Alternatively, polypeptide sequence identity can be calculated using the following equation: % identity—(the number of identical residues)/(alignment length in amino acid residues)*100. For this calculation, alignment length includes internal gaps but does not include terminal gaps.

[0622] TABLE 5

MA004 mRNA sequences			
Region	Sequence		SEQ ID NO
Full sequence	mRNA	AGGAAAU' AAGAGAGAAAAGAAGAGu' AAGAAGAAAU' Au' AAGAGCCACCAu' GAGCGAGGu' GGAGu' u' CAGCCA CGAGu' ACu' GGAu' GCGGCACGCCCu' GACCCu' GGCCAA GCGGGCCCGGGACGAGCGGGAGGu' GCCCCu' GGGCGC CGu' GCu' GGu' GCu' GAACAACCGGGu' GAu' CGGCGAGG GCu' GGAACCGGGCCAu' CGGCCu' GCACGACCCACCG CCCACGCCGAGAu' CAu' GGCCCu' GCGGCAGGGCGGGCCu' 'GGu' GAu' GCAGAACu' ACCGGCu' GAu' CGACGCCACCCu' 'Gu' ACGu' GACCu' u' CGAGCCCu' GCGu' GAu' Gu' GCGCCG GCGCCAu' GAu' CCACAGCCGGAu' CGGCCGGGu' GGu' Gu' u' CGGCGu' GCGGAACGCCAAGACCGGCGCCGCCGCA GCCu' GAu' GGACGu' GCu' GCACCACCCCGGCAu' GAACC ACCGGGu' GGAGAu' CACCGAGGGCAu' CCu' GGCCGACG AGu' GCGCCGCCCu' GCu' Gu' GCCGGu' u' Cu' u' CCGGAu' G CCCC GGCGGGu' Gu' u' CAACGCCCAGAAGAAGGCCAG	0001

		AGCAGCACCGACAGCGGCGGCAGCAGCGGCGGCAGCA GCGGCAGCGAGACACCCGGCACCAGCGAGAGCGCCAC CCCCGAGAGCAGCGGCGGCAGCAGCGGCGGCAGCGAC AAGAAGu'ACAGCAu'CGGCCu'GGCCAu'CGGCACCAAC AGCGu'GGGGu'GGGCCGu'GAu'CACCGACGAGu'ACAA GGu'GCCAGCAAGAAGu'u'CAAGGu'GGu'GGGCAACA CCGACCGGCACAGCAu'CAAGAAGAACCu'GAu'CGGCG CCCu'GGu'Gu'u'CGACAGCGGCGAGACAGCCGAGGCCA CCCGGGu'GAAGCGGACCGCCCGGCGGCGGu'ACACCC GGCGGAAGAACCGGAu'Cu'GGu'ACCu'GCAGGAGAu'Cu 'u'cAGCAACGAGAu'GGCCAAGGu'GGACGACAGCu'u'C u'u'CCACCGGGu'GGAGGAGAGCu'u'CCu'GGu'GGAGGA GGACAAGAAGCACGAGCGGCACCCCAu'Cu'u'CGGCAA CAu'CGu'GGACGAGGu'GGCCu'ACCACGAGAAGu'ACCC CACCAu'Cu'ACCACCu'GCGGAAGAAGCu'GGu'GGACAG CACCGACAAGGCCGACCu'GCGGGu'GAu'Cu'ACCu'GGC CCu'GGCCCACAu'GAu'CAAGu'u'CCGGGGCCACu'u'CCu 'GAu'CGAGGGCGACCu'GAACCCCGACAACAGCGACGu' GGACAAGCu'Gu'u'CAu'CCAGCu'GGu'GCAGACCu'ACA ACCAGCu'Gu'u'CGAGGAGAACCCCAu'CAACGCCAGCG GCGu'GGACGCCAAGGCCAu'CCu'GAGCGCCCGGGu'GA GCAAGAGCCGGCGGGu'GGAGAACCu'GAu'CGCCCAGC u'GCCCCGGCGAGAAGAAGAACGGCCu'Gu'u'CGGCAACC u'GAu'CGCCCu'GAGCCu'GGGCCu'GACCCCAACu'u'CA AGAGCAACu'u'CGACCu'GGCCGAGGACGCCAAGCu'GC AGCu'GAGCAAGGACACCu'ACGACGACGACCu'GGACA ACCu'GGu'GGCCCAGAu'CGGCGACCAGu'ACGCCGACC u'Gu'u'CCu'GGCCGCCAAGAACCu'GAGCGACGCCAu'CC u'GGu'GAGCGACAu'CCu'GCGGGu'GAACACCGAGAu'C ACCAAGGCCCCCCCu'GAGCGCCAGCAu'GAu'CAAGCGG u'ACGACGAGCACCAACAGGACCu'GACCCu'GGu'GAAG GCCCu'GGu'GCGGCAGCAGCu'GCCCAGAGAAGu'ACAAG GAGAu'Cu'u'Cu'u'CGACCAGAGCAAGAACGGCu'ACGC CGGGu'ACAu'CGACGGCGGCGCCAGCCAGGAGGAGu'u' Cu'ACAAGu'u'CAu'CAAGCCCAu'CCu'GGAGAAGAu'GG ACGGCACCGAGGAGCu'GGu'GGu'GAAGCu'GAACCGGG AGGACCu'GGu'GCGGAAGCAGCGGACCu'u'CGACAACG GCAGCAu'CCCCCACCAGAu'CCACCu'GGGCGAGCu'GC ACGCCAu'CCu'GCGGCGGCAGGAGGACu'u'Cu'ACCCCu' u'CCu'GAAGGACAACCGGGAGAAGAu'CGAGAAGAu'CC u'GACCu'u'CCGGAu'CCCCu'ACu'ACGu'GGGCCCCCu'G GCCCCGGGGCAACAGCCGGu'u'CGCCu'GGAu'GACCCGC AAGAGCGAGGAGACAAu'CACCCCCu'GGAACu'u'CGAG GAGGu'GGu'GGACAAGGGCGCCAGCGCCAGAGCu'u'C Au'CGAGCGGAu'GACCAACu'u'CGACAAGAACCu'GCCC AACGAGAAGGu'GGu'GCCCAAGCACAGCCu'GGu'Gu'AC GAGu'ACu'u'CACCGu'Gu'ACAACGAGCu'GACCAAGGu' GAAGu'ACGu'GACCGAGGGCAu'GCGGAAGCCCGCCu'u' CCu'GAGCGGCGAGCAGAAGAAGGCCAu'CGu'GGACCu' GGu'Gu'u'CAAGACCAACCGGAAGGu'GACCGu'GAAGC AGCu'GAAGGAGGACu'ACu'u'CAAGAAGAu'CGAGu'GC u'u'CGACAGCGu'GGAGAu'CAGCGGCGu'GGAGGACCG Gu'u'CAACGCCAGCCu'GGGCACCu'ACCACGACCu'GGu' GAAGAu'CAu'CAAGGACAAGGACu'u'CCu'GGACAACG AGGAGAACGAGGACAu'CCu'GGAGGACAu'CGu'GGu'G ACCCu'GACCCu'Gu'u'CGAGGACCGGGAGAu'GAu'CGA	
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		GGAGCGGCu'GAAGACCu'ACGCCCACCu'Gu'u'CGACGA CAAGGu'GAu'GAAGCAGCu'GAAGCGGCGGCGGu'ACAC CGGCu'GGGGCCGGCu'GAGCCGGAAGCu'GAu'CAACGG CAu'CCGGGACAAGCAGAGCGGCAAGACCAu'CCu'GGA Cu'u'CCu'CAAGAGCGACGGCu'u'CGCCAACCGGAACu'u 'CAu'GCAGCu'GAu'CCACGACGACAGCCu'GACCu'u'CA AGGAGGACAu'CCAGAAGGCCAGGu'GAGCGGCCAGG GCGACAGCCu'GCACGAGCACAu'CGCCAACCu'GGCCG GCAGCCCCGCCAu'CAAGAAGGGCAu'CCu'GCAGACCG u'GAAGGu'GGu'GGACGAGCu'GGu'GAAGGu'GAu'GGGC CGGCACAAGCCCGAGAACAu'CGu'GAu'CGAGAu'GGCC CGGGAGAACCAGACCACCAGAAGGGCCAGAAGAAC AGCCGGGAGCGGAu'GAAGCGGAu'CGAGGAGGGCAu'C AAGGAGCu'GGGCAGCCAGAu'CCu'GAAGGAGCACCCC Gu'GGAGAACACCCAGCu'GCAGAACGAGAAGCu'Gu'AC Cu'Gu'ACu'ACCu'GCAGAACGGCCGGGACAu'Gu'ACGu' GGACCAGGAGCu'GGACAu'CAACCGGCu'GAGCGACu'A CGACGu'GGACCACAu'CGu'GCCCCAGAGCu'u'CCu'GAA GGACGACAGCAu'CGACAACAAGGu'GCu'GACCCGGAG CGACAAGAACC GGCGCAAGAGCGACAACGu'GCCCAG CGAGGAGGu'GGu'GAAGAAGAu'GAAGAACu'ACu'GGC GGCAGCu'GCu'GAACGCCAAGCu'GAu'CACCCAGCGGA AGu'u'CGACAACCu'GACCAAGGCCGAGCGGGGCGGCC u'GAGCGAGCu'GGACAAGGCCGGCu'u'CAu'CAAGCGGC AGCu'GGu'GGAGACACGGCAGAu'CACCAAGCACGu'GG CCCAGAu'CCu'GGACAGCCGGAu'GAACACCAAGu'ACG ACGAGAACGACAAGCu'GAu'CCGGGAGGu'GAAGGu'G Au'CACCCu'CAAGAGCAAGCu'GGu'GAGCGACu'u'CCG GAAGGACu'u'CCAGu'u'Cu'ACAAGGu'GCGGGAGAu'CA ACAACu'ACCACCACGCCCACGACGCCu'ACCu'GAACG CCGu'GGu'GGGCACCGCCCu'GAu'CAAGAAGu'ACCCCA AGCu'GGAGAGCGAGu'u'CGu'Gu'ACGGCGACu'ACAAG Gu'Gu'ACGACGu'GCGGAAGAu'GAu'CGCCAAGAGCGA GCAGGAGAu'CGGCAAGGCCACCGCCAAGu'ACu'u'Cu'u 'Cu'ACAGCAACAu'CAu'GAACu'u'Cu'u'CAAGACCGAGA u'CACCCu'GGCCAACGGCGAGAu'CCGGAAGCGGCCCCu 'GAu'CGAGACAAACGGCGAGACAGGCGAGAu'CGu'Gu' GGGACAAGGGCCGGGACu'u'CGCCACCGu'GCGGAAGG u'GCu'GAGCAu'GCCCCAGGu'GAACAu'CGu'GAAGAAG ACCGAGGu'GCAGACCGGCGGCu'u'CAGCAAGGAGAGC Au'CCu'GCCCCAAGCGGAACAGCGACAAGCu'GAu'CGCC CGGAAGAAGGACu'GGGACCCCAAGAAGu'ACGGCGGC u'u'CGACAGCCCCACCGu'GGCCu'ACAGCGu'GCu'GGu' GGu'GGCCAAGGu'GGAGAAGGGCAAGAGCAAGAAGCu 'CAAGAGCGu'GAAGGAGCu'GCu'GGGCAu'CACCAu'CA u'GGAGCGGAGCAGCu'u'CGAGAAGAACCCCAu'CGACu' u'CCu'GGAGGCCAAGGGCu'ACAAGGAGGu'GAAGAAG GACCu'GAu'CAu'CAAGCu'GCCCAAGu'ACAGCCu'Gu'u' CGAGCu'GGAGAACGGCCGGAAGCGGAu'GCu'GGCCAG CGCCGGCGAGCu'GCAGAAGGGCAACGAGCu'GGCCCu' GCCCCAGCAAGu'ACGu'GAACu'u'CCu'Gu'ACCu'GGCCA GCCACu'ACGAGAAGCu'GAAGGGCAGCCCCGAGGACA ACGAGCAGAAGCAGCu'Gu'u'CGu'GGAGCAGCACAAGC ACu'ACCu'GGACGAGAu'CAu'CGAGCAGAu'CAGCGAGu 'u'CAGCAAGCGGGu'GAu'CCu'GGCCGACGCCAACCu'G GACAAGGu'GCu'GAGCGCCu'ACAACAAGCACCGGGAC	
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		AAGCCCAu'CCGGGAGCAGGCCGAGAACAu'CAu'CCAC Cu'Gu'u'CACCCu'GACCAACCu'GGGCGCCCCGCGCCu 'u'CAAGu'ACu'u'CGACACCACCAu'CGACCGGAAGCGGu 'ACACCAGCACCAAGGAGGu'GCu'GGACGCCACCCu'GA u'CCACCAGAGCAu'CACCGGCCu'Gu'ACGAGACACGGA u'CGACCu'GAGCCAGCu'GGGCGGCGACGAGGGCGCCG ACAAGCGGACCGCCGACGGCAGCGAGu'u'CGAGAGCC CCAAGAAGAAGCGGAAGGu'Gu'GAGCGGCCGCu'u'AAu 'u'AAGCu'GCCu'u'Cu'GCGGGGCu'u'GCCu'u'Cu'GGCCAu 'GCCCu'u'Cu'u'Cu'Cu'CCCu'u'GCACCu'Gu'ACCu'Cu'u'G Gu'Cu'u'u'GAAu'AAAGCCu'GAGu'AGGAAGu'Cu'AGA	
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[0623]

Target Sequences

[0624] The present disclosure provides active agents or therapeutic agents, such as genome editing compositions, and methods and compositions for targeted delivery thereof. The therapeutic agents described herein may comprise genome editing composition directed to and modify, alter, or cleave a target sequence on a target nucleic acid molecule. For example, the active agent may comprise a nucleic acid or a nucleic acid-protein complex capable of effecting a modification to a target sequence.

[0625] The target sequence may be a DNA sequence or a RNA sequence. In some embodiments, the active agent or therapeutic agent may comprise a RNA interference factor. In some embodiments, the active agent may comprise a siRNA, shRNA, antisense oligonucleotide, microRNA, anti-microRNA or antimir, supermir, antagomir, ribozyme, triplex-forming oligonucleotide, decoy oligonucleotide, splice-switching oligonucleotide, immunostimulatory oligonucleotide, RNA activator, or a UI adaptor. The active agent may recognize the target sequence and mediate cleavage and/or degradation of the target sequence. In some embodiments, the active or therapeutic agent may comprise a guide RNA. The guide RNA may be complexed with a nucleic acid guided programmable nuclease, such as a CRISPR enzyme, such as a Cas9, or a fusion protein thereof further comprising a functional domain. The target sequence may be recognized by the nucleic acid guided programmable nuclease domain. The target sequence may be cleaved by the nucleic acid guided programmable nuclease domain and/or modified by the functional domain, such as a deaminase domain, a methylase domain, a methyltransferase domain, an activation domain, a repressor domain, a nuclease domain, a transposase domain, or a recombinase domain. In some embodiments, a Cas9 protein may be directed by a guide RNA to a target sequence of a target nucleic acid molecule, where the guide RNA hybridizes with and the Cas protein cleaves the target sequence. In some embodiments, the target sequence may be complementary to the targeting sequence of the guide RNA. In some embodiments, the degree of complementarity between a targeting sequence of a guide RNA and its corresponding target

sequence may be about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100%. In some embodiments, the target sequence and the targeting sequence of the guide RNA may be 100% complementary. In other embodiments, the target sequence and the targeting sequence of the guide RNA may contain at least one mismatch. For example, the target sequence and the targeting sequence of the guide RNA may contain 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mismatches. In some embodiments, the target sequence and the targeting sequence of the guide RNA may contain 1-6 mismatches. In some embodiments, the target sequence and the targeting sequence of the guide RNA may contain 5 or 6 mismatches.

[0626] The length of the target sequence may depend on the nuclease system used. For example, the target sequence for a CRISPR/Cas system may comprise 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, or more than 50 nucleotides in length. In some embodiments, the target sequence may comprise 18-24 nucleotides in length. In some embodiments, the target sequence may comprise 19-21 nucleotides in length. In some embodiments, the target sequence may comprise 20 nucleotides in length. When nickases are used, the target sequence may comprise a pair of target sequences recognized by a pair of nickases on opposite strands of the DNA molecule.

[0627] In some embodiments, the active or therapeutic agent may comprise a meganuclease system. the target sequence for a meganuclease may comprise 12-40 or more nucleotides in length. When ZFNs are used, the target sequence may comprise two half target sequences recognized by a pair of ZFNs on opposite strands of the DNA molecule, with an interconnecting sequence in between. In some embodiments, each half target sequence for ZFNs may independently comprise 9, 12, 15, 18, or more nucleotides in length. In some embodiments, the interconnecting sequence for ZFNs may comprise 4-20 nucleotides in length. In some embodiments, the interconnecting sequence for ZFNs may comprise 5-7 nucleotides in length.

[0628] When TALENs are used, the target sequence may similarly comprise two half target sequences recognized by a pair of TALENs on opposite strands of the DNA molecule, with an interconnecting sequence in between. In some embodiments, each half target sequence for TALENs may independently comprise 10-20 or more nucleotides in length. In some embodiments, the interconnecting sequence for TALENs may comprise 4-20 nucleotides in length. In some embodiments, the interconnecting sequence for TALENs may comprise 12-19 nucleotides in length.

[0629] In some embodiments, the target sequence may be adjacent to a protospacer adjacent motif (PAM), a short sequence recognized by a CRISPR/Cas complex. The protospacer adjacent motif, or PAM, is essential for target binding for CRISPR/Cas complexes. Typically, a PAM is a 2-

6 base pair DNA sequence immediately following the DNA target sequence of the Cas nuclease. The PAM may be a 5' PAM or a 3' PAM. The exact sequence of PAM depends on the type of Cas protein. For example, a typical SpCas9 binding requires a 3'-NGG-5' PAM, also known as a canonical PAM, where the N is any one of A, G, C, or T. A SpCas9 with certain amino acid substitutions, e.g. D1135E, R1335Q, G1218R, and/or T1337R can recognize a NGA PAM or a NGCG PAM. A SaCas9 binding requires a 3'-NNGRRT-5' PAM. A SaCas9 with certain amino substitutions, e.g., K781E, K697N, H1014R, can recognize a NNNRRT PAM.

[0630] In some embodiments, the PAM may be adjacent to or within 1, 2, 3, or 4, nucleotides of the 3' end of the target sequence. The length and the sequence of the PAM may depend on the Cas9 protein used. For example, the PAM may be selected from a consensus or a particular PAM sequence for a specific Cas9 protein or Cas9 ortholog, including those disclosed in FIG. 1 of Ran et al., *Nature*, 520: 186-191 (2015), which is incorporated herein by reference. In some embodiments, the PAM may comprise 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. Non-limiting exemplary PAM sequences include NGG, NGGNG, NG, NAAAAN, NNAAA AW, NNNNACA, GNNNCNNA, and NNNNGATT (wherein N is defined as any nucleotide, and W is defined as either A or T). In some embodiments, the PAM sequence may be NGG. In some embodiments, the PAM sequence may be NGGNG. In some embodiments, the PAM sequence may be NNAAA AW. Additional evolved Cas variants and PAM sequences as described in Hu et al., *Evolved Cas9 variants with broad PAM compatibility and high DNA specificity*, *Nature* 2018 556(7699): 57-63 is incorporated herein in its entirety.

[0631] The target nucleic acid molecule may be any DNA or RNA molecule that is endogenous or exogenous to a cell. As used herein, the term "endogenous sequence" refers to a sequence that is native to the cell. The term "exogenous sequence" refers to a sequence that is not native to a cell, or a sequence whose native location in the genome of the cell is in a different location. In some embodiments, the target nucleic acid molecule may be a plasmid, a genomic DNA, or a chromosome from a cell or in the cell. In some embodiments, the target sequence of the target nucleic acid molecule may be a genomic sequence from a cell or in the cell. In some embodiments, the cell may be a prokaryotic cell. In other embodiments, the cell may be a eukaryotic cell. In some embodiments, the eukaryotic cell may be a mammalian cell. In some embodiments, the eukaryotic cell may be a rodent cell. In some embodiments, the eukaryotic cell may be a human cell. In some embodiments, the eukaryotic cell may be a liver cell. In some embodiments, the eukaryotic cell may be a hepatocyte. In some embodiments, the eukaryotic cell may be a parenchymal cell, a sinusoidal endothelial cell, a phagocytic Kupffer cell, or a stellate cell. In further embodiments, the target sequence may be a viral sequence. In yet other embodiments, the target sequence may be a

synthesized sequence. In some embodiments, the target sequence may be on a eukaryotic chromosome, such as a human chromosome.

[0632] In some embodiments, the target sequence may be located in a coding sequence of a gene, an intron sequence of a gene, a transcriptional control sequence of a gene, a translational control sequence of a gene, or a non-coding sequence between genes. In some embodiments, the gene may be a protein coding gene. In other embodiments, the gene may be a non-coding RNA gene. In some embodiments, the target sequence may comprise all or a portion of a disease-associated gene. In some embodiments, the target sequence may comprise all or a portion of a gene associated with a coronary disease. In some embodiments, the target sequence may comprise at least a portion of a gene encoding an apolipoprotein. In some embodiments, the target sequence may comprise at least a portion of a gene encoding Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), Angiopoietin-like protein 3 (ANGPTL3), Apolipoprotein C3 (APOC3), Apolipoprotein A (LPA), LDL Receptor (LDL-R), Myosin regulatory light chain interacting protein or inducible degrader of the LDL receptor (IDOL), Transthyretin (TTR), Antithrombin, AT3, Apolipoprotein B (ApoB), or Hup. The present disclosure also contemplates the use of modification to manipulate expression and activity of target genes, e.g., use of destabilizing mutations to counteract the effect of a gain-of-function PCSK9 variant.

[0633] The nucleic acid sequences of exemplary target genes and of other members of the family of human origin and those of a number of animals are publicly available, e.g., from the NCBI website or ENSEMBL website. Examples include, but are not limited to the following sequences: Wild Type PCSK9 Gene (NG_009061.1), Homo sapiens proprotein convertase subtilisin/kexin type 9 (PCSK9), RefSeqGene (LRG_275) on chromosome 1; human APOC3 Deposit No. NP_000031.1, GenBank Accession Nos.: NG_008949.1; Mouse, rat and monkey APOC3 nucleic acid sequences Ensembl accession number ENSMUSG000000032081, ENSRNOG000000047503, and ENSMFAG00000001837, respectively; human ANGPTL3 is provided, for example, in NG_028169.1; Mouse, rat, and monkey ANGPTL3 nucleic acid sequences Ensembl accession number ENSMUSG000000028553, ENSRNOG00000008638, and ENSMFAG00000007083, respectively; each of which sequences are incorporated herein in its entirety.

[0634] In some embodiments, contacting a target sequences with the genome editing composition described herein leads to a base editing event within or adjacent to the target sequence. For example, a target base (e.g. a C base) within or adjacent to a target sequence may be converted to a T base as the result of contact with the genome editing composition as disclosed in the present disclosure comprising a fusion protein comprising a nucleic acid guided nuclease domain and a

deaminase domain. In some embodiments, the target base is located upstream (5' end of) of the PAM. In some embodiments, the target base is located at a position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 base pairs upstream (5' end of) the PAM. In some embodiments, the target base is located at a position within 13 to 17 base pairs upstream (5' end) of the PAM. In some embodiments, the target base is located at a position outside of 13 to 17 base pairs upstream (5' end) of the PAM. In some embodiments, the target base pair is located at a position 10-15 base pairs upstream (5' end) of the PAM. In some embodiments, the target base is located at a position 11-12 base pairs upstream of the PAM. In some embodiments, the target base is 11 base pairs upstream (5' end) of the PAM. In some embodiments, the target base is located in the coding region (e.g., an exon) of the target sequence, e.g. the ANGPTL3 encoding polynucleotide (e.g., the ANGPTL3 gene locus). For example, conversion of a base in the coding region of the ANGPTL3 gene locus may result in an amino acid change in the ANGPTL3 protein sequence, i.e., a mutation. In some embodiments, the mutation is a loss of function mutation. In some embodiments, a mutation may introduce a pre-mature stop codon into the coding region the target sequence, e.g. coding region of the ANGPTL3 gene. In some embodiments, a loss-of-function mutation is a naturally occurring loss-of-function mutation. In some embodiments, the mutation is located in the coding region of the PCSK9 gene, e.g. a G106R, L253F, A443T, R93C, G24D, S47F, R46H, S 153N, or H193Y mutation. In some embodiments, the loss-of-function mutation introduces a pre-mature stop codon into the coding region of the ANGPTL3 gene. In some embodiments, a loss of function mutation may be introduced into the coding region of a APOC3 gene, e.g. a R19X mutation. In some embodiments, a loss of function mutation may be introduced into a Low-Density Lipoprotein Receptor (LDL-R) protein. In some embodiments, a loss of function mutation may be introduced into a Inducible Degradator of the LDL Receptor (IDOL) protein.

[0635] In some embodiments, a target sequence is located in a non-coding region of the target sequence, e.g., in an intron or a splicing site of a target gene. In some embodiments, a target sequence is located in a splicing site and the editing of such target base causes alternative splicing of the target gene mRNA. In some embodiments, the alternative splicing leads to leading to loss-of-function mutants. In some embodiments, the alternative splicing leads to introduction of a premature stop codon or a frameshift in the target mRNA, resulting in truncated, unstable, or folding-defective polypeptides. In some embodiments, stop codons may be introduced into the coding sequence of a apolipoprotein encoding gene upstream of the normal stop codon (referred to as a "premature stop codon"). In some embodiments, stop codons may be introduced into the

coding region of the target gene. Premature stop codons cause premature translation termination, in turn resulting in truncated and nonfunctional proteins and induces rapid degradation of the mRNA via the non-sense mediated mRNA decay pathway. See, e.g., Baker et al., *Current Opinion in Cell Biology* 16 (3): 293-299, 2004; Chang et al, *Annual Review of Biochemistry* 76: 51-74, 2007; and Behm-Ansmant et al, *Genes & Development* 20 (4): 391-398, 2006, each of which is incorporated herein by reference. The genome editing composition described herein may be used to introduce multiple editing events to the target sequence. For example, the genome editing composition may comprise a nucleic acid guide programmable nuclease that induces double strand breaks, deletions, insertions, frameshift, reversions, or other alterations in the target gene. For example, the genome editing composition may comprise a nucleic acid guided programmable nuclease-deaminase fusion protein that can convert several amino acids to create a stop codon (e.g., TAA, TAG, or TGA).

[0636] In some embodiments, simultaneous introduction of mutations into more than one protein factors in the LDL-mediated cholesterol clearance pathway are provided. For example, in some embodiments, a mutation may be simultaneously introduced into one or more, preferably at least two, of ANGPTL3, PCSK9, LDLR, APOB, APOE, IDOL, and other LDL-mediated pathway involved genes. In some embodiments, a loss-of-function mutation may be simultaneously introduced into one or more, preferably at least two, of ANGPTL3, PCSK9, APOB, and another LDL-mediated pathway involved gene. In some embodiments, mutations may be simultaneously introduced into ANGPTL3, PCSK9, LDLR, and IDOL. To simultaneously introduce of loss-of-function mutations into more than one protein, multiple guide nucleotide sequences are used.

[0637] In some embodiments, the target sequence may be located in a non-genic functional site in the genome that controls aspects of chromatin organization, such as a scaffold site or locus control region. In some embodiments, the target sequence may be a genetic safe harbor site, i.e., a locus that facilitates safe genetic modification.

Templates

[0638] In some embodiments, at least one template may be provided as a substrate during the repair of the cleaved target nucleic acid molecule. In some embodiments, the template may be used in homologous recombination, such as, e.g., high-fidelity homologous recombination. In some embodiments, the homologous recombination may result in the integration of the template sequence into the target nucleic acid molecule. In some embodiments, a single template or multiple copies of the same template may be provided. In other embodiments, two or more templates may be provided such that homologous recombination may occur at two or more target sites. For example, different templates may be provided to repair a single gene in a cell, or two different genes in a cell. In some

embodiments, the different templates may be provided in independent copy numbers.

[0639] In some embodiments, the template may be used in homology-directed repair, requiring DNA strand invasion at the site of the cleavage in the nucleic acid. In some embodiments, the homology-directed repair may result in the copying of the template sequence into the target nucleic acid molecule. In some embodiments, a single template or multiple copies of the same template may be provided. In other embodiments, two or more templates having different sequences may be inserted at two or more sites by homology-directed repair. For example, different templates may be provided to repair a single gene in a cell, or two different genes in a cell. In some embodiments, the different templates may be provided in independent copy numbers.

[0640] In some embodiments, the template may be incorporated into the cleaved nucleic acid as an insertion mediated by non-homologous end joining. In some embodiments, the template sequence has no similarity to the nucleic acid sequence near the cleavage site. In some embodiments, the template sequence (e.g., the coding sequence in the template) has no similarity to the nucleic acid sequence near the cleavage site. The template sequence may be flanked by target sequences that may have similar or identical sequence(s) to a target sequence near the cleavage site. In some embodiments, a single template or multiple copies of the same template may be provided. In other embodiments, two or more templates having different sequences may be inserted at two or more sites by non-homologous end joining. For example, different templates may be provided to insert a single template in a cell, or two different templates in a cell. In some embodiments, the different templates may be provided in independent copy numbers.

[0641] In some embodiments, the template sequence may correspond to an endogenous sequence of a target cell. In some embodiments, the endogenous sequence may be a genomic sequence of the cell. In some embodiments, the endogenous sequence may be a chromosomal or extrachromosomal sequence. In some embodiments, the endogenous sequence may be a plasmid sequence of the cell. In some embodiments, the template sequence may be substantially identical to a portion of the endogenous sequence in a cell at or near the cleavage site, but comprise at least one nucleotide change. In some embodiments, the repair of the cleaved target nucleic acid molecule with the template may result in a mutation comprising an insertion, deletion, or substitution of one or more nucleotides of the target nucleic acid molecule. In some embodiments, the mutation may result in one or more amino acid changes in a protein expressed from a gene comprising the target sequence. In some embodiments, the mutation may result in one or more nucleotide changes in an RNA expressed from the target gene. In some embodiments, the mutation may alter the expression level of the target gene. In some embodiments, the mutation may result in increased or decreased expression of the target gene. In some embodiments, the mutation may result in gene knockdown.

In some embodiments, the mutation may result in gene knockout. In some embodiments, the repair of the cleaved target nucleic acid molecule with the template may result in replacement of an exon sequence, an intron sequence, a transcriptional control sequence, a translational control sequence, or a non-coding sequence of the target gene.

[0642] In other embodiments, the template sequence may comprise an exogenous sequence. In some embodiments, the exogenous sequence may comprise a protein or RNA coding sequence operably linked to an exogenous promoter sequence such that, upon integration of the exogenous sequence into the target nucleic acid molecule, the cell is capable of expressing the protein or RNA encoded by the integrated sequence. In other embodiments, upon integration of the exogenous sequence into the target nucleic acid molecule, the expression of the integrated sequence may be regulated by an endogenous promoter sequence. In some embodiments, the exogenous sequence may be a chromosomal or extrachromosomal sequence. In some embodiments, the exogenous sequence may provide a cDNA sequence encoding a protein or a portion of the protein. In yet other embodiments, the exogenous sequence may comprise an exon sequence, an intron sequence, a transcriptional control sequence, a translational control sequence, or a non-coding sequence. In some embodiments, the integration of the exogenous sequence may result in gene knock-in.

[0643] The template may be of any suitable length. In some embodiments, the template may comprise 10, 15, 20, 25, 50, 75, 100, 150, 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, or more nucleotides in length. In some embodiments, the template may comprise a nucleotide sequence that is complementary to a portion of the target nucleic acid molecule comprising the target sequence (i.e., a “homology arm”). In some embodiments, a homology arm may comprise 10, 15, 20, 25, 50, 75, 100, 150, 200, 500, 1000, 1500, 2000, 2500, 3000 or more nucleotides in length. In some embodiments, the template may comprise a homology arm that is complementary to the sequence located upstream or downstream of the cleavage site on the target nucleic acid molecule. In some embodiments, the template may comprise a first nucleotide sequence and a second homology arm that are complementary to the sequences located upstream and downstream of the cleavage site, respectively. Where a template contains two homology arms, each arm can be the same length or different lengths, and the sequence between the homology arms can be substantially similar or identical to the target sequence between the homology arms, or be entirely unrelated. In some embodiments, the degree of complementarity between the first nucleotide sequence on the template and the sequence upstream of the cleavage site, and between the second nucleotide sequence on the template and the sequence downstream of the cleavage site, may permit homologous recombination, such as, e.g., high-fidelity homologous recombination, between the template and the target nucleic acid molecule. In some embodiments,

the degree of complementarity may be about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100%. In some embodiments, the degree of complementarity may be about 95%, 97%, 98%, 99%, or 100%. In some embodiments, the degree of complementarity may be about 98%, 99%, or 100%. In some embodiments, the degree of complementarity may be 100%. In some embodiments, for example those described herein where a template is incorporated into the cleaved nucleic acid as an insertion mediated by non-homologous end joining, the template has no homology arms. In some embodiments, a template having no homology arms comprises target sequences flanking one or both ends of the template sequence, e.g., as described herein. In some embodiments, a template having no homology arms comprises target sequences flanking both ends of the template sequence. In some embodiments, a target sequence flanking the end of the template sequence is about 10-50 nucleotides. In some embodiments, a target sequence flanking the end of the template sequence is about 10-20 nucleotides, about 15-20 nucleotides, about 20-25 nucleotides, or about 20-30 nucleotides. In some embodiments, a target sequence flanking the end of the template sequence is about 17-23 nucleotides. In some embodiments, a target sequence flanking the end of the template sequence is about 20 nucleotides.

[0644] In some embodiments, a nucleic acid molecule is expressed from the template if homologous recombination occurs between the template and the genomic sequence. In some embodiments, for example, the template does not have a promoter for expressing the nucleic acid molecule and/or the ATG transcriptional start site is removed from the coding sequence.

Delivery

[0645] Provided herein are methods and compositions for editing a nucleic acid molecule in a cell with a nuclease system and targeted delivery thereof. In some embodiments, the nucleic acid comprises a nucleic acid sequence encoding a gene. In some embodiments, the nucleic acid comprises a nucleic acid sequence encoding a gene associated with a disease or disorder.

[0646] The active agents comprising nucleic acids described herein, e.g. modified guide RNAs, may be conjugated with one or more targeting moieties for targeted delivery to desired in vivo locations. The guide RNA conjugates or guide RNA-protein complex conjugates may be introduced into the cell via any methods known in the art, such as, e.g., viral or bacteriophage infection, transfection, conjugation, protoplast fusion, lipofection, lipid particle or vesicle transduction, electroporation, calcium phosphate precipitation, polyethyleneimine (PEI)-mediated transfection, DEAE-dextran-mediated transfection, liposome-mediated transfection, e.g. transfection mediated by cationic liposomes, particle gun technology, calcium phosphate precipitation, shear-driven cell permeation, fusion to a cell-penetrating peptide followed by cell contact, microinjection, and

nanoparticle-mediated delivery. In some embodiments, the nuclease system may be introduced into the cell via viral infection. In some embodiments, the nuclease system may be introduced into the cell via bacteriophage infection. Liposomes may include those formed from 1,2-dioleoyloxy-N,N-dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from Marina Biotech (Bothell, WA), 1,2-dilinoleoyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and liposomes which may deliver small molecule drugs such as, but not limited to, DOXIL® (from Janssen Biotech, Inc. (Horsham, PA)).

[0647] In some embodiments, the methods and compositions provided herein may comprise introducing a vector system described herein into a cell. In some embodiments, the vector system encodes the nuclease system in whole or in part. In some embodiments, the vector system comprises one, two, three, or more vectors. In some embodiments, the introduction of the vector system into the cell may result in a stable cell line having the edited nucleic acid molecule while the vectors are lost, e.g., targeted for self-destruction. In some embodiments, the cell is a eukaryotic cell. Non-limiting examples of eukaryotic cells include yeast cells, plant cells, insect cells, cells from an invertebrate animal, cells from a vertebrate animal, mammalian cells, rodent cells, mouse cells, rat cells, and human cells. In some embodiments, the eukaryotic cell may be a mammalian cell. In some embodiments, the eukaryotic cell may be a rodent cell. In some embodiments, the eukaryotic cell may be a human cell. Similarly, the target sequence may be from any such cells or in any such cells.

[0648] In some embodiments, the polynucleotides or oligonucleotides provided herein, for example guide RNAs or mRNAs, may be formulated in a lipid vesicle which may have crosslinks between functionalized lipid bilayers, or lipid-polycation complex. The liposome formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size, or poly cationic composition. In one embodiment, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery in vitro and in vivo. The lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limited to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine, large intestine, colon, rectum), respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). The formulations may use nanoparticles

larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs which had been thought to be too large to rapidly diffuse through mucosal barriers. The dynamic transport of nanoparticles may be measured using fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). The formulations can be made for controlled release and/or targeted delivery. The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, mRNA, anionic protein (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecylammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocysteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β 4, dornase alfa, neltenequine, erdosteine) and various DNases including rhDNase. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed or dispersed (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle.

[0649] In a further embodiment, guide RNA of the present disclosure and the CRISPR system may be formulated as a lipoplex, such as, without limitation, the ATUPLEX™ system, the DACC system, the DBTC system and other siRNA-lipoplex technology. The liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of the modified guide RNAs for example by increasing cell transfection, increasing the translation of encoded protein or increasing the stability. A cell penetrating peptide may be used with the pharmaceutical formulations of the present disclosure such as a cell-penetrating peptide sequence attached to polycations that facilitates delivery to the intracellular space, e.g., HIV-derived TAT peptide, penetratins, transportans, or hCT derived cell-penetrating peptides. In another embodiment, lipid nanoparticles which target specific cell types may be used. Alternatively, the lipid nanoparticle may be encapsulated into any polymer or hydrogel known in the art which may form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable. In yet another embodiment, the pharmaceutical compositions may be sustained release formulations. In a further embodiment, the sustained release formulations may be for subcutaneous delivery. Sustained release formulations may include, but are not limited to, PLGA microspheres, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyne Therapeutics, San Diego, CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc

Deerfield, IL).

[0650] In some embodiments, the nucleic acids as described herein, such as a guide RNA, may be complexed with a CRISPR enzyme. In some embodiments, a part or all of the complex may be delivered via a vector system comprising one or more vectors. In some embodiments, the vector may be a DNA vector. In other embodiments, the vector may be an RNA vector. In some embodiments, the RNA vector may be an mRNA, e.g. an mRNA that encodes a nuclease such as Cas9. In some embodiments, the vector may be circular. In other embodiments, the vector may be linear. Non-limiting exemplary vectors include plasmids, phagemids, cosmids, artificial chromosomes, minichromosomes, transposons, viral vectors, and expression vectors. In some embodiments, the nuclease is provided by an RNA vector, e.g., as mRNA, and the template is provided by a viral vector. In some embodiments, the vector may be a viral vector. In some embodiments, the viral vector may be genetically modified from its wild-type counterpart. For example, the viral vector may comprise an insertion, deletion, or substitution of one or more nucleotides to facilitate cloning or such that one or more properties of the vector is changed. Such properties may include packaging capacity, transduction efficiency, immunogenicity, genome integration, replication, transcription, and translation. In some embodiments, a portion of the viral genome may be deleted such that the virus is capable of packaging exogenous sequences having a larger size. In some embodiments, the viral vector may have an enhanced transduction efficiency. In some embodiments, the immune response induced by the virus in a host may be reduced. In some embodiments, viral genes (such as, e.g., integrase) that promote integration of the viral sequence into a host genome may be mutated such that the virus becomes non-integrating. In some embodiments, the viral vector may be replication defective. In some embodiments, the viral vector may comprise exogenous transcriptional or translational control sequences to drive expression of coding sequences on the vector. In some embodiments, the virus may be helper-dependent. For example, the virus may need one or more helper virus to supply viral components (such as, e.g., viral proteins) required to amplify and package the vectors into viral particles. In such a case, one or more helper components, including one or more vectors encoding the viral components, may be introduced into a host cell along with the vector system described herein. In other embodiments, the virus may be helper-free. For example, the virus may be capable of amplifying and packaging the vectors without any helper virus. In some embodiments, the vector system described herein may also encode the viral components required for virus amplification and packaging.

