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(54) **MODIFIED SHORT INTERFERING NUCLEIC ACID (SINA) MOLECULES AND USES THEREOF**

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(73) Assignee: **Aligos Therapeutics, Inc.**, South San Francisco, CA (US)

(21) Appl. No.: **17/194,079**

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Publication Classification

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A61K 31/713	(2006.01)
A61P 31/20	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 15/1131*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 31/713*** (2013.01); ***A61P 31/20*** (2018.01); *C12N 2310/14* (2013.01); *C12N 2320/31* (2013.01); *C12N 2310/321* (2013.01); *C12N 2310/315* (2013.01); *C12N 2310/3231* (2013.01); *C12N 2310/351* (2013.01); *C12N 2310/322* (2013.01)

(57) **ABSTRACT**

Disclosed herein are short interfering nucleic acid (siNA) molecules comprising modified nucleotides and uses thereof. The siNA molecules may be double stranded and comprise modified nucleotides selected from 2'-O-methyl nucleotides and 2'-fluoro nucleotides. Further disclosed herein are siNA molecules comprising (a) a phosphorylation blocker, conjugated moiety, or 5'-stabilized end cap; and (b) a short interfering nucleic acid (siNA).

Specification includes a Sequence Listing.

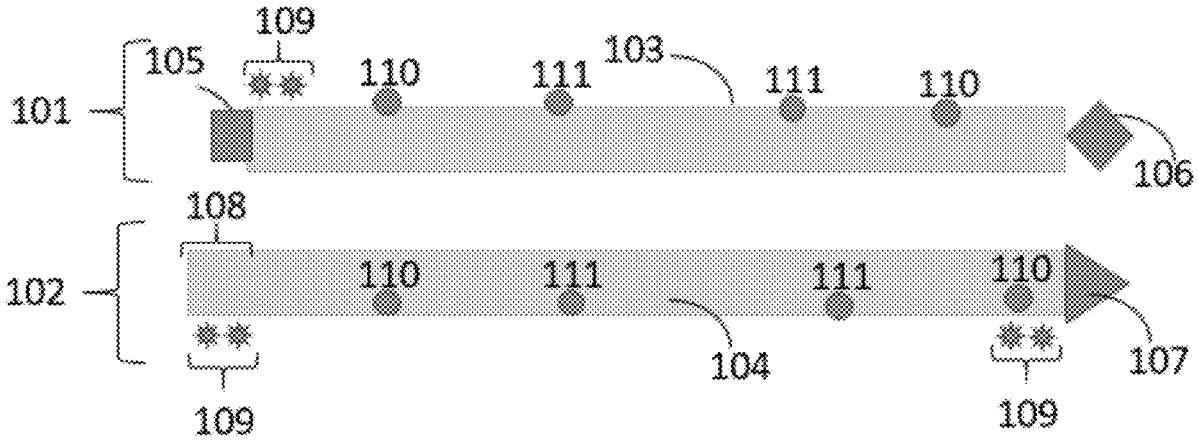


FIG. 1

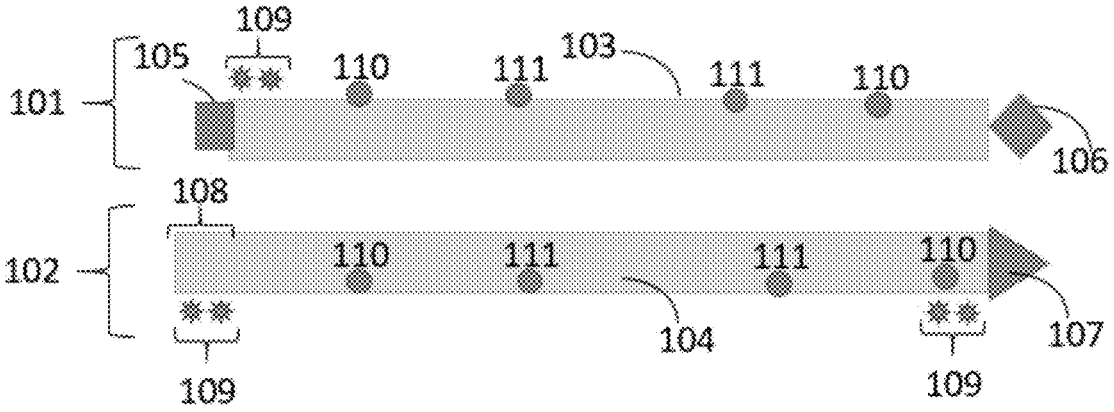

101
105
109
110
111
103
111
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106
102
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104
107
109
109

FIG. 2

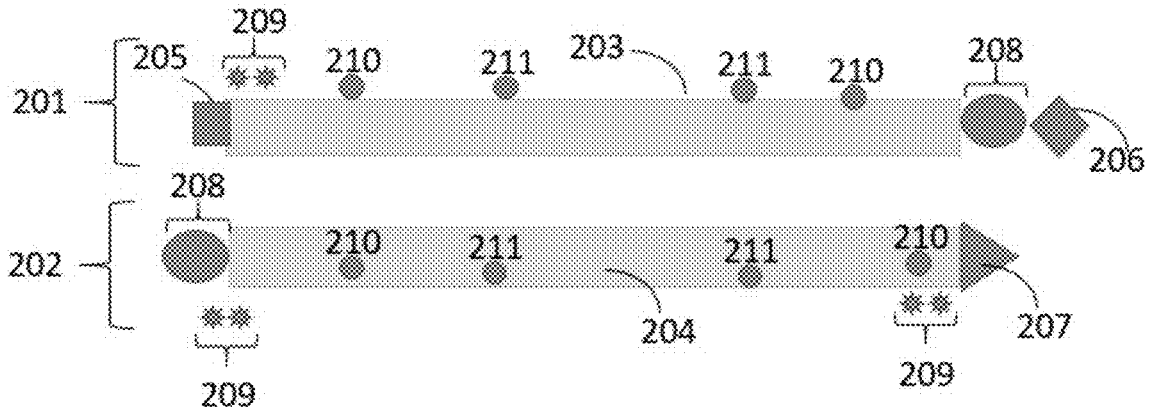

201
205
209
210
211
203
211
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206
202
208
210
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211
210
204
207
209
209

FIG. 3A

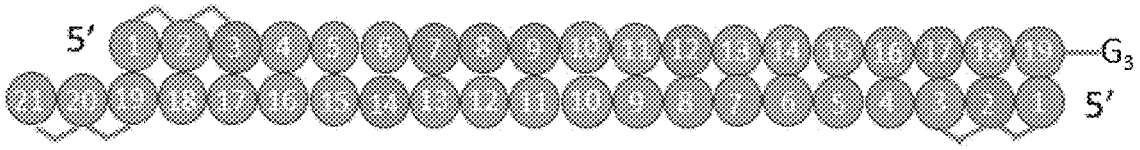


FIG. 3B

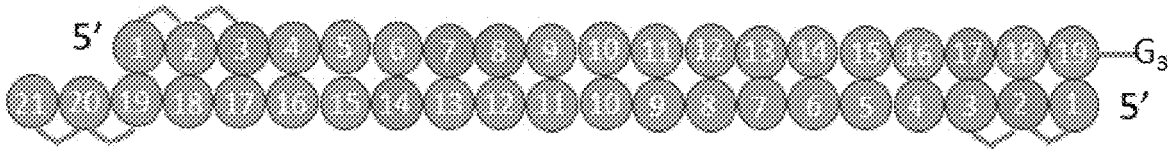


FIG. 3C

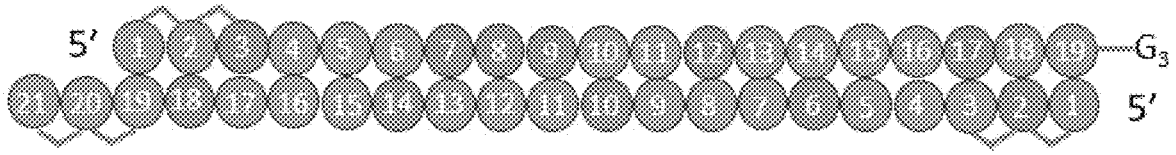
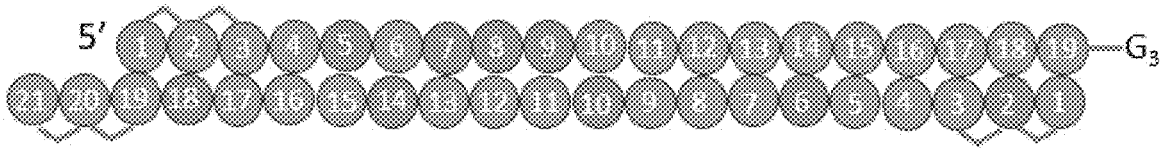


FIG. 3D



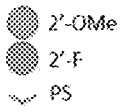


FIG. 3E

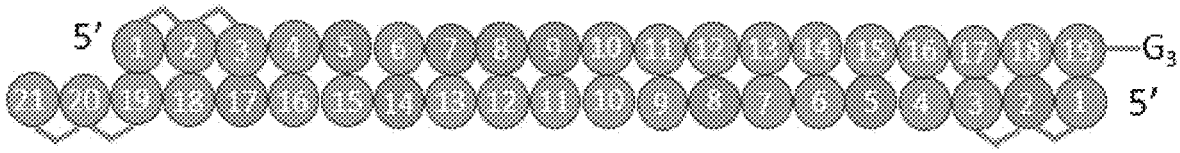


FIG. 3F

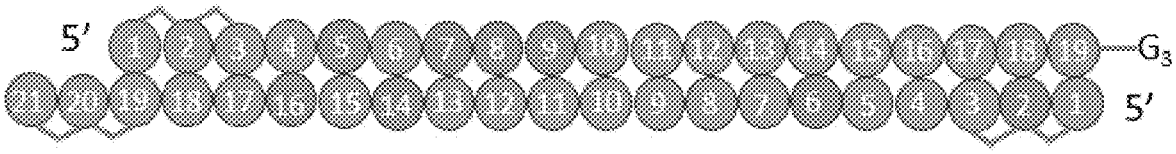


FIG. 3G

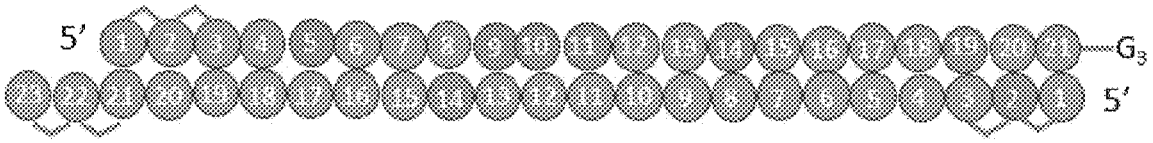




FIG. 4

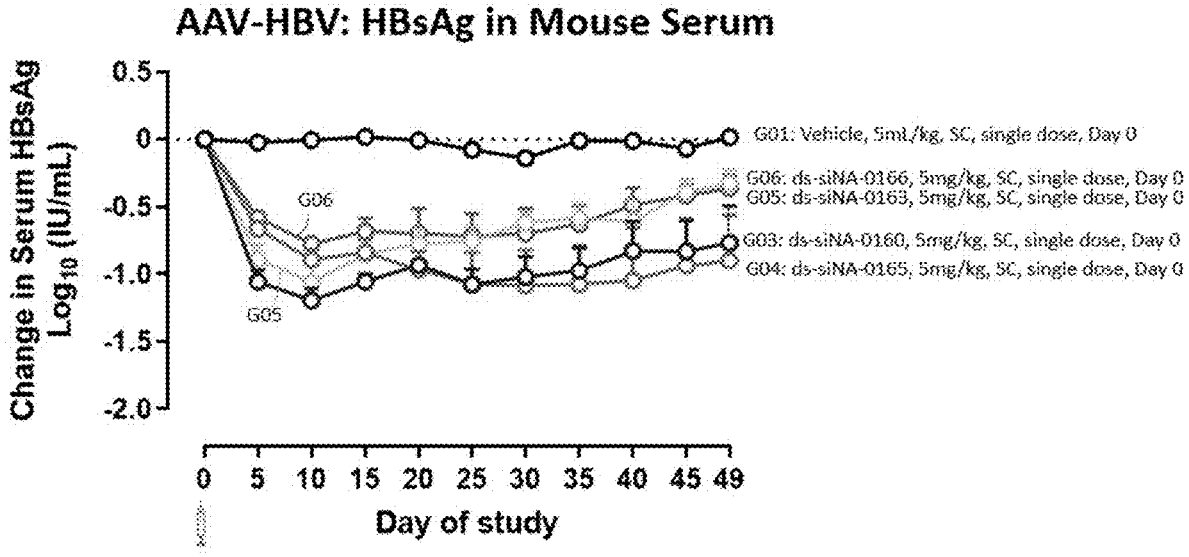

AAV-HBV: HBsAg in Mouse Serum
Change in Serum HBsAg
Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
G06
G05
G01: Vehicle, 5ml/kg, SC, single dose, Day 0
G06: ds-siNA-0166, 5mg/kg, SC, single dose, Day 0
G05: ds-siNA-0163, 5mg/kg, SC, single dose, Day 0
G03: ds-siNA-0160, 5mg/kg, SC, single dose, Day 0
G04: ds-siNA-0165, 5mg/kg, SC, single dose, Day 0
0 5 10 15 20 25 30 35 40 45 49
Day of study