[0651] Non-limiting exemplary viral vectors include adeno-associated virus (AAV) vector, lentivirus vectors, adenovirus vectors, herpes simplex virus (HSV-1) vectors, bacteriophage T4, baculovirus vectors, and retrovirus vectors. In some embodiments, the viral vector may be an AAV

vector. In other embodiments, the viral vector may be a lentivirus vector. In some embodiments, the lentivirus may be non-integrating. In some embodiments, the viral vector may be an adenovirus vector. In some embodiments, the adenovirus may be a high-cloning capacity or “gutless” adenovirus, where all coding viral regions apart from the 5' and 3' inverted terminal repeats (ITRs) and the packaging signal (Ψ) are deleted from the virus to increase its packaging capacity. In yet other embodiments, the viral vector may be an HSV-1 vector. In some embodiments, the HSV-1-based vector is helper dependent, and in other embodiments it is helper independent. For example, an amplicon vector that retains only the packaging sequence requires a helper virus with structural components for packaging, while a 30 kb-deleted HSV-1 vector that removes non-essential viral functions does not require helper virus. In additional embodiments, the viral vector may be bacteriophage T4. In some embodiments, the bacteriophage T4 may be able to package any linear or circular DNA or RNA molecules when the head of the virus is emptied. In further embodiments, the viral vector may be a baculovirus vector. In yet further embodiments, the viral vector may be a retrovirus vector. In embodiments using AAV or lentiviral vectors, which have smaller cloning capacity, it may be necessary to use more than one vector to deliver all the components of a vector system as disclosed herein. For example, one AAV vector may contain sequences encoding a Cas9 protein, while a second AAV vector may contain one or more guide sequences and one or more copies of template.

[0652] In certain embodiments, a viral vector may be modified to target a particular tissue or cell type. For example, viral surface proteins may be altered to decrease or eliminate viral protein binding to its natural cell surface receptor(s). In some embodiments, the vector may be modified for liver specific delivery. The surface proteins may also be engineered to interact with a receptor specific to a desired cell type. Viral vectors may have altered host tropism, including limited or redirected tropism. In some embodiments, the viral vector may be engineered to express or display a first binding moiety. The first binding moiety may be fused to a viral surface protein or glycoprotein, conjugated to a virus, chemically crosslinked to a virion, bound to a virus envelope, or joined to a viral vector by any other suitable method. The first binding moiety is capable of binding to a second binding moiety, which may be used to direct the virus to a desired cell type. In some embodiments, the first binding moiety is avidin, streptavidin, neutravidin, captavidin, or another biotin-binding moiety, and the second binding moiety is biotin or an analog thereof. A biotinylated targeting agent may then be bound to the avidin on the viral vector and used to direct the virus to a desired cell type. For example, a T4 vector may be engineered to display a biotin-binding moiety on one or more of its surface proteins. The cell-specificity of such a T4 vector may then be altered by binding a biotinylated antibody or ligand directed to a cell of choice. In alternate

embodiments, the first and second binding moieties are hapten and an anti-hapten binding protein; digoxigenin and an anti-digoxigenin binding protein; fluorescein and an anti-fluorescein binding protein; or any other suitable first and second binding moieties that are binding partners.

[0653] In some embodiments, the vector may be capable of driving expression of one or more coding sequences in a cell. In some embodiments, the cell may be a prokaryotic cell, such as, e.g., a bacterial cell. In some embodiments, the cell may be a eukaryotic cell, such as, e.g., a yeast, plant, insect, or mammalian cell. In some embodiments, the eukaryotic cell may be a mammalian cell. In some embodiments, the eukaryotic cell may be a rodent cell. In some embodiments, the eukaryotic cell may be a human cell. Suitable promoters to drive expression in different types of cells are known in the art. In some embodiments, the promoter may be wild-type. In other embodiments, the promoter may be modified for more efficient or efficacious expression. In yet other embodiments, the promoter may be truncated yet retain its function. For example, the promoter may have a normal size or a reduced size that is suitable for proper packaging of the vector into a virus.

[0654] In some embodiments, the vector may comprise a nucleotide sequence encoding the nuclease described herein. In some embodiments, the vector system may comprise one copy of the nucleotide sequence encoding the nuclease. In other embodiments, the vector system may comprise more than one copy of the nucleotide sequence encoding the nuclease. In some embodiments, the nucleotide sequence encoding the nuclease may be operably linked to at least one transcriptional or translational control sequence. In some embodiments, the nucleotide sequence encoding the nuclease may be operably linked to at least one promoter. In some embodiments, the nucleotide sequence encoding the nuclease may be operably linked to at least one transcriptional or translational control sequence.

[0655] In some embodiments, the promoter may be constitutive, inducible, or tissue-specific. In some embodiments, the promoter may be a constitutive promoter. Non-limiting exemplary constitutive promoters include cytomegalovirus immediate early promoter (CMV), simian virus (SV40) promoter, adenovirus major late (MLP) promoter, Rous sarcoma virus (RSV) promoter, mouse mammary tumor virus (MMTV) promoter, phosphoglycerate kinase (PGK) promoter, elongation factor-alpha (EF1 α) promoter, ubiquitin promoters, actin promoters, tubulin promoters, immunoglobulin promoters, a functional fragment thereof, or a combination of any of the foregoing. In some embodiments, the promoter may be a CMV promoter. In some embodiments, the promoter may be a truncated CMV promoter. In other embodiments, the promoter may be an EF1 α promoter. In some embodiments, the promoter may be an inducible promoter. Non-limiting exemplary inducible promoters include those inducible by heat shock, light, chemicals, peptides, metals, steroids, antibiotics, or alcohol. In some embodiments, the inducible promoter may be one

that has a low basal (non-induced) expression level, such as, e.g., the Tet-On® promoter (Clontech). In some embodiments, the promoter may be a tissue-specific promoter. In some embodiments, the tissue-specific promoter is exclusively or predominantly expressed in liver tissue. Non-limiting exemplary tissue-specific promoters include B29 promoter, CD14 promoter, CD43 promoter, CD45 promoter, CD68 promoter, desmin promoter, elastase-1 promoter, endoglin promoter, fibronectin promoter, Flt-1 promoter, GFAP promoter, GPIIb promoter, ICAM-2 promoter, INF- β promoter, Mb promoter, Nphs1 promoter, OG-2 promoter, SP-B promoter, SYN1 promoter, and WASP promoter.

[0656] In some embodiments, the vector may encode a Cas protein or a portion of a Cas protein, such as a Cas9 protein or Cpf1 protein. The vector system may further comprise a vector comprising a nucleotide sequence encoding the guide RNA described herein. In some embodiments, the vector system may comprise one copy of the guide RNA. In other embodiments, the vector system may comprise more than one copy of the guide RNA. In embodiments with more than one guide RNA, the guide RNAs may be non-identical such that they target different target sequences, or have other different properties, such as activity or stability within the Cas9 RNP complex. In some embodiments, the nucleotide sequence encoding the guide RNA may be operably linked to at least one transcriptional or translational control sequence. In some embodiments, the nucleotide sequence encoding the guide RNA may be operably linked to at least one promoter. In some embodiments, the promoter may be recognized by RNA polymerase III (Pol III). Non-limiting examples of Pol III promoters include U6, H1 and tRNA promoters. In some embodiments, the nucleotide sequence encoding the guide RNA may be operably linked to a mouse or human U6 promoter. In other embodiments, the nucleotide sequence encoding the guide RNA may be operably linked to a mouse or human H1 promoter. In some embodiments, the nucleotide sequence encoding the guide RNA may be operably linked to a mouse or human tRNA promoter. In embodiments with more than one guide RNA, the promoters used to drive expression may be the same or different. In some embodiments, the nucleotide encoding the crRNA of the guide RNA and the nucleotide encoding the tracr RNA of the guide RNA may be provided on the same vector. In some embodiments, the nucleotide encoding the crRNA and the nucleotide encoding the tracr RNA may be driven by the same promoter. In some embodiments, the crRNA and tracr RNA may be transcribed into a single transcript. For example, the crRNA and tracr RNA may be processed from the single transcript to form a double-molecule guide RNA. Alternatively, the crRNA and tracr RNA may be transcribed into a single-molecule guide RNA. In other embodiments, the crRNA and the tracr RNA may be driven by their corresponding promoters on the same vector. In yet other embodiments, the crRNA and the tracr RNA may be encoded by different vectors.

[0657] In some embodiments, the vector system may further comprise a vector comprising the template described herein. In some embodiments, the vector system may comprise one copy of the template. In other embodiments, the vector system may comprise more than one copy of the template. In some embodiments, the vector system may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, or more copies of the template. In some embodiments, the vector system may comprise 4, 5, 6, 7, 8, or more copies of the template. In some embodiments, the vector system may comprise 5, 6, 7, or more copies of the template. In some embodiments, the vector system may comprise 6 copies of the template. The multiple copies of the template may be located on the same or different vectors. The multiple copies of the template may also be adjacent to one another, or separated by other nucleotide sequences or vector elements. In other embodiments, two or more templates may be provided such that homologous recombination may occur at two or more target sites. For example, different templates may be provided to repair a single gene in a cell, or two different genes in a cell. In some embodiments, the different templates may be provided in independent copy numbers.

[0658] A vector system may comprise 1-3 vectors. In some embodiments, the vector system may comprise one single vector. In other embodiments, the vector system may comprise two vectors. In additional embodiments, the vector system may comprise three vectors.

[0659] In some embodiments, the nucleotide sequence encoding the nuclease and the template may be located on the same or separate vectors. In some embodiments, the nucleotide sequence encoding the nuclease and the template may be located on the same vector. In some embodiments, the nucleotide sequence encoding the nuclease and the template may be located on separate vectors. The sequences may be oriented in the same or different directions and in any order on the vector.

[0660] In some embodiments, the nucleotide sequence encoding a Cas9 protein and a template may be located on the same or separate vectors. In some embodiments, all of the sequences may be located on the same vector. In some embodiments, two or more sequences may be located on the same vector. The sequences may be oriented in the same or different directions and in any order on the vector. In some embodiments, the nucleotide sequence encoding the Cas9 protein and the nucleotide sequence encoding the guide RNA may be located on the same vector. In some embodiments, the nucleotide sequence encoding the Cas9 protein and the template may be located on the same vector. In a particular embodiment, the vector system may comprise a first vector comprising the nucleotide sequence encoding the Cas9 protein, and a second vector comprising the nucleotide sequence encoding the template or multiple copies of the template.

[0661] In some embodiments, the template may be released from the vector on which it is located by the nuclease system encoded by the vector system. In some embodiments, the template may be released from the vector by a Cas9 protein provided from an mRNA. The template may

comprise at least one target sequence that is recognized by the guide RNA. In some embodiments, the template may be flanked by a target sequence at the 5' and 3' ends of the template. Upon expression of Cas9 protein and delivery of the guide RNA, the guide RNA may hybridize with and the Cas9 protein may cleave the target sequence at both ends of the template such that the template is released from the vector. In additional embodiments, the template may be released from the vector by a nuclease encoded by the vector system by having a target sequence recognized by the nuclease at the 5' and 3' ends of the template. The target sequences at either end of the template may be oriented such that the PAM sequence is closer to the template. In such an orientation, fewer non-template nucleic acids remain on the ends of the template after release from the vector. In some embodiments, the target sequences flanking the template may be the same. In some embodiments, the target sequences flanking the template may be the same as the target sequence found at the cleavage site in which the template is incorporated, e.g., by HR, HDR, or non-homologous end joining. In other embodiments, the target sequences flanking the template may be different. For example, the target sequence at the 5' end of the template may be recognized by one guide RNA or nuclease, and the target sequence at the 3' end of the template may be recognized by another guide RNA or nuclease.

[0662] In some embodiments, the vector encoding the nuclease system may comprise at least one target sequence within the vector, to create a self-destroying (or “self-cleaving” or “self-inactivating”) vector system to control the amount of the nuclease system to be expressed. In some embodiments, the self-destroying vector system results in a reduction in the amount of nuclease activity. In further embodiments, the self-destroying vector system results in a reduction in the amount of vector nucleic acid. In embodiments in which the system comprises Cas9, it also comprises guide RNA(s) that recognize the target sequence. In this way, the residence time and/or the level of activity of the nuclease system may be temporally controlled to avoid adverse effects associated with overexpression of the nuclease system. Such adverse effects may include, e.g., an off-target effect by the nuclease. In some embodiments, one or more target sequences may be located at any place on the vector such that, upon expression of the nuclease, the nuclease recognizes and cleaves the target sequence in the vector that contains the nuclease-encoding sequence. The one or more target sequences of the self-destroying vector may be the same. Optionally, the self-destroying vector may comprise multiple target sequences. In some embodiments, the cleavage at a target sequence may reduce the expression of at least one component of the nuclease system, such as, for example, Cas9. In some embodiments, the cleavage may reduce the expression of the nuclease transcript. For example, a target sequence may be located within the nucleotide sequence encoding the nuclease such that the cleavage results in the

disruption of the coding region. In other embodiments, a target sequence may be located within a non-coding region on the vector encoding the nuclease. In some embodiments, a target sequence may be located within the promoter that drives the expression of the nuclease such that the cleavage results in the disruption of the promoter sequence. For example, the vector may contain a target sequence (and its corresponding guide RNA) that targets a Cas9 sequence. In certain embodiments, a target sequence may be located between the promoter and the nucleotide sequence encoding the nuclease such that the cleavage results in the separation of the coding sequence from its promoter. In certain embodiments, a target sequence outside the nuclease coding sequence and a target sequence within the nuclease coding sequence are included.

[0663] In some embodiments, the vector encoding a Cas9 protein may comprise at least one target sequence that is recognized by a guide RNA. In some embodiments, the target sequence may be located at any place on the vector such that, upon expression of the Cas9 protein and the guide RNA, the guide RNA hybridizes with and the Cas9 protein cleaves the target sequence in the vector encoding the Cas9 protein. In some embodiments, the cleavage at the target sequence may reduce the expression of the Cas9 protein transcript. For example, the target sequence may be located within the nucleotide sequence encoding the Cas9 protein such that the cleavage results in the disruption of the coding region. In other embodiments, the target sequence may be located within a non-coding region on the vector encoding the Cas9 protein. In some embodiments, the target sequence may be located within the promoter that drives the expression of the Cas9 protein such that the cleavage results in the disruption of the promoter sequence. In some embodiments, the target sequence may be located within the nucleotide sequence encoding the Cas9 protein such that the cleavage results in the disruption of the coding sequence. In other embodiments, the target sequence may be located between the promoter and the nucleotide sequence encoding the Cas9 protein such that the cleavage results in the separation of the coding sequence from its promoter.

[0664] The target sequences for release of the template, for vector self-destruction, and for targeting by the nuclease system in a cell may be the same or different. For example, the target sequence at the 3' end of the template may be present within the promoter driving the expression of the nuclease (e.g., the Cas9 protein) such that the release of the template simultaneously results in the disruption of the expression of the nuclease (e.g., the Cas9 protein). In some embodiments, both target sequences flanking the template, the target sequences for disrupting the expression of the nuclease (e.g., the Cas9 protein), and the target sequence in the target nucleic acid molecule in a cell may be the same sequence that is recognized by a single guide RNA or nuclease. Thus, in some embodiments, the vector system may comprise only one type of target sequence, and the nuclease system may comprise only one guide RNA. In other embodiments, these target sequences may

comprise different sequences that are recognized by different guide RNAs.

[0665] In some embodiments, the vector system may comprise inducible promoters to start expression only after it is delivered to a target cell. Non-limiting exemplary inducible promoters include those inducible by heat shock, light, chemicals, peptides, metals, steroids, antibiotics, or alcohol. In some embodiments, the inducible promoter may be one that has a low basal (non-induced) expression level, such as, e.g., the Tet-On® promoter (Clontech).

[0666] In additional embodiments, the vector system may comprise tissue-specific promoters to start expression only after it is delivered into a specific tissue. Non-limiting exemplary tissue-specific promoters include albumin promoter, α -1 antitrypsin promoter, hemopexin promoter, B29 promoter, CD14 promoter, CD43 promoter, CD45 promoter, CD68 promoter, desmin promoter, elastase-1 promoter, endoglin promoter, fibronectin promoter, Flt-1 promoter, GFAP promoter, GPIIb promoter, ICAM-2 promoter, INF- β promoter, Mb promoter, Nphsl promoter, OG-2 promoter, SP-B promoter, SYN1 promoter, and WASP promoter. In particular embodiments, the tissue specific promoter is an albumin promoter, a α -1 antitrypsin promoter, a hepatitis B virus core promoter, or a hemopexin gene promoter. Methods of examining liver specific promoters are described in Kramer et al., Molecular Therapy 7(3): 375-385 (2003), which is incorporated herein in its entirety by reference.

[0667] In some embodiments of the present disclosure, the activity of the nuclease system may be temporally regulated by adjusting the residence time, the amount, and/or the activity of the expressed components of the nuclease system. For example, as described herein, the nuclease may be fused with a protein domain that is capable of modifying the intracellular half-life of the nuclease. In certain embodiments involving two or more vectors (e.g., a vector system in which the components described herein are encoded on two or more separate vectors), the activity of the nuclease system may be temporally regulated by controlling the timing in which the vectors are delivered. For example, in some embodiments a vector encoding the nuclease system may deliver the nuclease prior to the vector encoding the template. In other embodiments, the vector encoding the template may deliver the template prior to the vector encoding the nuclease system. In some embodiments, the vectors encoding the nuclease system and template are delivered simultaneously. In certain embodiments, the simultaneously delivered vectors temporally deliver, e.g., the nuclease, template, and/or guide RNA components. In further embodiments, the RNA (such as, e.g., the nuclease transcript) transcribed from the coding sequence on the vectors may further comprise at least one element that is capable of modifying the intracellular half-life of the RNA and/or modulating translational control. In some embodiments, the half-life of the RNA may be increased. In some embodiments, the half-life of the RNA may be decreased. In some embodiments, the

element may be capable of increasing the stability of the RNA. In some embodiments, the element may be capable of decreasing the stability of the RNA. In some embodiments, the element may be within the 3' UTR of the RNA. In some embodiments, the element may include a polyadenylation signal (PA). In some embodiments, the element may include a cap, e.g., an upstream mRNA end. In some embodiments, the PA may be added to the 3' UTR of the RNA. In some embodiments, the RNA may comprise no PA such that it is subject to quicker degradation in the cell after transcription. In some embodiments, the element may include at least one AU-rich element (ARE). The AREs may be bound by ARE binding proteins (ARE-BPs) in a manner that is dependent upon tissue type, cell type, timing, cellular localization, and environment. In some embodiments the destabilizing element may promote RNA decay, affect RNA stability, or activate translation. In some embodiments, the ARE may comprise 50 to 150 nucleotides in length. In some embodiments, the ARE may comprise at least one copy of the sequence AUUUA. In some embodiments, at least one ARE may be added to the 3' UTR of the RNA. In some embodiments, the element may be a Woodchuck Hepatitis Virus (WHP) Posttranscriptional Regulatory Element (WPRE), which creates a tertiary structure to enhance expression from the transcript. In further embodiments, the element is a modified and/or truncated WPRE sequence that is capable of enhancing expression from the transcript, as described, for example in Zufferey et al., J Virol, 73(4): 2886-92 (1999) and Flajolet et al., J Virol, 72(7): 6175-80 (1998). In some embodiments, the WPRE or equivalent may be added to the 3' UTR of the RNA. In some embodiments, the element may be selected from other RNA sequence motifs that are enriched in either fast- or slow-decaying transcripts.

[0668] Embodiments of the disclosure also encompass treating a patient with the vector system described herein. In some embodiments, the method may comprise administering the vector system described herein to the patient. The method may be used as a single therapy or in combination with other therapies available in the art. In some embodiments, the patient may have a mutation (such as, e.g., insertion, deletion, substitution, chromosome translocation) in a disease-associated gene. In some embodiments, administration of the vector system may result in a mutation comprising an insertion, deletion, or substitution of one or more nucleotides of the disease-associated gene in the patient. Certain embodiments may include methods of repairing the patient's mutation in the disease-associated gene. In some embodiments, the mutation may result in one or more amino acid changes in a protein expressed from the disease-associated gene. In some embodiments, the mutation may result in one or more nucleotide changes in an RNA expressed from the disease-associated gene. In some embodiments, the mutation may alter the expression level of the disease-associated gene. In some embodiments, the mutation may result in increased or decreased expression of the gene. In some embodiments, the mutation may result in gene knockdown in the

patient. In some embodiments, the administration of the vector system may result in the correction of the patient's mutation in the disease-associated gene. In some embodiments, the administration of the vector system may result in gene knockout in the patient. In some embodiments, the administration of the vector system may result in replacement of an exon sequence, an intron sequence, a transcriptional control sequence, a translational control sequence, or a non-coding sequence of the disease-associated gene.

[0669] In some embodiments, the administration of the vector system may result in integration of an exogenous sequence of the template into the patient's genomic DNA. In some embodiments, the exogenous sequence may comprise a protein or RNA coding sequence operably linked to an exogenous promoter sequence such that, upon integration of the exogenous sequence into the patient's genomic DNA, the patient is capable of expressing the protein or RNA encoded by the integrated sequence. The exogenous sequence may provide a supplemental or replacement protein coding or non-coding sequence. For example, the administration of the vector system may result in the replacement of the mutant portion of the disease-associated gene in the patient. In some embodiments, the mutant portion may include an exon of the disease-associated gene. In other embodiments, the integration of the exogenous sequence may result in the expression of the integrated sequence from an endogenous promoter sequence present on the patient's genomic DNA. For example, the administration of the vector system may result in supply of a functional gene product of the disease-associated gene to rectify the patient's mutation. In some embodiments, the administration of the vector system may result in integration of a cDNA sequence encoding a protein or a portion of the protein. In yet other embodiments, the administration of the vector system may result in integration of an exon sequence, an intron sequence, a transcriptional control sequence, a translational control sequence, or a non-coding sequence into the patient's genomic DNA. In some embodiments, the administration of the vector system may result in gene knockin in the patient.

Administration

[0670] Provided herein are methods and compositions for editing a target nucleic acid in a cell. Further provided herein are pharmaceutical compositions and methods for modifying the function and activity of a target gene in a cell of a subject. The genome editing compositions described herein may be administered to a subject in need thereof in a therapeutically effective amount, to treat conditions related to high circulating cholesterol levels and/or coronary disease, e.g. hypercholesterolemia, elevated total cholesterol levels, elevated low-density lipoprotein (LDL) levels, elevated LDL-cholesterol levels, reduced high-density lipoprotein levels, liver steatosis,

coronary heart disease, ischemia, stroke, peripheral vascular disease, thrombosis, type 2 diabetes, high elevated blood pressure, atherosclerosis, obesity, Alzheimer's disease, neurodegeneration, and combinations thereof can be administered to the subject in a variety of ways, including parenterally, intravenously, intradermally, intramuscularly, colonically, rectally or intraperitoneally. In some embodiments, the pharmaceutical composition may be co-administered with pharmaceutically acceptable salt by intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject. In some embodiments, the pharmaceutical composition may be directly injected to a specific tissue, such as the liver tissue. In some embodiments, the pharmaceutical compositions can be administered parenterally, intravenously, intramuscularly or orally. The oral formulations can be further coated or treated to prevent or reduce dissolution in stomach. The compositions of the present disclosure can be administered to a subject using any suitable methods known in the art. Suitable formulations for use in the present disclosure and methods of delivery are generally well known in the art. For example, the composition of the present disclosure can be formulated as pharmaceutical compositions with a pharmaceutically acceptable diluent, carrier or excipient. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions including pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, such as, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

[0671] Pharmaceutical formulations described herein can be administrable to a subject in a variety of ways by multiple administration routes, including but not limited to, oral, parenteral (*e.g.*, intravenous, subcutaneous, intramuscular, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intralymphatic, intranasal injections), intranasal, buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[0672] In some embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulations containing an composition or inhibitory agent described herein are in the form of a capsule. In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions or solutions selected from the group including, but not limited to, aqueous oral dispersions, emulsions, solutions, elixirs, gels, and

syrups.

[0673] For administration by inhalation, a composition or inhibitory agent described herein can be formulated for use as an aerosol, a mist or a powder. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner. In some embodiments, a composition or inhibitory agent described herein can be prepared as transdermal dosage forms. In some embodiments, a composition or inhibitory agent described herein can be formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection. In some embodiments, a composition or inhibitory agent described herein can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. In some embodiments, a composition or inhibitory agent described herein can be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas.

Dosage

[0674] Appropriate dosage or effective amounts for administration vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual subject parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. Factors involved in dosage determination are known to those of ordinary skill in the art without additional experimentation other than routine test. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. Empirical considerations, such as the half-life, generally will contribute to the determination of the dosage. For example, therapeutic agents that are compatible with the human immune system, such as polypeptides comprising regions from humanized antibodies or fully human antibodies, may be used to prolong half-life of the polypeptide and to prevent the polypeptide being attacked by the host's immune system.

[0675] Frequency of administration may be determined and adjusted over the course of therapy, and is generally, but not necessarily, based on treatment and/or suppression and/or amelioration and/or delay of a disease. Alternatively, sustained continuous release formulations of a polypeptide or a polynucleotide may be appropriate. Various formulations and devices for achieving sustained release are known in the art. In some embodiments, dosage is daily, every other day, every three days, every four days, every five days, or every six days. In some embodiments,

dosing frequency is once every week, every 2 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, or every 10 weeks; or once every month, every 2 months, or every 3 months, or longer. The progress of this therapy is easily monitored by conventional techniques and assays.

[0676] The dosing regimen can vary over time. In some embodiments, for an adult subject of normal weight, doses ranging from about 0.01 to 1000 mg/kg may be administered. In some embodiments, the dose is between 1 to 200 mg. In some embodiments, the doses may range from about 0.01 to 0.05mg/kg, between about 0.01 to 0.1mg/kg, between about 0.01 to 1mg/kg, between about 0.01 to 10mg/kg, between about 0.01 to 100 mg/kg, between 0.01 to 500mg/kg, between about 0.1 to 1mg/kg, between about 0.1 to 5mg/kg, between about 0.1 to 10mg/kg, between about 0.1 to 100mg/kg, between about 0.1 to 500mg/kg, between about 0.1 to 1000mg/kg, between about 1 to 5mg/kg, between about 1 to 10mg/kg, between about 1 to 100mg/kg, between about 1 to 500mg/kg, between about 1 to 1000mg/kg, between about 10 to 100mg/kg, between about 10 to 500mg/kg, between about 10 to 1000mg/kg, or between about 100 to 1000 mg/kg. The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular subject and that subject's medical history, as well as the properties of the polypeptide or the polynucleotide (such as the half-life of the polypeptide or the polynucleotide, and other considerations well known in the art).

[0677] As will be apparent to those skilled in the art, the appropriate dosage of a therapeutic agent as described herein will depend on the specific agent (or compositions thereof) employed, the formulation and route of administration, the type and severity of the disease, whether the polypeptide or the polynucleotide is administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the antagonist, and the discretion of the attending physician. Typically the clinician will administer a polypeptide until a dosage is reached that achieves the desired result.

[0678] Administration of one or more therapeutic compositions, e.g. polypeptides, polynucleotides, or RNPs, can be continuous or intermittent, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of a polypeptide may be essentially continuous over a preselected period of time or may be in a series of spaced dose, e.g., either before, during, or after developing a disease.

Biological samples

[0679] A sample, e.g., a biological sample can be taken from a subject. A biological sample can

comprise a plurality of biological samples. The plurality of biological samples can contain two or more biological samples; for examples, about 2–1000, 2–500, 2–250, 2–100, 2–75, 2–50, 2–25, 2–10, 10–1000, 10–500, 10–250, 10–100, 10–75, 10–50, 10–25, 25–1000, 25–500, 25–250, 25–100, 25–75, 25–50, 50–1000, 50–500, 50–250, 50–100, 50–75, 60–70, 100–1000, 100–500, 100–250, 250–1000, 250–500, 500–1000, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, or more biological samples. The biological samples can be obtained from a plurality of subjects, giving a plurality of sets of a plurality of samples. The biological samples can be obtained from about 2 to about 1000 subjects, or more; for example, about 2–1000, 2–500, 2–250, 2–100, 2–50, 2–25, 2–20, 2–10, 10–1000, 10–500, 10–250, 10–100, 10–50, 10–25, 10–20, 15–20, 25–1000, 25–500, 25–250, 25–100, 25–50, 50–1000, 50–500, 50–250, 50–100, 100–1000, 100–500, 100–250, 250–1000, 250–500, 500–1000, or at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 68, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 or more subjects.

[0680] The biological samples can be obtained from human subjects. The biological samples can be obtained from human subjects at different ages. The human subject can be prenatal (*e.g.*, a fetus), a child (*e.g.*, a neonate, an infant, a toddler, a preadolescent), an adolescent, a pubescent, or an adult (*e.g.*, an early adult, a middle aged adult, a senior citizen). The human subject can be between about 0 months and about 120 years old, or older. The human subject can be between about 0 and about 12 months old; for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months old. The human subject can be between about 0 and 12 years old; for example, between about 0 and 30 days old; between about 1 month and 12 months old; between about 1 year and 3 years old; between about 4 years and 5 years old; between about 4 years and 12 years old; about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 years old. The human subject can be between about 13 years and 19 years old; for example, about 13, 14, 15, 16, 17, 18, or 19 years old. The human subject can be between about 20 and about 39 year old; for example, about 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, or 39 years old. The human subject can be between about 40 to about 59 years old; for example, about 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59 years old. The human subject can be greater than 59 years old; for example, about 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, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, or 120 years old. The human subjects can include living subjects or deceased subjects. The human subjects can include male subjects and/or female subjects.

[0681] Biological samples can be obtained from any suitable source that allows determination of expression levels of genes, *e.g.*, from cells, tissues, bodily fluids or secretions, or a gene expression product derived therefrom (*e.g.*, nucleic acids, such as DNA or RNA; polypeptides, such as protein or protein fragments). The nature of the biological sample can depend upon the nature of the subject. If a biological sample is from a subject that is a unicellular organism or a multicellular organism with undifferentiated tissue, the biological sample can comprise cells, such as a sample of a cell culture, an excision of the organism, or the entire organism. If a biological sample is from a multicellular organism, the biological sample can be a tissue sample, a fluid sample, or a secretion.

[0682] The biological samples can be obtained from different tissues. The term tissue is meant to include ensembles of cells that are of a common developmental origin and have similar or identical function. The term tissue is also meant to encompass organs, which can be a functional grouping and organization of cells that can have different origins. The biological sample can be obtained from any tissue.

[0683] The biological samples can be obtained from different tissue samples from one or more humans or non-human animals. Suitable tissues can include connective tissues, muscle tissues, nervous tissues, epithelial tissues or a portion or combination thereof. Suitable tissues can also include all or a portion of a lung, a heart, a blood vessel (*e.g.*, artery, vein, capillary), a salivary gland, a esophagus, a stomach, a liver, a gallbladder, a pancreas, a colon, a rectum, an anus, a hypothalamus, a pituitary gland, a pineal gland, a thyroid, a parathyroid, an adrenal gland, a kidney, a ureter, a bladder, a urethra, a lymph node, a tonsil, an adenoid, a thymus, a spleen, skin, muscle, a brain, a spinal cord, a nerve, an ovary, a fallopian tube, a uterus, vaginal tissue, a mammary gland, a testicle, a vas deferens, a seminal vesicle, a prostate, penile tissue, a pharynx, a larynx, a trachea, a bronchi, a diaphragm, bone marrow, a hair follicle, or a combination thereof. A biological sample from a human or non-human animal can also include a bodily fluid, secretion, or excretion; for example, a biological sample can be a sample of aqueous humour, vitreous humour, bile, blood, blood serum, breast milk, cerebrospinal fluid, endolymph, perilymph, female ejaculate, amniotic fluid, gastric juice, menses, mucus, peritoneal fluid, pleural fluid, saliva, sebum, semen, sweat, tears, vaginal secretion, vomit, urine, feces, or a combination thereof. The biological sample can be from healthy tissue, diseased tissue, tissue suspected of being diseased, or a combination thereof.

[0684] In some embodiments, the biological sample is a fluid sample, for example a sample of

blood, serum, sputum, urine, semen, or other biological fluid. In certain embodiments the sample is a blood sample. In some embodiments the biological sample is a tissue sample, such as a tissue sample taken to determine the presence or absence of disease in the tissue. In certain embodiments the sample is a sample of thyroid tissue.

[0685] The biological samples can be obtained from subjects in different stages of disease progression or different conditions. Different stages of disease progression or different conditions can include healthy, at the onset of primary symptom, at the onset of secondary symptom, at the onset of tertiary symptom, during the course of primary symptom, during the course of secondary symptom, during the course of tertiary symptom, at the end of the primary symptom, at the end of the secondary symptom, at the end of tertiary symptom, after the end of the primary symptom, after the end of the secondary symptom, after the end of the tertiary symptom, or a combination thereof. Different stages of disease progression can be a period of time after being diagnosed or suspected to have a disease; for example, at least about, or at least, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 hours; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 days; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 years after being diagnosed or suspected to have a disease. Different stages of disease progression or different conditions can include before, during or after an action or state; for example, treatment with drugs, treatment with a surgery, treatment with a procedure, performance of a standard of care procedure, resting, sleeping, eating, fasting, walking, running, performing a cognitive task, sexual activity, thinking, jumping, urinating, relaxing, being immobilized, being emotionally traumatized, being shock, and the like.

[0686] The methods of the present disclosure provide for analysis of a biological sample from a subject or a set of subjects. The subject(s) may be, *e.g.*, any animal (*e.g.*, a mammal), including but not limited to humans, non-human primates, rodents, dogs, cats, pigs, fish, and the like. The present methods and compositions can apply to biological samples from humans, as described herein.

[0687] A biological sample can be obtained by methods known in the art such as the biopsy methods provided herein, swabbing, scraping, phlebotomy, or any other suitable method. The biological sample can be obtained, stored, or transported using components of a kit of the present disclosure. In some cases, multiple biological samples, such as multiple thyroid samples, can be obtained for analysis, characterization, or diagnosis according to the methods of the present disclosure. In some cases, multiple biological samples, such as one or more samples from one

tissue type (*e.g.*, thyroid) and one or more samples from another tissue type (*e.g.*, buccal) can be obtained for diagnosis or characterization by the methods of the present disclosure. In some cases, multiple samples, such as one or more samples from one tissue type (*e.g.*, thyroid) and one or more samples from another tissue (*e.g.*, buccal) can be obtained at the same or different times. In some cases, the samples obtained at different times are stored and/or analyzed by different methods. For example, a sample can be obtained and analyzed by cytological analysis (*e.g.*, using routine staining). In some cases, a further sample can be obtained from a subject based on the results of a cytological analysis. The diagnosis of a disease or condition, *e.g.* a coronary disease can include examination of a subject by a physician, nurse or other medical professional. The examination can be part of a routine examination, or the examination can be due to a specific complaint including, but not limited to, one of the following: pain, illness, anticipation of illness, presence of a suspicious lump or mass, a disease, or a condition. The subject may or may not be aware of the disease or condition. The medical professional can obtain a biological sample for testing. In some cases the medical professional can refer the subject to a testing center or laboratory for submission of the biological sample. The methods of obtaining provided herein include methods of biopsy including fine needle aspiration, core needle biopsy, vacuum assisted biopsy, incisional biopsy, excisional biopsy, punch biopsy, shave biopsy or skin biopsy. In some cases, the methods and compositions provided herein are applied to data only from biological samples obtained by FNA. In some cases, the methods and compositions provided herein are applied to data only from biological samples obtained by FNA or surgical biopsy. In some cases, the methods and compositions provided herein are applied to data only from biological samples obtained by surgical biopsy. A biological sample can be obtained by non-invasive methods, such methods including, but not limited to: scraping of the skin or cervix, swabbing of the cheek, saliva collection, urine collection, feces collection, collection of menses, tears, or semen. The biological sample can be obtained by an invasive procedure, such procedures including, but not limited to: biopsy, alveolar or pulmonary lavage, needle aspiration, or phlebotomy. The method of biopsy can further include incisional biopsy, excisional biopsy, punch biopsy, shave biopsy, or skin biopsy. The method of needle aspiration can further include fine needle aspiration, core needle biopsy, vacuum assisted biopsy, or large core biopsy. Multiple biological samples can be obtained by the methods herein to ensure a sufficient amount of biological material. Generic methods for obtaining biological samples are also known in the art and further described in for example Ramzy, Ibrahim *Clinical Cytopathology and Aspiration Biopsy* 2001 which is herein incorporated by reference in its entirety. The biological sample can be a fine needle aspirate of a thyroid nodule or a suspected thyroid tumor. The fine needle aspirate sampling procedure can be guided by the use of an ultrasound, X-ray, or other

imaging device.

[0688] In some cases, the subject can be referred to a specialist such as an oncologist, surgeon, or endocrinologist for further diagnosis. The specialist can likewise obtain a biological sample for testing or refer the individual to a testing center or laboratory for submission of the biological sample. In any case, the biological sample can be obtained by a physician, nurse, or other medical professional such as a medical technician, endocrinologist, cytologist, phlebotomist, radiologist, or a pulmonologist. The medical professional can indicate the appropriate test or assay to perform on the sample, or the molecular profiling business of the present disclosure can consult on which assays or tests are most appropriately indicated. The molecular profiling business can bill the individual or medical or insurance provider thereof for consulting work, for sample acquisition and or storage, for materials, or for all products and services rendered.

[0689] A medical professional need not be involved in the initial diagnosis or sample acquisition. An individual can alternatively obtain a sample through the use of an over the counter kit. The kit can contain a means for obtaining said sample as described herein, a means for storing the sample for inspection, and instructions for proper use of the kit. In some cases, molecular profiling services are included in the price for purchase of the kit. In other cases, the molecular profiling services are billed separately.

[0690] A biological sample suitable for use by the molecular profiling business can be any material containing tissues, cells, nucleic acids, genes, gene fragments, expression products, gene expression products, and/or gene expression product fragments of an individual to be tested. Methods for determining sample suitability and/or adequacy are provided. The biological sample can include, but is not limited to, tissue, cells, and/or biological material from cells or derived from cells of an individual. The sample can be a heterogeneous or homogeneous population of cells or tissues. The biological sample can be obtained using any method known to the art that can provide a sample suitable for the analytical methods described herein.

[0691] Obtaining a biological sample can be aided by the use of a kit. A kit can be provided containing materials for obtaining, storing, and/or shipping biological samples. The kit can contain, for example, materials and/or instruments for the collection of the biological sample (*e.g.*, sterile swabs, sterile cotton, disinfectant, needles, syringes, scalpels, anesthetic swabs, knives, curette blade, liquid nitrogen, *etc.*). The kit can contain, for example, materials and/or instruments for the storage and/or preservation of biological samples (*e.g.*, containers; materials for temperature control such as ice, ice packs, cold packs, dry ice, liquid nitrogen; chemical preservatives or buffers such as formaldehyde, formalin, paraformaldehyde, glutaraldehyde, alcohols such as ethanol or methanol, acetone, acetic acid, HOPE fixative (Hepes–glutamic acid buffer–mediated organic

solvent protection effect), heparin, saline, phosphate buffered saline, TAPS, bicine, Tris, tricine, TAPSO, HEPES, TES, MOPS, PIPES, cadodylate, SSC, MES, phosphate buffer; protease inhibitors such as aprotinin, bestatin, calpain inhibitor I and II, chymostatin, E-64, leupeptin, alpha-2-macroglobulin, pefabloc SC, pepstatin, phenylmethanesulfonyl fluoride, trypsin inhibitors; DNase inhibitors such as 2-mercaptoethanol, 2-nitro-5-thicyanobenzoic acid, calcium, EGTA, EDTA, sodium dodecyl sulfate, iodoacetate, *etc.*; RNase inhibitors such as ribonuclease inhibitor protein; double-distilled water; DEPC (diethyprocarbonate) treated water, *etc.*). The kit can contain instructions for use. The kit can be provided as, or contain, a suitable container for shipping. The shipping container can be an insulated container. The shipping container can be self-addressed to a collection agent (*e.g.*, laboratory, medical center, genetic testing company, *etc.*). The kit can be provided to a subject for home use or use by a medical professional. Alternatively, the kit can be provided directly to a medical professional.

[0692] One or more biological samples can be obtained from a given subject. In some cases, between about 1 and about 50 biological samples are obtained from the given subject; for example, about 1-50, 1-40, 1-30, 1-25, 1-20, 1-15, 1-10, 1-7, 1-5, 5-50, 5-40, 5-30, 5-25, 5-15, 5-10, 10-50, 10-40, 10-25, 10-20, 25-50, 25-40, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 biological samples can be obtained from the given subject. Multiple biological samples from the given subject can be obtained from the same source (*e.g.*, the same tissue), *e.g.*, multiple blood samples, or multiple tissue samples, or from multiple sources (*e.g.*, multiple tissues). Multiple biological samples from the given subject can be obtained at the same time or at different times. Multiple biological samples from the given subject can be obtained at the same condition or different condition. Multiple biological samples from the given subject can be obtained at the same disease progression or different disease progression of the subject. If multiple biological samples are collected from the same source (*e.g.*, the same tissue) from the particular subject, the samples can be combined into a single sample. Combining samples in this way can ensure that enough material is obtained for testing and/or analysis.

[0693] Also described herein is an RNA molecule comprising the IVT mRNA sequence initiator described herein. In some embodiments, the RNA comprises a guide RNA or a nuclease mRNA.

[0694] Also described herein is a cell containing an RNA molecule comprising the IVT mRNA sequence initiator described herein.

[0695] Also described herein is a cell containing a polypeptide translated from an RNA molecule comprising the IVT mRNA sequence initiator described herein.

- [0696] Also described herein is a method for synthesizing an RNA molecule comprising:
- introducing the IVT mRNA sequence initiator described herein into a mixture comprising an RNA polymerase, and
 - incubating the mixture for a time sufficient to allow for transcription of the RNA molecule.

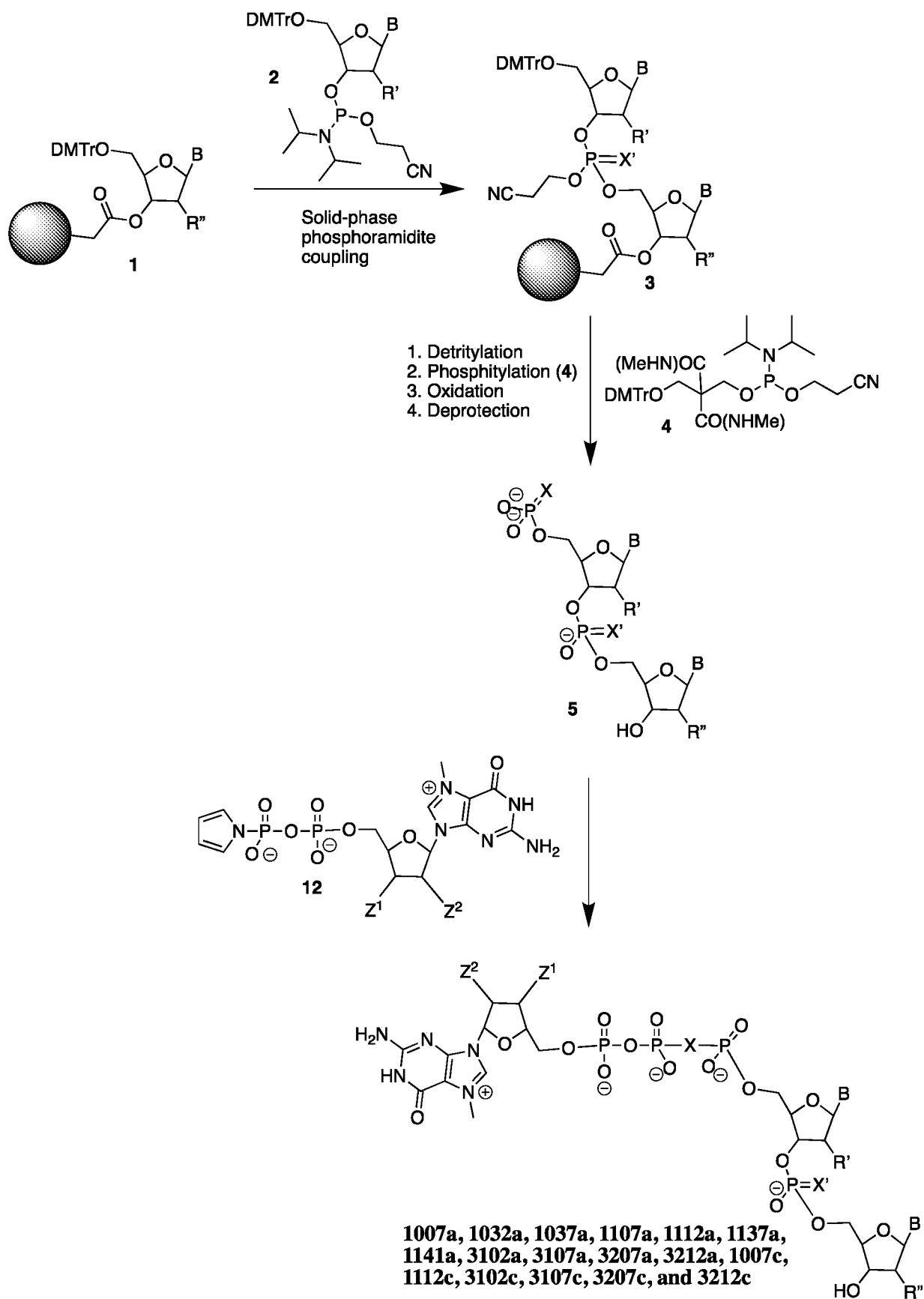
[0697] Also described herein is a method of gene editing comprising introducing into a cell an RNA molecule described herein, or pharmaceutical composition described herein, wherein the RNA molecule comprises guide RNA or a nuclease mRNA, wherein the RNA molecule is translated in the cell.

EXAMPLES

[0698] The following examples are provided to better illustrate the present disclosure and are not to be interpreted as limiting the scope of the disclosure. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the disclosure. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the disclosure.

Synthesis of cap structures

Example 1. Preparation of trinucleotide caps 1007a, 1032a, 1037a, 1107a, 1112a, 1137a, 1141a, 3102a, 3107a, 3207a, 3212a, 1007c, 1112c, 3102c, 3107c, 3207c, and 3212c



[0699] The dinucleotide 5'-phosphate 7 is prepared from the solid support 1 and phosphoramidite 3 by following standard solid phase oligonucleotide synthesis and deprotection protocol (Methods in Molecular Biology, 1993, 20, 81-114; ACS Chem. Biol. 2015, 10,

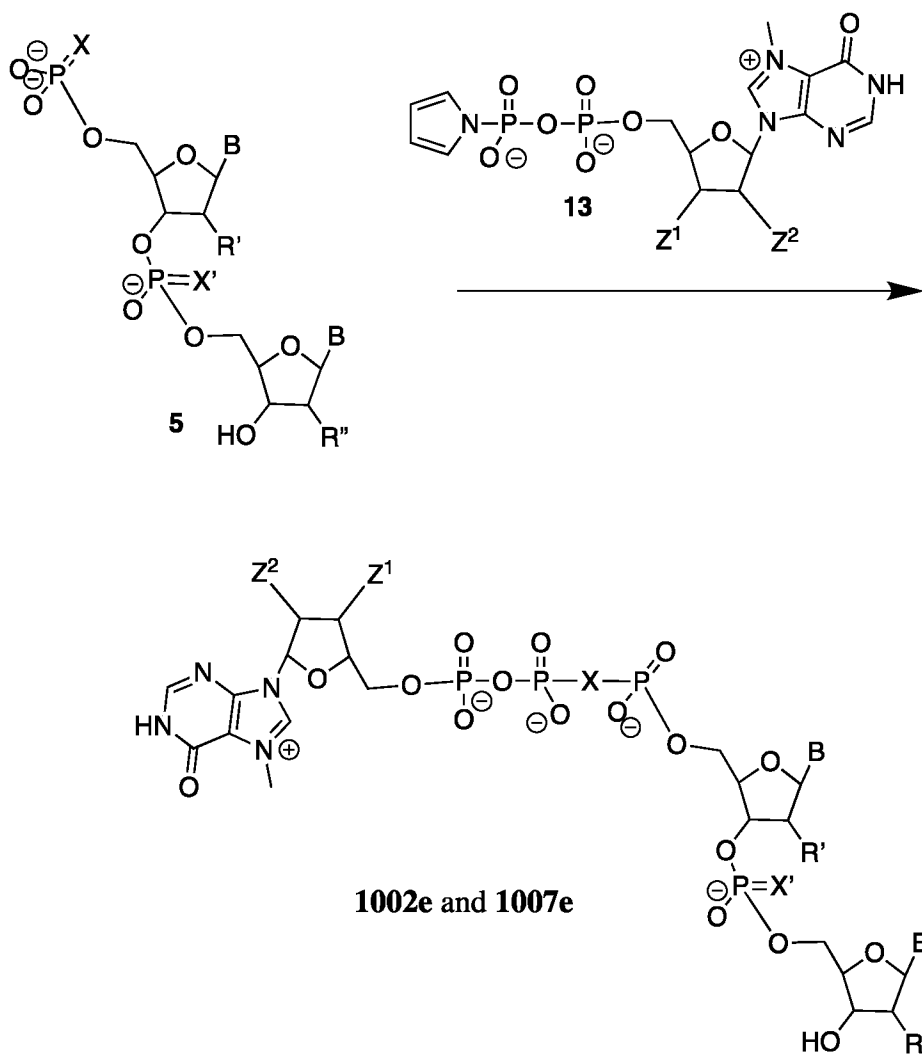
1181–1187, incorporated herein by reference in its entirety). The phosphoramidite **2** are purchased from commercial sources and/or custom synthesized. The detritylation of support bound fully protected dinucleotide **3** affords the 5'-deprotected dinucleotide intermediate on the support. The intermediate thus obtained is reacted with the 5'-phosphorylating agent **4** according to reported procedures (EP 816368 A1, <https://www.glenresearch.com/solid-chemical-phosphorylation-reagent-ii.html>, The Glen Report, 2011, 23, 10-11). After coupling and oxidation, the 5'-phosphorylated dinucleotide is treated with base followed by HPLC purification to obtain the fully deprotected dinucleotide 5'-phosphate **5** (<https://www.glenresearch.com/solid-chemical-phosphorylation-reagent-ii.html>).

[0700] Compound **12** is prepared from guanosine or 2' and/or 3' sugar-modified guanosine according to reported procedure (*Nucleic Acids Research*, **2016**, *44*, 9578; *RNA*, **2001**, *7*, 1486; WO 2017/053297 A1). Compound **12** is coupled with the dinucleotide 5'-monophosphate **5** as described in the literature (*Nucleic Acids Research*, **2016**, *44*, 9578, WO 2017/053297 A1) to afford the desired compounds **1007a**, **1032a**, **1037a**, **1107a**, **1112a**, **1137a**, **1141a**, **3102a**, **3107a**, **3207a**, **3212a**, **1007c**, **1112c**, **3102c**, **3107c**, **3207c**, and **3212c**.

[0701] As generally described here in Example 1, compounds **1007a** and **1107a** (Fig. 1) were synthesized. A final amount of about 1 gram of compound **1007a** was produced; this material was characterized by mass spectrometry and HPLC to have an actual mass of 1161 daltons and purity of 98.4%. Additionally, a final amount of about 250 milligrams of compound **1107a** was produced; this material was characterized by mass spectrometry and HPLC to have an actual mass of 1161 daltons and purity of 97.5%. These compounds were used as mRNA initiators, as described in Example 5.

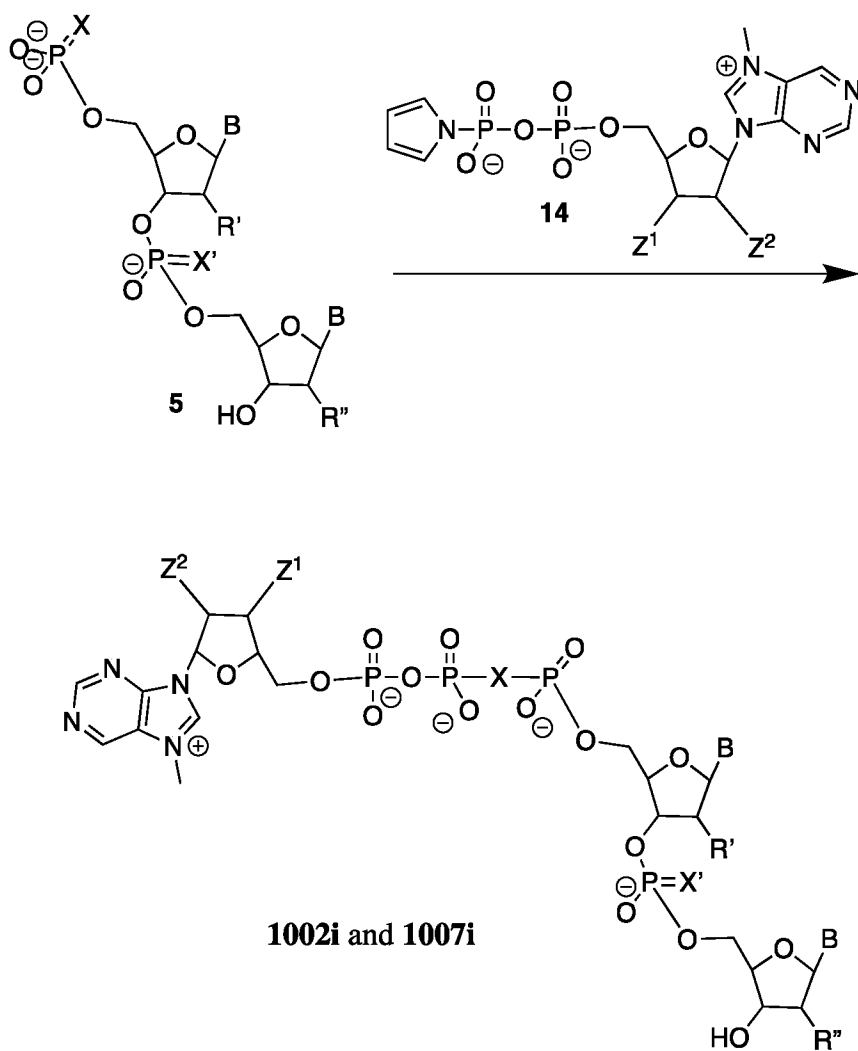
[0702]

Example 2. Preparation of trinucleotide caps 1002e and 1007e



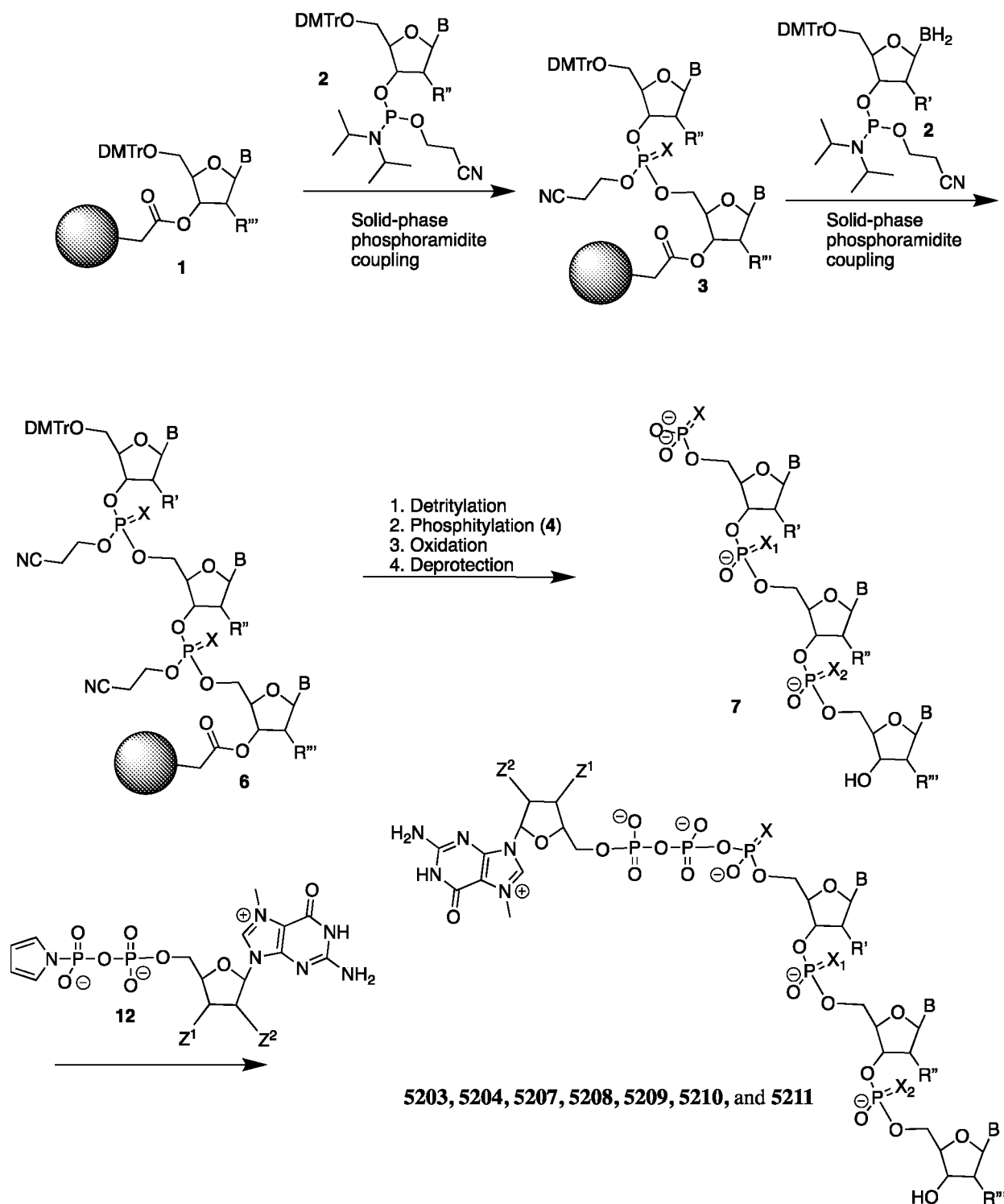
[0703] Compound **13** is prepared from inosine or 2' and/or 3' sugar-modified inosine (*Nucleic Acids Research*, **2016**, 44, 9578; *RNA*, **2001**, 7, 1486; WO 2017/053297 A1). Compound **13** is then coupled with dinucleotide 5'-monophosphate **5** to afford compounds **1002e** and **1007e** as described above in Example 1

Example 3. Preparation of trinucleotide caps **1002i** and **1007i**



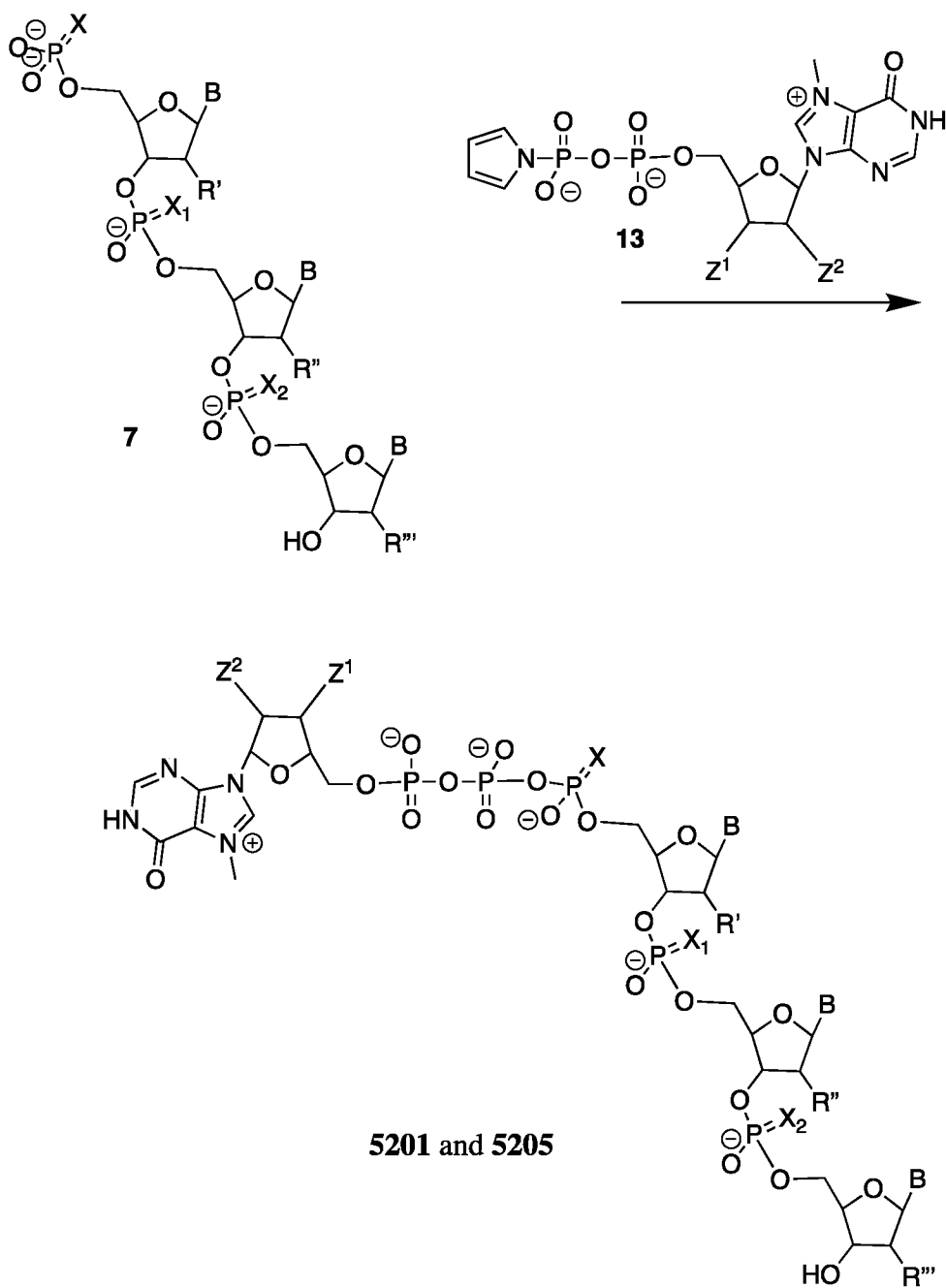
[0704] Compound **14** is prepared from nebularine or 2' and/or 3' sugar-modified nebularine. Compound **13** is then coupled with dinucleotide 5'-monophosphate **5** to afford compounds **1002i** and **1007i** as described above in Example 1.

Example 4. Preparation of tetranucleotide caps 5203, 5204, 5207, 5208, 5209, 5210, and 5211



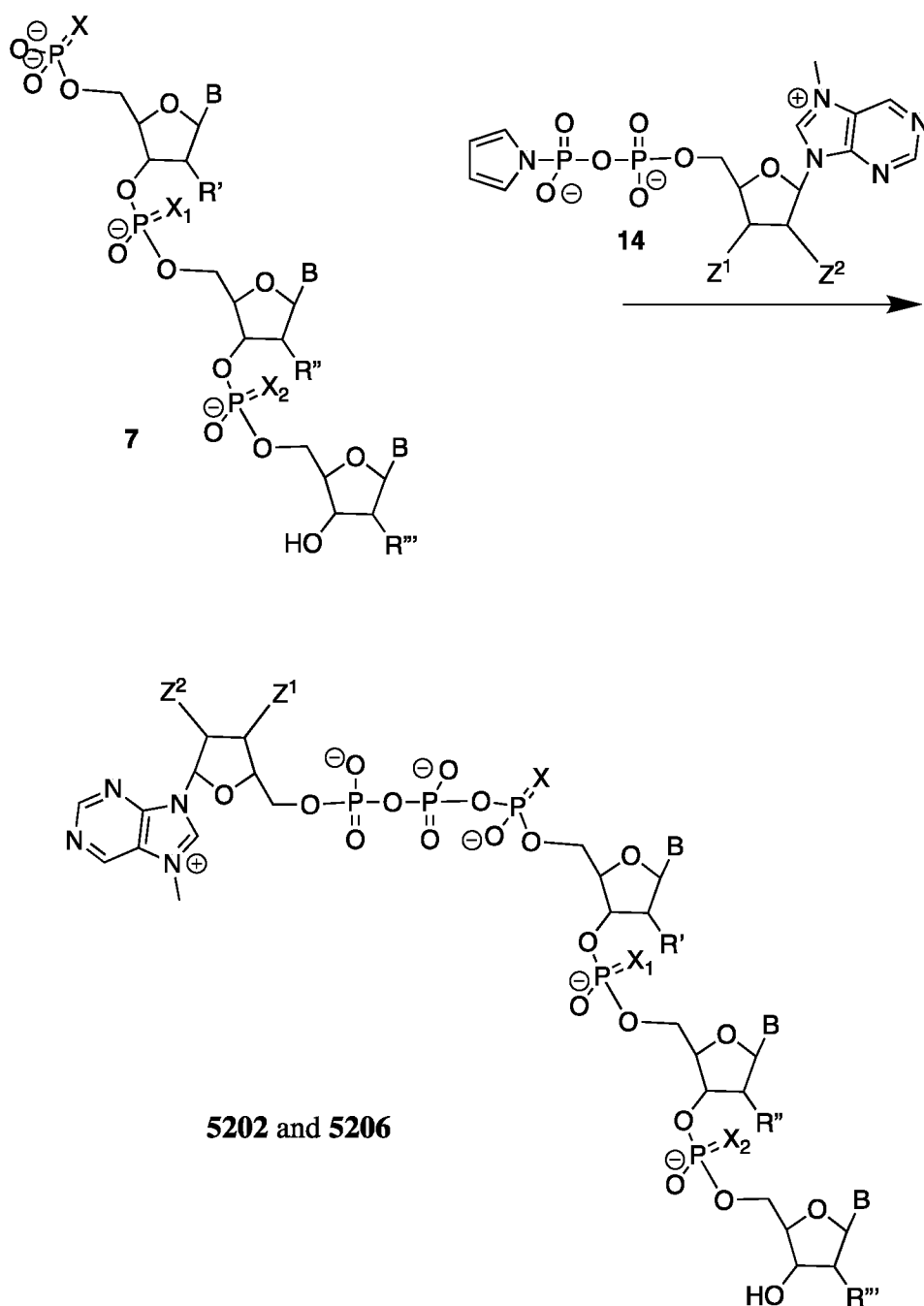
[0705] The trinucleotide 5'-monophosphate **7** is prepared from the solid support **1** by following a similar procedure described in Example 1 for the synthesis of the dinucleotide 5'-monophosphate. An additional phosphoramidite is coupled to the 5'-end of the fully-protected solid support bound dinucleotide under standard solid phase oligonucleotide conditions prior to reacting with the 5'-phosphorylating agent **4**. Compound **7** thus obtained is then reacted with compound **12** to afford compounds **5203**, **5204**, **5207**, **5208**, **5209**, **5210**, and **5211**.

Example 5. Preparation of tetranucleotide caps **5201** and **5205**



[0706] The desired compounds **5201** and **5205** are prepared from compound **7** and compound **13** as described in Examples 1-4.

Example 6. Preparation of tetranucleotide caps **5202** and **5206**



The desired compounds **5202** and **5206** are prepared from compound **7** and compound **14** as described in Examples 1-4.

Example 7. One-pot preparation of 5' capped mRNA

A. mRNA production

[0707] The 5' end initiator, **1007a**, (FIG. 1A) was used to prepare capped mRNAs that encode for ABE and luciferase proteins. In this Example and for all others described herein, the ABE mRNA sequence was MA004 (SEQ. 0001) and the luciferase mRNA sequence was the *Photinus pyralis* (Firefly) luciferase sequence described in NCBI reference sequence XM_031473197.1. These mRNA can be produced by different methods well known in the art. One of such methods

used herein was *in vitro* transcription (IVT) using T7 polymerase; or in other embodiments, additional RNA polymerase variants. This IVT reaction to produce mRNA used a linearized DNA template that comprised a T7 polymerase promoter and associated regulatory sequences, mRNA coding sequence (CDS), 3' and 5' untranslated regions (UTRs), poly A tail, and additional sequence elements to facilitate and modulate mRNA stability and *in vivo* performance. Prior to IVT, the DNA template was in the form of a plasmid; in other embodiments the DNA template is in the form of a PCR product, synthetic DNA product, or any other double-stranded DNA construct. Linearization of the DNA template with a restriction digestion enzyme was performed in order to promote run-off transcription. The typical IVT reaction included T7 polymerase, DNA template, RNase inhibitor, cap analog, inorganic pyrophosphatase, and the naturally occurring ribonucleoside triphosphates (NTPs) such as GTP, ATP, CTP, and N1-methyl pseudouridine triphosphate; in some embodiments NTPs include UTP or modified NTPs such as pseudouridine, 5'methyl cytidine, 5-methoxy uridine, N6-methyl adenosine, and N4-acetyl cytidine. The **1007a** 5' end initiator was added to the IVT reaction along with ATP, GTP, CTP, and N1-methyl pseudouridine triphosphate at a 1:1 initiator-to-NTP molar ratio and additional ratios described in Example 5(B). Poly A tail was encoded in the DNA template that was added to the mRNA during transcription; in some instances, poly A tail is added to the mRNA after the IVT reaction using an RNA ligase enzyme. Finally, T7 RNA polymerase was added to the mixture and the IVT reaction was run at 37°C for about 1-4 hours. After IVT, DNase was added to the transcription mixture to remove DNA template; in some instances, residual DNA is removed with chromatography. This mRNA was purified to remove residual reaction products and impurities, and stored in 1 mM citrate buffer. Characterization of production yield and mRNA full-length purity was performed by UV spectrometry and capillary gel electrophoresis methods, which are known in the art. The final production yield for ABE encoding mRNA with 5' end region motif, **1007a**, was about 3.3 mg per 1 ml of IVT reaction (FIG. 2) and the mRNA had a full-length purity of about 88% (FIG. 3). As a comparison, the production yield for ABE encoding mRNA with 5' end motif, **1002a**, a commercially available capping compound known in the art, was about 3.8 mg per 1 ml of IVT reaction (FIG. 2) and the mRNA had a full-length purity of about 86% (FIG. 3). Similar IVT and purification process are used to produce mRNA encoding SpCas9, Cas12b, CBE, and other ABEs; in all cases the DNA template, reaction conditions, and purification parameters are optimized for the specific gene of interest.

[0708] Similarly, ABE encoding mRNA with 5' end region, **1107a**, (FIG. 1B) was produced and characterized as described in the paragraph above. The final production yield for mRNA with 5' end region, **1107a**, was about 3.3 mg per 1 ml of IVT reaction (FIG. 2) and had a full-length

purity of about 86% (FIG. 3).

[0709] Similarly, exemplary trinucleotide 5' end initiators **1007e, 1007i, 1002e, 1002i, 1032a, 1037a, 1112a, 1137a, 1141a, 3102a, 3107a, 3207a, 3212a, 1007c, 1107c, 1112c, 3102c, 3107c, 3207c, 3212c, 5212, 5213, and 5214** (described in Table 1) that include additional modifications to the triphosphate bridge, phosphodiester linkages, ribose ring functional groups, and tetranucleotide bases and other modifications are used to produce 5' capped mRNA as described above.

[0710] Similarly, exemplary tetranucleotide 5' end initiators **5201, 5202, 5203, 5204, 5205, 5206, 5207, 5208, 5209, 5210, and 5211** (described in Table 1) are used to produce 5' capped mRNA as described above.

[0711] Similarly, in other embodiments, trinucleotide and tetranucleotide 5' end initiators shown in Table 1 can be used to produce 5' capped mRNA as described in the paragraph above, and As noted by this example and the data generated, these will exhibit similar properties based on the results of this example.

B. Adjustment of mRNA 5' end initiator-to-NTP molar ratio

[0712] The amount of capped mRNA produced in an IVT reaction is directly proportional to the ratio of cap to NTPs in the reaction mixture (Stepinski, J. et al., *RNA*. 2006, 7, 1486-1495). The 5' end initiator-to-NTP ratio in an IVT reaction impacts the amount of mRNA that becomes capped primarily because cap can compete with NTPs for insertion at the 5' end of mRNA. A typical initiator-to-NTP ratio for a dinucleotide cap structure is 4:1 and a typical molar initiator-to-NTP ratio for a trinucleotide cap structure is 1:1; where NTP represents either GTP, ATP, CTP, UTP, or modified NTPs such as N1-methyl pseudouridine. At both a 4:1 ratio for a dinucleotide cap and 1:1 ratio for a trinucleotide cap, the resultant mRNA will have a mixture of transcripts of which at least 80% are capped at the 5' end and up to 20% are uncapped, this is also described as a capping efficiency of 80%. Capping efficiency is the measured amount of capped mRNA divided by the total amount of capped mRNA plus uncapped mRNA. Therefore, trinucleotide caps can be considered more efficient capping compounds than dinucleotide caps since less input cap is required to produce a final mRNA product that contains a similar amount of capped 5' ends. The ability of trinucleotide caps to produce a high (>90%) capping efficiency at a lower initiator-to-NTP ratio than dinucleotide caps, in some instances, can be attributed to the increased affinity of a trinucleotide cap for the DNA template. In some cases, the optimal cap-to-NTP ratio may vary with the composition of the cap structure, wherein modification of cap structures may affect capping efficiency. For example, cap structures with phosphorothioate backbone modifications may exhibit reduced capping efficiency at a 1:1 initiator-to-NTP ratio compared to conventional phosphodiester backbones since phosphorothioate groups can weaken hybridization strength of complementary

nucleic acids. Unexpectedly, mRNA capped with phosphorothioate-containing compound **1007a** had a capping efficiency of greater than 90% at an initiator-to-NTP ratio ranging from 1:1 down to 1:2.5 (FIG. 4); this was similar to the capping efficiency of mRNA capped with the conventional phosphodiester-containing 5' end initiator, **1002a**, using similar production conditions. Similarly, trinucleotide initiators, **1007e**, **1007i**, **1037a**, **1112a**, **1141a**, **3107a**, **3212a**, **1007c**, **1112c**, **3107c**, **3212c**, **5214** and other trinucleotide cap structures described in Table 1 with phosphorothioate linkage between the first two initiating nucleotides are expected to also have similar capping efficiencies as compared to compound **1002a** based on the observations seen in the previous example.

[0713] Phosphorothioate modification of the triphosphate bridge in a cap structure is not expected to reduce capping efficiency and production of mRNA containing triphosphate bridge-modified dinucleotide caps is well known in the art. Interestingly, mRNA was produced with cap compound **1107a** (FIG. 2), which demonstrated that trinucleotide caps containing phosphorothioate modification of the triphosphate bridge can be incorporated into mRNA with >90% capping efficiency at an initiator-to-NTP ratio ranging from 1:1 down to 1:1.67 (FIG. 4). Similarly, trinucleotide cap structures with triphosphate bridge phosphorothioate modifications described in Table 1 are expected to have similar capping efficiencies as compared to 5' end initiator, **1107a**, based on the observations seen in the previous example.

[0714] Additionally, tetranucleotide cap compounds **5201**, **5202**, **5203**, **5204**, **5205**, **5206**, **5207**, **5208**, **5209**, **5210**, **5211**, and other cap structures described in Table 1 may also produce mRNA with >90% capping efficiency at an initiator-to-NTP ratio of 1:1 and below due to the increased hybridization strength of the tetranucleotide cap compared to trinucleotide and dinucleotide caps.

[0715] Furthermore, as seen with mRNA made with compounds **1007a** and **1107a**, an initiator-to-NTP ratio ranging from 1:1 down to 1:5 did not reduce the amount of full-length mRNA produced (FIG 3), and so the chemically modified cap compounds described herein were able to function as mRNA initiators across a range of reaction conditions. As noted by this example and the data generated, it is contemplated that the remaining compounds described in Table 1 will exhibit similar properties based on the results of this example.

C. Determination of mRNA capping efficiency

[0716] The amount of capped mRNA relative to the total amount of mRNA that is present, i.e. capping efficiency, can be measured by numerous methods well known in the art. One of such methods is digestion of the mRNA into small fragments followed by chromatographic separation and detection. In some cases, digestion is performed with sequence-specific RNA or DNA nucleases or cleavage enzymes. Chromatographic separation and measurement of capped RNA is

typically performed by HPLC, FPLC, thin layer chromatography, gel electrophoresis, or capillary gel electrophoresis techniques. Identity of capped RNA and uncapped mRNA is verified by mass spectrometry.

Example 8. Measurement of capped mRNA stability

[0717] Removal of the cap from mRNA, i.e. decapping, is a common initiating step in the degradation of mRNA within cells. Reported methods for measuring decapping and mRNA degradation are used to evaluate the stability of capped mRNA (Grudzien, E. et al., *J. Biol. Chem.* 2006, 281, 1857-1867). Cap structures that prevent the interaction of decapping enzymes may improve mRNA stability and half-life in cells. For example, mRNA with 5' end region motifs, **1032a, 1037a, 1107a, 5207a, 1112a, 1137a, 1141a, 5208, 3207a, 3212a, 1107c, 1112c, 3207c, and 3212c**, contain phosphorothioate modifications in the triphosphate linkage that may inhibit the activity of dcp2 decapping enzyme. Similarly, other compounds as described in Table 1 containing phosphorothioate modifications in the triphosphate linkage may also inhibit the activity of dcp2 decapping enzyme based on the results of the previous examples. Stability of mRNA may also be improved with cap modifications that inhibit exonuclease activity. For example, introduction of phosphorothioate modifications between the first two or three initiating nucleotides in the cap structure, as present in mRNA with 5' end region motifs, **1007a, 1007e, 1007i, 1037a, 1112a, 1141a, 3107a, 3212a, 1007c, 1112c, 3107c, 3212c, 5203, 5204, 5205, 5206, 5209, 5210, 5211, 5214**, may reduce the rate of mRNA degradation in cells. Similarly, other compounds as described in Table 1 with a phosphorothioate modification between the first two or three initiating nucleotides in the cap structure may also reduce the rate of mRNA degradation in cells as seen by the previous example.