FIG. 5A

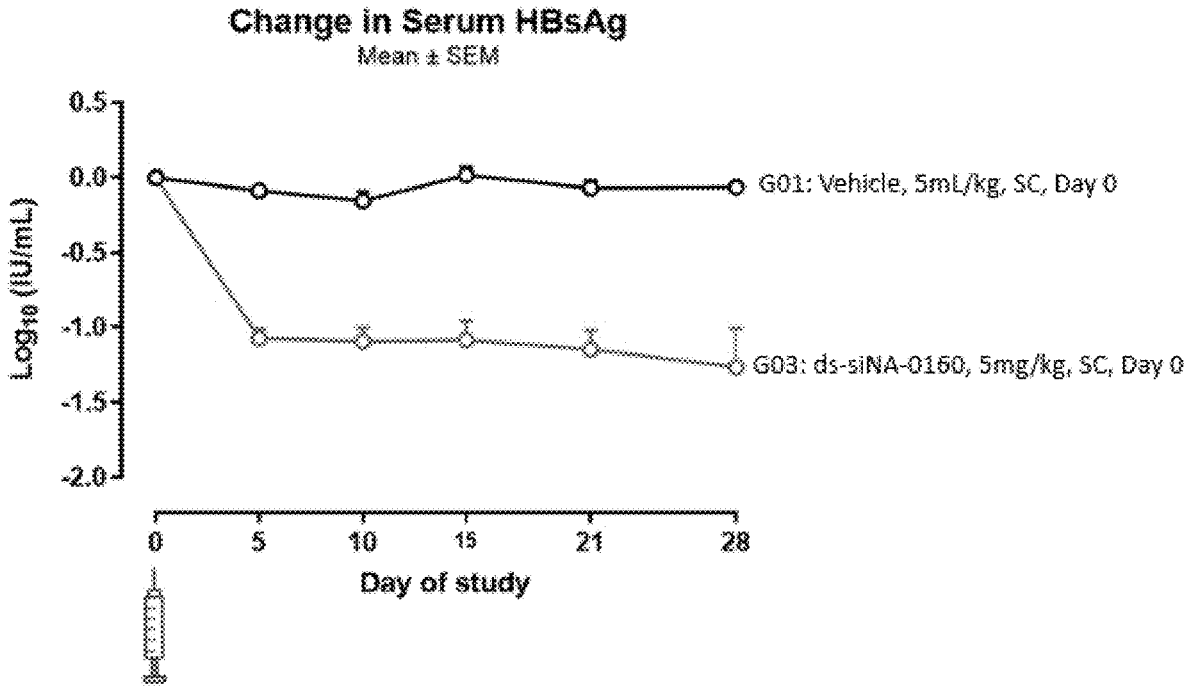

Change in Serum HBsAg
Mean ± SEM
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G03: ds-siNA-0160, 5mg/kg, SC, Day 0
0
5
10
15
21
28
Day of study

FIG. 5B

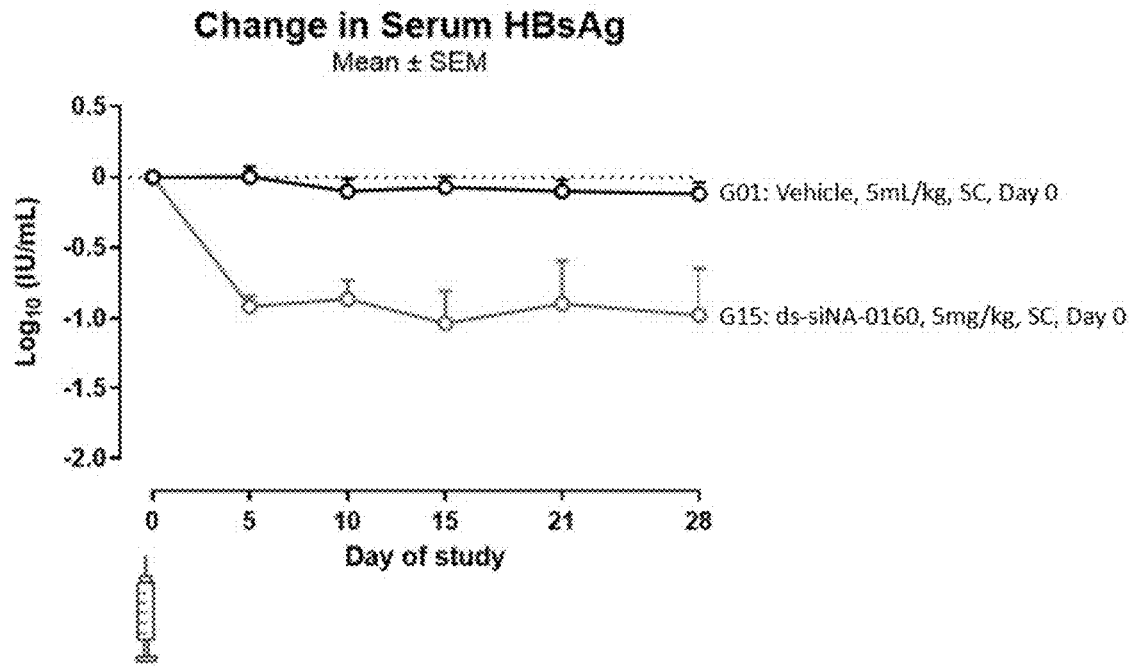

Change in Serum HBsAg
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G15: ds-siNA-0160, 5mg/kg, SC, Day 0
0
5
10
15
21
28
Day of study

FIG. 5C

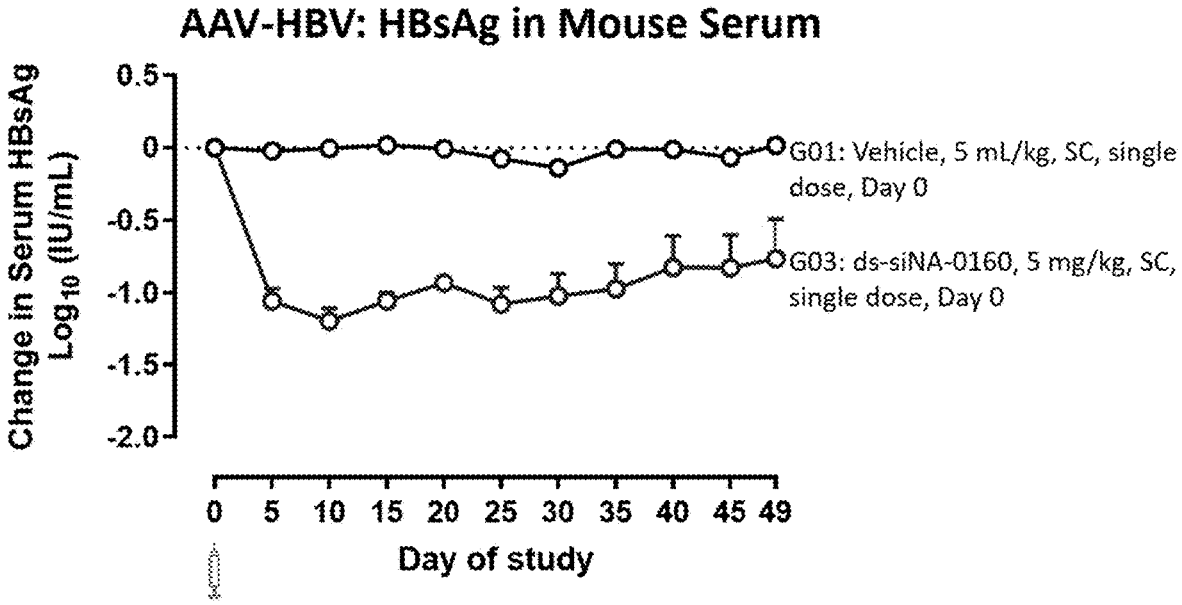

AAV-HBV: HBsAg in Mouse Serum
Change in Serum HBsAg Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
0 5 10 15 20 25 30 35 40 45 49
Day of study
G01: Vehicle, 5 mL/kg, SC, single dose, Day 0
G03: ds-siNA-0160, 5 mg/kg, SC, single dose, Day 0

FIG. 5D

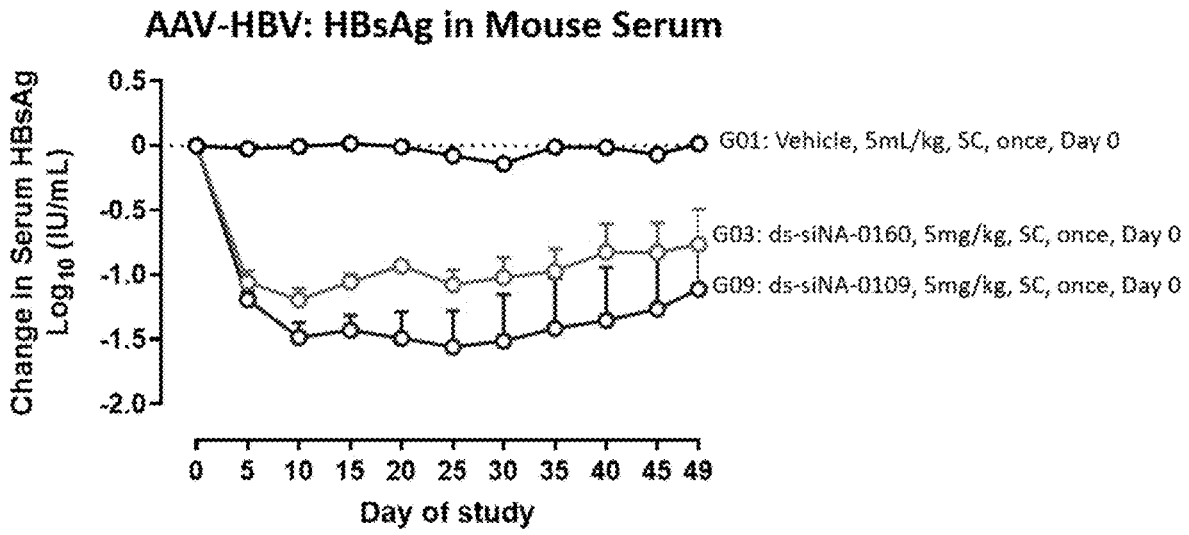

AAV-HBV: HBsAg in Mouse Serum
Change in Serum HBsAg Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
0 5 10 15 20 25 30 35 40 45 49
Day of study
G01: Vehicle, 5mL/kg, SC, once, Day 0
G03: ds-siNA-0160, 5mg/kg, SC, once, Day 0
G09: ds-siNA-0109, 5mg/kg, SC, once, Day 0

FIG. 5E

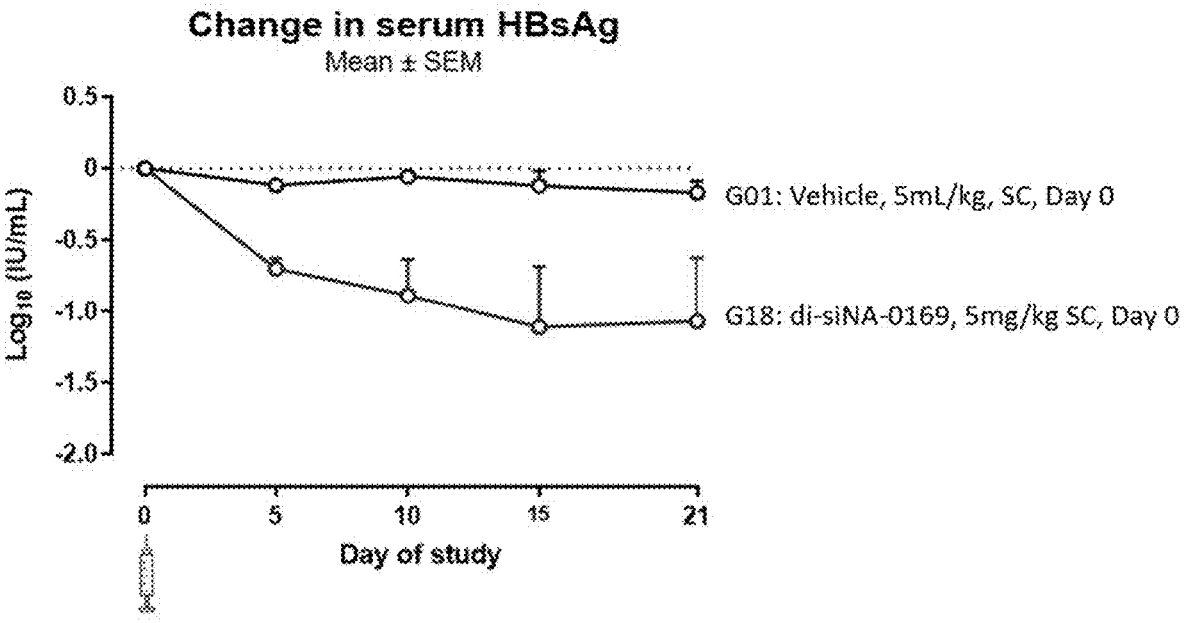

Change in serum HBsAg
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
0
5
10
15
21
Day of study
G01: Vehicle, 5mL/kg, SC, Day 0
G18: di-siNA-0169, 5mg/kg SC, Day 0