Example 9. Translation of capped luciferase mRNA in HeLa cells and lysates

[0718] HeLa cells are cultured in RPMI with 10% FBS at 37°C under 5% CO₂ atmosphere. Cells are plated into an appropriately sized well plate per manufacturer's recommended seeding conditions. After overnight incubation, cells are checked for monolayer formation and then transfected using a transfection agent such as MessengerMAX. Solution A: the desired amount of luciferase mRNA is diluted in OptiMEM and mixed with Solution B: MessengerMAX in OptiMEM. After mixing solutions A and B, the mixture is incubated at room temperature for 20 minutes, and then added dropwise to each well of cells. The cells are then incubated at 37°C for 12-72 hours to allow for expression of mRNA into protein. Cells are harvested and prepared for measuring luciferase protein levels per Promega luciferase assay system protocol. In some

instances, mRNA is directly administered to HeLa lysates that contain the cellular components for protein expression, this approach does not require the use of a transfection agent. For example, luciferase encoding mRNA with 5' end region motif, **1007a**, was added to a commercially available HeLa lysate *in vitro* translation kit to produce luciferase protein. Luciferase protein activity as measured by luminescent light production in the presence of a luciferin substrate, was measured with a luminescence-detecting plate reader. Relative light units measured per this assay are proportional to the amount of luciferase protein translated from mRNA. The results of this Example were compared using a mRNA made with a commercially available 5' end initiator, **1002a**, as a reference. In this example, the mRNA with initiator **1007a** produced around 2x greater luciferase activity than the mRNA with initiator **1002a** (FIG. 5). As noted by this example and the data generated, it is contemplated that the remaining compounds described in Table 1 will exhibit similar properties based on the results of this example.

Example 10. Translation of capped mRNA in primary hepatocyte cells for genome editing

[0719] Primary human liver hepatocytes (hPH), primary cynomolgus liver hepatocytes (cPH), or primary mouse liver hepatocytes (mPH) are cultured per the manufacturer's protocol. In brief, the cells are thawed and resuspended in hepatocyte thawing medium followed by centrifugation at 100 g for 10 min at 4°C. The supernatant is discarded, and the pelleted cells resuspended in hepatocyte plating medium. Each vial contains ~5 million cells that are used for plating one 24-well plate. Plated cells are allowed to settle and adhere for 4-6 h in a tissue culture incubator at 37 °C under 5% CO₂ atmosphere. After incubation, cells are checked for monolayer formation. The incubating media is then replaced with fresh hepatocyte maintenance media. The cells thus are ready for transfection using a transfection agent such as MessengerMAX. Solution A: desired amount of single guide RNA (sgRNA) is mixed with 1:1 wt ratio of mRNA in OptiMEM. Solution B: MessengerMAX in OptiMEM. After mixing solutions A and B, the mixture is incubated at room temperature for 20 minutes, and then the incubated solution is added dropwise to each well of cells. The cells are then allowed to remain at 37 °C for 3 days. Cells are harvested and prepared for genomic DNA extraction using Thermo Kingfisher instrument. Extracted genomic DNA is processed by PCR, and amplified PCR product was then subjected to NGS (MiSeq) to analyze genome editing. In some instances, hPH are transfected with ABE encoding mRNA as described above and the levels of translated ABE protein are used to assess the mRNA function. For example, mRNA with 5' end region motifs, **1007a** and **1107a**, were transfected to hPH cells as described above, the cells were lysed, and ABE protein levels were measured by ELISA. The results of this example were compared using ABE mRNA made with a commercially available initiator, **1002a**,

as a reference. In this example, the mRNAs with 5' end region motifs, **1007a** and **1107a**, produced similar ABE protein levels as compared to the mRNA with 5' end region motif, **1002a** (FIG. 6). As noted by this example and the data generated, it is contemplated that the remaining compounds described in Table 1 will exhibit similar properties based on the results of this example.

Example 11. Translation of capped mRNA *in vivo* in mouse for genome editing

A. LNP Preparation for *in vitro* transfection and *in vivo* evaluation

[0720] Lipid nanoparticles (LNPs) are generated by microfluidic mixing using the Precision Nanosystems NanoAssemblr system according to the manufacturer's protocol, with some optimization for individual payloads. The resulting LNPs are filtered using 0.2-micron filters and stored at 4°C or frozen at 80°C.

B. *in vivo* evaluation in mice

[0721] LNPs used in these studies are prepared as described above in Example 6(A), comprising chemically synthesized sgRNAs targeting the mouse ANGPTL3 (mANGPTL3) and/or mouse PCSK9 (mPCSK9) genes and SpCas9 or ABE8.8 mRNA in a 1:1 weight ratio, are administered to C57BL/6 mice (n = 5) intravenously via the lateral tail vein or retro-orbital sinus in a total volume of 5-10 ml/kg. 4 or 5 days post dose at necropsy, livers and blood are collected for NGS measurements of editing efficiency, and serum PCSK9, triglyceride and cholesterol analyses.

C. Genomic DNA isolation

[0722] Genomic DNA is isolated from approximately 20 microliters of whole mouse liver lysate using a bead-based extraction kit, MagMAX-96 DNA Multi-Sample Kit on the KingFisher Flex automated extraction instrument according to the manufacturer's protocols. Mouse whole liver is lysed using the FastPrep-24 system according to the manufacturer's protocol. Livers are loaded into 2 mL lysing matrix tubes with 0.5 mL of PBS. Extracted genomic DNA is stored at 4 °C until further use or at -80 °C for long term storage.

D. Next Generation Sequencing (NGS) and Analysis of Editing Efficiency

[0723] Next generation sequencing, or deep sequencing, is performed on the region of interest to determine the extent of gene editing. Samples are prepared using the Nextera XT DNA library preparation kit (Illumina) according to the manufacturer's protocol. Briefly, two rounds of PCR are performed first to amplify the region of interest and second to add DNA sequences required for deep sequencing and sample identification to the initial product. The final amplicon is sequenced on the Illumina MiSeq instrument according to the manufacturer's protocol.

[0724] Paired-end reads are analyzed with the CRISPResso2 pipeline (Clement, K. et al., *Nat. Biotech.* 2019, 37, 224-226). Briefly, low-quality reads are filtered out, adapter sequences are

trimmed from the reads, and the paired-end reads are merged and aligned to the amplicon sequence. The editing percentage is calculated as the number of reads supporting an insertion or a deletion, over the total number of aligned reads. For ABE, the editing percentage is calculated as the number of reads supporting an insertion or a deletion, over the total number of aligned reads.

[0725] In some instances, LNPs were formulated with sgRNA targeting mPCSK9 and ABE encoding mRNAs with 5' end region motif, **1007a**, administered *in vivo* to mice, and editing efficiency was assessed as described in Example 11. The results of this example were compared using ABE encoding mRNA made with a commercially available 5' end initiator, **1002a**, as a reference. In this example, the mRNA with 5' end region motif, **1007a**, produced similar hepatocyte editing levels as compared to the mRNA with 5' end region motif, **1002a** (FIG. 7). As noted by this example and the data generated, it is contemplated that the remaining compounds in Table 1 will exhibit similar properties based on the results of this example.

Example 12. Determination of immune stimulation of capped mRNA *in vivo* in mouse or in an *in vitro* HEK293 cell model

[0726] LNPs are prepared and administered *in vivo* to mice as in Example 11(A,B). Blood is collected at appropriate time points, typically at intervals between 1-48 hours post-dose and terminal end point, and processed to serum or plasma per techniques well known in the art. Serum or plasma cytokine and chemokine levels are measured using V-PLEX cytokine and chemokine detection kits. Cytokine and chemokine levels are compared to animals treated with buffer alone as well as pre-dose sampling of the treatment animals. In some instances, the immune stimulation of capped mRNA is assessed after *in vitro* transfection to reporter cell lines such as HEK-Lucia RIG-I cell reporter model, which produces luciferase signal in the presence of IFN-stimulated response elements such as uncapped mRNA. This cell model is cultured and transfected as described in Example 7, and luciferase activity is measured using a luciferase activity kit and plate reader. It is known in the art that uncapped mRNA produces a RIG-I-dependent IFN immune response, and capped mRNA lessens this immune stimulation. In this example, mRNA with 5' end region motif, **1007a**, showed reduced RIG-I activity as compared to uncapped mRNA using the HEK-Lucia RIG-I cell reporter model (FIG. 8). Furthermore, mRNA with 5' end region motif, **1007a**, did not appear to increase RIG-I activation as a result of the chemical modifications to the cap structure. The results of this example were compared using mRNA made with a commercially available 5' end initiator, **1002a**, as a reference. As noted by this example and the data generated, it is contemplated that the remaining compounds in Table 1 will exhibit similar properties based on the results of this example.

Other Embodiments

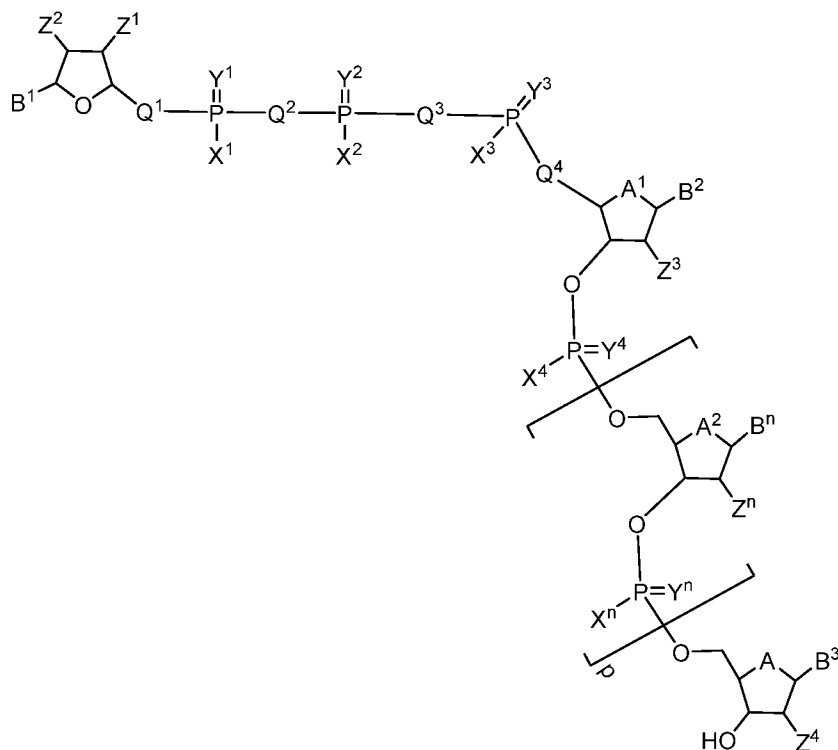
[0727] From the foregoing description, it will be apparent that variations and modifications may be made to the disclosure described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

[0728] The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0729] All patents and publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent patent and publication was specifically and individually indicated to be incorporated by reference.

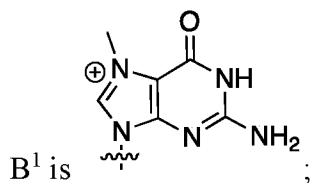
[0730] While specific examples and numerous embodiments have been provided to illustrate aspects and combinations of aspects of the foregoing, it should be appreciated and understood that any aspect, or combination thereof, of an exemplary or disclosed embodiment may be excluded therefrom to constitute another embodiment without limitation and that it is contemplated that any such embodiment can constitute a separate and independent claim. Similarly, it should be appreciated and understood that any aspect or combination of aspects of one or more embodiments may also be included or combined with any aspect or combination of aspects of one or more embodiments and that it is contemplated herein that all such combinations thereof fall within the scope of this disclosure and can be presented as separate and independent claims without limitation. Accordingly, it should be appreciated that any feature presented in one claim may be included in another claim; any feature presented in one claim may be removed from the claim to constitute a claim without that feature; and any feature presented in one claim may be combined with any feature in another claim, each of which is contemplated herein. The following enumerated clauses are further illustrative examples of aspects and combination of aspects of the foregoing embodiments and examples:

1. An in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (I) or a salt or solvate thereof:



Formula (I)

wherein



each B^2 , B^3 , and B^n is independently a natural, a modified, or an unnatural nucleobase;
each Z^1 and Z^2 is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z^3 , Z^4 , and Z^n is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q^1 and Q^4 is independently -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q^2 and Q^3 is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X^1 , X^2 , X^3 , X^4 , and X^n is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

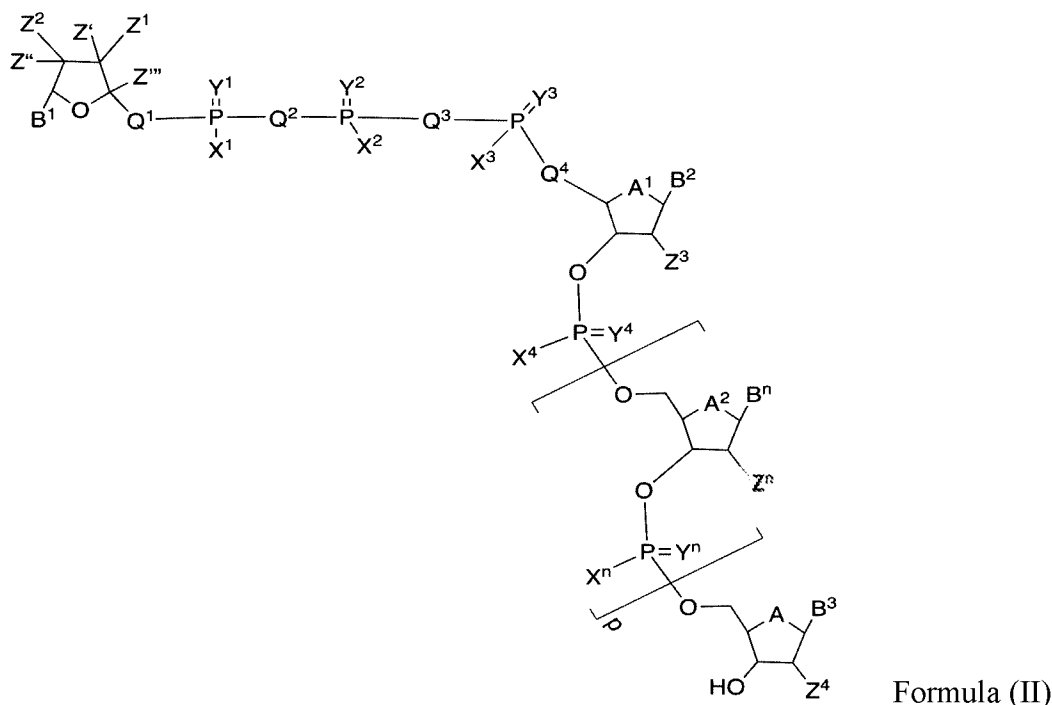
each A, A^1 , and A^2 is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-; and

$p = 0, 1, 2, 3, 4, 5$ or 6 ,

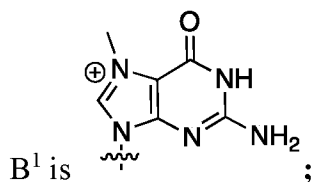
provided that the compound of Formula (I) satisfies one or more of the following proviso (i)

to (iii): (i) at least one of X^1 , X^2 , X^3 , X^4 , and X^n is -SH or -S⁻; (ii) at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S; and (iii) at least one of A, A^1 , and A^2 is -S-

2. The IVT mRNA sequence initiator of clause 1, wherein at least one of X^1 , X^2 , X^3 , X^4 , and X^n is -SH or -S⁻; at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S; or at least one of A, A^1 , and A^2 is -S-
3. An in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B^2 , B^3 , and B^n is independently a natural, a modified, or an unnatural nucleobase;

each Z^1 and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

each Z^2 and Z'' is independently fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z^3 , Z^4 , and Z^n is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q^1 and Q^4 is independently $-\text{CH}=\text{CH}-$, $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CF}_2-$, $-\text{CH}_2\text{NH}_2-$, $-\text{CH}_2\text{NH}(\text{CH}_3)-$, or $-\text{CH}_2\text{N}(\text{C}(=\text{O})\text{CH}_3)-$;

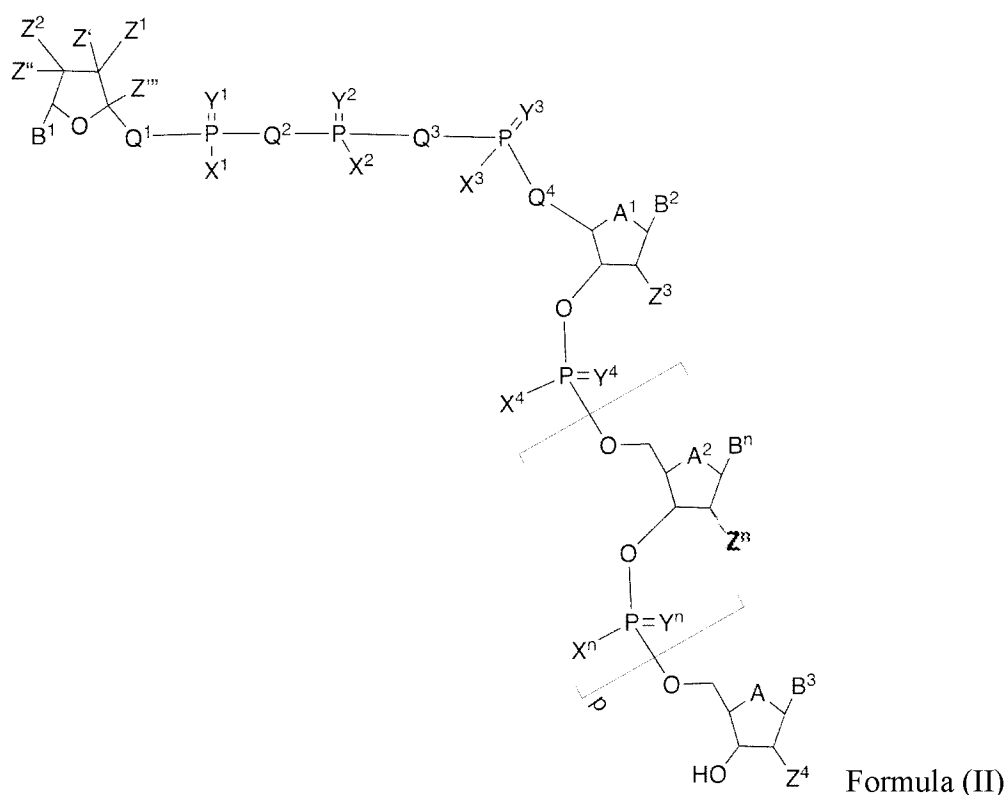
each Q^2 and Q^3 is independently $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, or $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$;

each X^1 , X^2 , X^3 , X^4 , and X^n is independently $-\text{OH}$, $-\text{SH}$, $-\text{O}^-$, $-\text{S}^-$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$ or $-\text{OCH}_2\text{CH}_3$;

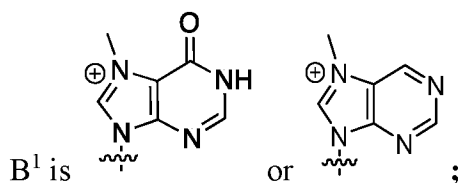
each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently $=\text{O}$, $=\text{S}$, $=\text{NH}$, or $=\text{NCH}_3$;

each A , A^1 , and A^2 is independently $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$ or $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$; and
 $p = 0, 1, 2, 3, 4, 5$ or 6 .

4. An in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B^2 , B^3 , and B^n is independently a natural, a modified, or an unnatural nucleobase;

each Z^1 and Z^n is independently is hydrogen, fluorine, $-\text{OH}$, $-\text{SH}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{NH}(\text{CH}_3)$, $-\text{NH}_2$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, or $-\text{SCH}_3$;

Z''' is hydrogen, fluorine, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, or $-\text{OCH}_2\text{CH}_3$;

each Z^1 and Z^2 is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z^3 , Z^4 , and Z^n is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q^1 and Q^4 is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q^2 and Q^3 is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X^1 , X^2 , X^3 , X^4 , and X^n is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

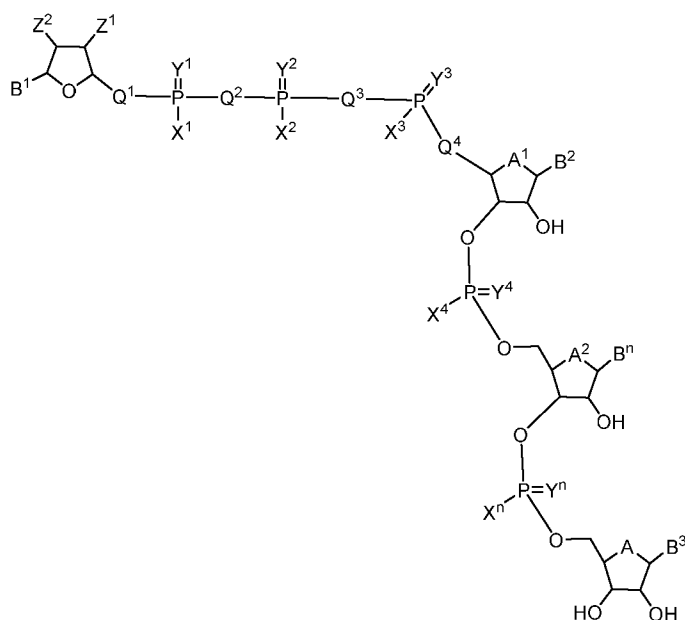
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

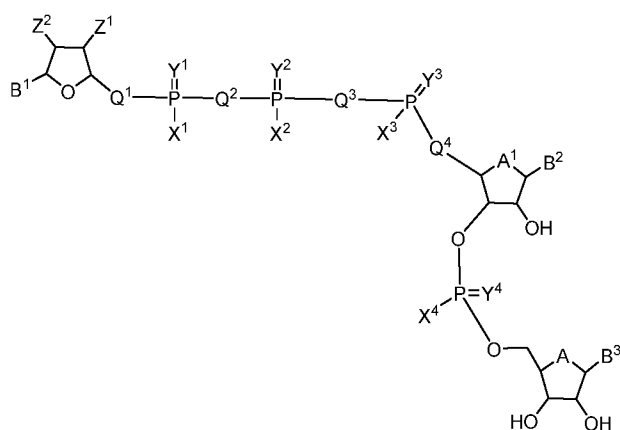
p = 0, 1, 2, 3, 4, 5 or 6.

5. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-a):



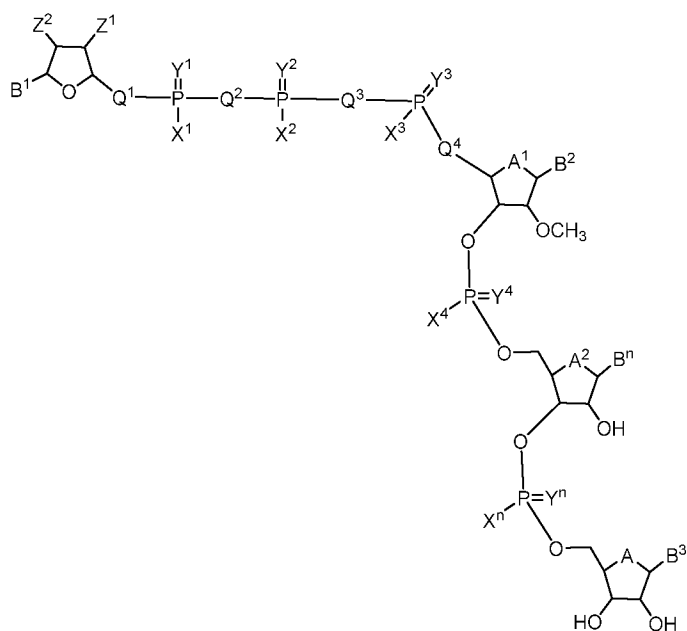
Formula (I-a).

6. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-b):



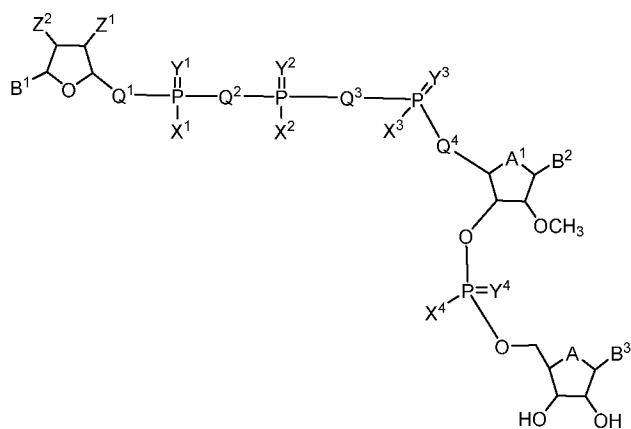
Formula (I-b).

7. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-c):



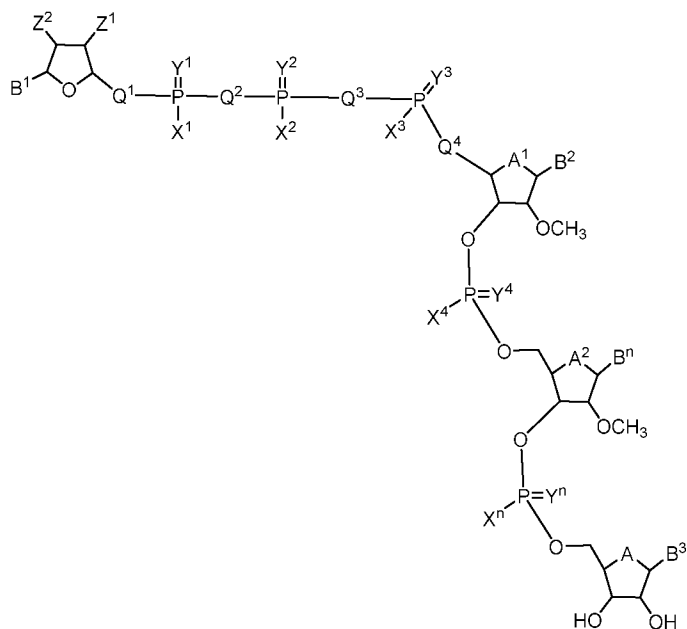
Formula (I-c).

8. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-d):



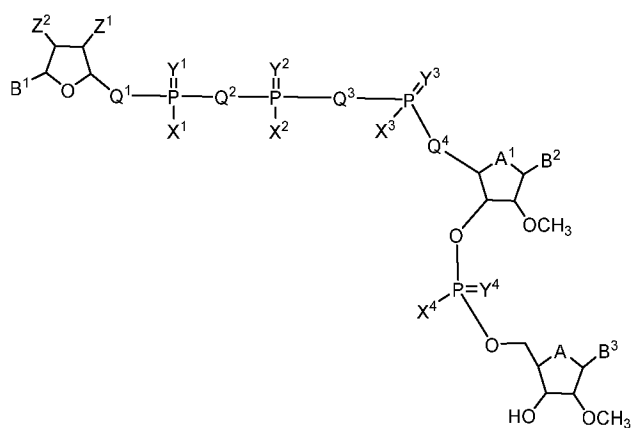
Formula (I-d).

9. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-e):



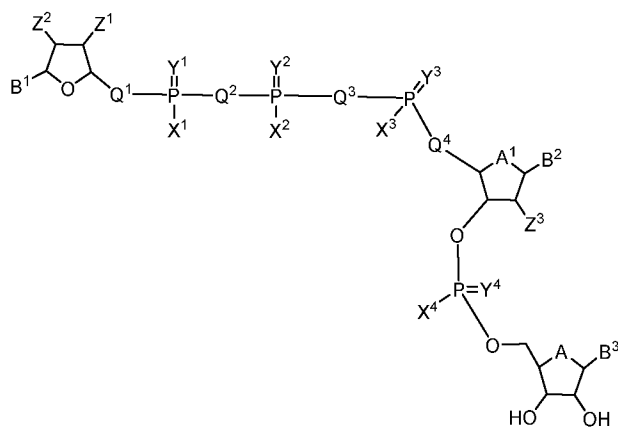
Formula (I-e).

10. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-f):



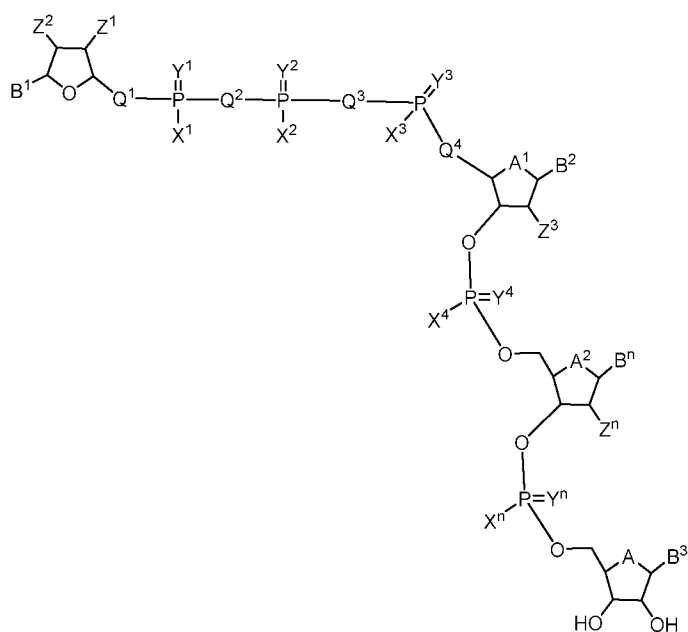
Formula (I-f).

11. The IVT mRNA sequence initiator of clause 1, wherein the initiator has a structure of Formula (I-g):



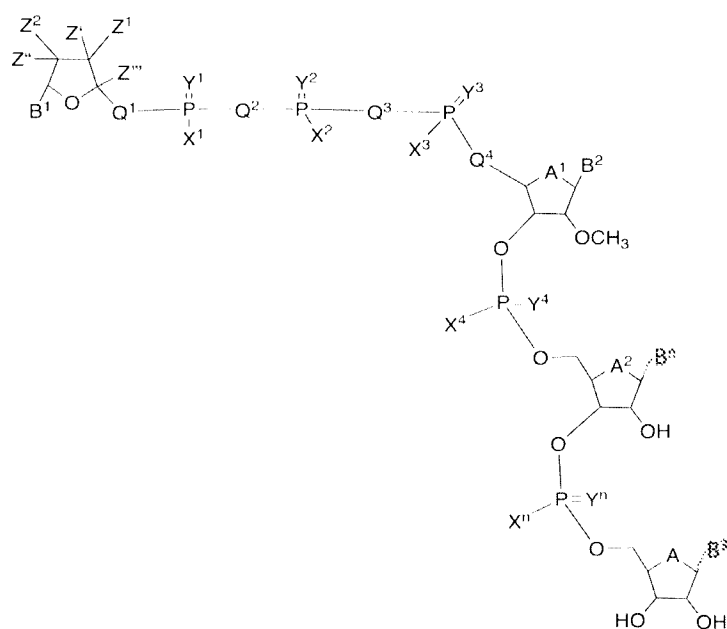
Formula (I-g).

12. The IVT mRNA sequence initiator of clam 1, wherein the initiator has a structure of Formula (I-h):



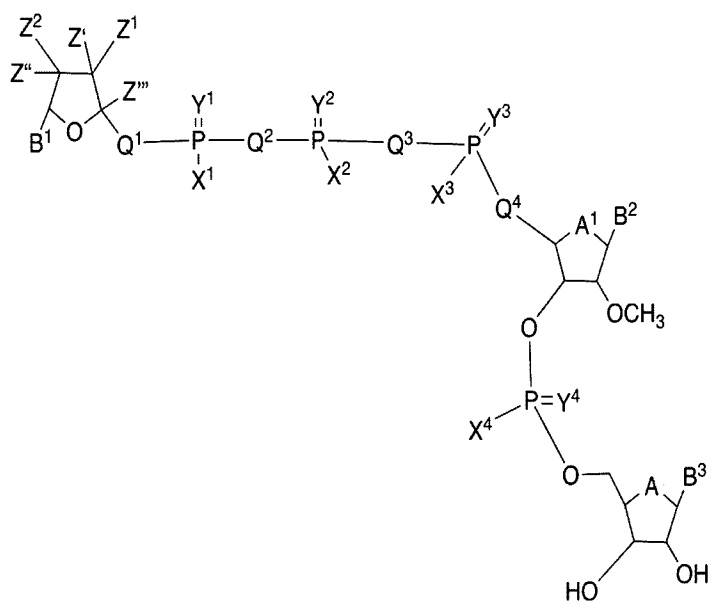
Formula (I-h).

13. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-a):



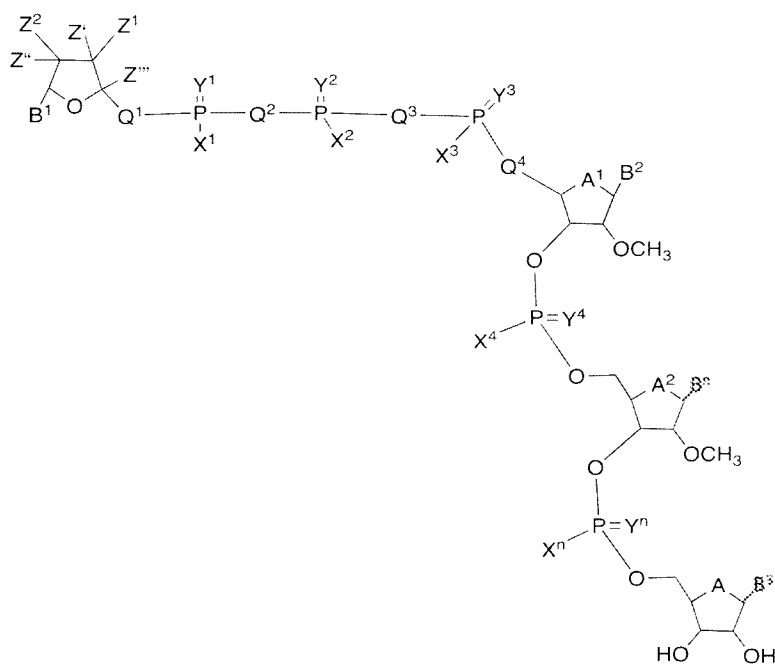
Formula (II-a).

14. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-b):



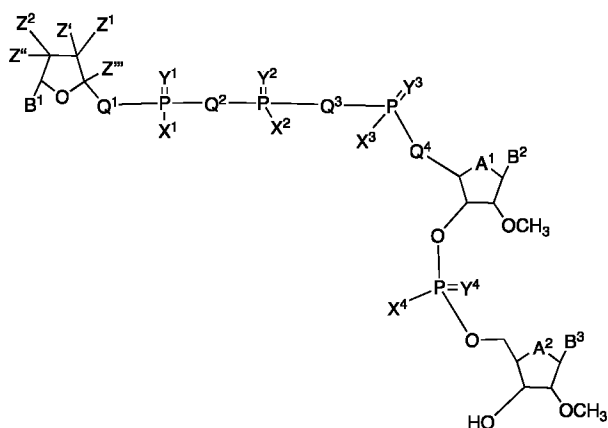
Formula (II-b).

15. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-c):



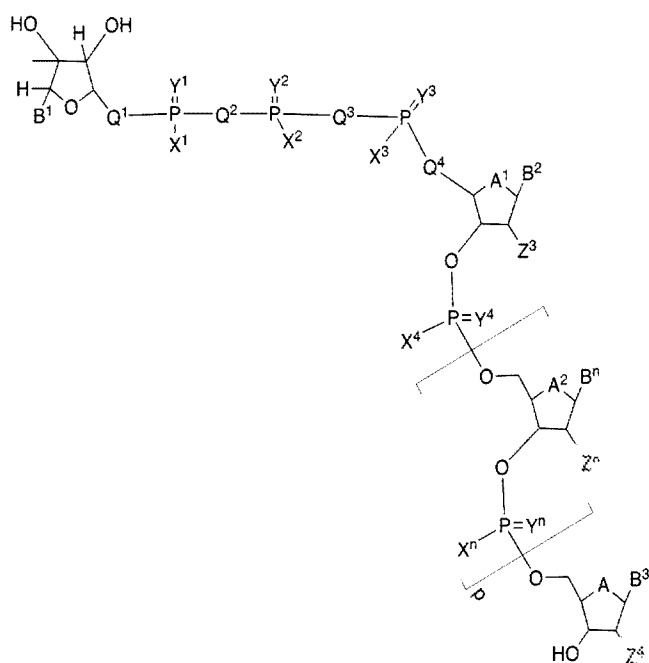
Formula (II-c).

16. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-d):



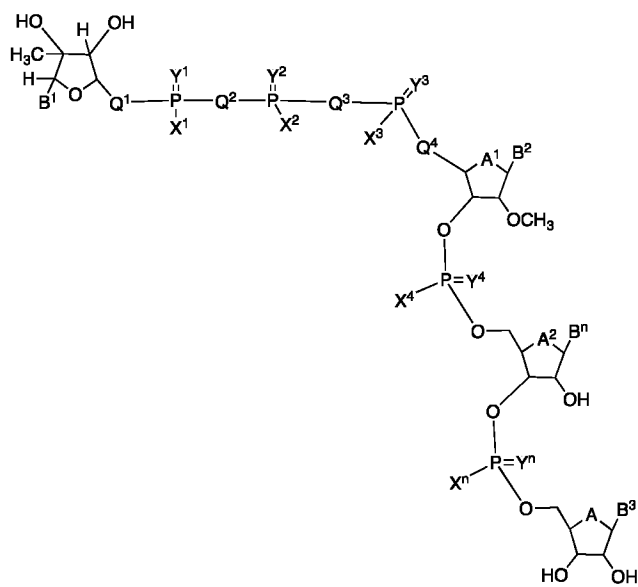
Formula (II-d).

17. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-e):



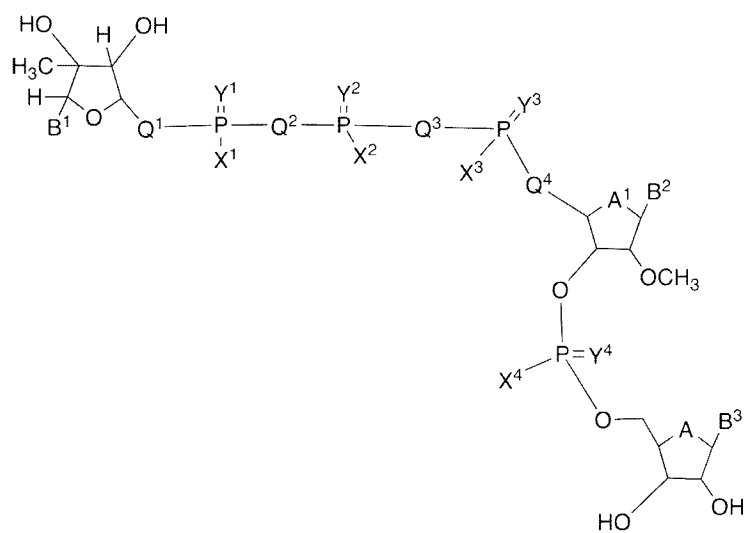
Formula (II-e).

18. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-f):



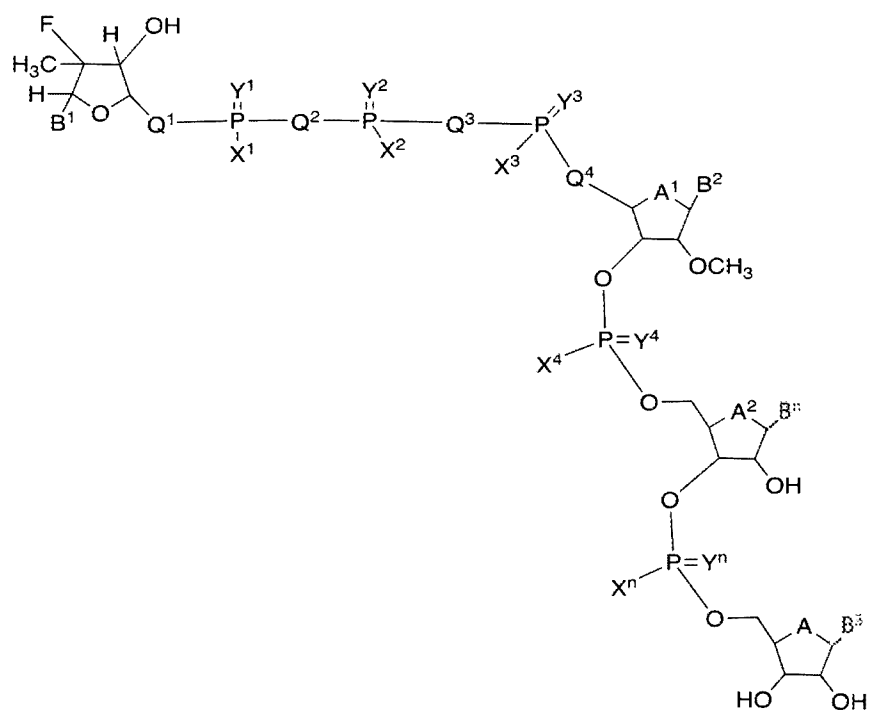
Formula (II-f).

19. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-g):



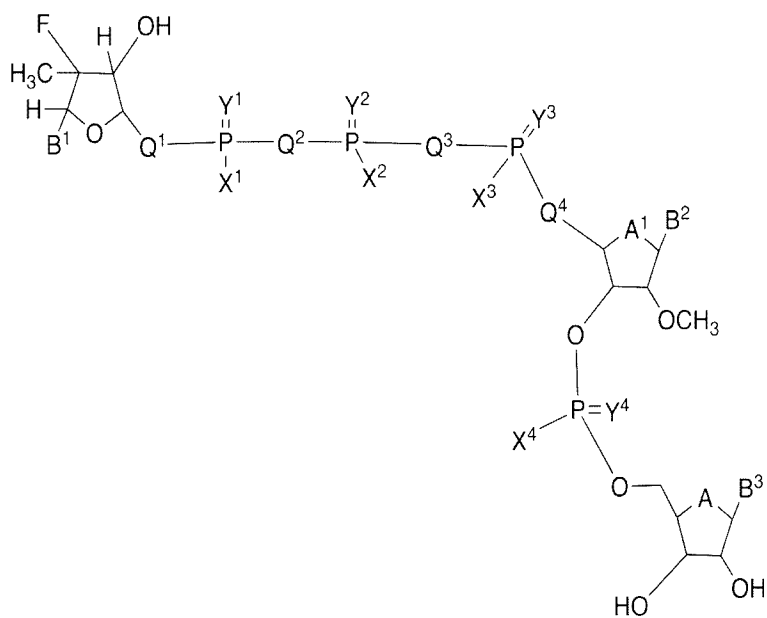
Formula (II-g).

20. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-h):



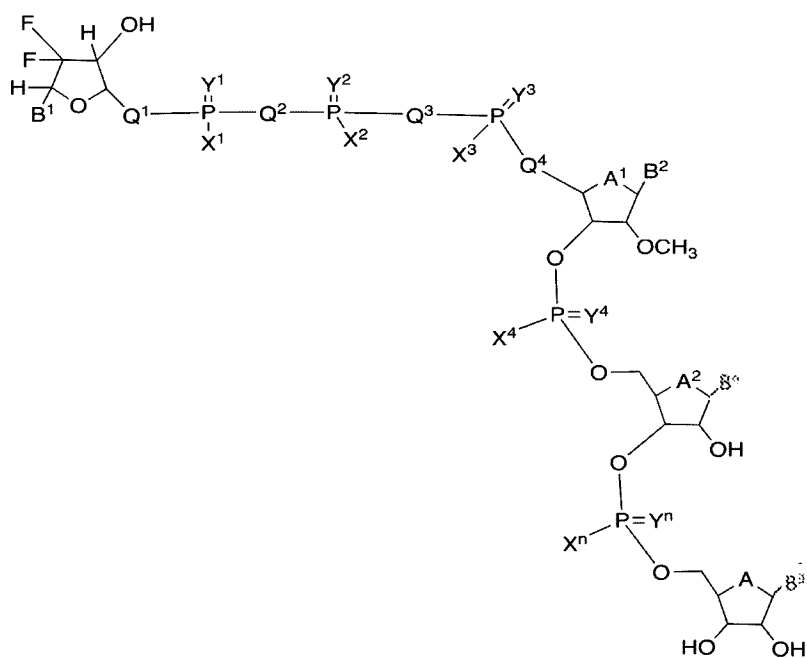
Formula (II-h).

21. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-i)



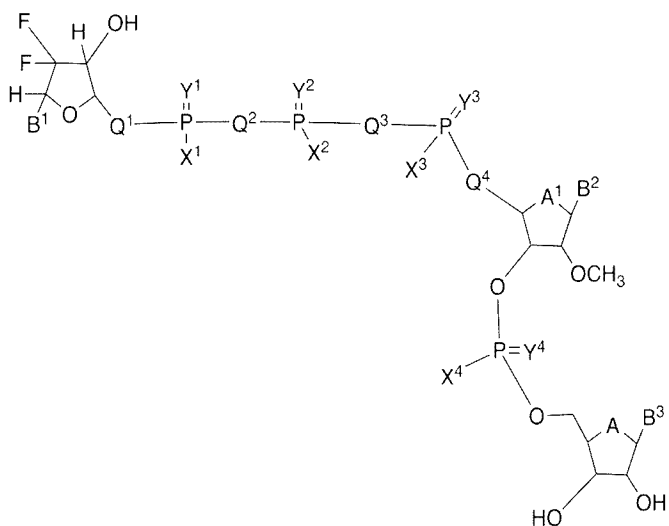
Formula (II-i).

22. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-j):



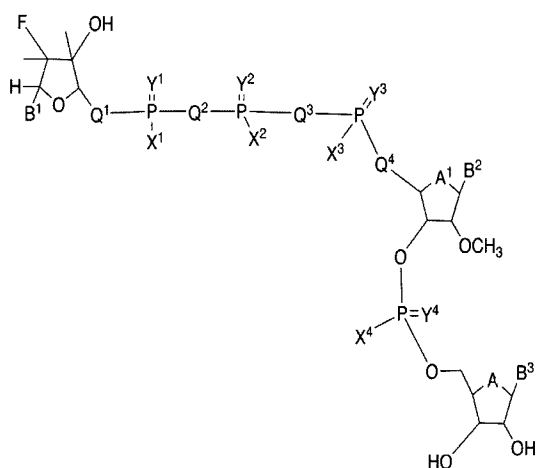
Formula (II-j).

23. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-k):



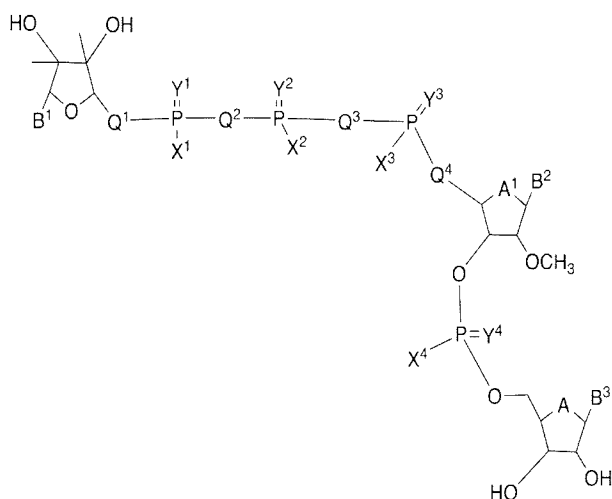
Formula (II-k).

24. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-l):



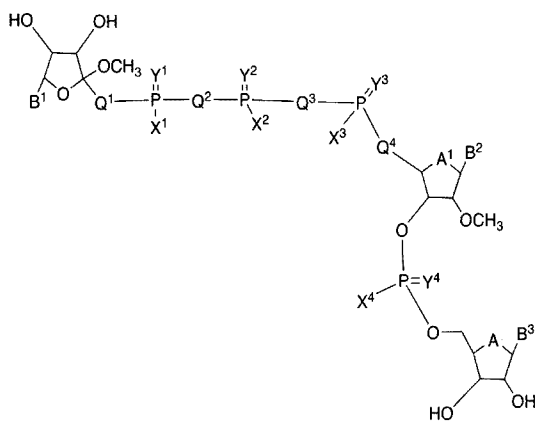
Formula (II-l).

25. The IVT mRNA sequence initiator of clause 17 or 18, wherein the initiator has a structure of Formula (II-m):



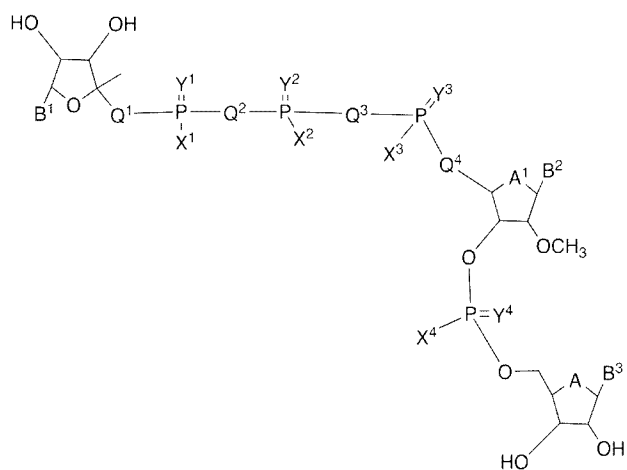
Formula (II-m).

26. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-n):



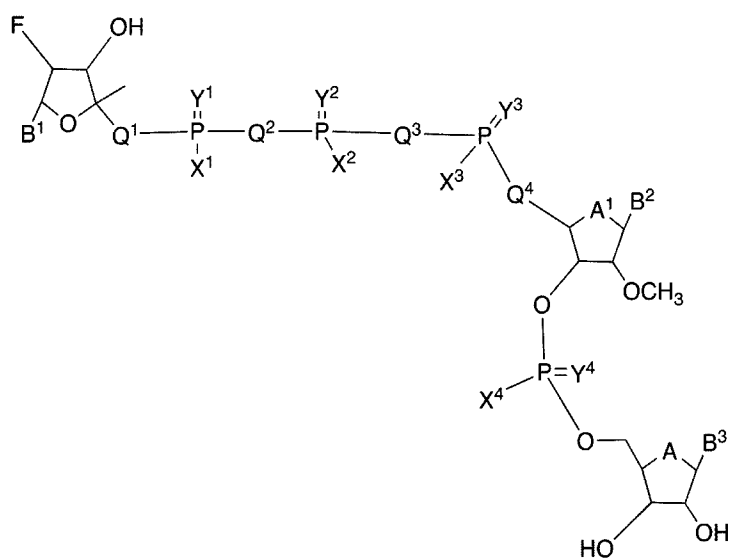
Formula (II-n).

27. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-o):



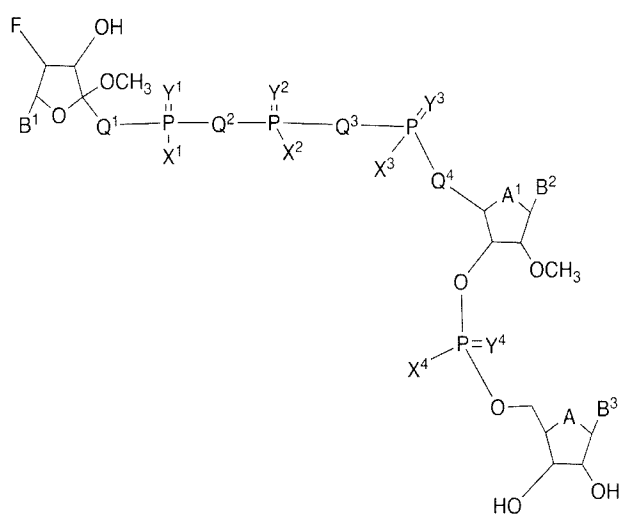
Formula (II-o).

28. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-p):



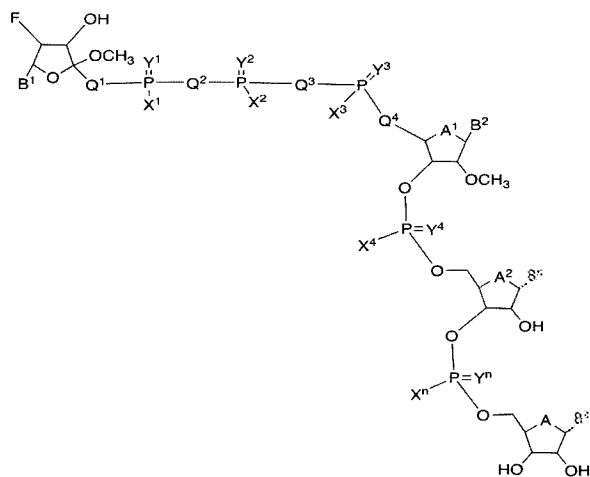
Formula (II-p).

29. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-q):



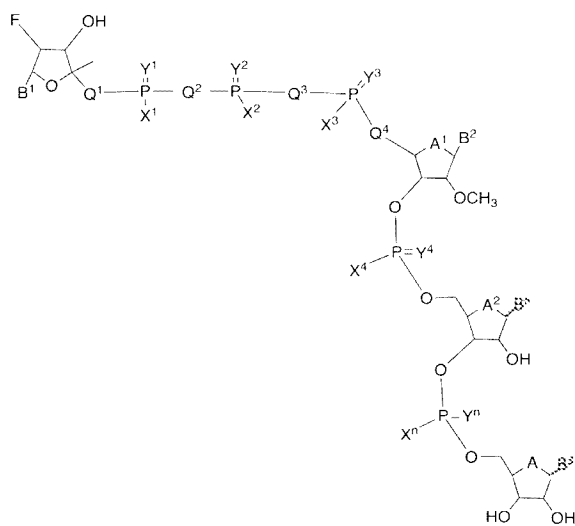
Formula (II-q).

30. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-r):



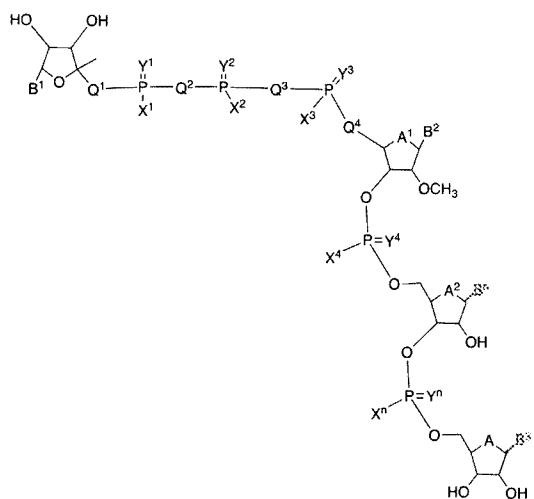
Formula (II-r).

31. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-s):



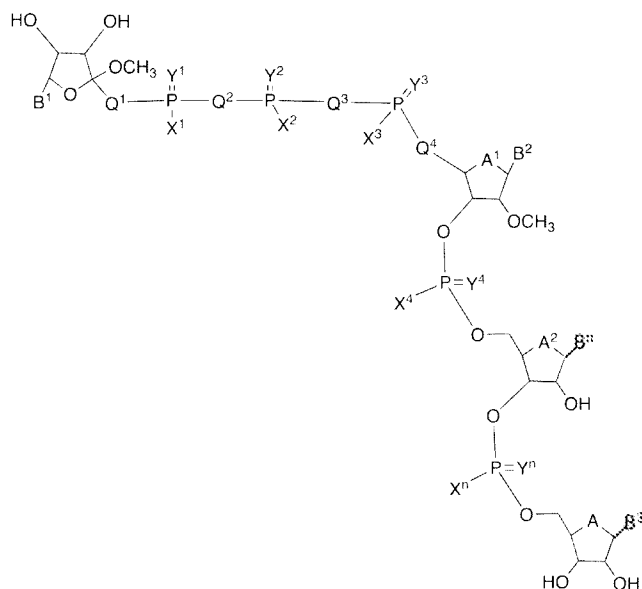
Formula (II-s).

32. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-t):



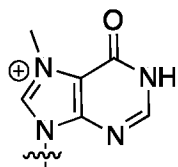
Formula (II-t).

33. The IVT mRNA sequence initiator of clause 18, wherein the initiator has a structure of Formula (II-u):

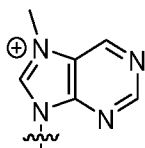


Formula (II-u).

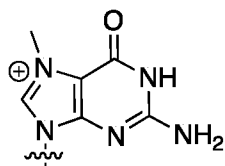
34. The IVT mRNA sequence initiator of any one of clauses 1-18, wherein Z^3 is hydrogen, fluorine, -OH, -OCH₃, - or -OCH₂CH₃.
35. The IVT mRNA sequence initiator of clause 48, wherein Z^3 is -OCH₃.
36. The IVT mRNA sequence initiator of clause 48, wherein each Z^4 and Z^n is independently -OH or -OCH₃.
37. The IVT mRNA sequence initiator of any one of clauses 1-18, wherein each Z^3 , Z^4 , and Z^n is independently -OH or -OCH₃.
38. The IVT mRNA sequence initiator of any one of clauses 18 or 25-51, wherein B¹ is



39. The IVT mRNA sequence initiator of any one of clauses 18 or 25-51, wherein B¹ is

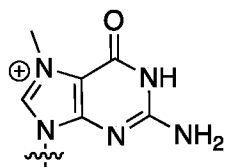


40. The IVT mRNA sequence initiator of any one of clauses 18 or 25-51, wherein B¹ is



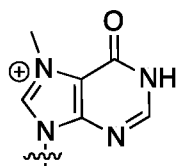
41. The IVT mRNA sequence initiator of any one of clauses 1-30, wherein Z^1 is fluorine, -OH, or -OCH₃.
42. The IVT mRNA sequence initiator of clause 55, wherein Z^1 is fluorine.
43. The IVT mRNA sequence initiator of clause 55, wherein Z^1 is -OH.
44. The IVT mRNA sequence initiator of clause 55, wherein Z^1 is -OCH₃.
45. The IVT mRNA sequence initiator of any one of clauses 1-30, wherein Z^2 is fluorine, -OH, or -OCH₃.
46. The IVT mRNA sequence initiator of clause 59, wherein Z^2 is fluorine.
47. The IVT mRNA sequence initiator of clause 59, wherein Z^2 is -OH.
48. The IVT mRNA sequence initiator of clause 59, wherein Z^2 is -OCH₃.
49. The IVT mRNA sequence initiator of any one of clauses 1-62, wherein Q^1 and Q^4 is -CH₂O-.
50. The IVT mRNA sequence initiator of any one of clauses 1-63, wherein each Q^2 and Q^3 is -O-.
51. The IVT mRNA sequence initiator of any one of clauses 1-64, wherein each Y^1 and Y^3 is =O.
52. The IVT mRNA sequence initiator of any one of clauses 1-64, wherein each Y^2 , Y^4 , and Y^n is independently =O or =S.
53. The IVT mRNA sequence initiator of any one of clauses 1-64, wherein one or more of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S.
54. The IVT mRNA sequence initiator of clause 67, wherein Y^2 is =S.
55. The IVT mRNA sequence initiator of clause 67, wherein Y^4 is =S.
56. The IVT mRNA sequence initiator of any one of clauses 1-64, wherein each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =O.
57. The IVT mRNA sequence initiator of any one of clauses 1-70, wherein each X^1 , X^4 , and X^n is -O⁻.
58. The IVT mRNA sequence initiator of any one of clauses 1-70, wherein each X^2 and X^3 is independently -O⁻ or -S⁻.
59. The IVT mRNA sequence initiator of clause 72, wherein X^3 is -O⁻.
60. The IVT mRNA sequence initiator of any one of clauses 1-70, wherein one or more of X^1 , X^2 , X^3 , X^4 , and X^n is -S⁻.
61. The IVT mRNA sequence initiator of clause 74, wherein X^2 is -S⁻.
62. The IVT mRNA sequence initiator of clause 74, wherein X^4 is -S⁻.
63. The IVT mRNA sequence initiator of any one of clauses 1-70, wherein each X^1 , X^2 , X^3 , X^4 , and X^n is -O⁻.
64. The IVT mRNA sequence initiator of any one of clauses 1-77, wherein each A, A^1 , and A^2 is -O-.

65. The IVT mRNA sequence initiator of any one of clauses 1-77, wherein one or more of A, A¹, and A² is -S-.
66. The IVT mRNA sequence initiator of any one of clauses 1-77 or 79, wherein A is -S- and A¹ and A² is -O-.
67. The IVT mRNA sequence initiator of any one of clauses 1-77 or 79, wherein A² is -S- and A and A¹ is -O-.
68. The IVT mRNA sequence initiator of any one of clauses 1-77, wherein A, A¹, and A² is -O-.
69. The IVT mRNA sequence initiator of any one of clauses 1, 17, or 48-81, wherein p is 0.
70. The IVT mRNA sequence initiator of any one of clauses 1, 17, or 48-81, wherein p is 1.
71. The IVT mRNA sequence initiator of any one of clauses 1, 17, or 48-81, wherein p is 2.
72. The IVT mRNA sequence initiator of any one of clauses 1-85, wherein each B², B³, and Bⁿ is independently adenine, cytosine, guanine, uracil, thymine, hypoxanthine, or purine.
73. The IVT mRNA sequence initiator of clause 86, wherein B² is adenine and B³ is guanine.
74. The IVT mRNA sequence initiator of clause 86, wherein B² is guanine and B³ is adenine.
75. The IVT mRNA sequence initiator of any one of clauses 1 to 88, wherein protein expression is increased.
76. The IVT mRNA sequence initiator of clauses 18-47, wherein Q¹ and Q⁴ are -CH₂O-; Q² and Q³ are -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently =O or =S;



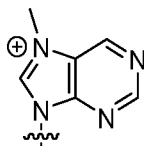
and B¹ is

77. The IVT mRNA sequence initiator of clauses 18-47, wherein Q¹ and Q⁴ are -CH₂O-; Q² and Q³ are -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently =O or =S;



and B¹ is

78. The IVT mRNA sequence initiator of clauses 18-47, wherein Q¹ and Q⁴ are -CH₂O-; Q² and Q³ are -O-; each Xⁿ is independently -OH, -SH, O⁻, or S⁻; each Yⁿ is independently =O or =S;



and B¹ is

79. The IVT mRNA sequence initiator of clauses 86-92, wherein B² is adenine.
80. The IVT mRNA sequence initiator of clauses 86-92, wherein B³ is guanine.

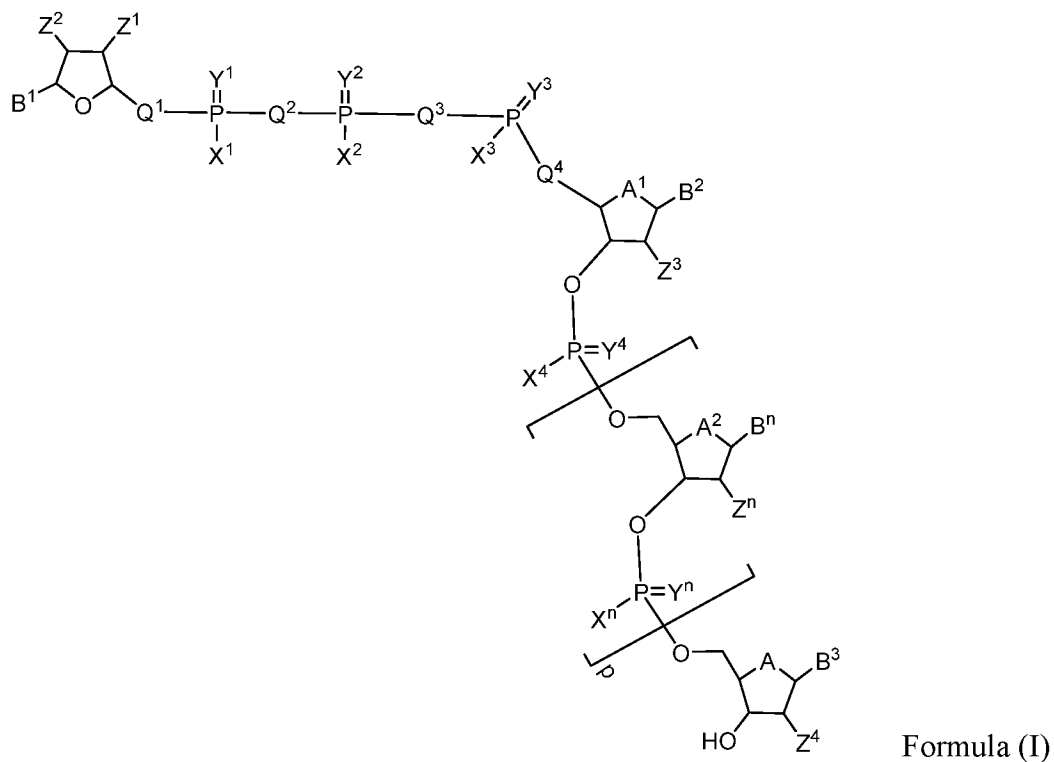
81. A complex comprising an IVT mRNA sequence initiator and a DNA template, wherein the IVT mRNA sequence initiator comprises a compound of any one of clauses 1-94, wherein the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1, a second nucleotide at nucleotide position +2, and a third nucleotide at nucleotide position +3; and wherein the IVT mRNA sequence initiator is hybridized to the DNA template at least at nucleotide positions +1, +2, and +3.
82. A complex comprising an IVT mRNA sequence initiator and a DNA template, wherein the IVT mRNA sequence initiator comprises a compound of any one of clauses 1-94, wherein the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1 and a second nucleotide at nucleotide position +2; and wherein the IVT mRNA sequence initiator is hybridized to the DNA template at least at nucleotide positions +1 and +2.
83. An RNA molecule comprising the IVT mRNA sequence initiator according to any one of clauses 1-94.
84. The RNA of clause 97, wherein the RNA comprises a guide RNA or a nuclease mRNA.
85. The RNA of clause 97, wherein the RNA comprises an mRNA.
86. A method of expressing an mRNA comprising (a) contacting the mRNA of clause 99 with a cell or a cell lysate thereof and (b) expressing the mRNA
87. The method of clause 100, further comprising measuring the expression level of the mRNA.
88. The method of clause 100, wherein the expression level of the mRNA is at least 6-fold, 8-fold, or 20-fold greater compared to a corresponding mRNA without the the IVT mRNA sequence initiator.
89. The method of clause 100, wherein the cell is a HeLa cell.
90. A method of reducing cellular immune stimulation of capped mRNA comprising (a) contacting a capped mRNA according to any one of clauses 1 to 94 with a cell reporter line and (b) measuring RIG-I activation in said cell reporter line.
91. The method of clause 104, wherein said cell reporter line is HEK-Lucia RIG-I model.
92. The method of any one of clauses 104 or 105, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 20%.
93. The method of clause 106, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 50%.

94. The method of clause 107, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 70%.
95. The method of clause 108, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 100%.
96. The method of clause 109, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 150%.
97. A cell containing an RNA molecule comprising the IVT mRNA sequence initiator according to any one of clauses 1-94.
98. A cell containing a polypeptide translated from an RNA molecule comprising the IVT mRNA sequence initiator according to any one of clauses 1-94.
99. A pharmaceutical composition comprising an RNA molecule comprising the IVT mRNA sequence initiator according to any one of clauses 1-94 and one or more of pharmaceutically acceptable excipients.
100. The pharmaceutical composition of clause 126, comprising lipid nanoparticles.
101. The pharmaceutical composition of clause 126, wherein the RNA is encapsulated in a lipid nanoparticle.
102. A method for synthesizing an RNA molecule comprising:
 - a. introducing the IVT mRNA sequence initiator according to any one of clauses 1-94 into a mixture comprising an RNA polymerase, and
 - b. incubating the mixture for a time sufficient to allow for transcription of the RNA molecule.
103. The method of clause 81 wherein the mixture further comprises a DNA template and nucleoside triphosphates.
104. A method of gene editing comprising introducing into a cell an RNA molecule of clause 97 or 98, or pharmaceutical composition of any one of clauses 126-129, wherein the RNA molecule comprises guide RNA or a nuclease mRNA, wherein the RNA molecule is translated in the cell.
105. A method for reducing the risk of coronary disease in a subject in need thereof, comprising administering to the subject an effective amount of a pharmaceutical composition of any one of clauses 126-129.

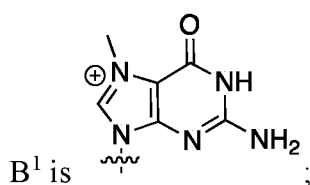
CLAIMS

We claim:

1. An in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (I) or a salt or solvate thereof:



wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

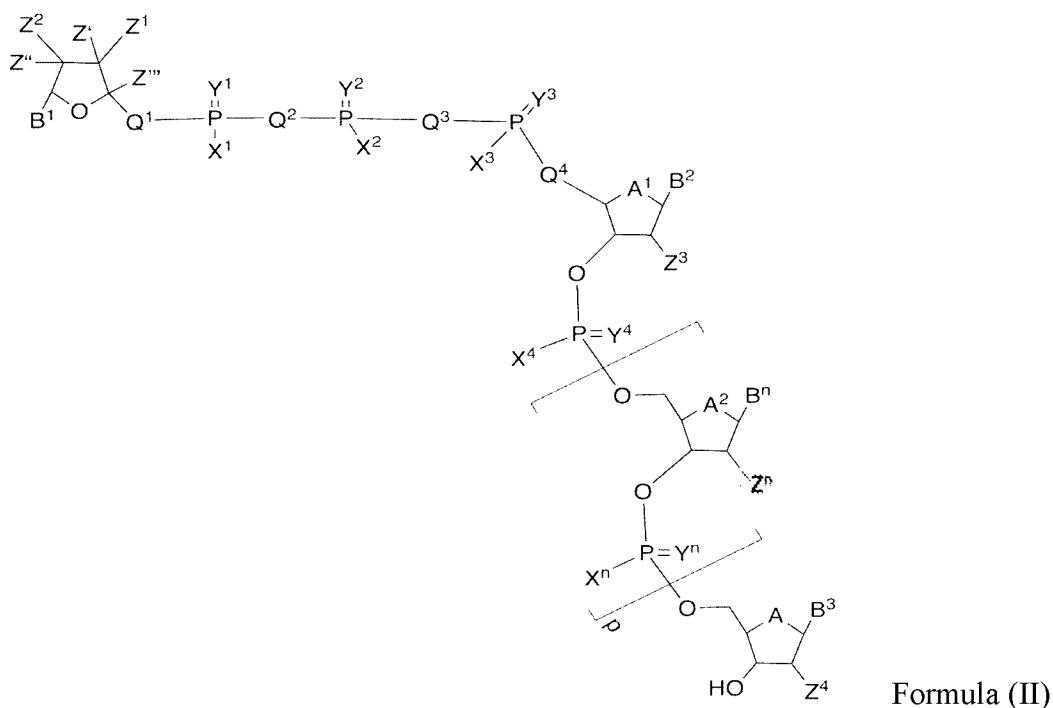
each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH₂-, -CH=CH-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

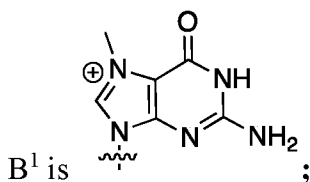
each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X^1 , X^2 , X^3 , X^4 , and X^n is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃, or -OCH₂CH₃;
 each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;
 each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and
 $p = 0, 1, 2, 3, 4, 5$ or 6 ,
 provided that the compound of Formula (I) satisfies one or more of the following proviso (i) to (iii): (i) at least one of X^1 , X^2 , X^3 , X^4 , and X^n is -SH or -S⁻; (ii) at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S; and (iii) at least one of A, A¹, and A² is -S-.

2. The IVT mRNA sequence initiator of claim 1, wherein at least one of X^1 , X^2 , X^3 , X^4 , and X^n is -SH or -S⁻; at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S; or at least one of A, A¹, and A² is -S-.
3. An in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z^1 and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

each Z^2 and Z'' is independently fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z^3 , Z^4 , and Z^n is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q^1 and Q^4 is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-

each Q^2 and Q^3 is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-

each X^1 , X^2 , X^3 , X^4 , and X^n is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

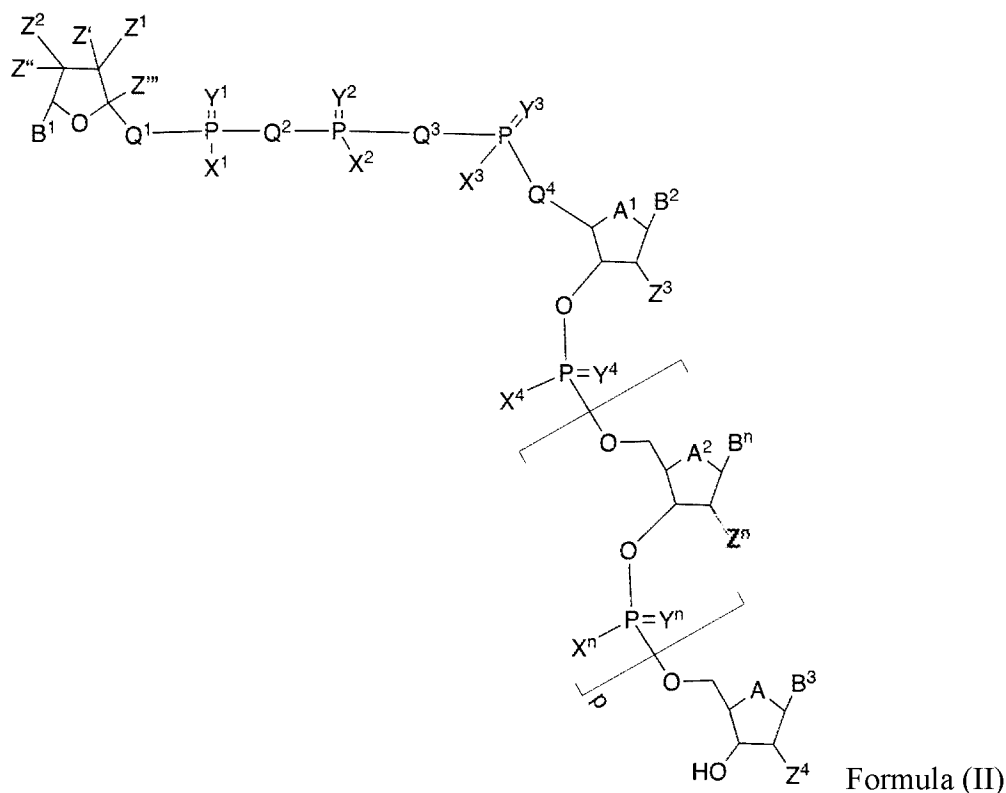
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

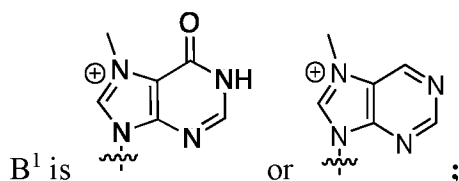
each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-

and $p = 0, 1, 2, 3, 4, 5$ or 6 .

4. An in vitro-transcribed (IVT) mRNA sequence initiator comprising a compound of Formula (II) or a salt or solvate thereof:



wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z' and Z'' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-;

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-;

each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

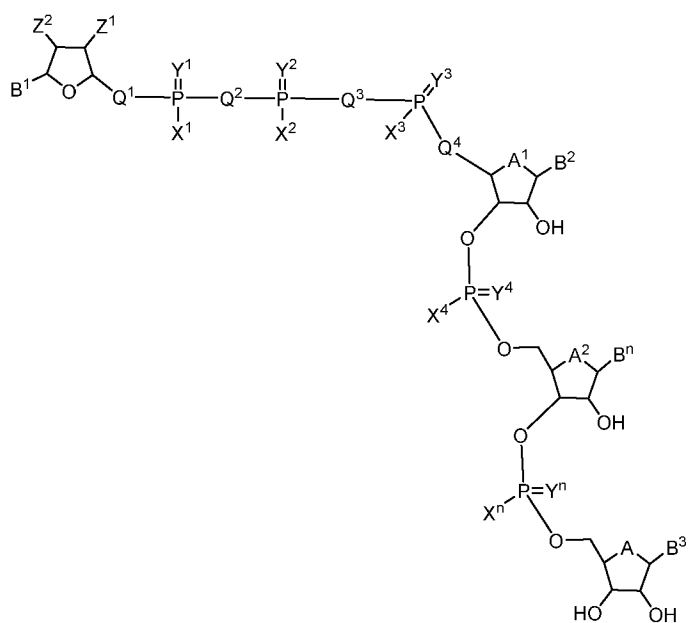
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y¹, Y², Y³, Y⁴, and Yⁿ is independently =O, =S, =NH, or =NCH₃;

each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-; and

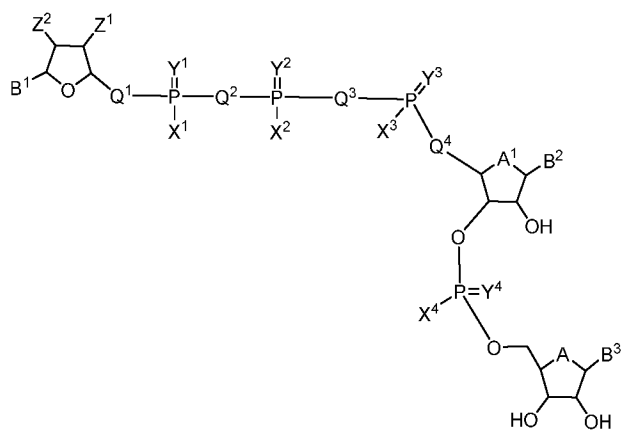
p = 0, 1, 2, 3, 4, 5 or 6.

5. The IVT mRNA sequence initiator of claim 1, wherein the initiator has a structure of Formula (I-a):



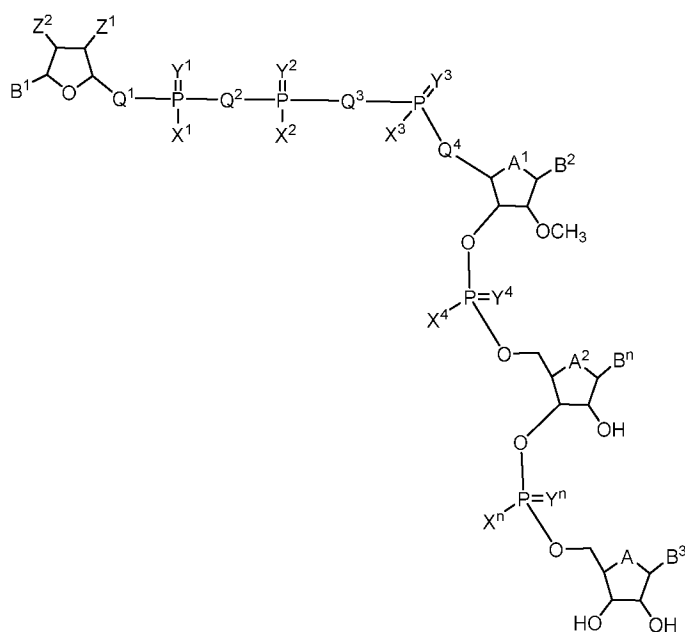
Formula (I-a).