FIG. 5F

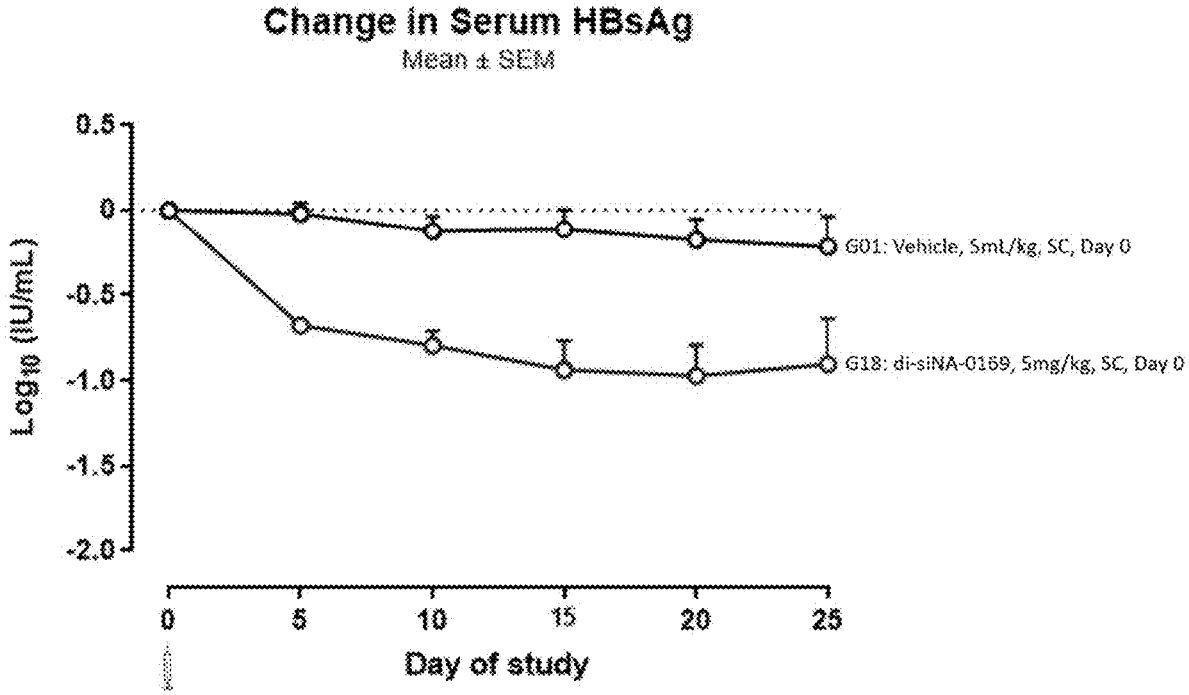

Change in Serum HBsAg
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G18: di-siNA-0169, 5mg/kg, SC, Day 0
0
5
10
15
20
25
Day of study

FIG. 5G

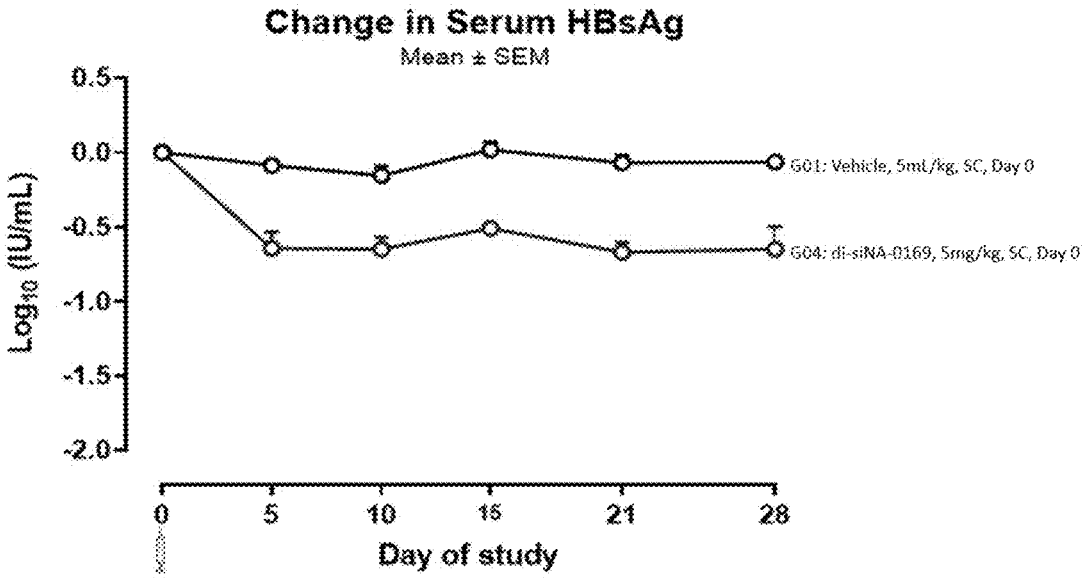

Change in Serum HBsAg
Mean ± SEM
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G04: di-siNA-0169, 5mg/kg, SC, Day 0
0
5
10
15
21
28
Day of study

FIG. 5H

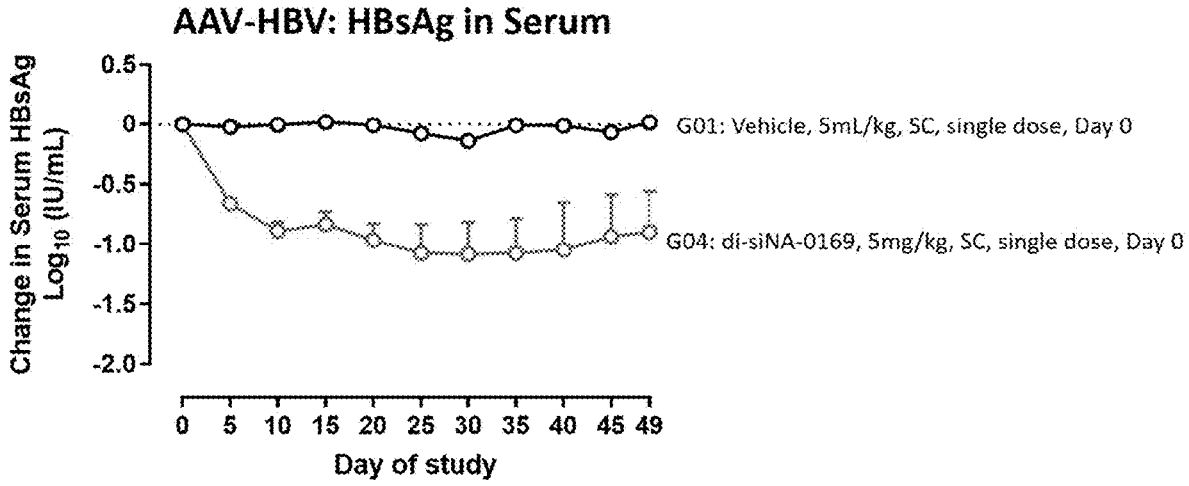

AAV-HBV: HBsAg in Serum
Change in Serum HBsAg Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
0 5 10 15 20 25 30 35 40 45 49
Day of study
G01: Vehicle, 5mL/kg, SC, single dose, Day 0
G04: di-siNA-0169, 5mg/kg, SC, single dose, Day 0

FIG. 5I

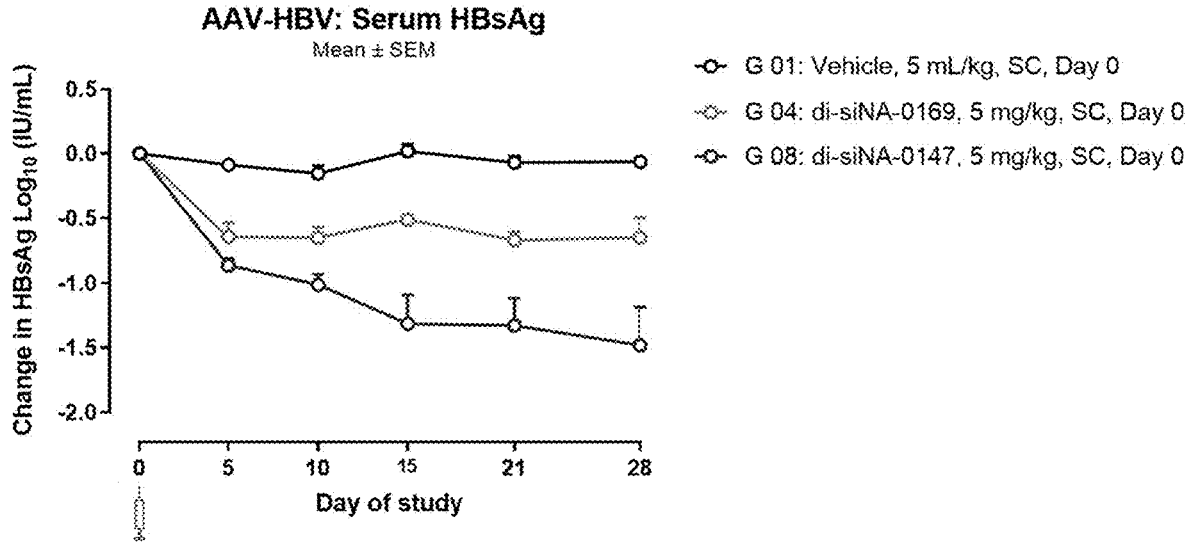

AAV-HBV: Serum HBsAg
Mean ± SEM
Change in HBsAg Log10 (IU/mL)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0 5 10 15 21 28
Day of study
G 01: Vehicle, 5 mL/kg, SC, Day 0
G 04: di-siNA-0169, 5 mg/kg, SC, Day 0
G 08: di-siNA-0147, 5 mg/kg, SC, Day 0

FIG. 5J

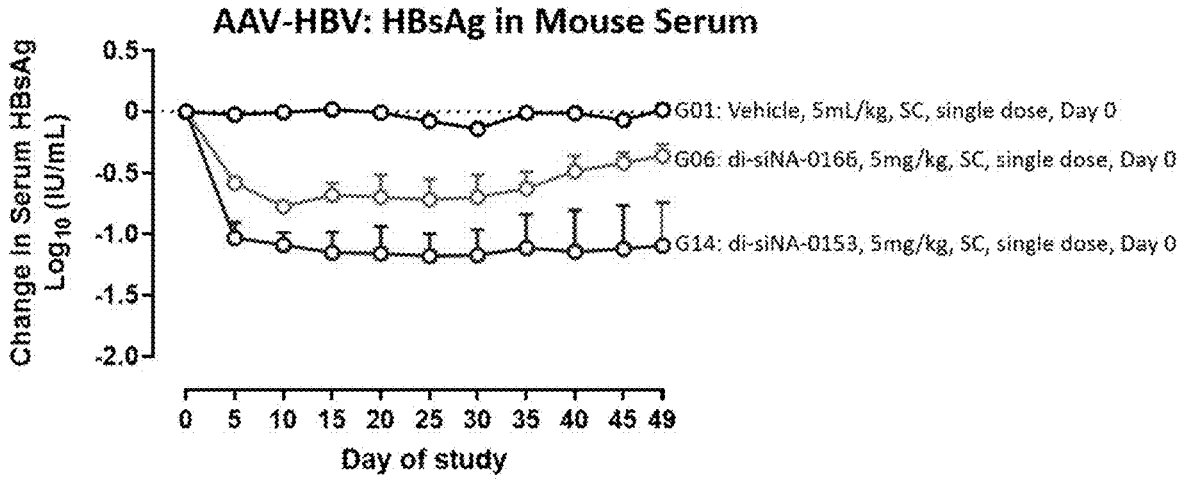

AAV-HBV: HBsAg in Mouse Serum
Change in Serum HBsAg
Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
0 5 10 15 20 25 30 35 40 45 49
Day of study
G01: Vehicle, 5mL/kg, SC, single dose, Day 0
G06: di-siNA-0166, 5mg/kg, SC, single dose, Day 0
G14: di-siNA-0153, 5mg/kg, SC, single dose, Day 0

FIG. 5K

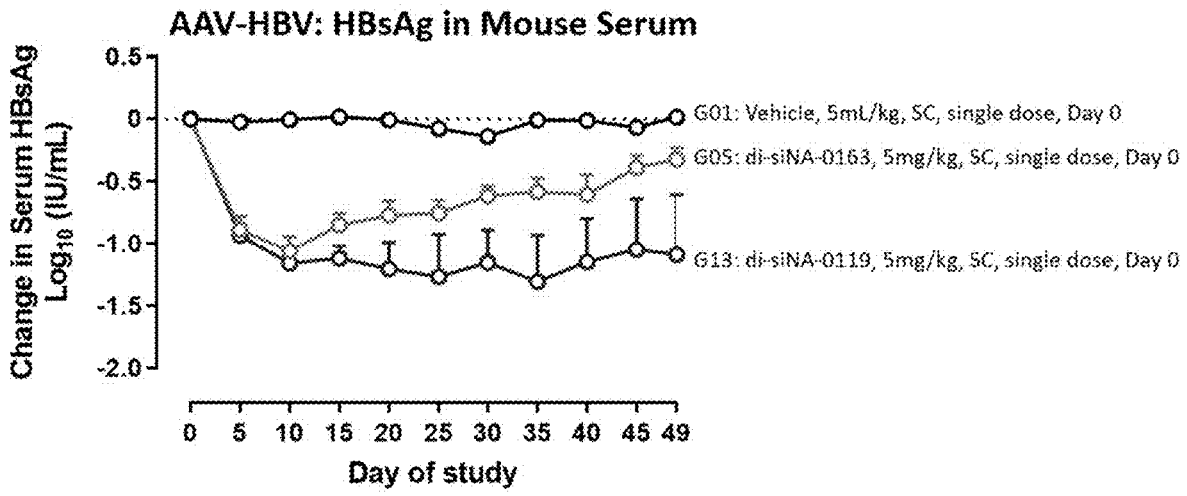

AAV-HBV: HBsAg in Mouse Serum
Change in Serum HBsAg
Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
0 5 10 15 20 25 30 35 40 45 49
Day of study
G01: Vehicle, 5mL/kg, SC, single dose, Day 0
G05: di-siNA-0163, 5mg/kg, SC, single dose, Day 0
G13: di-siNA-0119, 5mg/kg, SC, single dose, Day 0