6. The IVT mRNA sequence initiator of claim 1, wherein the initiator has a structure of Formula (I-b):



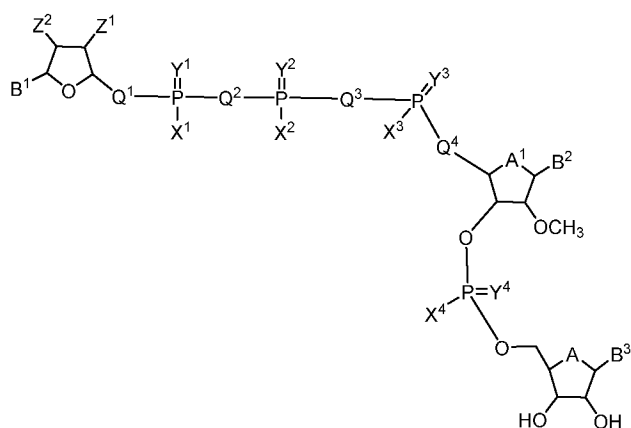
Formula (I-b).

7. The IVT mRNA sequence initiator of claim 1, wherein the initiator has a structure of Formula (I-c):



Formula (I-c).

8. The IVT mRNA sequence initiator of claim 1, wherein the initiator has a structure of Formula (I-d):



Formula (I-d).

9. The IVT mRNA sequence initiator of any one of claims 1-4, wherein Z^3 is hydrogen, fluorine, -OH, -OCH₃, - or -OCH₂CH₃.

10. The IVT mRNA sequence initiator of claim 9, wherein Z^3 is -OCH₃.

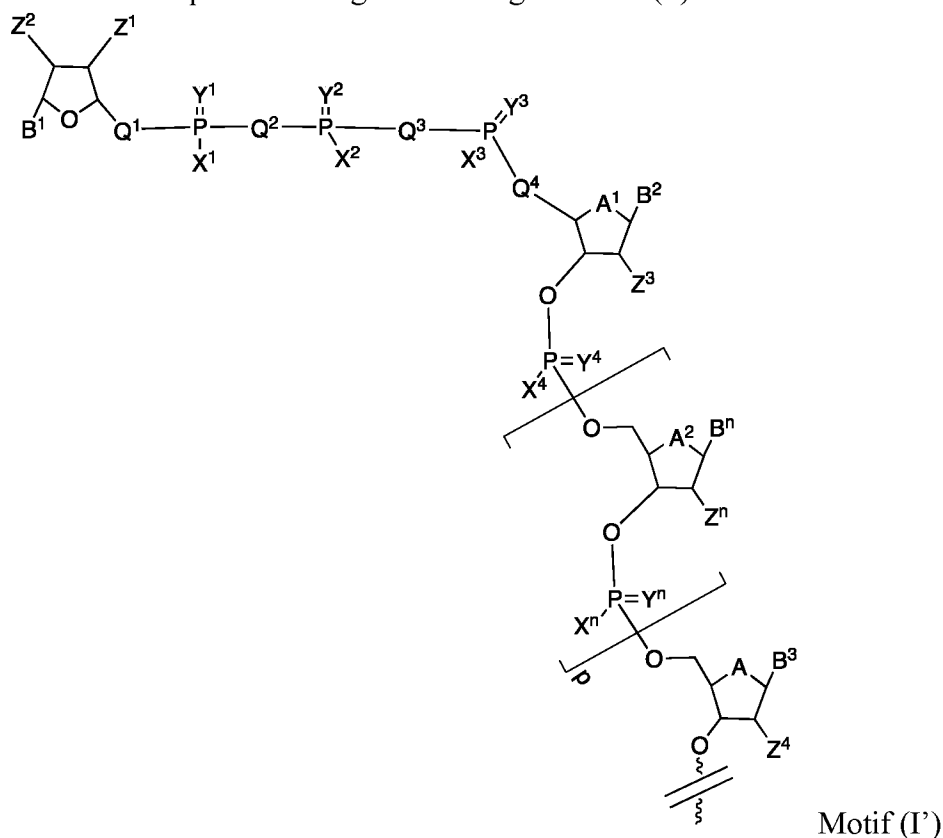
11. The IVT mRNA sequence initiator of claim 9, wherein each Z^4 and Z^n is independently -OH or -OCH₃.

12. The IVT mRNA sequence initiator of any one of claims 1-11, wherein each Z^3 , Z^4 , and Z^n is independently -OH or -OCH₃.

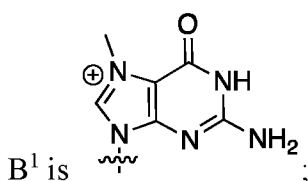
13. The IVT mRNA sequence initiator of any one of claims 1-12, wherein each Y^2 , Y^4 , and Y^n is independently =O or =S.

14. The IVT mRNA sequence initiator of any one of claims 1-13, wherein each X^2 and X^3 is independently $-O^-$ or $-S^-$.

15. An mRNA sequence having a 5'-end region motif (I'):



wherein



each B^2 , B^3 , and B^n is independently a natural, a modified, or an unnatural nucleobase;

each Z^1 and Z^2 is independently hydrogen, fluorine, $-OH$, $-SH$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-SCH_3$, $-NH_2$, $NHCH_3$, or $NHC(=O)CH_3$;

each Z^3 , Z^4 , and Z^n is independently hydrogen, fluorine, $-OH$, $-SH$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-NH(C(=O)CH_3)$, $-OCH_2CH_3$, $-OCH_2OCH_3$, $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$, $-SCH_3$, or $-OCH_2CH_2OCH_3$;

each Q^1 and Q^4 is independently $-CH_2-$, $-CH=CH-$, $-CH_2O-$, $-CH_2S-$, $-CH_2CH_2-$, $-CH_2CF_2-$, $-CH_2NH_2-$, $-CH_2NH(CH_3)-$, or $-CH_2N(C(=O)CH_3)-$;

each Q^2 and Q^3 is independently $-O-$, $-S-$, $-CH_2-$, $-CF_2-$, $-NH-$, $-N(CH_3)-$, or $-N(C(=O)CH_3)-$;

each X^1 , X^2 , X^3 , X^4 , and X^n is independently $-\text{OH}$, $-\text{SH}$, $-\text{O}^-$, $-\text{S}^-$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{OCH}_3$, or $-\text{OCH}_2\text{CH}_3$;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently $=\text{O}$, $=\text{S}$, $=\text{NH}$, or $=\text{NCH}_3$;

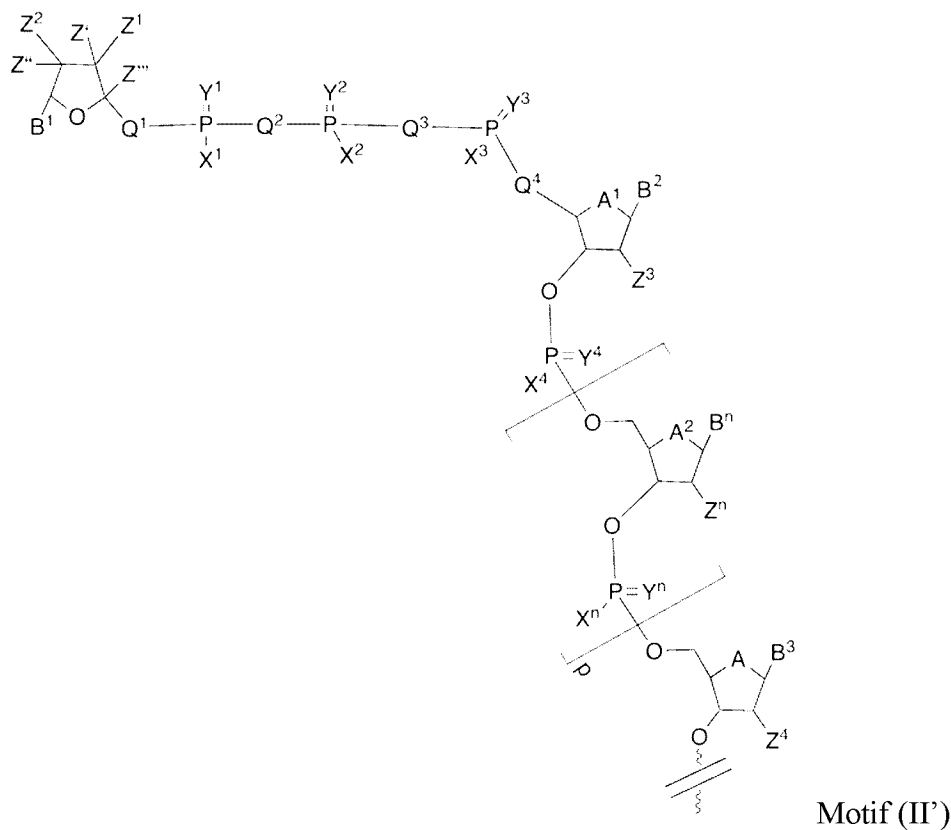
each A , A^1 , and A^2 is independently $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$ or $-\text{N}(\text{C}(=\text{O})\text{CH}_3)-$; and

$p = 0, 1, 2, 3, 4, 5$ or 6 ,

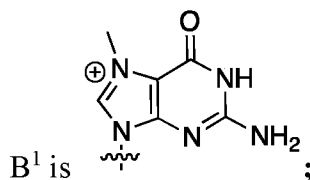
provided that the compound of Formula (I) satisfies one or more of the following proviso (i) to (iii): (i) at least one of X^1 , X^2 , X^3 , X^4 , and X^n is $-\text{SH}$ or $-\text{S}^-$; (ii) at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is $=\text{S}$; and (iii) at least one of A , A^1 , and A^2 is $-\text{S}-$.

16. The mRNA sequence having a 5'-end region motif of claim 15, wherein at least one of X^1 , X^2 , X^3 , X^4 , and X^n is $-\text{SH}$ or $-\text{S}^-$; at least one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is $=\text{S}$; or at least one of A , A^1 , and A^2 is $-\text{S}-$.

17. An mRNA sequence having a 5' end region motif (II'):



wherein



each B^2 , B^3 , and B^n is independently a natural, a modified, or an unnatural nucleobase;

each Z^1 and Z' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

each Z^2 and Z'' is independently fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z^3 , Z^4 , and Z^n is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q^1 and Q^4 is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-

each Q^2 and Q^3 is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-

each X^1 , X^2 , X^3 , X^4 , and X^n is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

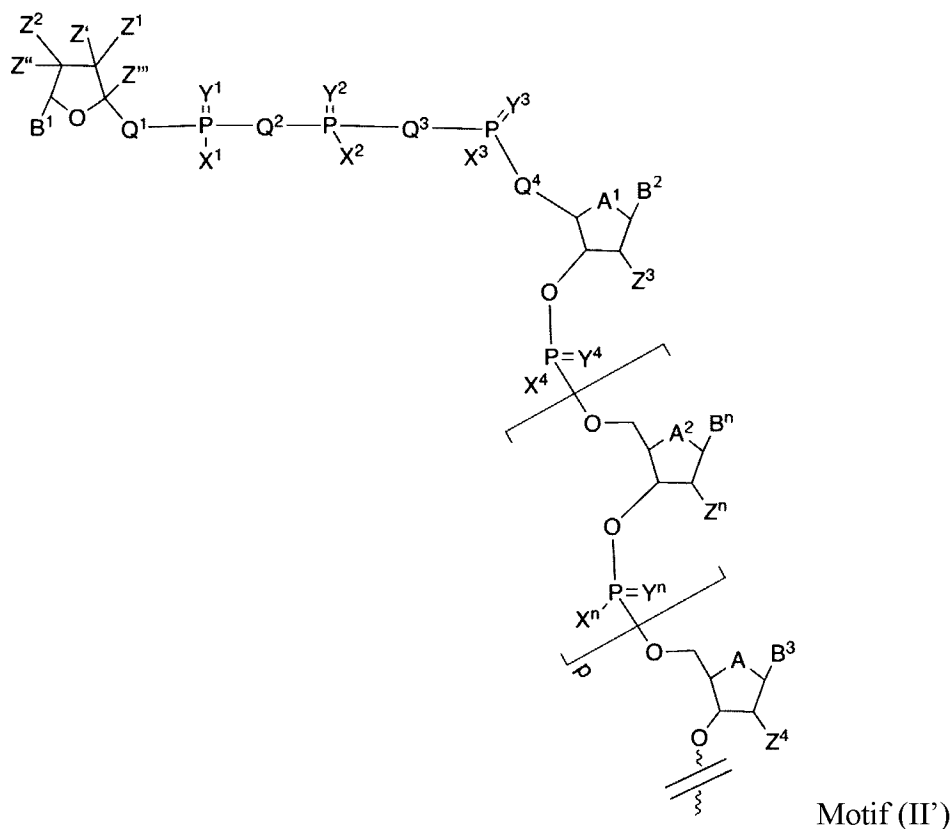
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is independently =O, =S, =NH, or =NCH₃;

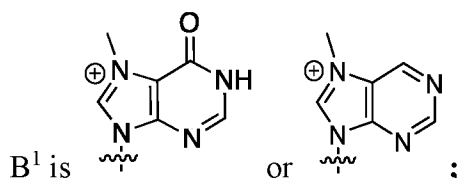
each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-

and $p = 0, 1, 2, 3, 4, 5$ or 6 .

18. An mRNA sequence having a 5'-end region motif (II''):



wherein



each B², B³, and Bⁿ is independently a natural, a modified, or an unnatural nucleobase;

each Z' and Z'' is independently is hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -NH(CH₃), -NH₂, -NH(C(=O)CH₃), or -SCH₃;

Z''' is hydrogen, fluorine, -CH₃, -CH₂CH₃, -OCH₃, or -OCH₂CH₃;

each Z¹ and Z² is independently hydrogen, fluorine, -OH, -SH, -CH₃, -CH₂CH₃, -OCH₃, -SCH₃, -OCH₂CH₃, -NH₂, NHCH₃, or NHC(=O)CH₃;

each Z³, Z⁴, and Zⁿ is independently hydrogen, fluorine, -OH, -CH₃, -CH₂CH₃, -OCH₃, -NH₂, -NHCH₃, -NH(C(=O)CH₃), -OCH₂CH₃, -OCH₂OCH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -SCH₃, or -OCH₂CH₂OCH₃;

each Q¹ and Q⁴ is independently -CH=CH-, -CH₂-, -CH₂O-, -CH₂S-, -CH₂CH₂-, -CH₂CF₂-, -CH₂NH₂-, -CH₂NH(CH₃)-, or -CH₂N(C(=O)CH₃)-

each Q² and Q³ is independently -O-, -S-, -CH₂-, -CF₂-, -NH-, -N(CH₃)-, or -N(C(=O)CH₃)-

each X¹, X², X³, X⁴, and Xⁿ is independently -OH, -SH, -O⁻, -S⁻, -NH₂, -NHCH₃, -

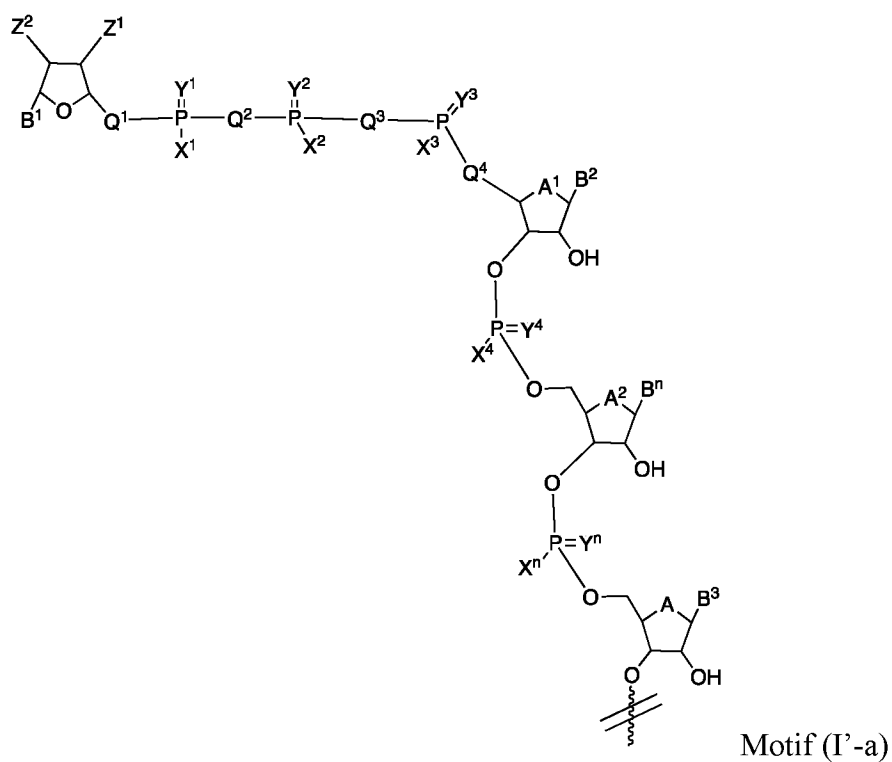
NH(C(=O)CH₃), -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -OCH₃ or -OCH₂CH₃;

each Y¹, Y², Y³, Y⁴, and Yⁿ is independently =O, =S, =NH, or =NCH₃;

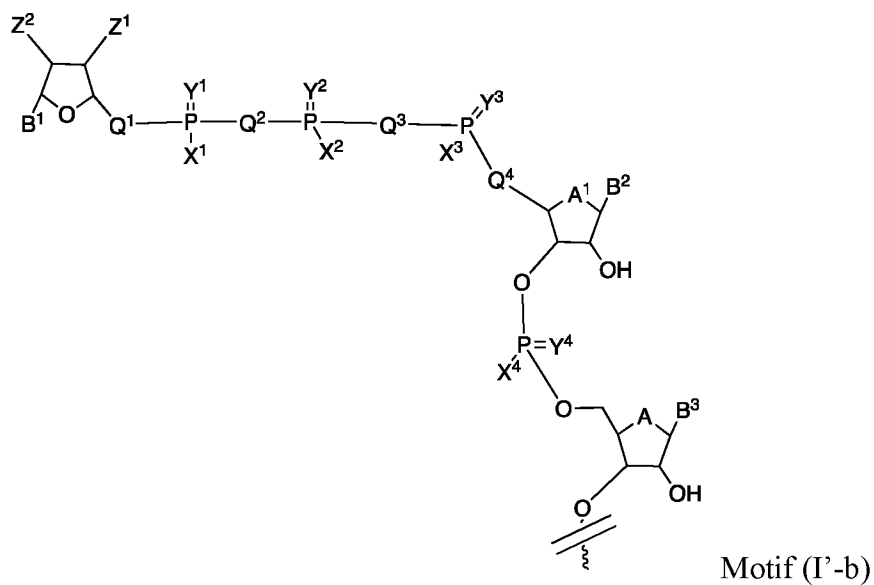
each A, A¹, and A² is independently -O-, -S-, -CH₂-, -NH-, -N(CH₃)- or -N(C(=O)CH₃)-

and p = 0, 1, 2, 3, 4, 5 or 6.

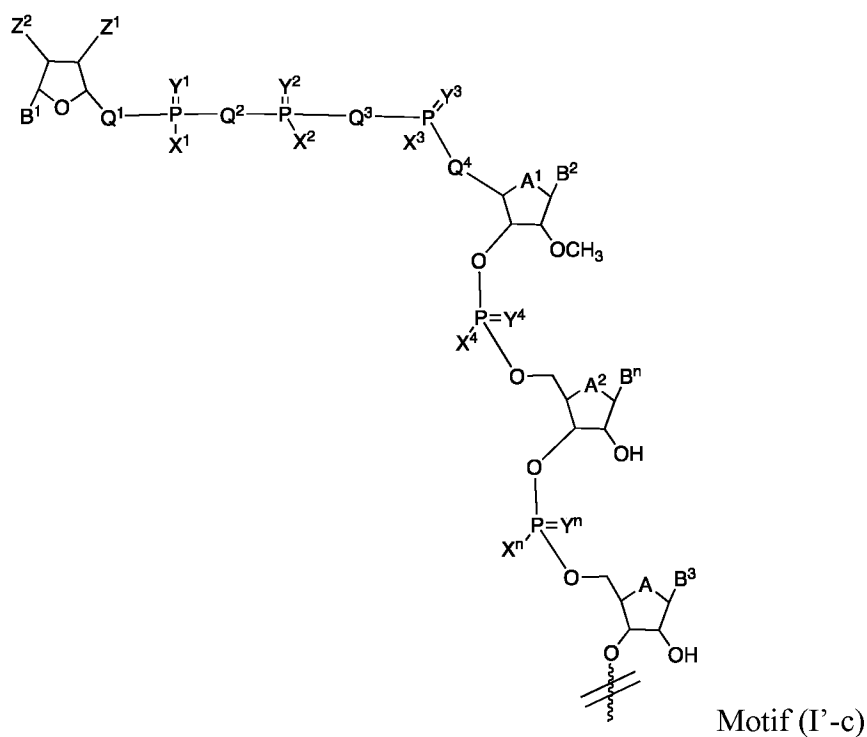
19. The mRNA sequence having a 5'-end region motif (I'-a) of claim 15, wherein the motif has a structure of Motif (I'-a):



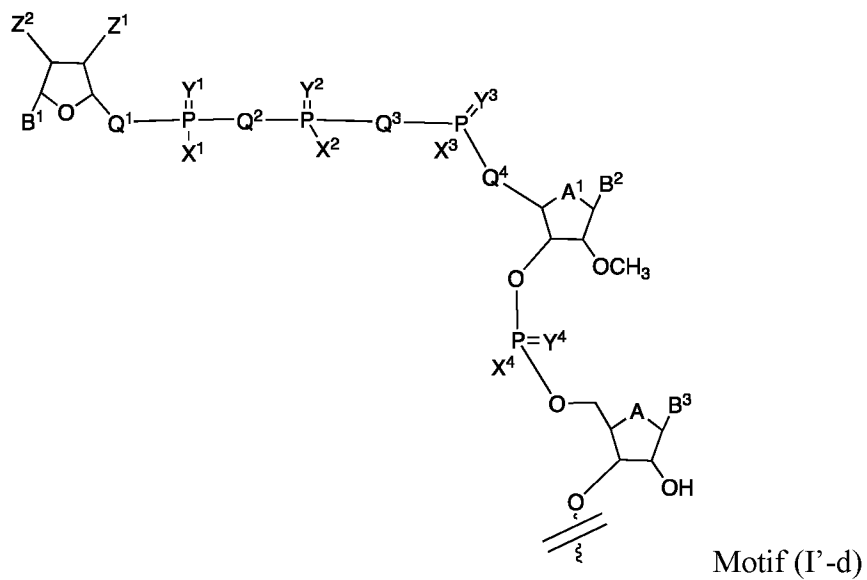
20. The mRNA sequence having a 5'-end region motif (I'-b) of claim 15, wherein the motif has a structure of Motif (I'-b):



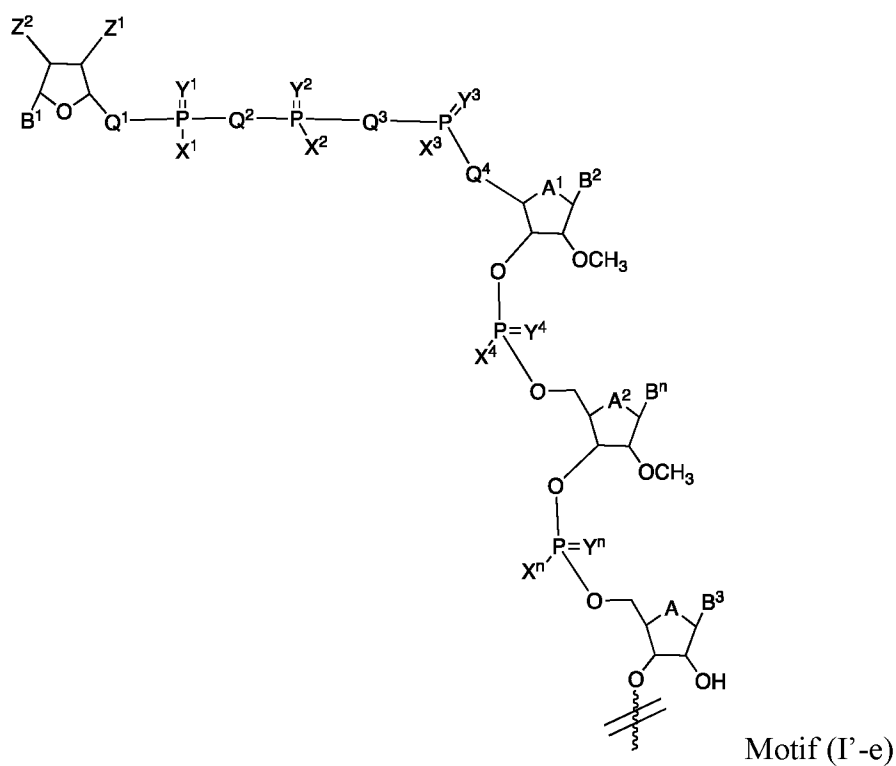
21. The mRNA sequence having a 5'-end region motif (I'-c) of claim 15, wherein the motif has a structure of Motif (I'-c):



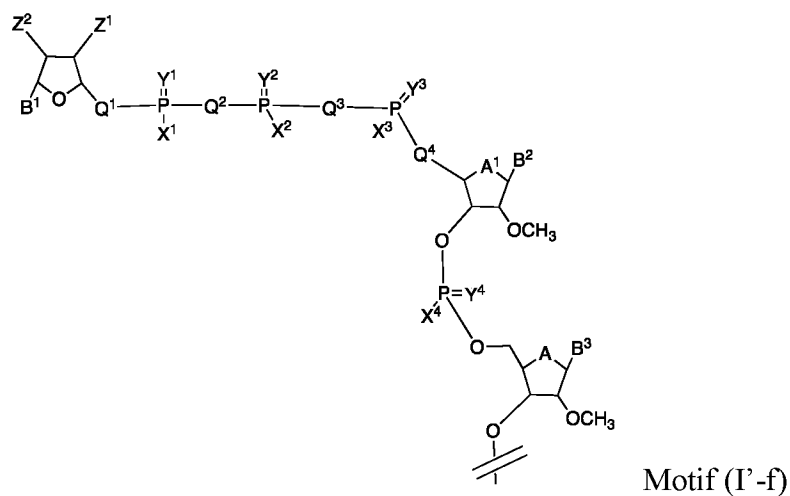
22. The mRNA sequence having a 5'-end region motif (I'-d) of claim 15, wherein the motif has a structure of Motif (I'-d):



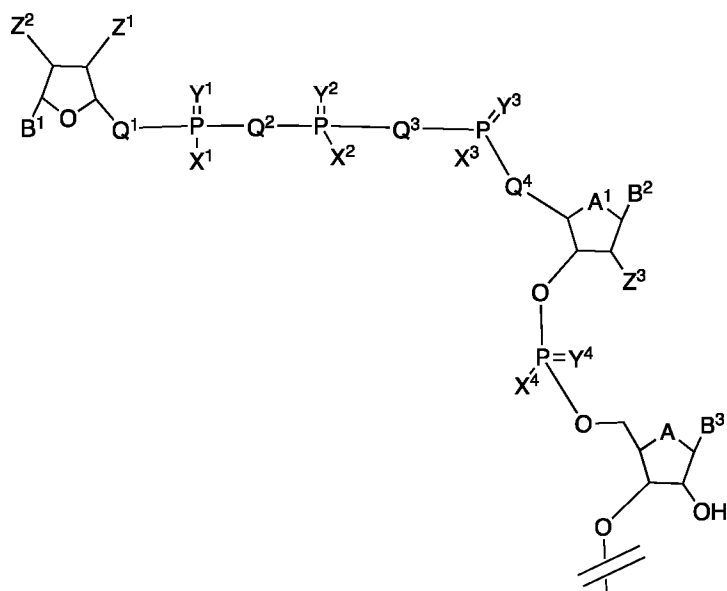
23. The mRNA sequence having a 5'-end region motif (I'-e) of claim 15, wherein the motif has a structure of Motif (I'-e):



24. The mRNA sequence having a 5'-end region motif (I'-f) of claim 15, wherein the motif has a structure of Motif (I'-f):

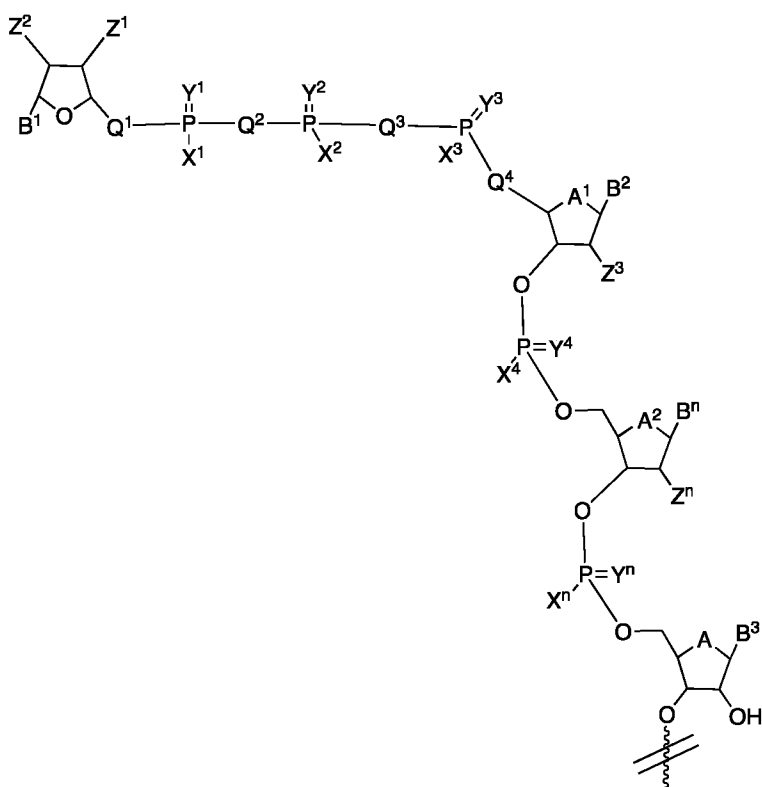


25. The mRNA sequence having a 5'-end region motif (I'-g) of claim 15, wherein the motif has a structure of Motif (I'-g):



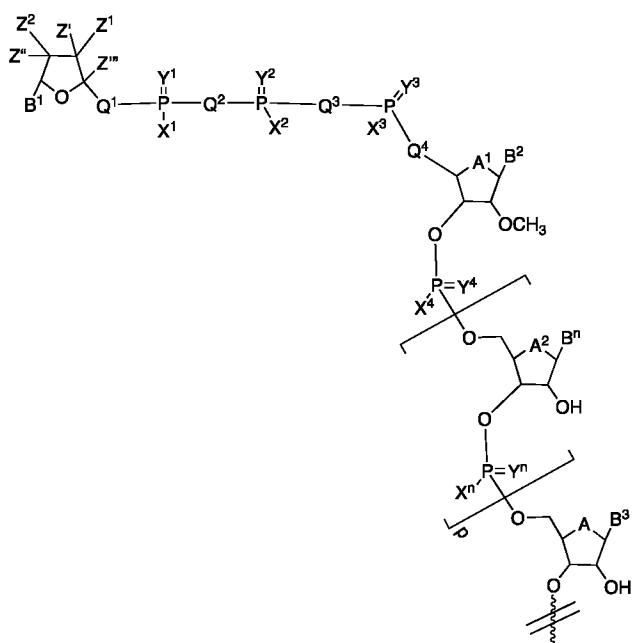
Motif (I'-g)

26. The mRNA sequence having a 5'-end region motif (I'-h) of clam 15, wherein the motif has a structure of Motif (I'-h):



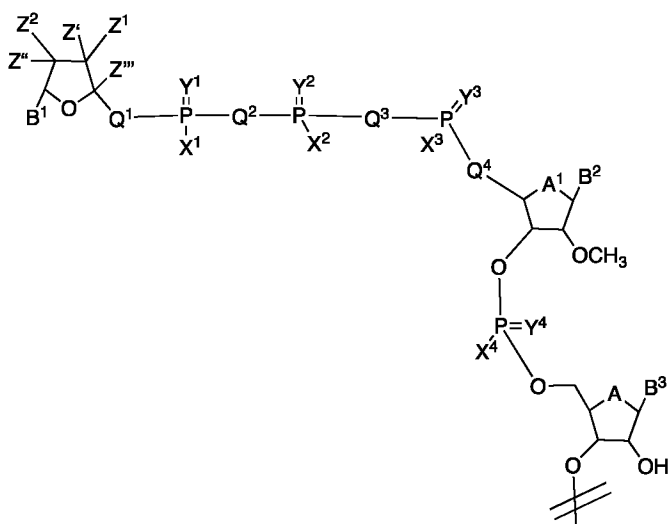
Motif (I'-h)

27. The mRNA sequence having a 5'-end region motif (II'-a) of claim 17 or 18, wherein the motif has a structure of Motif (II'-a):



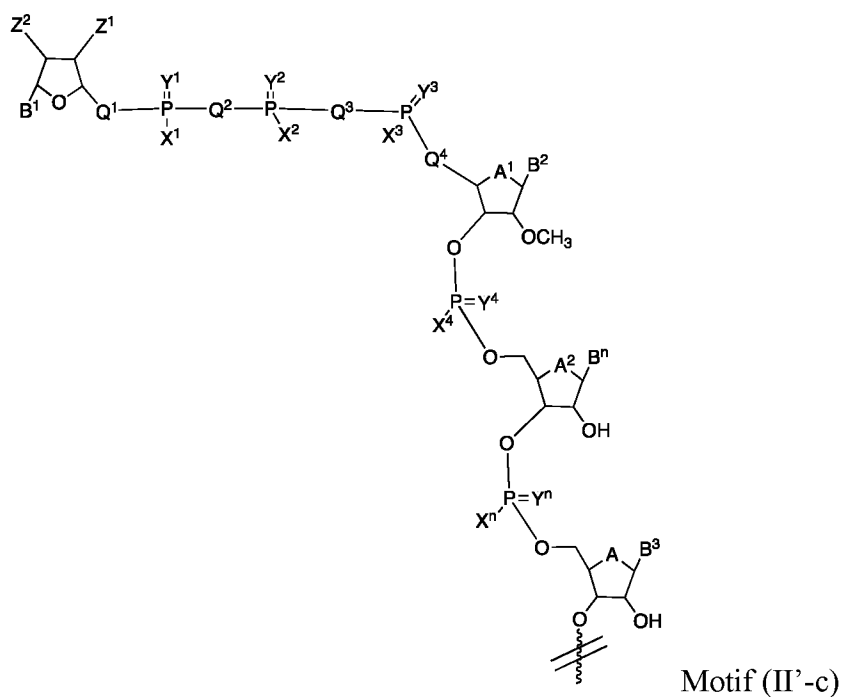
Motif (II'-a)

28. The mRNA sequence having a 5'-end region motif (II'-b) of claim 17 or 18, wherein the motif has a structure of Motif (II'-b):

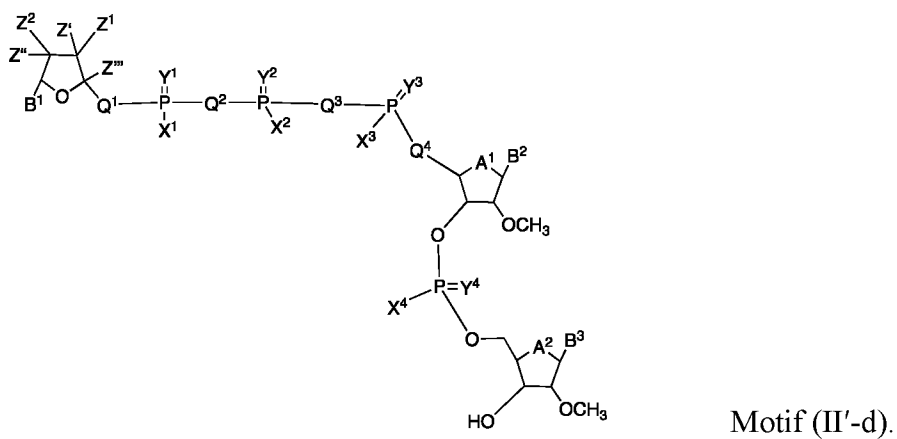


Motif (II'-b)

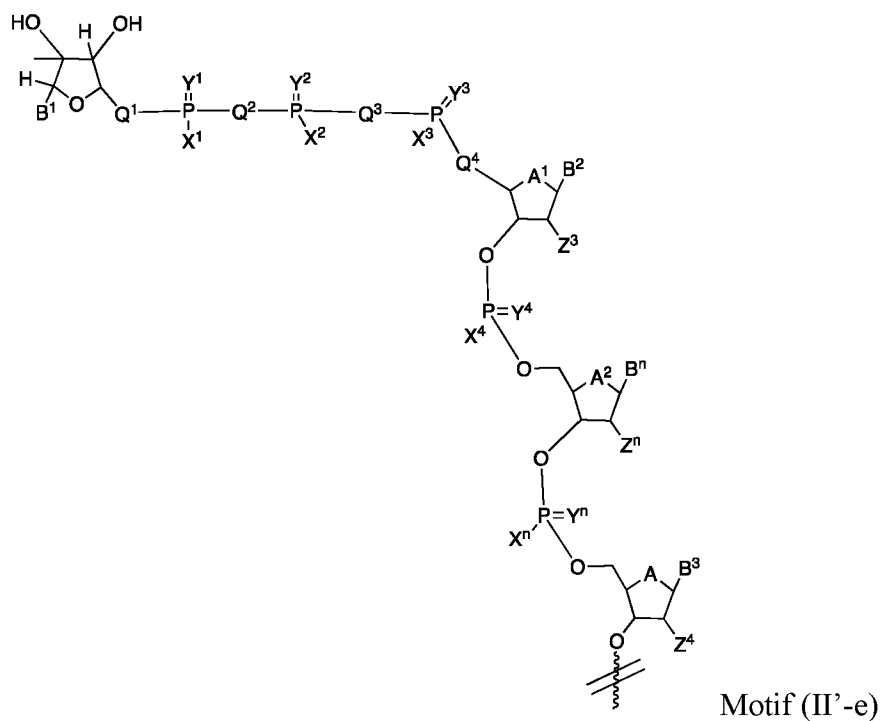
29. The mRNA sequence having a 5'-end region motif (II'-c) of claim 17 or 18, wherein the motif has a structure of Motif (II'-c):