FIG. 6A

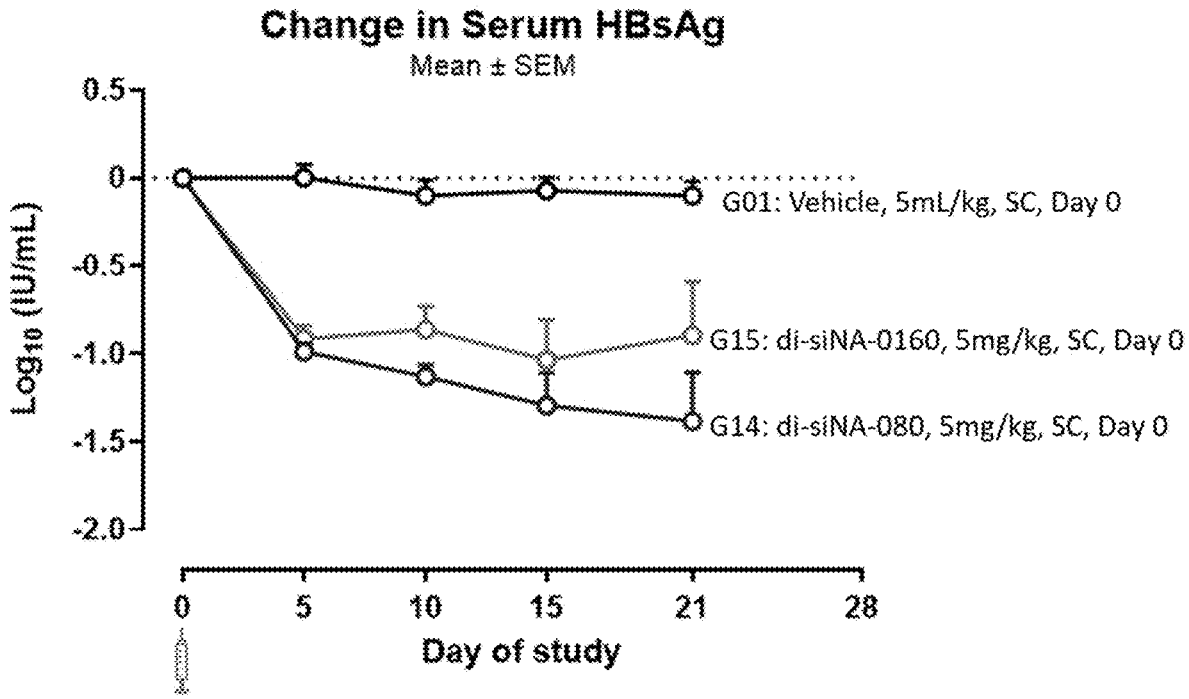

Change in Serum HBsAg
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G15: di-siNA-0160, 5mg/kg, SC, Day 0
G14: di-siNA-080, 5mg/kg, SC, Day 0
0
5
10
15
21
28
Day of study

FIG. 6B

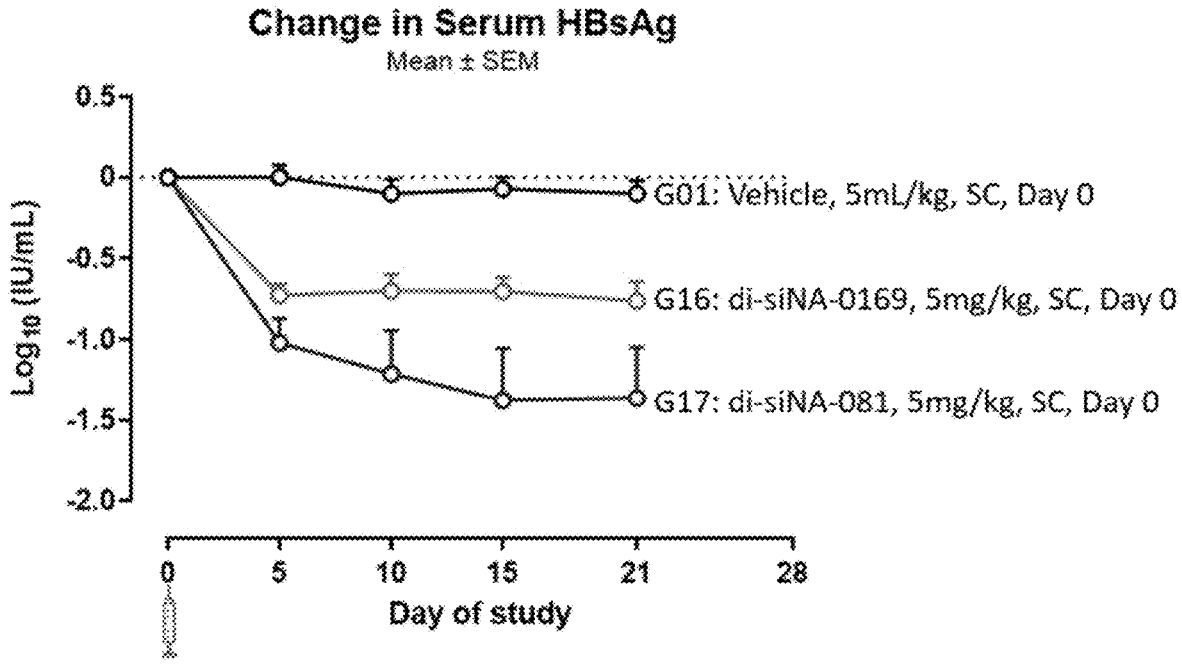

Change in Serum HBsAg
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G16: di-siNA-0169, 5mg/kg, SC, Day 0
G17: di-siNA-081, 5mg/kg, SC, Day 0
0
5
10
15
21
28
Day of study

FIG. 7A

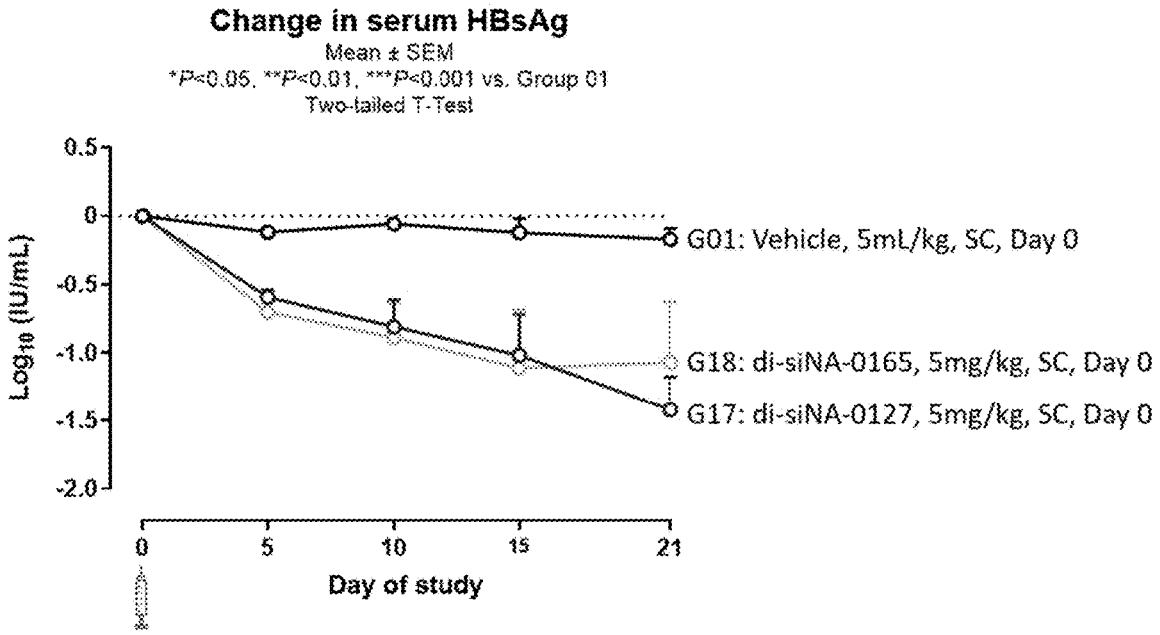

Change in serum HBsAg
Mean ± SEM
*P<0.05, **P<0.01, ***P<0.001 vs. Group 01
Two-tailed T-Test
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G18: di-siNA-0165, 5mg/kg, SC, Day 0
G17: di-siNA-0127, 5mg/kg, SC, Day 0
0
5
10
15
21
Day of study

FIG. 7B

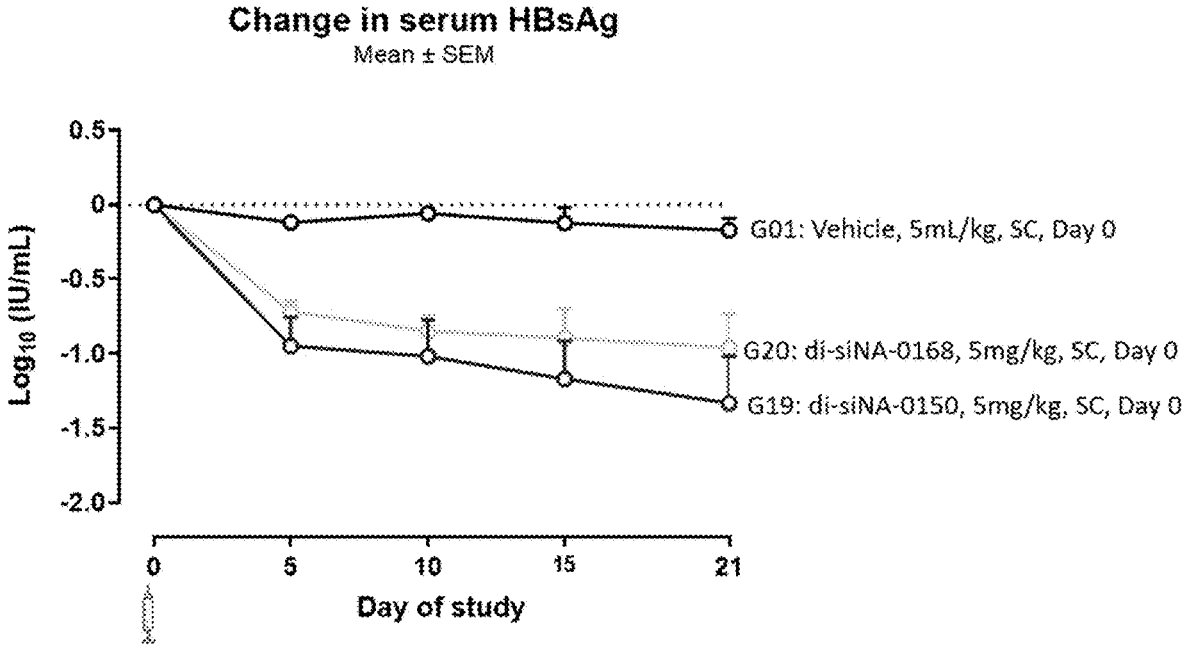

Change in serum HBsAg
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
-2.0
Log10 (IU/mL)
G01: Vehicle, 5mL/kg, SC, Day 0
G20: di-siNA-0168, 5mg/kg, SC, Day 0
G19: di-siNA-0150, 5mg/kg, SC, Day 0
0
5
10
15
21
Day of study

FIG. 8A

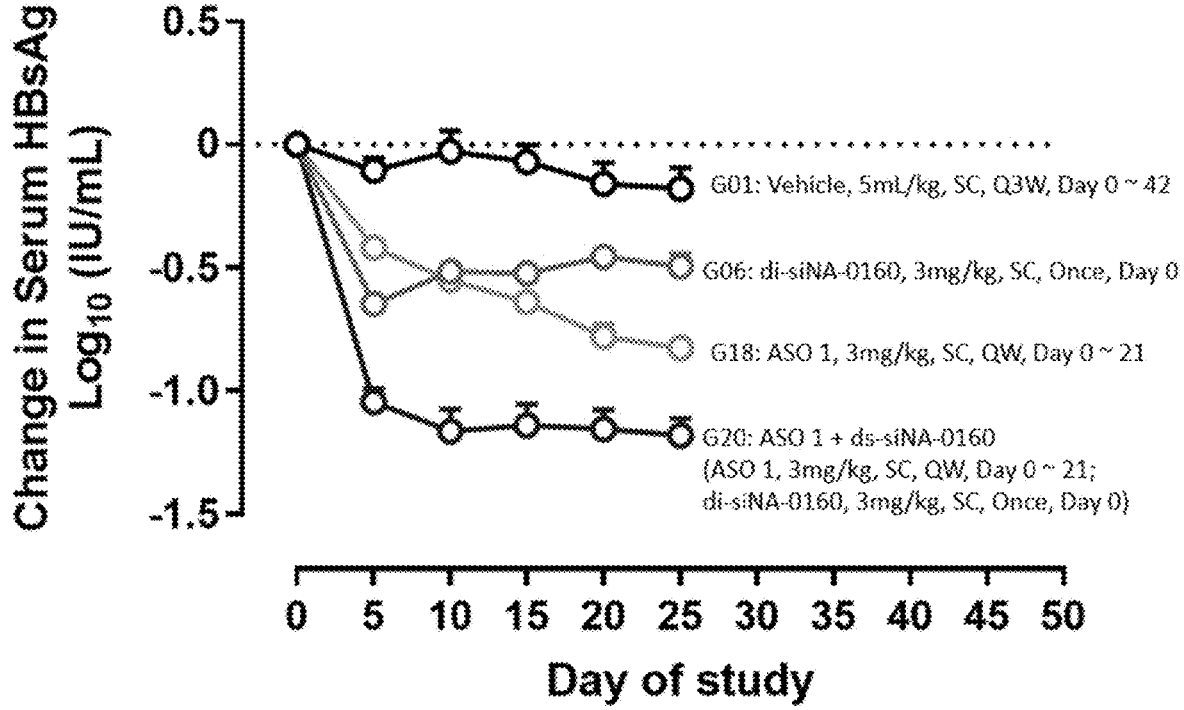

Change in Serum HBsAg
Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
G01: Vehicle, 5mL/kg, SC, Q3W, Day 0 ~ 42
G06: di-siNA-0160, 3mg/kg, SC, Once, Day 0
G18: ASO 1, 3mg/kg, SC, QW, Day 0 ~ 21
G20: ASO 1 + ds-siNA-0160
(ASO 1, 3mg/kg, SC, QW, Day 0 ~ 21;
di-siNA-0160, 3mg/kg, SC, Once, Day 0)
0 5 10 15 20 25 30 35 40 45 50
Day of study

FIG. 8B

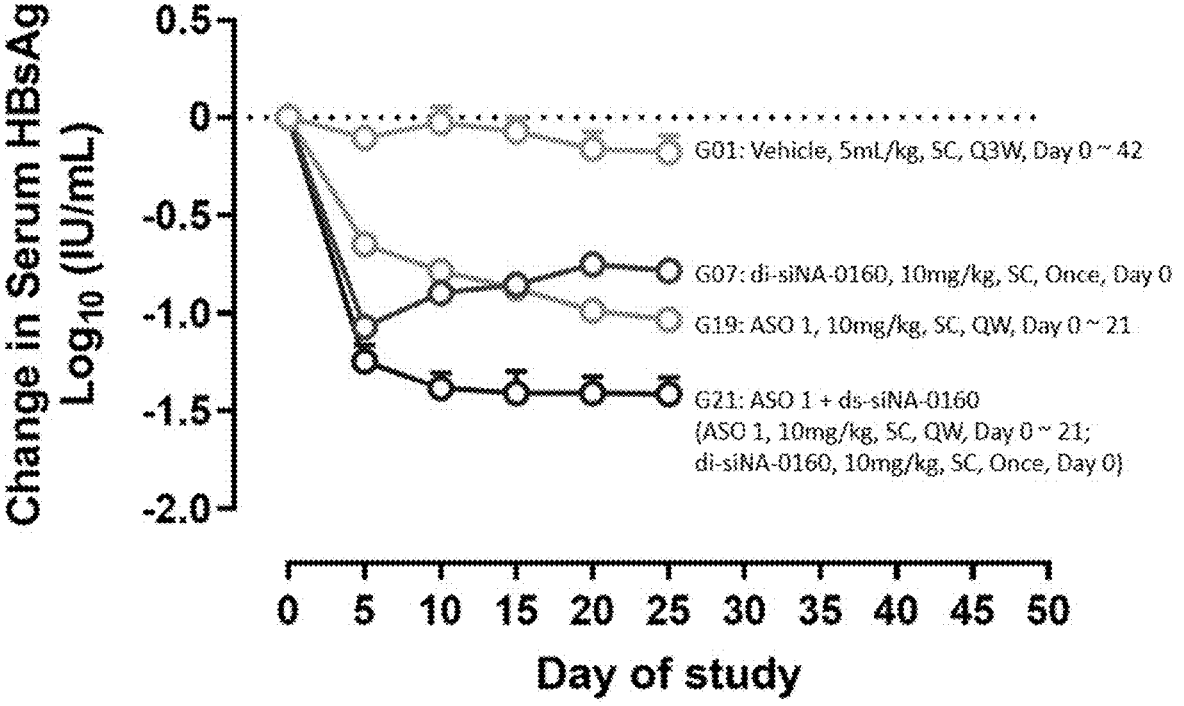

Change in Serum HBsAg
Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
-2.0
G01: Vehicle, 5mL/kg, SC, Q3W, Day 0 ~ 42
G07: di-siNA-0160, 10mg/kg, SC, Once, Day 0
G19: ASO 1, 10mg/kg, SC, QW, Day 0 ~ 21
G21: ASO 1 + ds-siNA-0160
(ASO 1, 10mg/kg, SC, QW, Day 0 ~ 21;
di-siNA-0160, 10mg/kg, SC, Once, Day 0)
0 5 10 15 20 25 30 35 40 45 50
Day of study

FIG. 8C

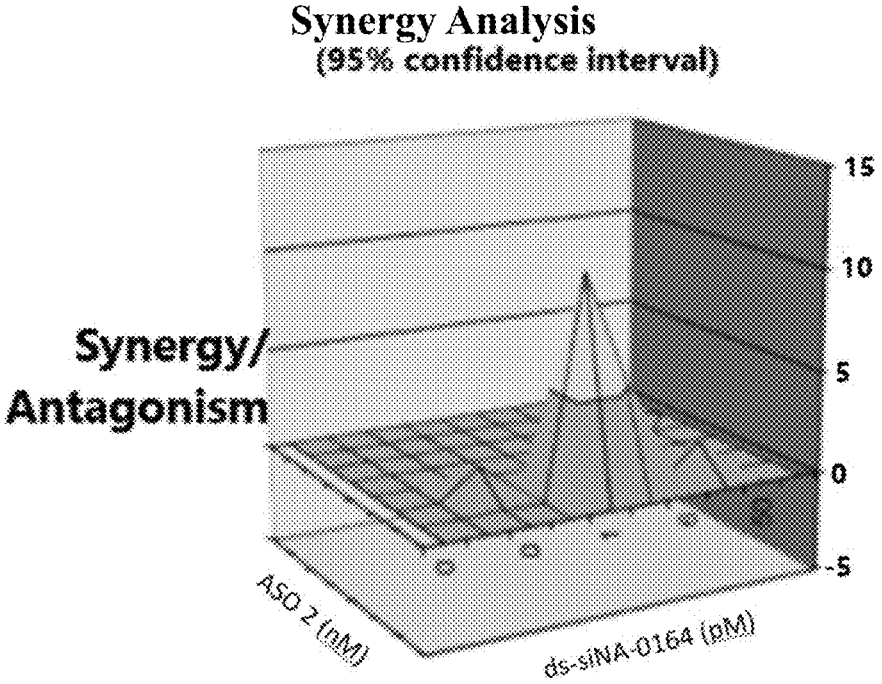

Synergy Analysis
(95% confidence interval)
Synergy/
Antagonism
15
10
5
0
-5
ASO 2 (nM)
ds-siNA-0164 (pM)

FIG. 9

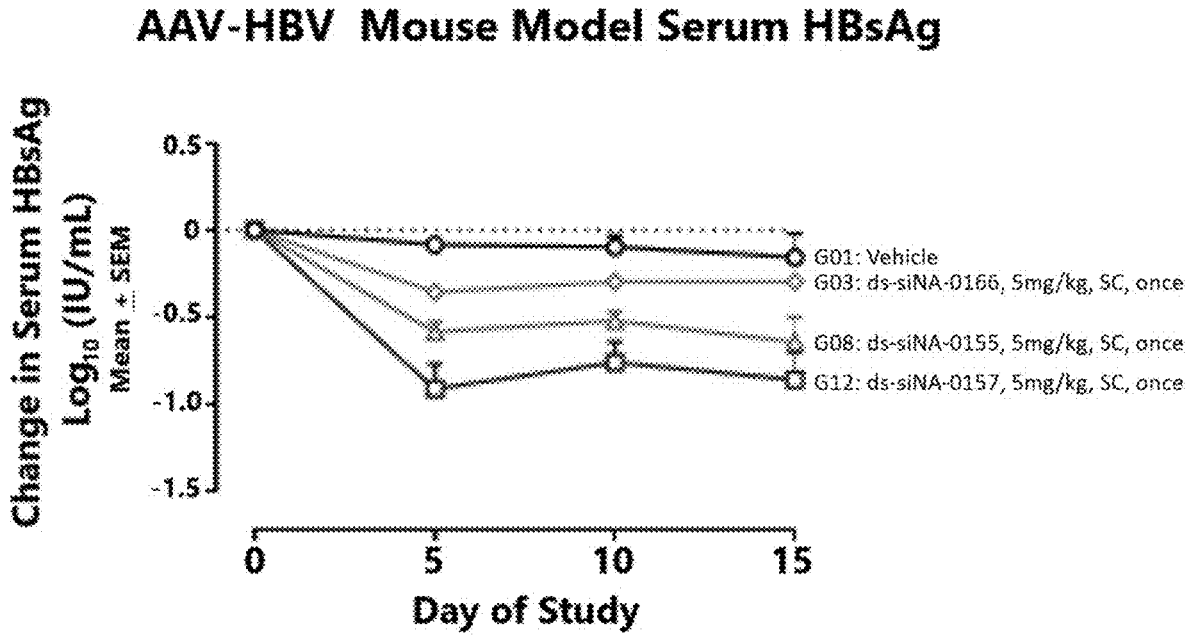

AAV-HBV Mouse Model Serum HBsAg
Change in Serum HBsAg
Log10 (IU/mL)
Mean + SEM
0.5
0
-0.5
-1.0
-1.5
0
5
10
15
Day of Study
G01: Vehicle
G03: ds-siNA-0166, 5mg/kg, SC, once
G08: ds-siNA-0155, 5mg/kg, SC, once
G12: ds-siNA-0157, 5mg/kg, SC, once

FIG. 10

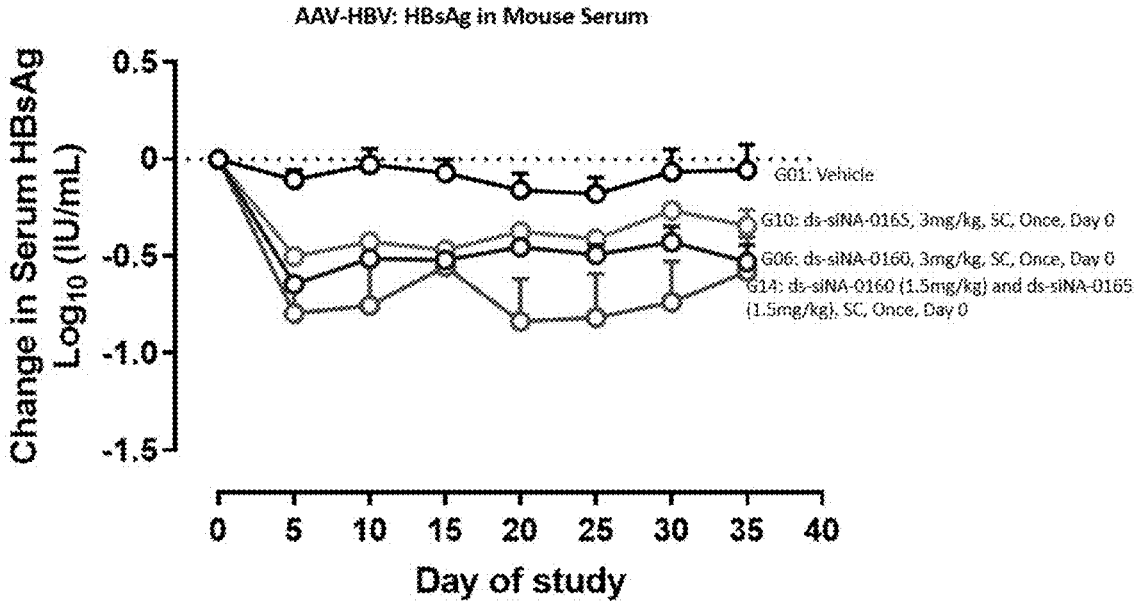

AAV-HBV: HBsAg in Mouse Serum
Change in Serum HBsAg
Log10 (IU/mL)
0.5
0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
35
40
Day of study
G01: Vehicle
G10: ds-siNA-0165, 3mg/kg, SC, Once, Day 0
G06: ds-siNA-0160, 3mg/kg, SC, Once, Day 0
G14: ds-siNA-0160 (1.5mg/kg) and ds-siNA-0165 (1.5mg/kg), SC, Once, Day 0

FIG. 11

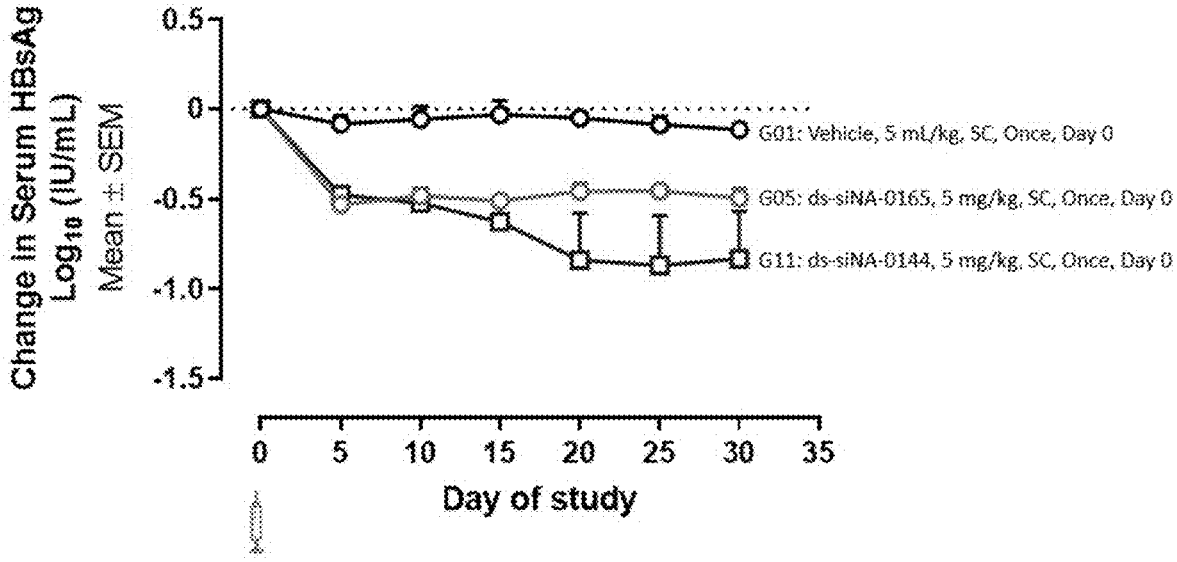

Change in Serum HBsAg
Log10 (IU/mL)
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
35
Day of study
G01: Vehicle, 5 mL/kg, SC, Once, Day 0
G05: ds-siNA-0165, 5 mg/kg, SC, Once, Day 0
G11: ds-siNA-0144, 5 mg/kg, SC, Once, Day 0