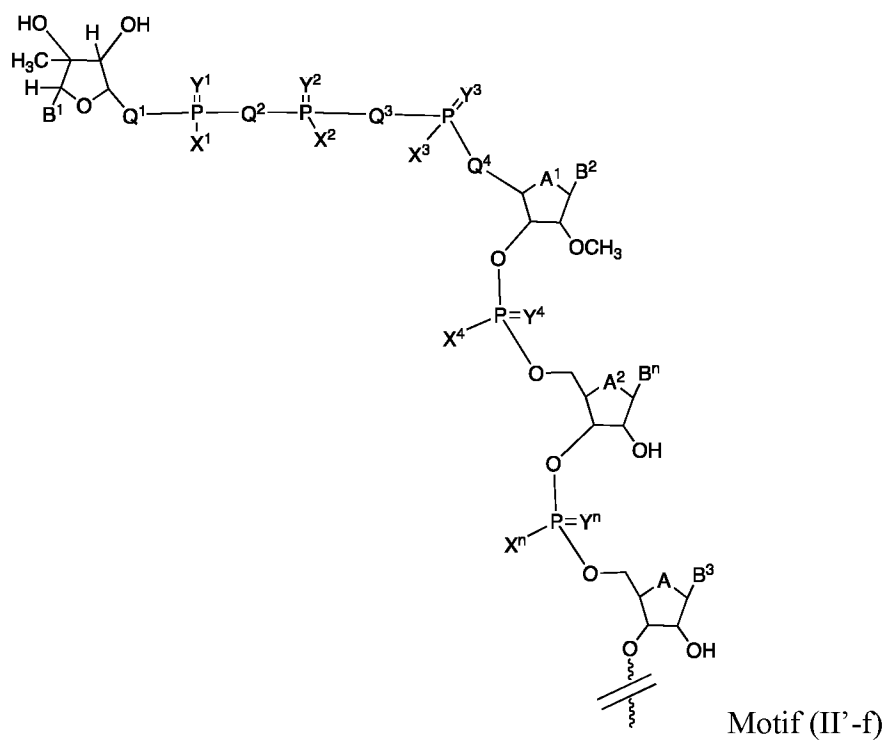
30. The mRNA sequence having a 5'-end region motif (II'-d) of claim 17 or 18, wherein the motif has a structure of Motif (II'-d):



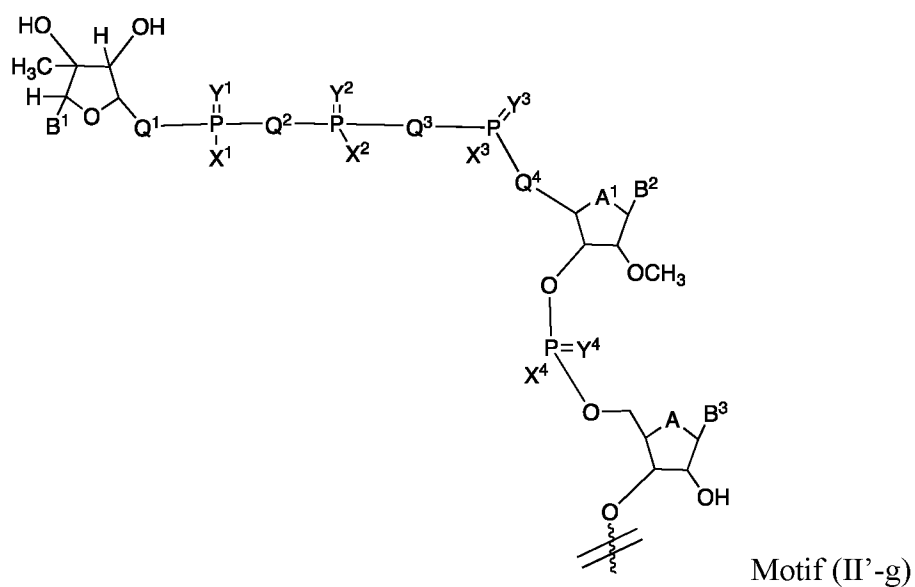
31. The mRNA sequence having a 5'-end region motif (II'-e) of claim 17 or 18, wherein the motif has a structure of Motif (II'-e):



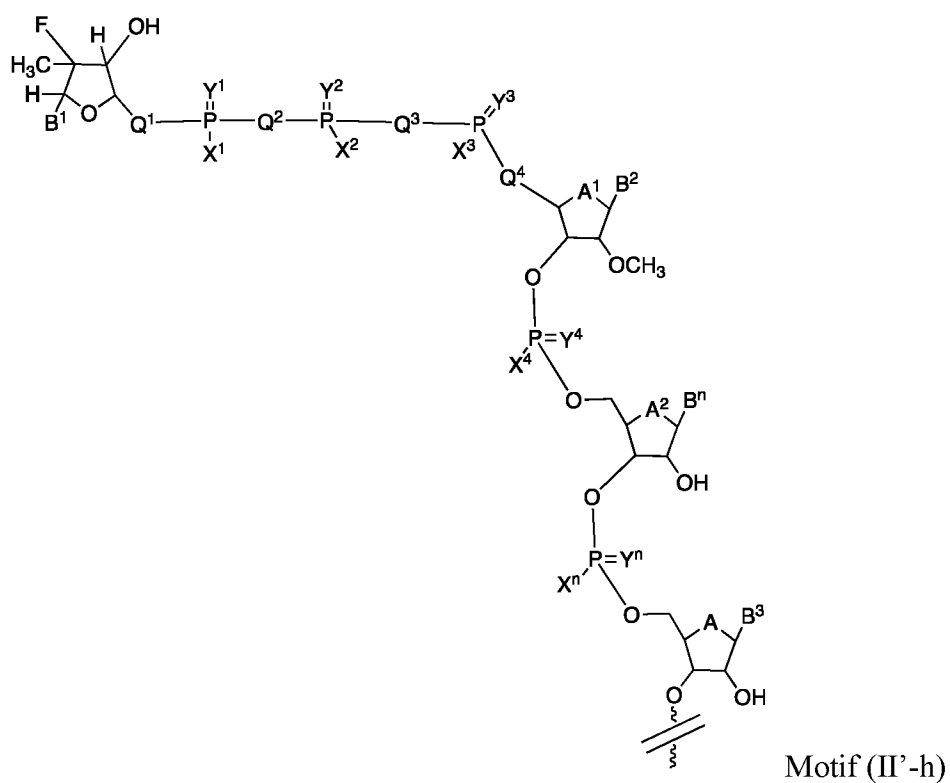
32. The mRNA sequence having a 5'-end region motif (II'-f) of claim 17 or 18, wherein the motif has a structure of Motif (II'-f):



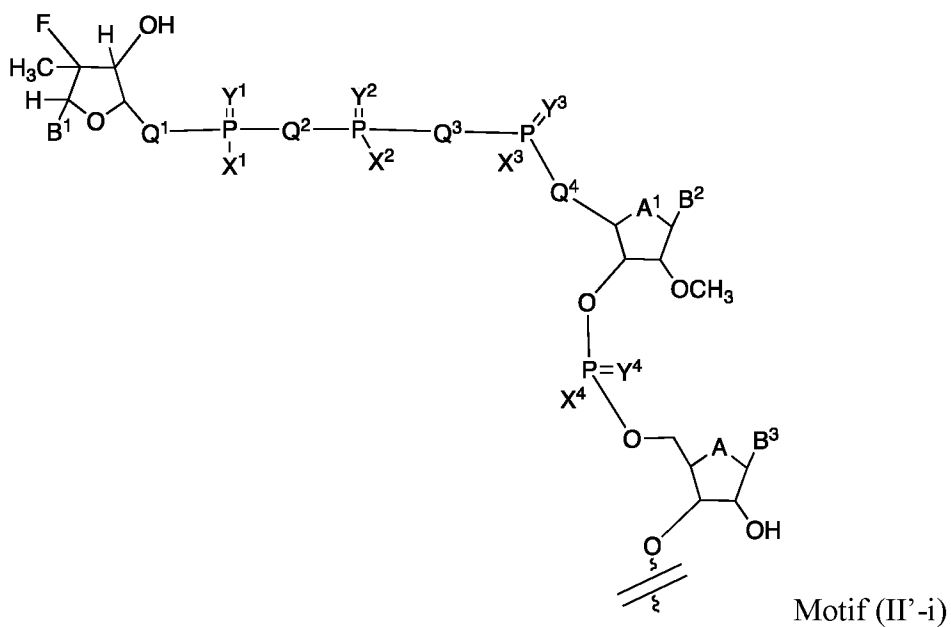
33. The mRNA sequence having a 5'-end region motif (II'-g) of claim 17 or 18, wherein the motif has a structure of Motif (II'-g):



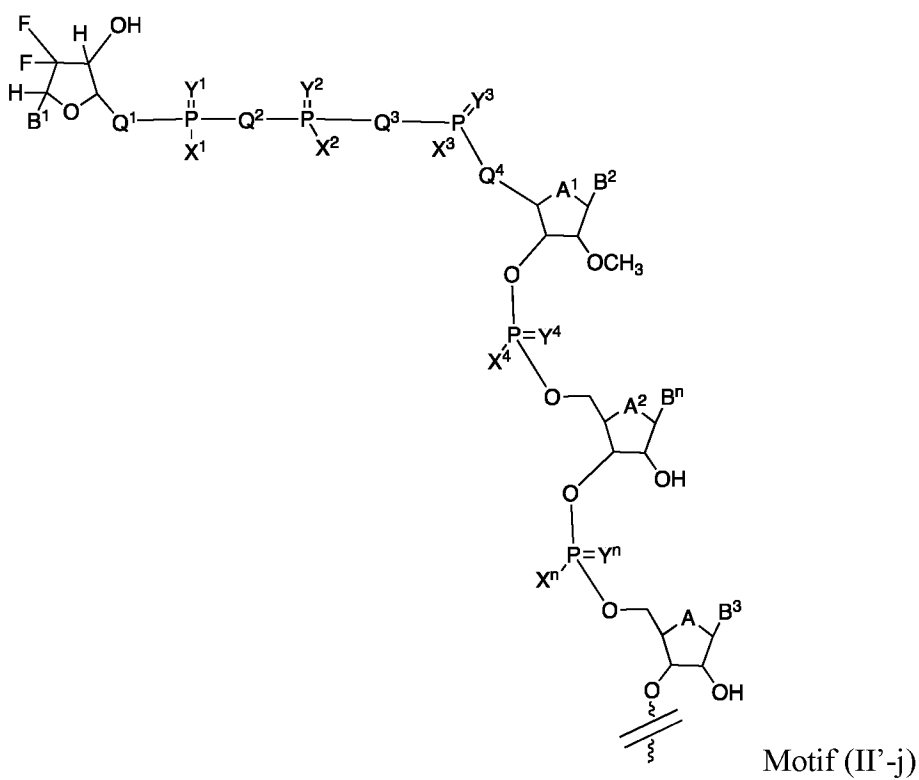
34. The mRNA sequence having a 5'-end region motif (II-h) of claim 17 or 18, wherein the motif has a structure of Motif (II'-h):



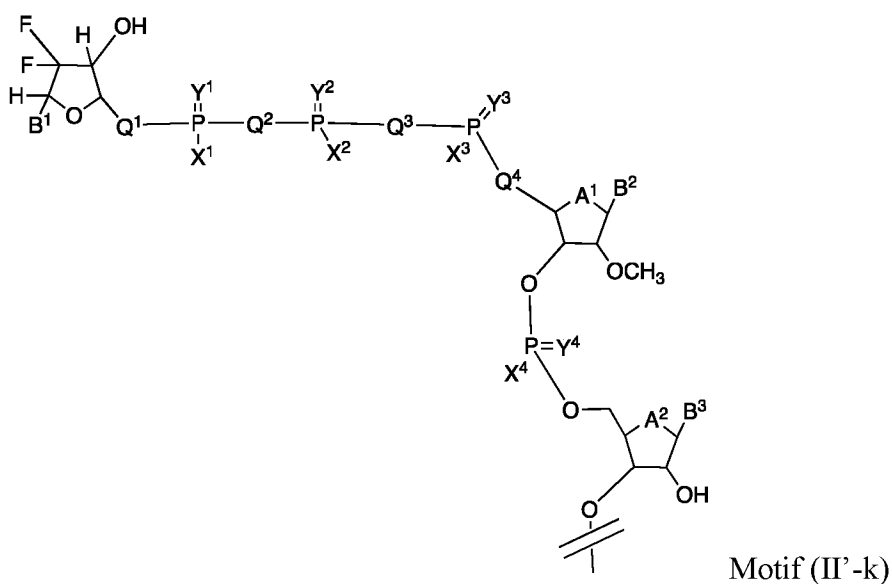
35. The mRNA sequence having a 5'-end region motif (II'-i) of claim 17 or 18, wherein the motif has a structure of Motif (II'-i)



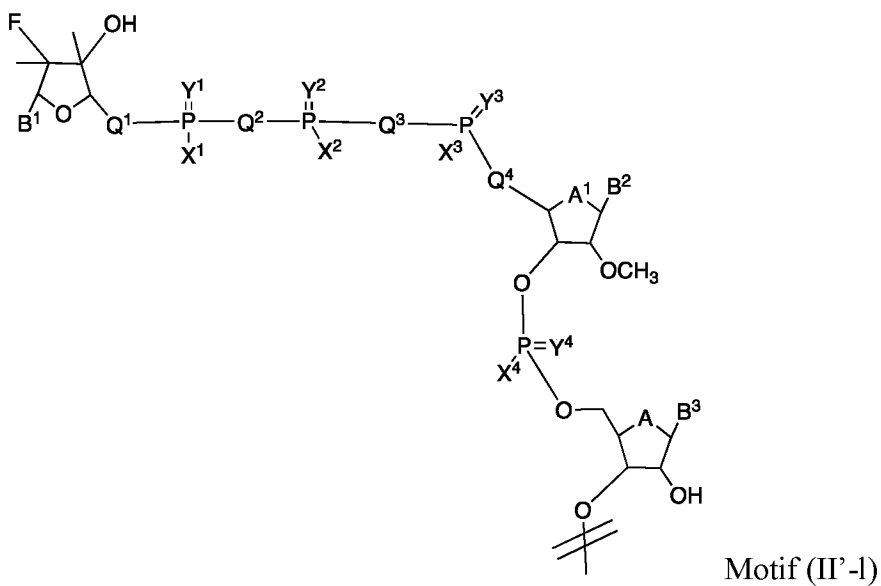
36. The mRNA sequence having a 5'-end region motif (II'-j) of claim 17 or 18, wherein the motif has a structure of Motif (II'-j):



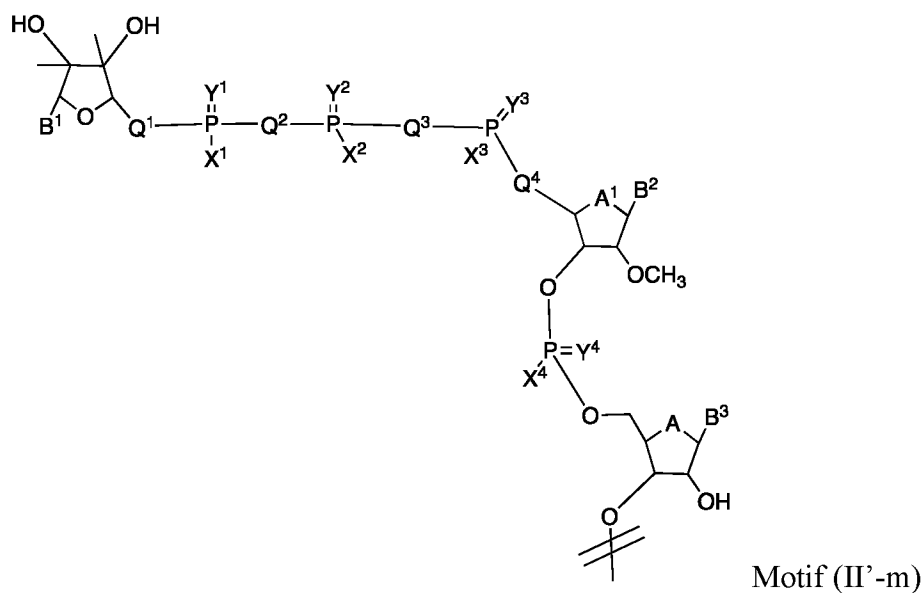
37. The mRNA sequence having a 5'-end region motif (II'-k) of claim 17 or 18, wherein the motif has a structure of Motif (II'-k):



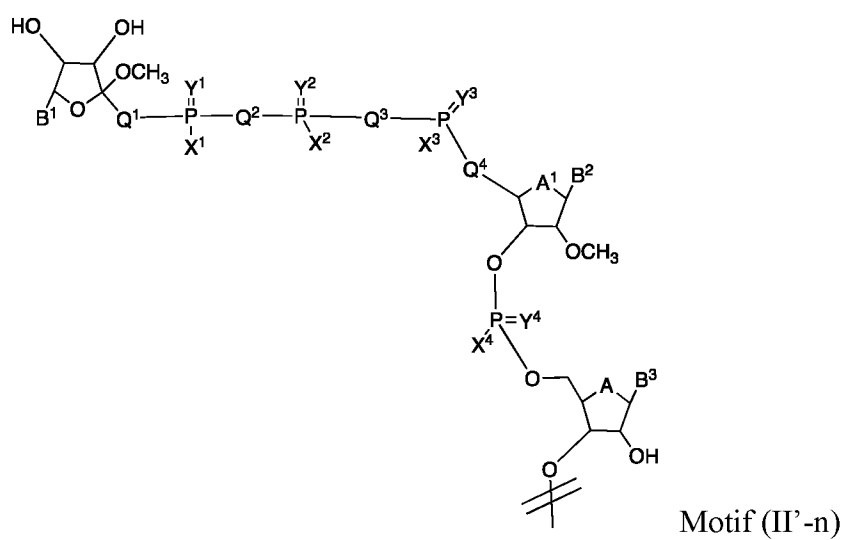
38. The mRNA sequence having a 5'-end region motif (II'-1) of claim 17 or 18, wherein the motif has a structure of Motif (II'-1):



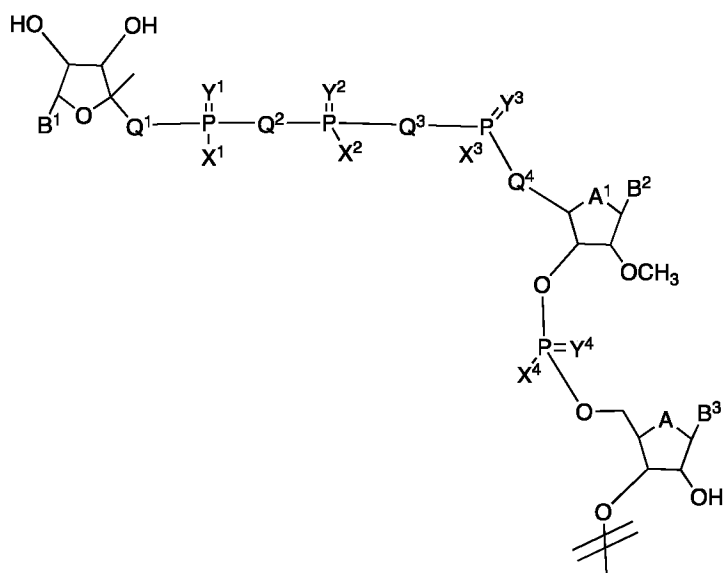
39. The mRNA sequence having a 5'-end region motif (II'-m) of claim 17 or 18, wherein the motif has a structure of Motif (II'-m):



40. The mRNA sequence having a 5'-end region motif (II''-n) of claim 18, wherein the motif has a structure of Motif (II'-n):

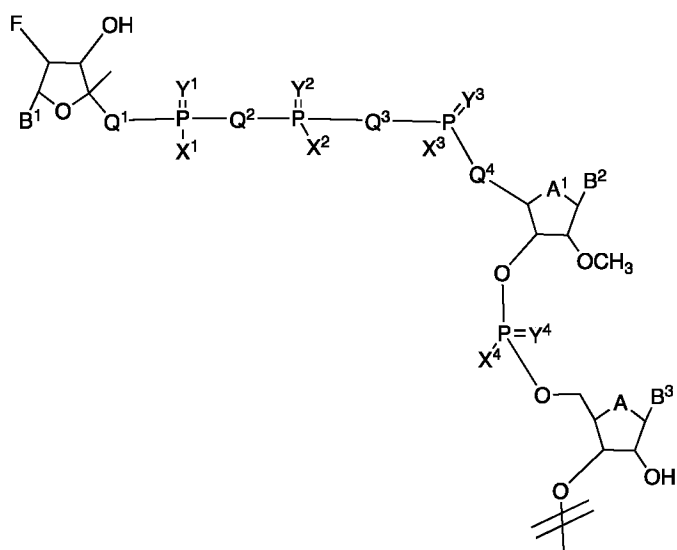


41. The mRNA sequence having a 5'-end region motif (II'-o) of claim 18, wherein the motif has a structure of Motif (II'-o):



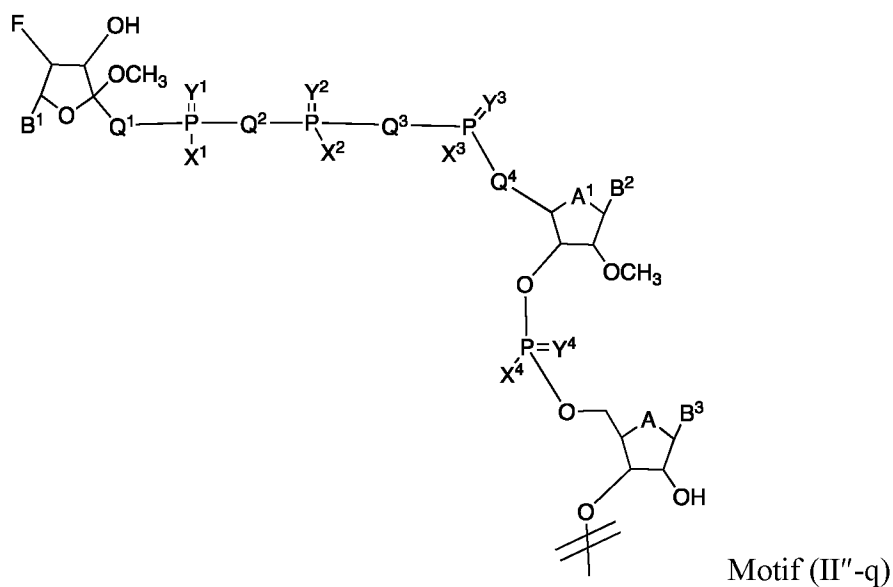
Motif (II''-o)

42. The mRNA sequence having a 5'-end region motif (II'-p) of claim 18, wherein the motif has a structure of Motif (II'-p):

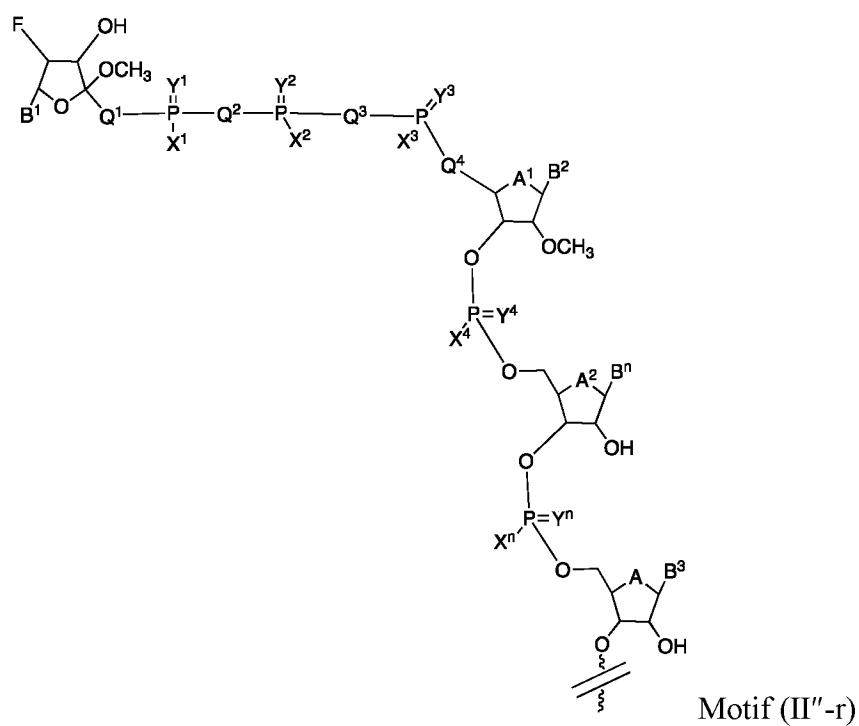


Motif (II''-p)

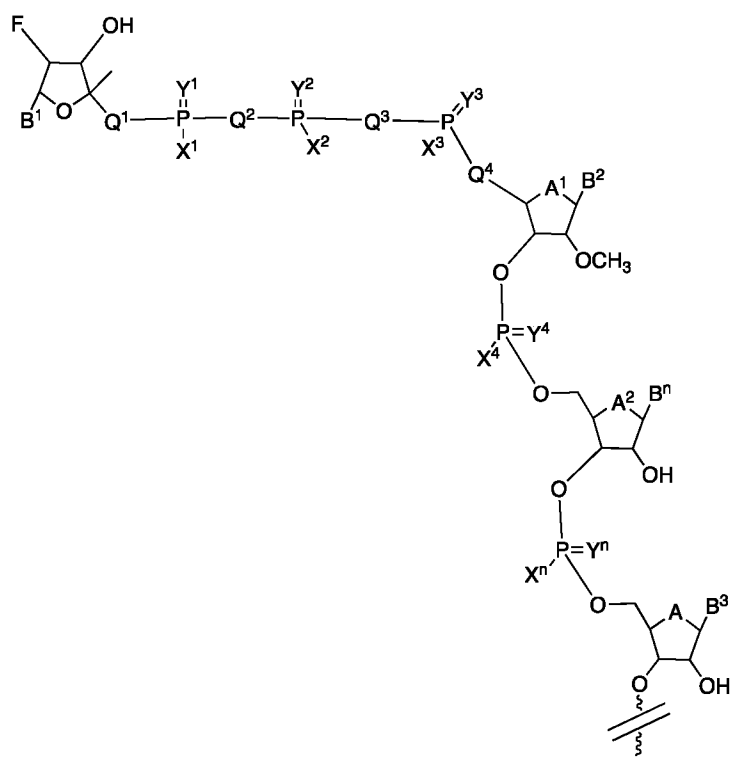
43. The mRNA sequence having a 5'-end region motif (II'-q) of claim 18, wherein the motif has a structure of Motif (II'-q):



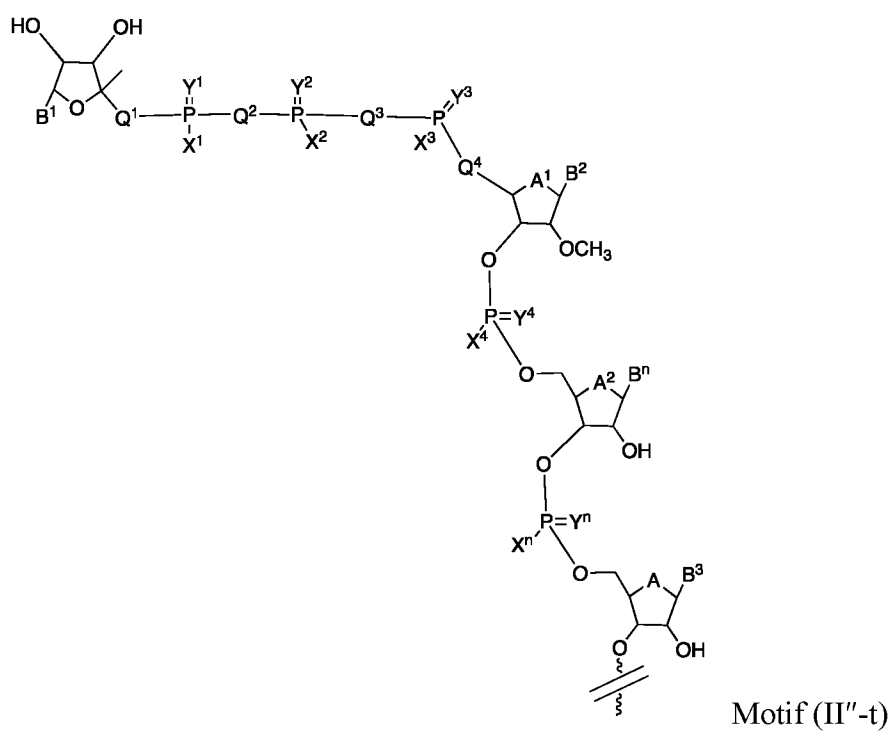
44. The mRNA sequence having a 5'-end region motif (II'-r) of claim 18, wherein the motif has a structure of Motif (II'-r):



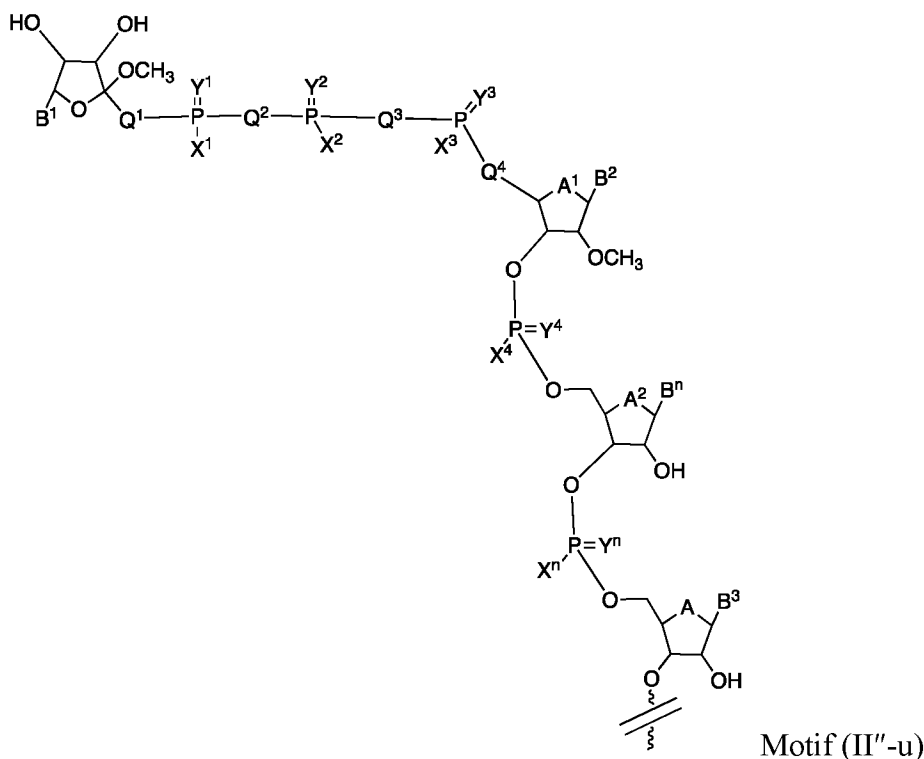
45. The mRNA sequence having a 5'-end region motif (II'-s) of claim 18, wherein the motif has a structure of Motif (II'-s):



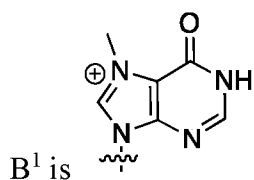
46. The mRNA sequence having a 5'-end region motif (II'-t) of claim 18, wherein the motif has a structure of Motif (II'-t):



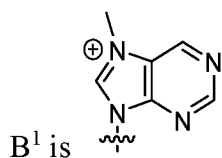
47. The mRNA sequence having a 5'-end region motif (II'-u) of claim 18, wherein the motif has a structure of Motif (II'-u):



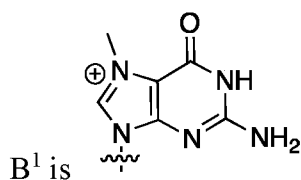
48. The mRNA sequence having a 5'-end region motif of any one of claims 15-18, wherein Z^3 is hydrogen, fluorine, -OH, -OCH₃, - or -OCH₂CH₃.
49. The mRNA sequence having a 5'-end region motif of claim 48, wherein Z^3 is -OCH₃.
50. The mRNA sequence having a 5'-end region motif of claim 48, wherein each Z^4 and Z^n is independently -OH or -OCH₃.
51. The mRNA sequence having a 5'-end region motif of any one of claims 15-18, wherein each Z^3 , Z^4 , and Z^n is independently -OH or -OCH₃.
52. The mRNA sequence having a 5'-end region motif of any one of claims 18 or 25-51, wherein



53. The mRNA sequence having a 5'-end region motif of any one of claims 18 or 25-51, wherein

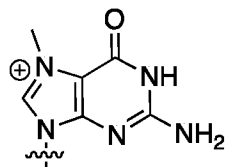


54. The mRNA sequence having a 5'-end region motif of any one of claims 18 or 25-51, wherein



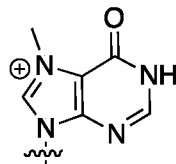
55. The mRNA sequence having a 5'-end region motif of any one of claims 15-30, wherein Z^1 is fluorine, -OH, or -OCH₃.
56. The mRNA sequence having a 5'-end region motif of claim 55, wherein Z^1 is fluorine.
57. The mRNA sequence having a 5'-end region motif of claim 55, wherein Z^1 is -OH.
58. The mRNA sequence having a 5'-end region motif of claim 55, wherein Z^1 is -OCH₃.
59. The mRNA sequence having a 5'-end region motif of any one of claims 15-30, wherein Z^2 is fluorine, -OH, or -OCH₃.
60. The mRNA sequence having a 5'-end region motif of claim 59, wherein Z^2 is fluorine.
61. The mRNA sequence having a 5'-end region motif of claim 59, wherein Z^2 is -OH.
62. The mRNA sequence having a 5'-end region motif of claim 59, wherein Z^2 is -OCH₃.
63. The mRNA sequence having a 5'-end region motif of any one of claims 15-62, wherein Q^1 and Q^4 is -CH₂O-.
64. The mRNA sequence having a 5'-end region motif of any one of claims 15-63, wherein each Q^2 and Q^3 is -O-.
65. The mRNA sequence having a 5'-end region motif of any one of claims 15-64, wherein each Y^1 and Y^3 is =O.
66. The mRNA sequence having a 5'-end region motif of any one of claims 15-64, wherein each Y^2 , Y^4 , and Y^n is independently =O or =S.
67. The mRNA sequence having a 5'-end region motif of any one of claims 15-64, wherein one or more of Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =S.
68. The mRNA sequence having a 5'-end region motif of claim 67, wherein Y^2 is =S.
69. The mRNA sequence having a 5'-end region motif of claim 67, wherein Y^4 is =S.
70. The mRNA sequence having a 5'-end region motif of any one of claims 15-64, wherein each Y^1 , Y^2 , Y^3 , Y^4 , and Y^n is =O.
71. The mRNA sequence having a 5'-end region motif of any one of claims 15-70, wherein each X^1 , X^4 , and X^n is -O[•].
72. The mRNA sequence having a 5'-end region motif of any one of claims 15-70, wherein each X^2 and X^3 is independently -O[•] or -S[•].
73. The mRNA sequence having a 5'-end region motif of claim 72, wherein X^3 is -O[•].
74. The mRNA sequence having a 5'-end region motif of any one of claims 15-70, wherein one or more of X^1 , X^2 , X^3 , X^4 , and X^n is -S[•].
75. The mRNA sequence having a 5'-end region motif of claim 74, wherein X^2 is -S[•].
76. The mRNA sequence having a 5'-end region motif of claim 74, wherein X^4 is -S[•].

77. The mRNA sequence having a 5'-end region motif of any one of claims 15-70, wherein each X^1 , X^2 , X^3 , X^4 , and X^n is -O-.
78. The mRNA sequence having a 5'-end region motif of any one of claims 15-77, wherein each A, A^1 , and A^2 is -O-.
79. The mRNA sequence having a 5'-end region motif of any one of claims 15-77, wherein one or more of A, A^1 , and A^2 is -S-.
80. The mRNA sequence having a 5'-end region motif of any one of claims 15-77 or 79, wherein A is -S- and A^1 and A^2 is -O-.
81. The mRNA sequence having a 5'-end region motif of any one of claims 15-77 or 79, wherein A^2 is -S- and A and A^1 is -O-.
82. The mRNA sequence having a 5'-end region motif of any one of claims 15-77, wherein A, A^1 , and A^2 is -O-.
83. The mRNA sequence having a 5'-end region motif of any one of claims 15, 17, or 48-81, wherein p is 0.
84. The mRNA sequence having a 5'-end region motif of any one of claims 15, 17, or 48-81, wherein p is 1.
85. The mRNA sequence having a 5'-end region motif of any one of claims 15, 17, or 48-81, wherein p is 2.
86. The mRNA sequence having a 5'-end region motif of any one of claims 15-85, wherein each B^2 , B^3 , and B^n is independently adenine, cytosine, guanine, uracil, thymine, hypoxanthine, or purine.
87. The mRNA sequence having a 5'-end region motif of claim 86, wherein B^2 is adenine and B^3 is guanine.
88. The mRNA sequence having a 5'-end region motif of claim 86, wherein B^2 is guanine and B^3 is adenine.
89. The mRNA sequence having a 5'-end region motif of any one of claims 15 to 88, wherein protein expression is increased.
90. The mRNA sequence having a 5'-end region motif of claims 18-47, wherein Q^1 and Q^4 are -CH₂O-; Q^2 and Q^3 are -O-; each X^n is independently -OH, -SH, O⁻, or S⁻; each Y^n is



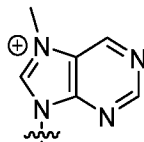
independently =O or =S; and B^1 is

91. The mRNA sequence having a 5'-end region motif of claims 18-47, wherein Q^1 and Q^4 are $-CH_2O-$; Q^2 and Q^3 are $-O-$; each X^n is independently $-OH$, $-SH$, O^- , or S^- ; each Y^n is



independently $=O$ or $=S$; and B^1 is

92. The mRNA sequence having a 5'-end region motif of claims 18-47, wherein Q^1 and Q^4 are $-CH_2O-$; Q^2 and Q^3 are $-O-$; each X^n is independently $-OH$, $-SH$, O^- , or S^- ; each Y^n is



independently $=O$ or $=S$; and B^1 is

93. The mRNA sequence having a 5'-end region motif of claims 86-92, wherein B^2 is adenine.
 94. The mRNA sequence having a 5'-end region motif of claims 86-92, wherein B^3 is guanine.
 95. A complex comprising an mRNA sequence having a 5' end region motif and a DNA template, wherein the mRNA sequence having a 5'-end region motif comprises a compound of any one of claims 15-94, wherein

the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1, a second nucleotide at nucleotide position +2, and a third nucleotide at nucleotide position +3; and

wherein the mRNA sequence having a 5'-end region motif is hybridized to the DNA template at least at nucleotide positions +1, +2, and +3.

96. A complex comprising an mRNA sequence having a 5'-end region motif and a DNA template, wherein the mRNA sequence having a 5' end region motif comprises a compound of any one of claims 15-94, wherein

the DNA template comprises a promoter region comprising a transcriptional start site having a first nucleotide at nucleotide position +1 and a second nucleotide at nucleotide position +2; and

wherein the mRNA sequence having a 5'-end region motif is hybridized to the DNA template at least at nucleotide positions +1 and +2.

97. An RNA molecule comprising the mRNA sequence having a 5'-end region motif according to any one of claims 15-94.
 98. The RNA of claim 97, wherein the RNA comprises a guide RNA or a nuclease mRNA.
 99. The RNA of claim 97, wherein the RNA comprises an mRNA.
 100. A method of expressing an mRNA comprising introducing the mRNA of claim 99 into a cell lysate to express the mRNA.