FIG. 12

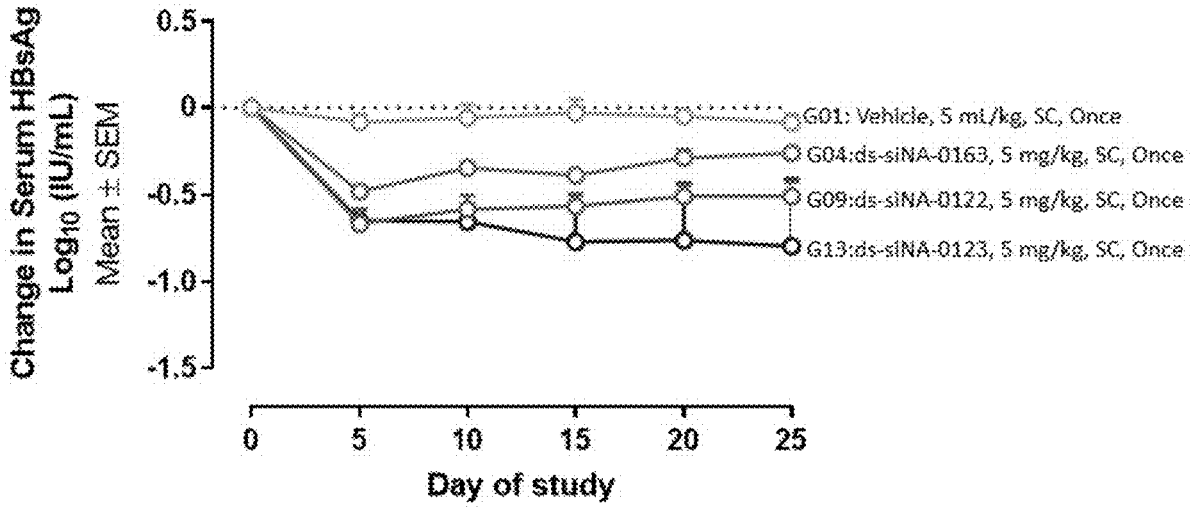

Change in Serum HBsAg
Log10 (IU/mL)
Mean ± SEM
0.5
0
-0.5
-1.0
-1.5
0
5
10
15
20
25
Day of study
G01: Vehicle, 5 mL/kg, SC, Once
G04:ds-siNA-0163, 5 mg/kg, SC, Once
G09:ds-siNA-0122, 5 mg/kg, SC, Once
G13:ds-siNA-0123, 5 mg/kg, SC, Once

FIG. 13

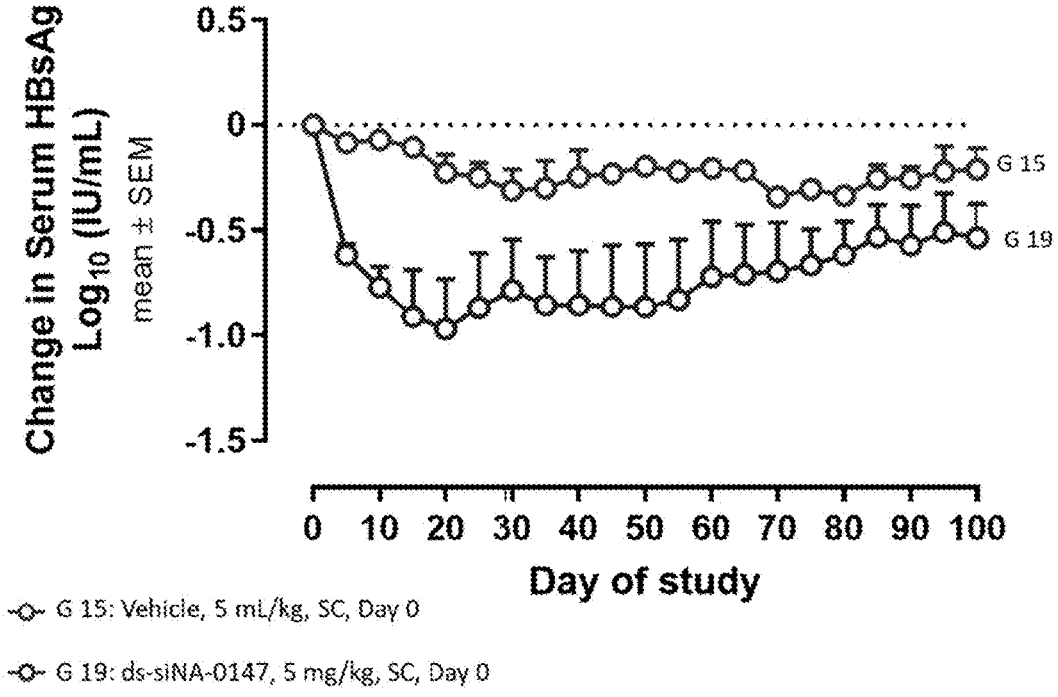

Change in Serum HBsAg
Log10 (IU/mL)
mean ± SEM
0.5
0
-0.5
-1.0
-1.5
0
10
20
30
40
50
60
70
80
90
100
Day of study
G 15
G 19
G 15: Vehicle, 5 mL/kg, SC, Day 0
G 19: ds-siNA-0147, 5 mg/kg, SC, Day 0

FIG. 14

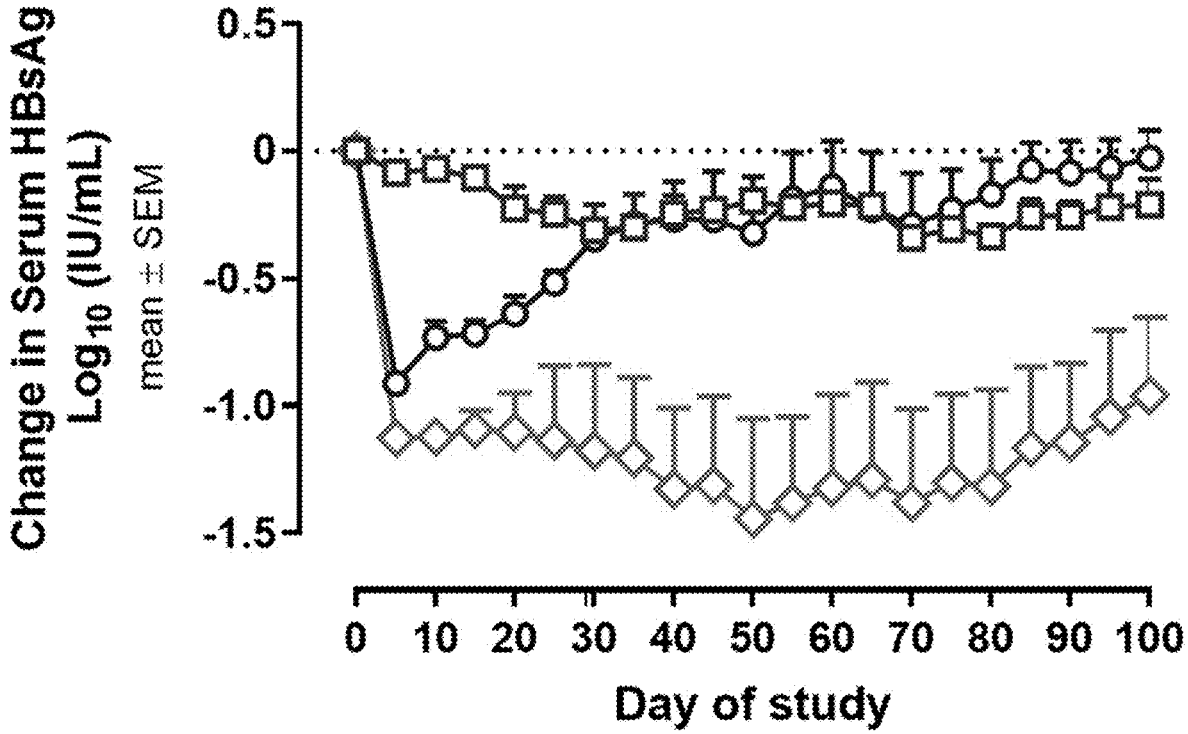

Change in Serum HBsAg
Log10 (IU/mL)
mean ± SEM
0.5
0
-0.5
-1.0
-1.5
0 10 20 30 40 50 60 70 80 90 100
Day of study
G 15: Vehicle, 5 mL/kg, SC, Day 0
G 21: ds-siNA-0109, 5 mg/kg, SC, Day 0
G 27: ds-siNA-0172, 5 mg/kg, SC, Day 0

FIG. 15

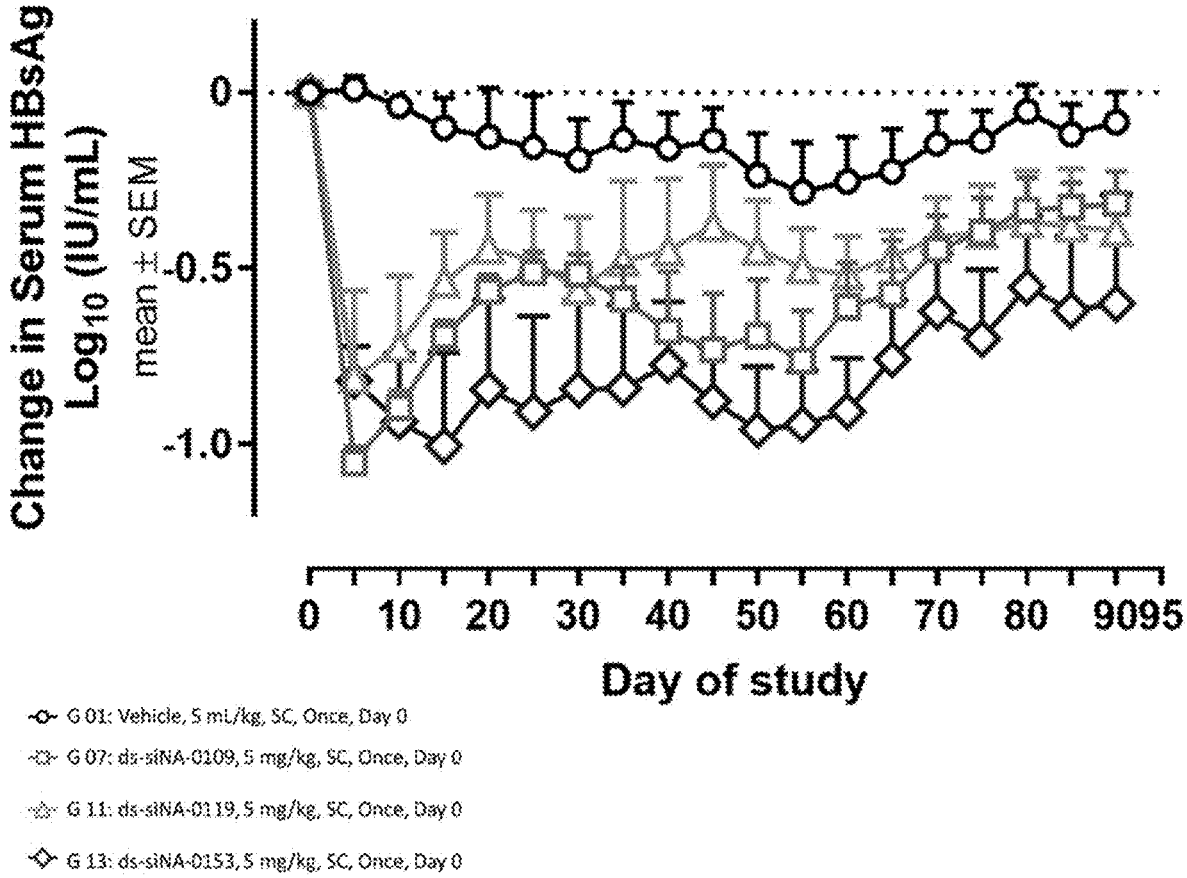

Change in Serum HBsAg
Log10 (IU/mL)
mean ± SEM
0
-0.5
-1.0
0 10 20 30 40 50 60 70 80 9095
Day of study
G 01: Vehicle, 5 mL/kg, SC, Once, Day 0
G 07: ds-siNA-0109, 5 mg/kg, SC, Once, Day 0
G 11: ds-siNA-0119, 5 mg/kg, SC, Once, Day 0
G 13: ds-siNA-0153, 5 mg/kg, SC, Once, Day 0

FIG. 16

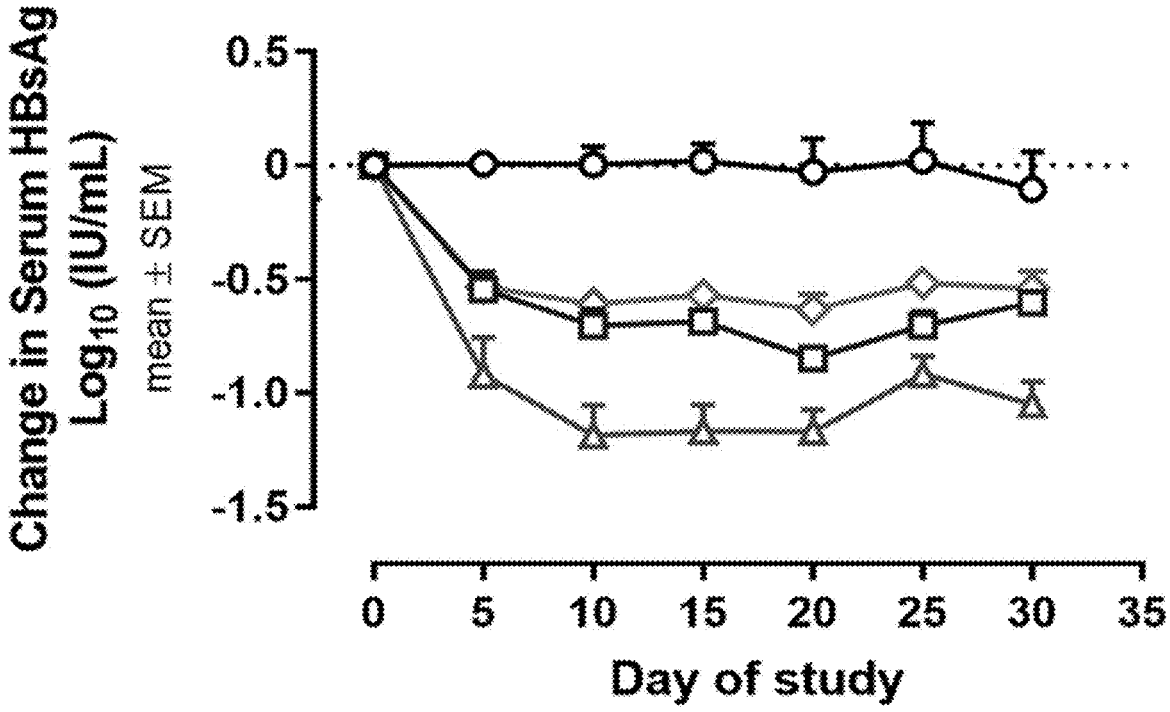
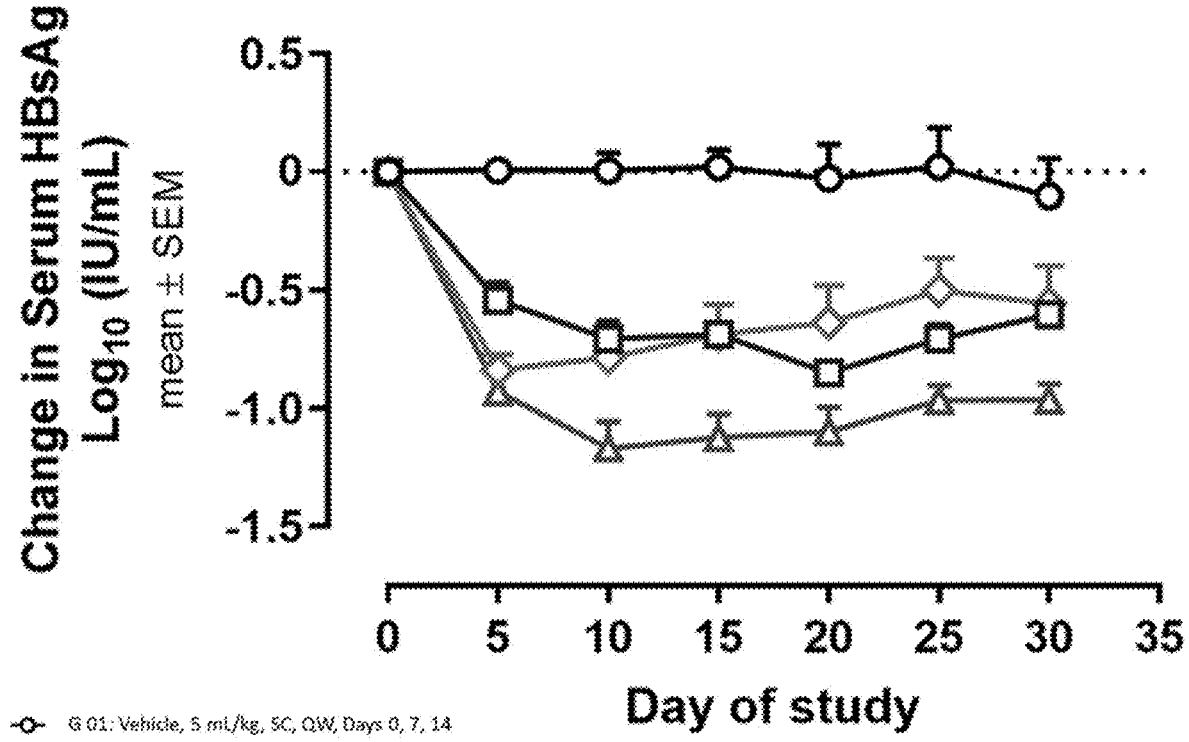

Change in Serum HBsAg
Log10 (IU/mL)
mean ± SEM
0.5
0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
35
Day of study
G 01: Vehicle, 5 mL/kg, SC, QW, Days 0, 7, 14
G 20: ASO 1, 5 mg/kg, SC, QW, Days 0, 7, 14
G 24: ds-siNA-0147, 5 mg/kg, SC, Once, Day 0
G 25: ds-siNA-0147 + ASO 1 (ds-siNA-0147: 5 mg/kg, SC, Once, Day 0; ASO 1: 5 mg/kg, SC, QW, Days 0, 7, 14)

FIG. 17


Change in Serum HBsAg
Log10 (IU/mL)
mean ± SEM
0.5
0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
35
Day of study
G 01: Vehicle, 5 mL/kg, SC, QW, Days 0, 7, 14
G 20: ASO 1, 5 mg/kg, SC, QW, Days 0, 7, 14
G 26: ds-siNA-0109, 5 mg/kg, SC, Once, Day 0
G 27: ds-siNA-0109 + ASO 1 (ds-siNA-0109: 5 mg/kg, SC, Once, Day 0; ASO 1: 5 mg/kg, SC, QW, Days 0, 7, 14)

MODIFIED SHORT INTERFERING NUCLEIC ACID (SINA) MOLECULES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/986,150, filed Mar. 6, 2020, and U.S. Provisional Application No. 63/109,196, filed Nov. 3, 2020, the disclosures of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] Described are short interfering nucleic acid (siNA) molecules comprising modified nucleotides, compositions, and uses thereof.

BACKGROUND OF THE INVENTION

[0003] RNA interference (RNAi) is a biological response to double-stranded RNA that mediates resistance to both endogenous parasitic and exogenous pathogenic nucleic acids, and regulates the expression of protein-coding genes. The short interfering nucleic acids (siNA), such as siRNA, have been developed for RNAi therapy to treat a variety of diseases. For instance, RNAi therapy has been proposed for the treatment of metabolic diseases, neurodegenerative diseases, cancer, and pathogenic infections (See e.g., Rondindone, *Biotechniques,* 2018, 40(4S), doi.org/10.2144/000112163, Boudreau and Davidson, *Curr Top Dev Biol,* 2006, 75:73-92, Chalbatani et al., *Int J Nanomedicine,* 2019, 14:3111-3128, Arbuthnot, *Drug News Perspect,* 2010, 23(6):341-50, and Chernikov et. al., *Front. Pharmacol.,* 2019, doi.org/10.3389/fphar.2019.00444, each of which are incorporated by reference in their entirety). However, major limitations of RNAi therapy are the ability to effectively deliver siRNA to target cells and the degradation of the siRNA.

[0004] The present disclosure improves the delivery and stability of siNA molecules by providing siNA molecules comprising modified nucleotides. The siNA molecules of the present disclosure provide optimized combinations and numbers of modified nucleotides, nucleotide lengths, design (e.g., blunt ends or overhangs, internucleoside linkages, conjugates), and modification patterns for improving the delivery and stability of siNA molecules.

SUMMARY OF THE INVENTION

[0005] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

[0006] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

[0007] In some embodiments, the first nucleotide sequence comprises 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the first nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, between 2 to 15 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 10 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 2, 3, 4, 5, or 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between about 2 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 2 to 20 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 5 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 10 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 12 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides.

[0008] In some embodiments, the second nucleotide sequence comprises 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the second nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, between 2 to 15 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 10 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 2, 3, 4, 5, or 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between about 2 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 2 to 20 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 5 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 10 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 12 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides.

[0009] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (iii) comprises 1 or more phosphorothioate internucleoside linkage; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (iii) comprises 1 or more phosphorothioate internucleoside linkage.

[0010] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide, wherein the siNA further comprises a phosphorylation blocker, a galactosamine, or 5'-stabilized end cap.

[0011] In some embodiments, at least 1, 2, 3, 4, 5, 6, or 7 nucleotides at position 3, 5, 7, 8, 9, 10, 11, 12, and/or 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 3 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 5 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 7 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 8 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 9 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 12 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, nucleotide at position 10 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 11 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

[0012] In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 nucleotides at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 2 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 5 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 6 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 8 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 10 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 14 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotides at position 16 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 17 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

[0013] In some embodiments, the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides. In some embodiments, the alternating 1:3 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:3 modification pattern occur consecutively. In some embodiments, at least two of the alternating 1:3 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand.

[0014] In some embodiments, the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides. In some embodiments, the alternating 1:2 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:2 modification pattern occurs consecutively. In some embodiments, at least two of the alternating 1:2 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:2 modification pattern begins at nucleotide position 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 5 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 8 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 17 from the 5' end of the antisense strand.

[0015] Disclosed herein is a short interfering nucleic acid (siNA) molecule represented by Formula (VIII):

$$5'\text{-}A_n{}^1B_n{}^2A_n{}^3B_n{}^4A_n{}^5B_n{}^6A_n{}^7B_n{}^8A_n{}^9\text{-}3'$$

$$3'\text{-}C_q{}^1A_q{}^2B_q{}^3A_q{}^4B_q{}^5A_q{}^6B_q{}^7A_q{}^8B_q{}^9A_q{}^{10}B_q{}^{11}A_q{}^{12}\text{-}5'$$

wherein:

the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5'-stabilized end cap or a phosphorylation blocker;

B is a 2'-fluoro nucleotide;

C represents overhanging nucleotides and is a 2'-O-methyl nucleotide;

n^1=1-4 nucleotides in length;

each n^2, n^6, n^8, q^3, q^5, q^7, q^9, q^{11}, and q^{12} is independently 0-1 nucleotides in length;

each n^3 and n^4 is independently 1-3 nucleotides in length;

n^5 is 1-10 nucleotides in length;

n^7 is 0-4 nucleotides in length;

each n^9, q^1, and q^2 is independently 0-2 nucleotides in length;

q^4 is 0-3 nucleotides in length;

q^6 is 0-5 nucleotides in length;

q^8 is 2-7 nucleotides in length; and

q^{10} is 2-11 nucleotides in length.

[0016] Disclosed herein is a short interfering nucleic acid (siNA) molecule represented by Formula (IX):

$$5'\text{-}A_{2-4}B_1A_{1-3}B_{2-3}A_{2-10}B_{0-1}A_{0-4}B_{0-1}A_{0-2}\text{-}3'$$

$$3'\text{-}C_2A_{0-2}B_{0-1}A_{0-3}B_{0-1}A_{0-5}B_{0-1}A_{2-7}B_1A_{2-11}B_1A_1\text{-}5'$$

wherein:

the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5'-stabilized end cap or a phosphorylation blocker;

B is a 2'-fluoro nucleotide;

C represents overhanging nucleotides and is a 2'-O-methyl nucleotide.

[0017] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12, and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, and 13-16 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end of the second nucleotide sequence. In some embodiments, the first nucleotide sequence consists of 19 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence. In some embodiments, the second

nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

[0018] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7, 8, and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, and 9-16 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the first nucleotide sequence; and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end of the first nucleotide sequence. In some embodiments, the first nucleotide sequence consists of 19 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence. In some embodiments, the second nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

[0019] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12 and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, and 13-16 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides. In some embodiments, the first nucleotide sequence consists of 19 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence. In some embodiments, the second nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 19-21 from the 5' end of the second nucleotide sequence. In some embodiments, the alternating 1:3 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:3 modification pattern occur consecutively. In some embodiments, at least two of the alternating 1:3 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand.

[0020] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides. In some embodiments, the first nucleotide sequence consists of 19 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence. In some embodiments, the second nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 19-21 from the 5' end of the second nucleotide sequence. In some embodiments, the alternating 1:3 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:3 modification pattern occur consecutively. In some embodiments, at least two of the alternating 1:3 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand.

[0021] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides. In some embodiments, the first nucleotide sequence consists of 19 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence. In some embodiments, the second nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence. In some embodiments, the alternating 1:2 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:2 modification pattern occur consecutively. In some embodiments, at least two of the alternating 1:2 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:2 modification pattern begins at nucleotide position 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 5 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 8 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position

14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 17 from the 5' end of the antisense strand.

[0022] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2, 6, 14, and 16 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-5, 7-13, 15, and 17 from the 5' end the second nucleotide sequence. In some embodiments, the first nucleotide sequence consists of 19 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence. In some embodiments, the second nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

[0023] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5, 9-11, and 14 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6-8, and 12-17 from the 5' end of the first nucleotide sequence; and (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end the second nucleotide sequence. In some embodiments, the first nucleotide sequence consists of 21 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the first nucleotide sequence. In some embodiments, the second nucleotide sequence consists of 23 nucleotides. In some embodiments, 2'-O-methyl nucleotides are at positions 18-23 from the 5' end of the second nucleotide sequence.