101. The method of claim 100, further comprising measuring the expression level of the mRNA.
102. The method of claim 100, wherein the expression level of the mRNA is at least 2-fold, 3-fold, 4-fold, 6-fold, 8-fold, or 20-fold greater compared to a corresponding mRNA without the the mRNA sequence having a 5'-end region motif.
103. The method of claim 100, wherein the cell is a HeLa cell.
104. A method of detecting cellular immune stimulation resulting from mRNA comprising (a) contacting a formulation comprising capped mRNA according to any one of claims 15 to 94 with a cell reporter line and (b) measuring RIG-I activation in said cell reporter line.
105. The method of claim 104, wherein said cell reporter line is HEK-Lucia RIG-I model.
106. The method of any one of claims 104 or 105, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 20%.
107. The method of claim 106, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 50%.
108. The method of claim 107, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 70%.
109. The method of claim 108, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 100%.
110. The method of claim 109, wherein cellular immune stimulation is reduced compared to an uncapped mRNA by at least 150%.
111. A method of producing an mRNA sequence having a 5'-end region motif of any one of claims 15-99 using an IVT reaction comprising (a) mixing a DNA template, polymerase enzyme, mRNA sequence initiator comprising a phosphorothioate group, and nucleoside triphosphates (NTPs) at a specified molar ratio of said mRNA sequence initiator to said NTPs to generate a mixture (b) incubating said mixture at a specified temperature and duration and (c) harvesting and purifying said mRNA sequence having a 5'-end region motif from said mixture.
112. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:5, and wherein said method is capable of producing a yield of at least 80% with a capping efficiency of at least 80%.
113. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is 1:2.5, and wherein said method is capable of producing a yield of at least 80% with a capping efficiency of at least 85%.
114. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:1.67, and wherein said method is capable of producing a yield of at least 80% with a capping efficiency of at least 90%.

115. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:1.25, and wherein said method is capable of producing a yield of at least 80% with a capping efficiency of at least 90%.
116. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:1, and wherein said method is capable of producing a yield of at least 80% with a capping efficiency of at least 90%.
117. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:5, and wherein said method is capable of producing a yield of at least 3 mg of mRNA per milliliter (mL) of IVT reaction with a capping efficiency of at least 80%.
118. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:2.5, and wherein said method is capable of producing a yield of at least 3 mg of mRNA per mL of IVT reaction with a capping efficiency of at least 85%.
119. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:1.67, and wherein said method is capable of producing a yield of at least 3 mg of mRNA per mL of IVT reaction with a capping efficiency of at least 90%.
120. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:1.25, and wherein said method is capable of producing a yield of at least 3 mg of mRNA per mL of IVT reaction with a capping efficiency of at least 90%.
121. The method of claim 111, wherein said molar ratio of the mRNA sequence initiator to NTPs is about 1:1, and wherein said method is capable of producing a yield of at least 3 mg of mRNA per mL of IVT reaction with a capping efficiency of at least 90%.
122. The method of claim 111, wherein said NTPs is GTP, ATP, CTP, UTP, or a modified NTP, or a combination thereof.
123. The method of claim 122, wherein said modified NTP is 5'-triphosphate of N1-methyl pseudouridine.
124. A cell containing an RNA molecule comprising the mRNA sequence having a 5' end region motif according to any one of claims 15-94.
125. A cell containing a polypeptide or protein translated from an RNA molecule comprising the mRNA sequence having a 5' end region motif according to any one of claims 15-94.
126. A pharmaceutical composition comprising an RNA molecule comprising the mRNA sequence having a 5' end region motif according to any one of claims 15-94 and one or more of pharmaceutically acceptable excipients.

127. The pharmaceutical composition of claim 126, further comprising one or more single guide RNA designed to target one or more specific locations of one or more genes of interest to elicit pharmacological effect upon administration into a mammal.
128. The pharmaceutical composition of claim 126, comprising lipid nanoparticles.
129. The pharmaceutical composition of claim 126, wherein the RNA is encapsulated in a lipid nanoparticle.
130. A method for synthesizing an RNA molecule comprising:
- a. introducing the mRNA sequence having a 5' end region motif according to any one of claims 15-94 into a mixture comprising an RNA polymerase, and
 - b. incubating the mixture for a time sufficient to allow for transcription of the RNA molecule.
131. The method of claim 81 wherein the mixture further comprises a DNA template and nucleoside triphosphates.
132. A method of gene editing comprising introducing into a cell an RNA molecule of claim 97 or 98, or pharmaceutical composition of any one of claims 126-129, wherein the RNA molecule comprises guide RNA or a nuclease mRNA, wherein the RNA molecule is translated in the cell.
133. A method for reducing the risk of coronary disease in a subject in need thereof, comprising administering to the subject an effective amount of a pharmaceutical composition of any one of claims 126-129.

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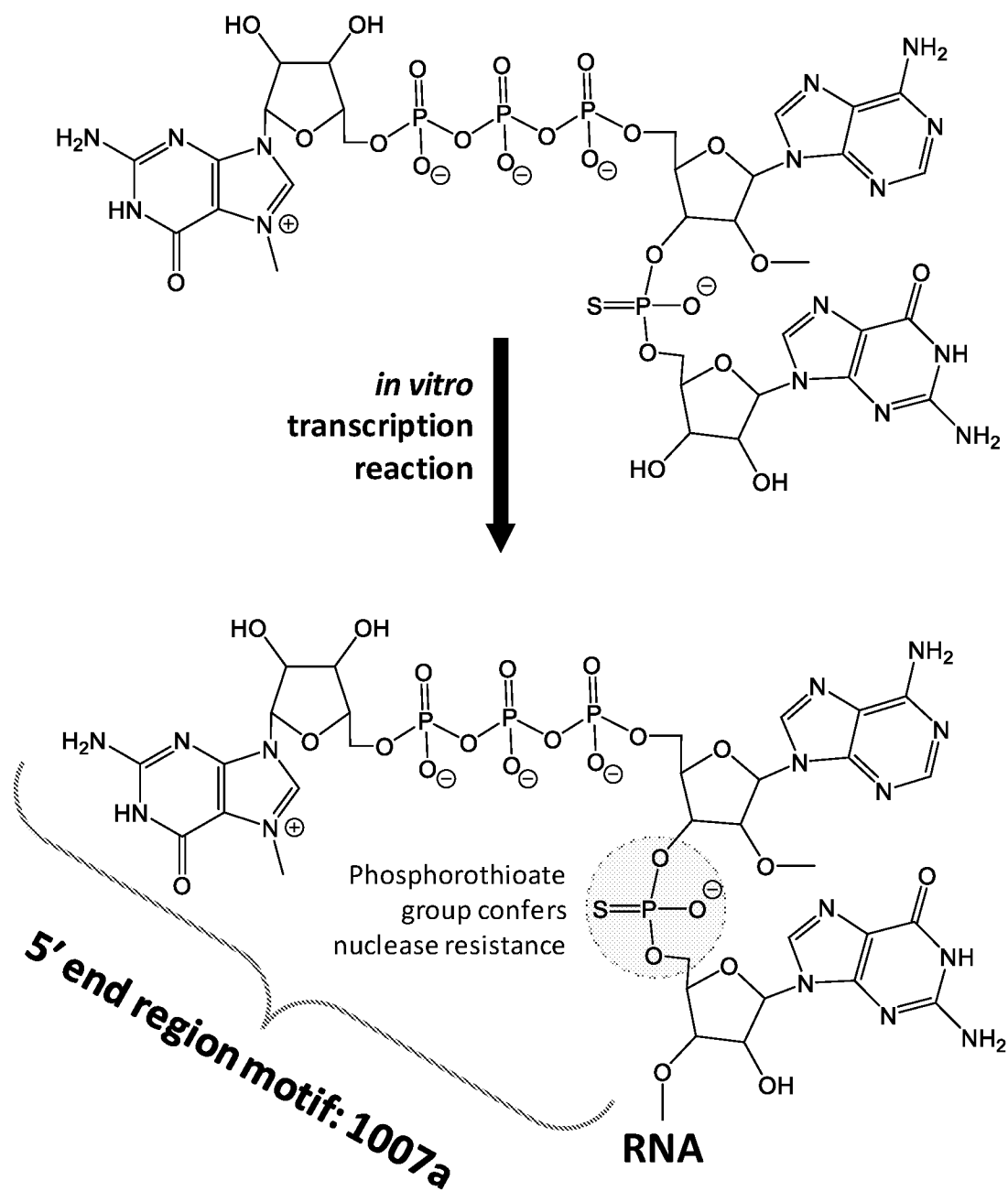
5' end initiator: 1007a

FIG. 1A

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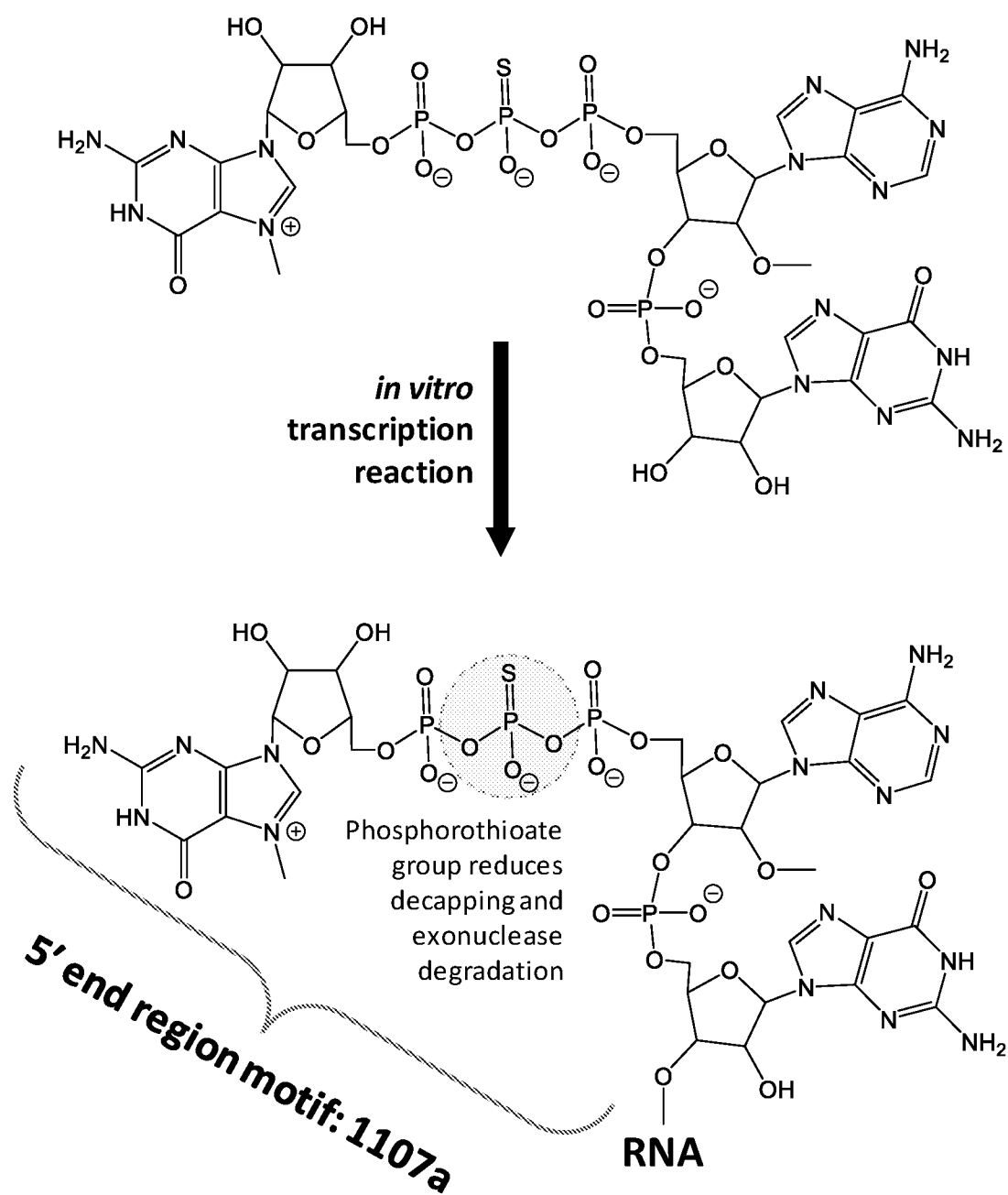
5' end initiator: 1107a

FIG. 1B

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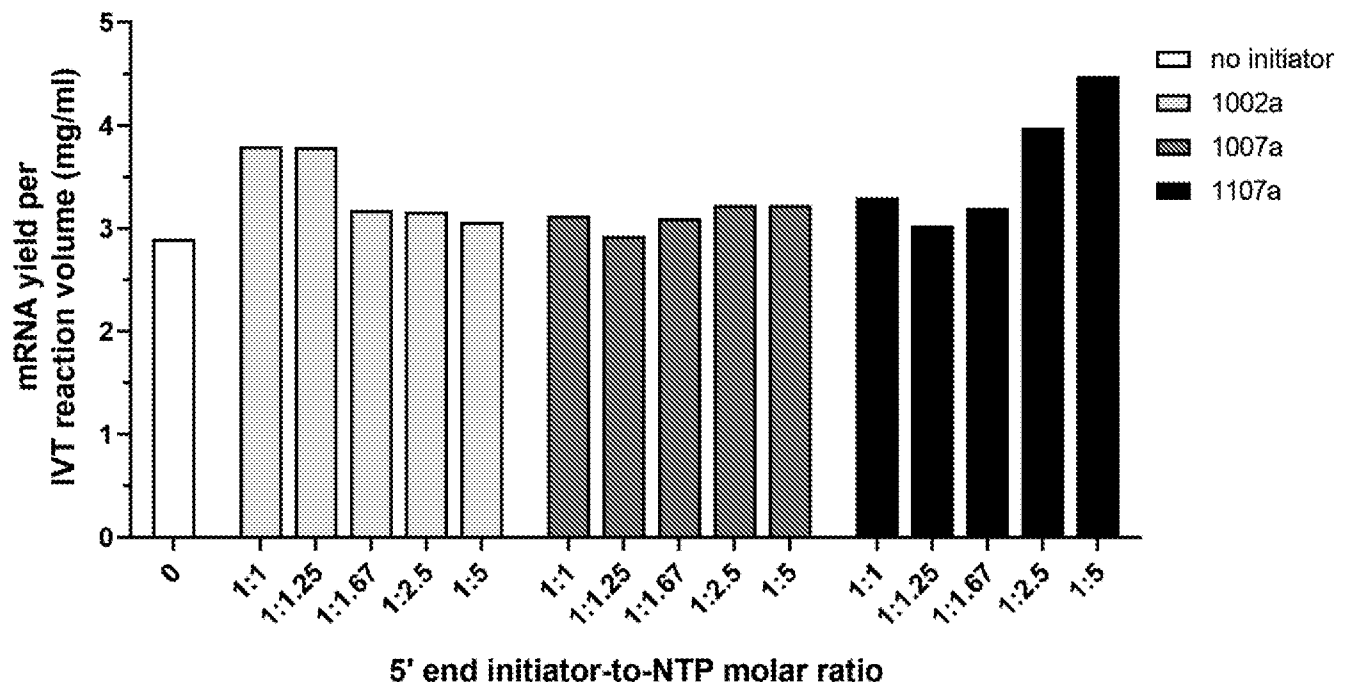


FIG. 2

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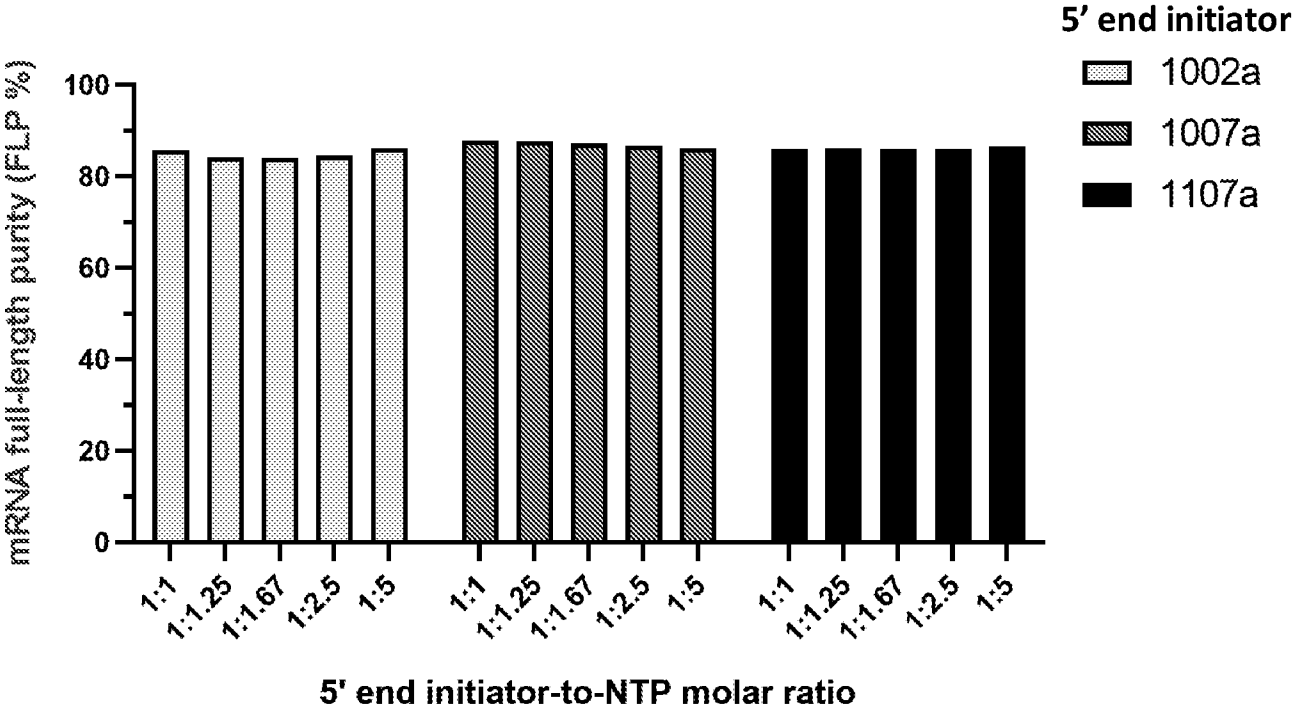


FIG. 3

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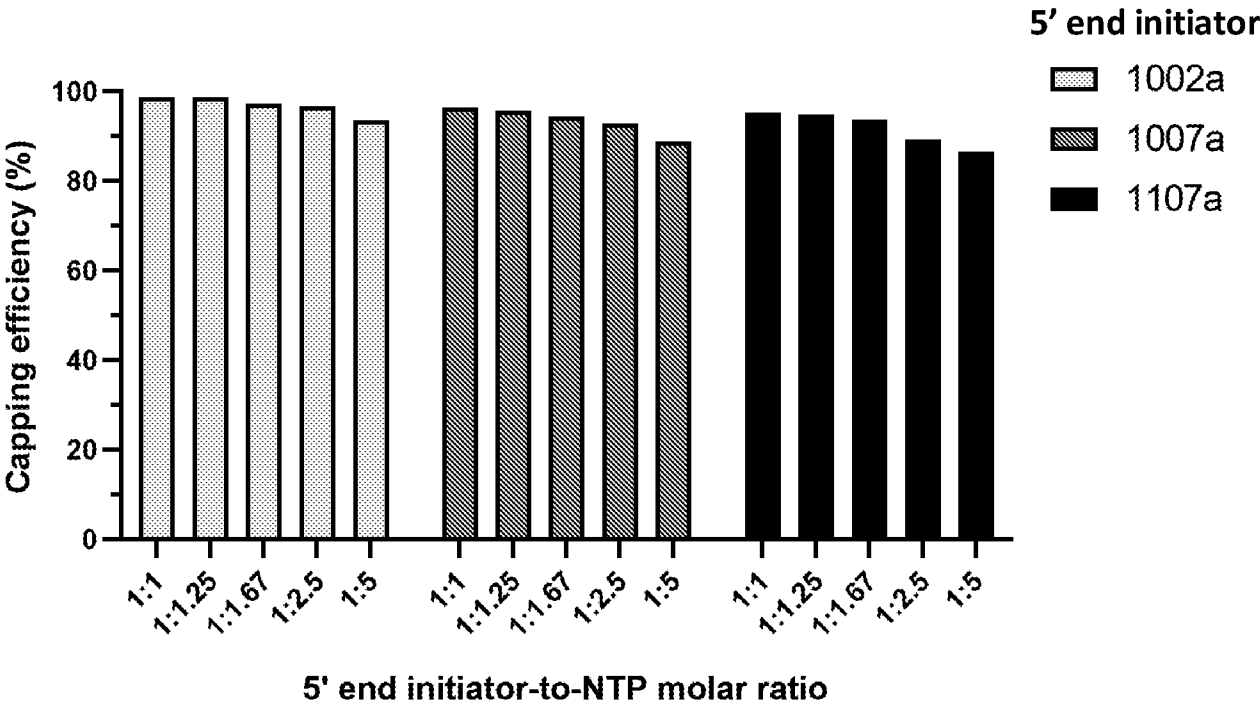


FIG. 4

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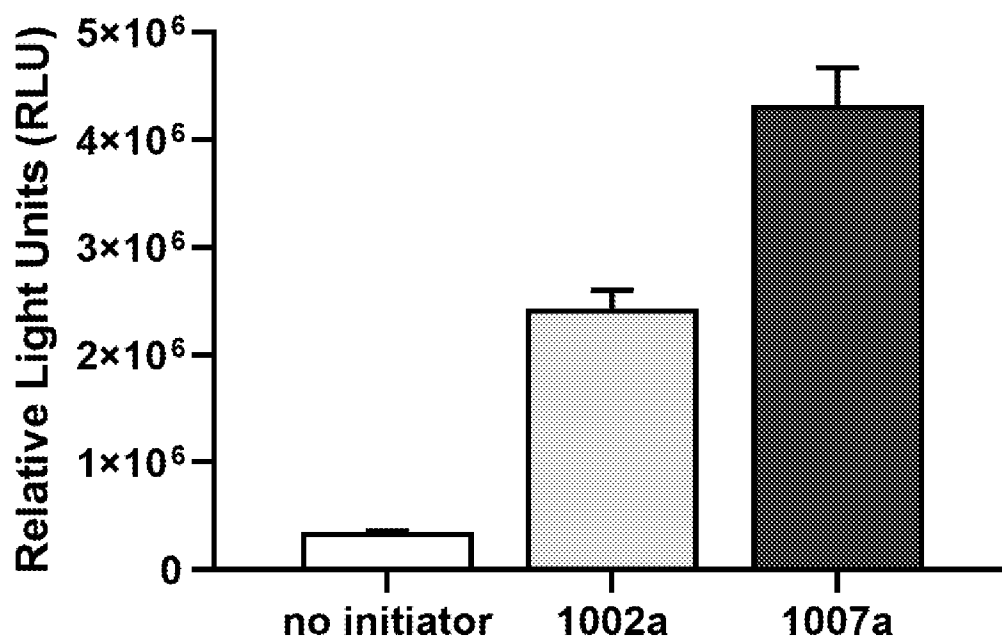


FIG. 5

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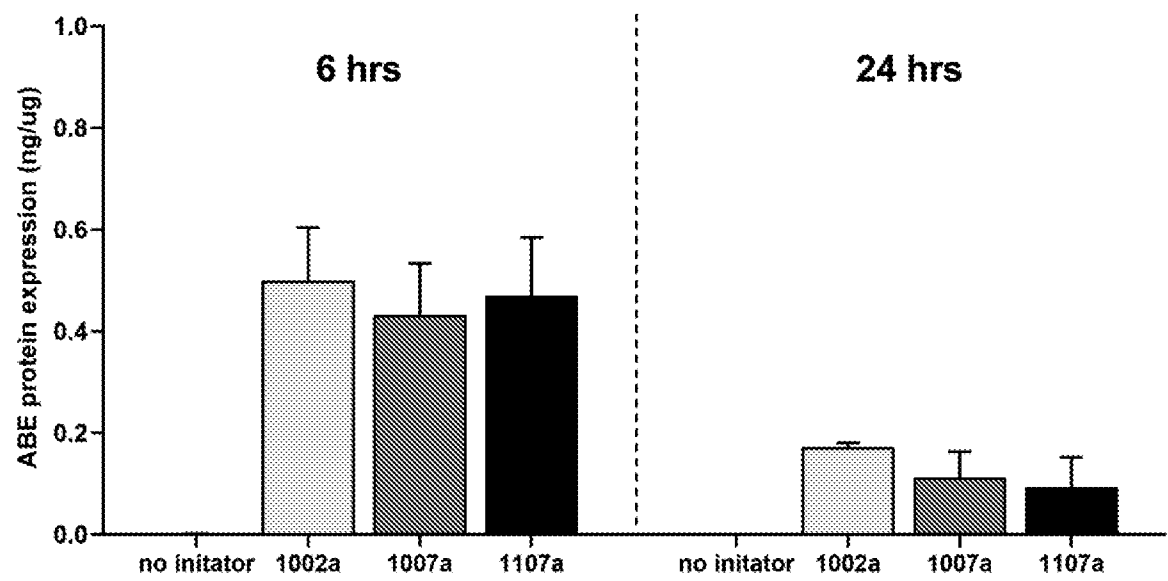


FIG. 6

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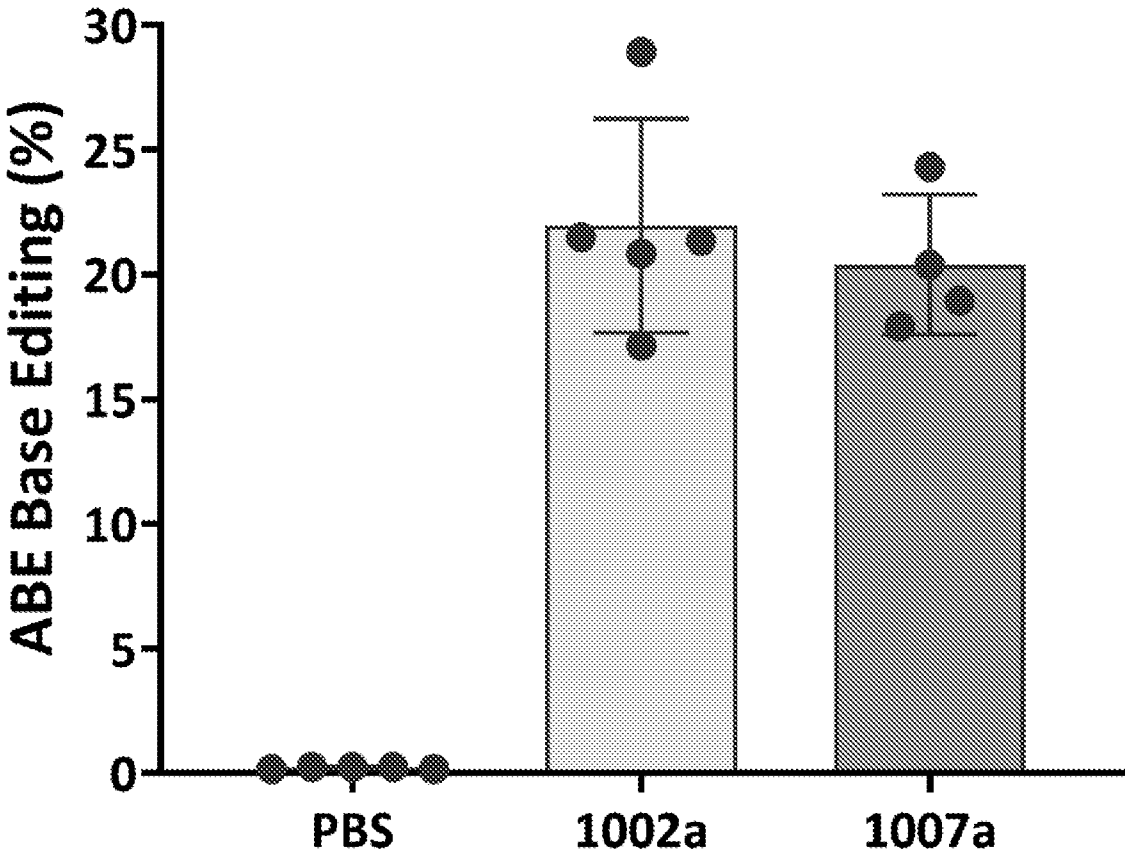


FIG. 7

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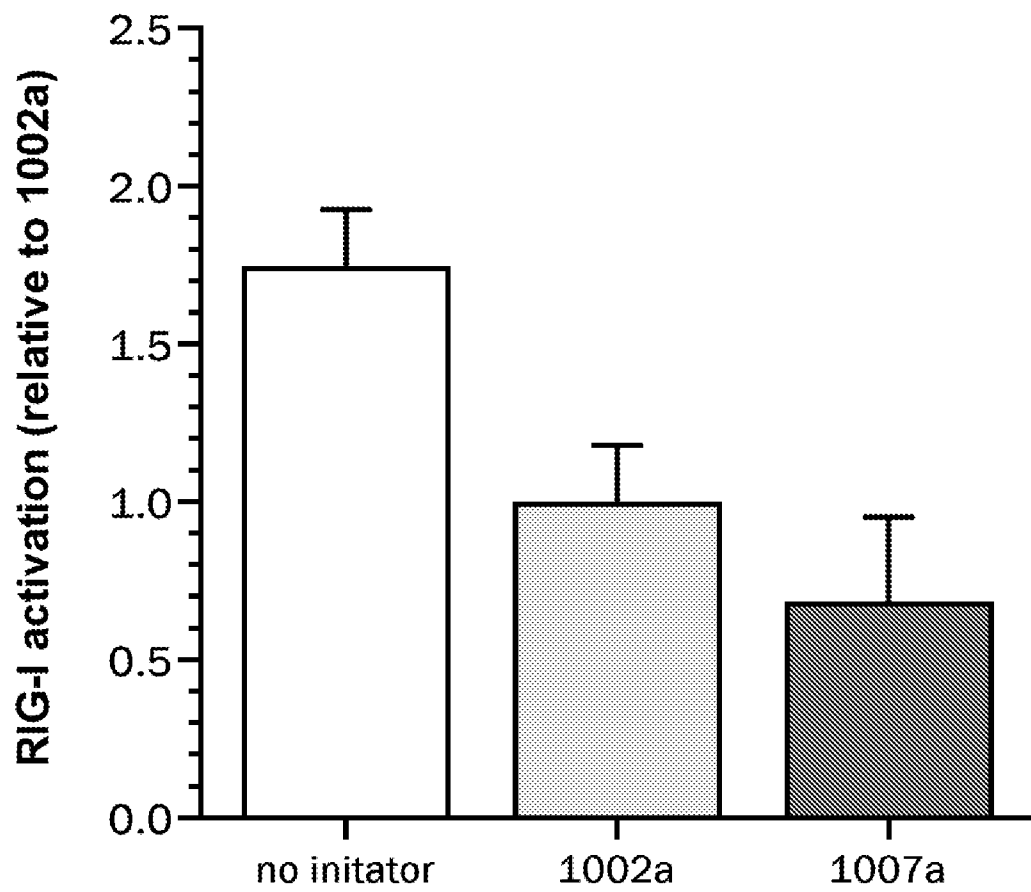


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/49158

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/712; A61K 31/7115; A61K 31/7125; C07H 21/02; C07H 21/04 (2021.01)

CPC - A61K 31/7115; A61K 31/712; A61K 31/7125; C07H 21/02; C07H 21/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	WO 2017/066797 A1 (MODERNATX, INC.) 20 April 2017; abstract; paragraphs [006], [008], [011], [021], [0176], [0297], [0308], [0318], [0436], [0462], [0674]-[0675]	1-3, 6, 8, 9/1-3, 10/9/1-3, 15-17, 20, 25, 48/15-17 --- 4-5, 7, 9/4, 10/9/4, 11, 18, 19, 21-24, 26, 27-33, 41, 46, 48/18, 49-51 --- 34-40, 42-45, 47
Y --- A	WO 2017/053297 A1 (TRILINK BIOTECHNOLOGIES, INC.) 30 March 2017; abstract; paragraph [0051]; figure 10A, 10B, 10H	1, 5, 7, 11/9/1-3, 19, 21-24, 26, 27-33, 49-51 --- 34-40, 42-45, 47
Y --- A	(SENTHILVELAN, A et al.) Highly regioselective methylation of inosine nucleotide: an efficient synthesis of 7-methylinosine nucleotide. Nucleosides, Nucleotides and Nucleic Acids. 19 March 2020, Vol. 39, No. 7; pages 1011-1019; abstract; page 1, first paragraph; page 2, first and second paragraphs; page 5, scheme 3; DOI: 10.1080/15257770.2020.1738457	18, 27/18, 28/18, 29/18, 30/18, 31/18, 32/18, 33/18, 48/18, 49/48/18, 50/48/18, 51/18
Y --- A	US 2013/0123481 A1 (MODERNA THERAPEUTICS) 16 May 2013; paragraphs [0008], [0035], [0043], [0060], [0933]	41, 46 --- 40, 42-45, 47
A	US 2012/0245335 A1 (CLARK, J) 27 September 2012; paragraph [0165]	34-39

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 2022 (27.01.2022)

Date of mailing of the international search report

FEB 15 2022

Name and mailing address of the ISA/US

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Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/49158

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	- (SIKORSKI, PJ et al.) The identity and methylation status of the first transcribed nucleotide in eukaryotic mRNA 5' cap modulates protein expression in living cells. Nucleic Acids Research. 2020, Epub 27 January 2020, Vol. 48, No. 4; pages 1607-1626; DOI: 10.1093/nar/gkaa032	1
A	WO 2017/066781 A1 (MODERNATX, INC.) 20 April 2017; entire publication	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/49158

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item I.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter I(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
 - ☒ in the form of an Annex C/ST.25 text file (Rule 13ter I(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter I(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US21/49158

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.: 12-14, 52-133
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:
-***-Please See Supplemental Page-***-

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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.

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-3, 5-8, 9-11 (each in part) are directed toward the compound of Formula I or Formula II comprising terminal nucleoside having 7-methylguanosine as a base at the 5' end of the sequence and the hydroxy group attached to the C3 carbon atom of the nucleoside at the 3' terminal.

Group II, Claims 4, 9-11 (each in part) are directed toward the compound of Formula II comprising terminal nucleoside having 7-methyladenosine or 7-methylpurine as a base at the 5' end of the sequence and the hydroxy group attached to the C3 carbon atom of the nucleoside at the 3' terminal.

Group III, Claims 15-17, 19-26, 27-39 (each in part), 48-51 (each in part) are directed toward the mRNA sequence Motif I' or Motif II', comprising terminal nucleoside having 7-methylguanosine as a base at the 5' end of the sequence and the mRNA sequence attached to the C3 carbon atom of the nucleoside at the 3' terminal.

Group IV- Claims 18, 27-39 (each in part), 40-47, 48-51 (each in part) are directed toward the mRNA sequence Motif II', comprising terminal nucleoside having 7-methyladenosine or 7-methylpurine as a base at the 5' end of the sequence and the mRNA sequence attached to the C3 carbon atom of the nucleoside at the 3' terminal.

The inventions listed as Groups I, II, III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include the compound of Formula I or Formula II comprising terminal nucleoside having 7-methylguanosine as a base at the 5' end of the sequence and the hydroxy group attached to the C3 carbon atom of the nucleoside at the 3' terminal, which are not present in Groups II-IV; the special technical features of Group II include the compound of Formula II comprising terminal nucleoside having 7-methyladenosine or 7-methylpurine as a base at the 5' end of the sequence and the hydroxy group attached to the C3 carbon atom of the nucleoside at the 3' terminal, which are not present in Groups I and III-IV; the special technical features of Group III include the mRNA sequence Motif I' or Motif II', comprising terminal nucleoside having 7-methylguanosine as a base at the 5' end of the sequence and the mRNA sequence attached to the C3 carbon atom of the nucleoside at the 3' terminal, which are not present in Groups I-II and IV; the special technical features of Group IV include the mRNA sequence Motif II', comprising terminal nucleoside having 7-methyladenosine or 7-methylpurine as a base at the 5' end of the sequence and the mRNA sequence attached to the C3 carbon atom of the nucleoside at the 3' terminal, which are not present in Groups I-III.

The common technical features of Groups I-IV include a polynucleotide sequence comprising at least one triphosphate bridge and at least one monophosphate bridge of general Formula I, wherein each B2 and B3 is a natural nucleobase, each Z1 and Z2 is -OH, each Z3 is -OH, Z4 is -OH, each Q1 and Q4 is -CH2-, each Q2 and Q3 is -O-, each X1, X2, X3 and X4 is -OH, each Y1, Y2, Y3 and Y4 is =O, each A and A1, is -O-, and Bn, Zn, Xn, Yn, A2 are not chosen, p = 0, provided that the compound of Formula I satisfies one proviso i at least one X4 is -SH. However, these common technical features are disclosed by WO 2017/066797 A1 (MODERNATX, INC.) (hereinafter "MODERNATX").

MODERNATX discloses a compound of formula similar to the Formula I, as shown (formula GpppGpG; paragraph [0674]) wherein each B2 and B3 is a natural nucleobase (guanosine bases are in the second and the third nucleotides of the trinucleotide GpppGpG; paragraph [0674]); each Z1 and Z2 is -OH (the hydroxy groups are attached to the C2' and C3' carbon atoms of the sugar moiety of the first nucleotide of the trinucleotide GpppGpG; paragraph [0674]); each Z3 is -OH, Z4 is -OH (the hydroxy groups are attached to the C2' carbon atoms of the sugar moiety of the second and third nucleotides of the trinucleotide GpppGpG; paragraph [0674]); each Q1 and Q4 is -CH2- (two hydrogen atoms are attached to the C5' carbon atoms of the sugar moiety of the first and the second nucleotides of the trinucleotide GpppGpG; paragraph [0674]); each Q2 and Q3 is -O- (the oxygen atoms are connecting the second phosphate atom with the first and the third phosphate atoms in the triphosphate moiety; paragraph [0674]); each X1, X2, X3 and X4 is -OH (the hydroxy groups are attached to the phosphorus atoms of the triphosphate moiety and the phosphorus atom of the monophosphate bridge; paragraph [0674]); each Y1, Y2, Y3 and Y4 is =O (the oxo groups are attached to the phosphorus atoms of the triphosphate moiety and the phosphorus atom of the monophosphate bridge; paragraph [0674]); each A and A1, is -O- (the oxygen bridge is in the sugar rings of the second the third nucleotides of the trinucleotide; paragraph [0674]); and Bn, Zn, Xn, Yn, A2 are not chosen, p = 0 (the second nucleotide is linked directly to the third nucleotide, p = 0, and Bn, Zn, Xn, Yn, A2 are not chosen; paragraph [0674]), and in a separate embodiment MODERNATX further discloses provided that the compound of Formula I satisfies one proviso i at least one X4 is -SH (in general formula Ia1, R4 is SH; paragraphs [0176], [0297]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by MODERNATX, in order to have provided for provided that the compound of Formula I satisfies one proviso i at least one X4 is -SH, as previously disclosed by MODERNATX in a separate embodiment (paragraphs [0176], [0297], [0436]), for modifying the compound to improve the interaction of the compound with the initiation factor 4E and improve the effectiveness of synthesizing an mRNA molecule in vitro (abstract; paragraphs [0011], [0021], [0318]). Further, provided that in all embodiments MODERNATX discloses the methods and compounds for synthesizing an mRNA molecule in vitro (abstract; paragraphs [0011], [0021], [0318]), the modification to MODERNATX's compound, of providing for provided that the compound of Formula I satisfies one proviso i at least one X4 is -SH, would provide the benefit of modifying the compound to improve the interaction of the compound with the initiation factor 4E and improve the effectiveness of synthesizing an mRNA molecule in vitro (abstract; paragraphs [0011], [0021], [0318]).

Since the common technical features are previously disclosed by MODERNATX, these common features are not special and so Groups I-IV lack unity.