[0024] In some embodiments, any of the sense strands disclosed herein further comprise a TT sequence adjacent to the first nucleotide sequence.

[0025] In some embodiments, any of the sense strands disclosed herein further comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate internucleoside linkages. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the first nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the first nucleotide sequence.

[0026] In some embodiments, any of the antisense strands disclosed herein further comprise TT sequence adjacent to the second nucleotide sequence. In some embodiments, the antisense strand further comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate internucleoside linkages. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the second nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the second nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 3' end of the second nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 3' end of the second nucleotide sequence.

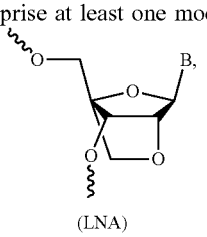
[0027] In some embodiments, the first nucleotide from the 5' end of any of the first nucleotide sequences disclosed herein comprises a 5' stabilizing end cap.

[0028] In some embodiments, the first nucleotide from the 5' end of any of the second nucleotide sequences disclosed herein comprise a 5' stabilizing end cap.

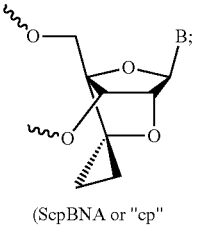
[0029] In some embodiments, the first nucleotide from the 5' end of any of the first nucleotide sequences disclosed herein comprises a phosphorylation blocker.

[0030] In some embodiments, the first nucleotide from the 5' end of any of the second nucleotide sequences disclosed herein comprises a phosphorylation blocker.

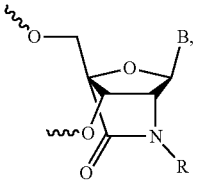
[0031] In some embodiments, any of the first nucleotide sequences or second nucleotide sequences disclosed herein comprise at least one modified nucleotide selected from



(LNA)

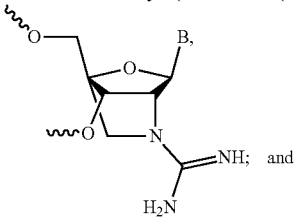


(ScpBNA or "cp"

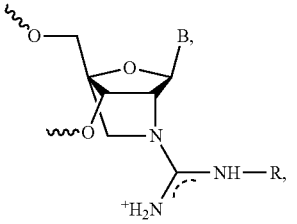


(AmNA)

where R is H or alkyl (or AmNA(N-Me)) when R is alkyl;



(GuNA)

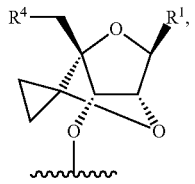


GuNA(N-R),
R = Me, Et, iPr, tBu,

wherein B is a nucleobase.

[0032] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising:

(a) a phosphorylation blocker of Formula (IV):



wherein

R^1 is a nucleobase,

R^4 is —O—R^{30} or —$NR^{31}R^{32}$,

R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and

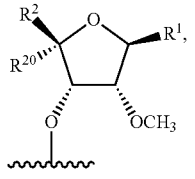
R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or

unsubstituted heterocyclic ring; and

(b) a short interfering nucleic acid (siNA). In some embodiments, the siNA is any of the siNAs disclosed herein. In some embodiments, the siNA comprises any of the sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein. In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0033] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising:

(a) a 5'-stabilized end cap of Formula (Ia):

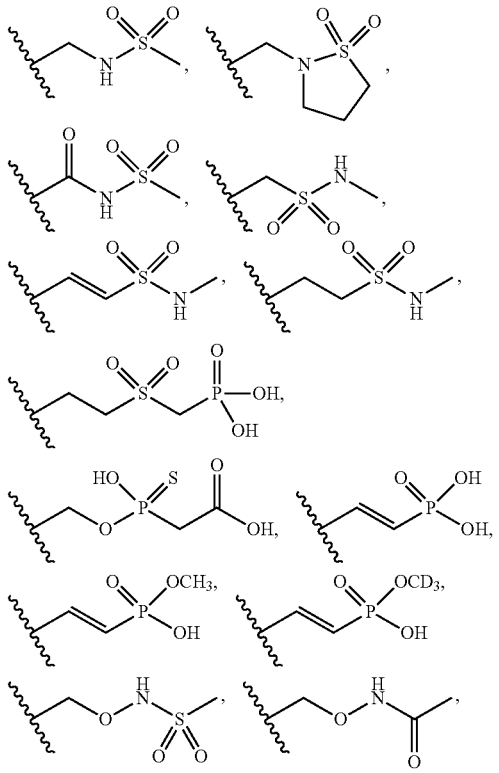


wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0034]



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl; R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

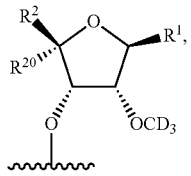
m is 1, 2, 3, or 4; and

(b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ

ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0035] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising:

(a) a 5'-stabilized end cap of Formula (Ib):

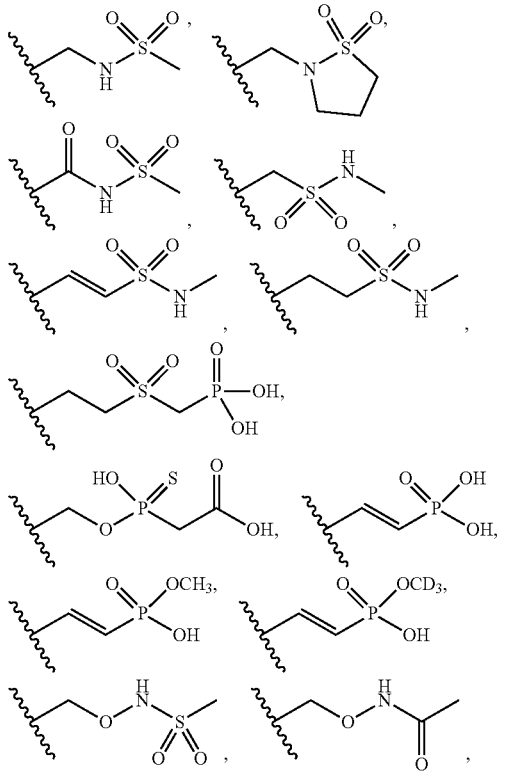


wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0036]



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl; R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

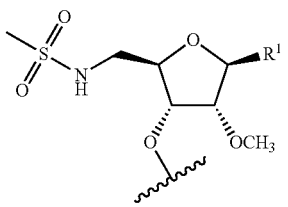
R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4; and

(b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

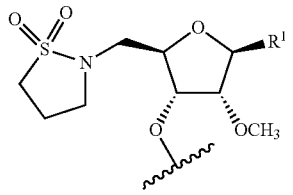
[0037] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising: (a) a 5'-stabilized end cap selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

Formula (1)

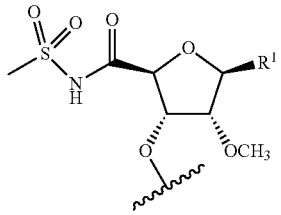


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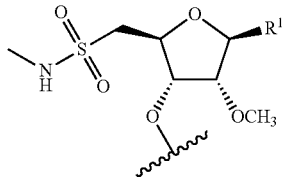
Formula (2)



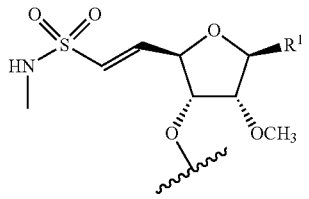
Formula (3)



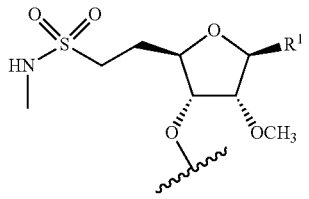
Formula (4)



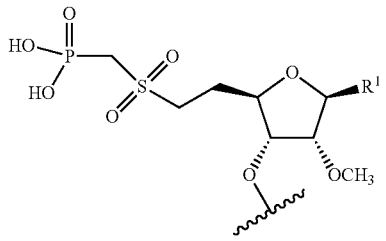
Formula (5)



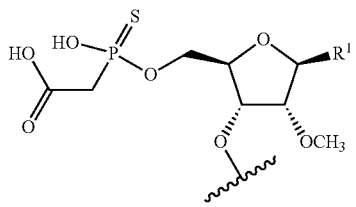
Formula (6)



Formula (7)

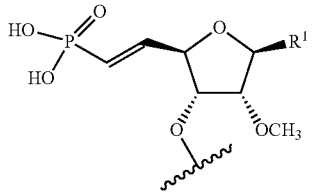


Formula (8)

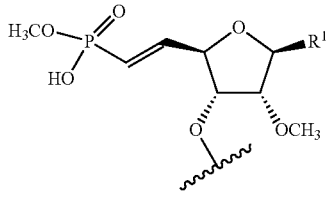


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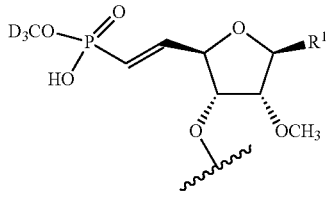
Formula (9)



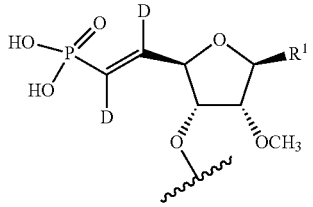
Formula (9X)



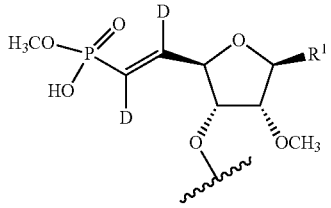
Formula (9Y)



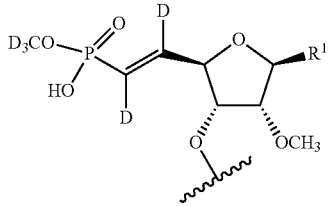
Formula (10)



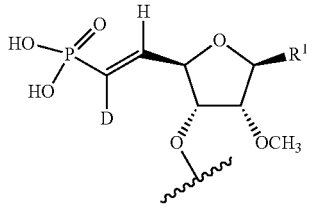
Formula (10X)



Formula (10Y)

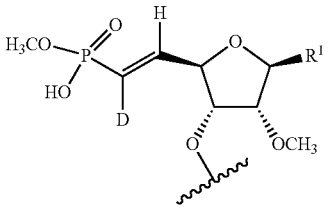


Formula (11)

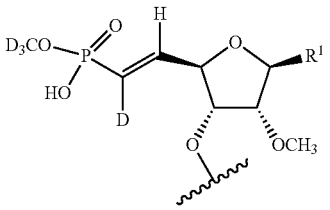


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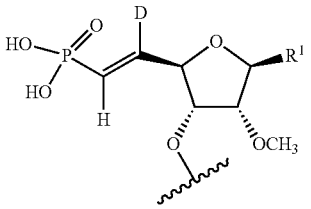
Formula (11X)



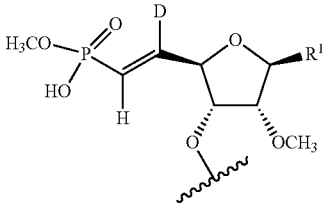
Formula (11Y)



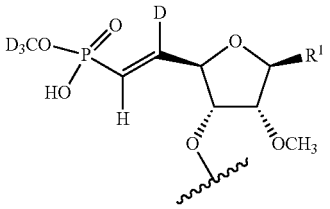
Formula (12)



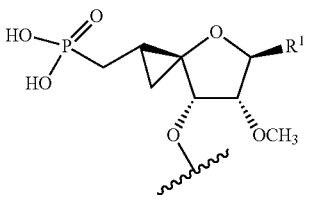
Formula (12X)



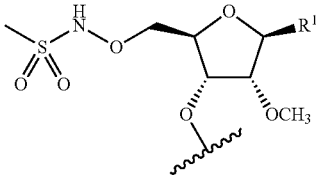
Formula (12Y)



Formula (13)

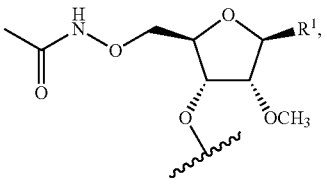


Formula (14)



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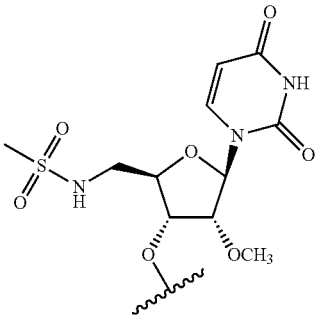
Formula (15)



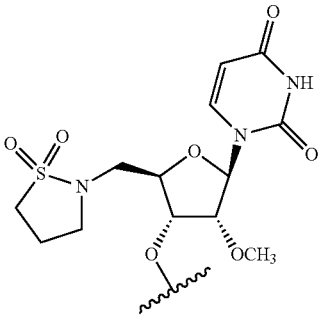
wherein R^1 is a nucleobase, aryl, heteroaryl, or H; and (b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0038] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising: (a) a 5'-stabilized end cap selected from the group consisting of Formulas (1A)-(15A), Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

Formula (1A)

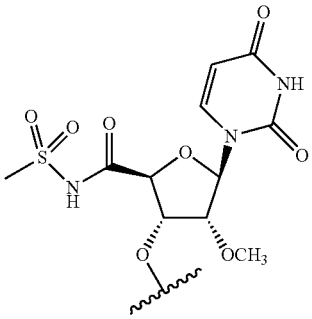


Formula (2A)

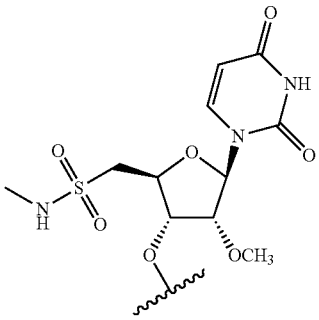


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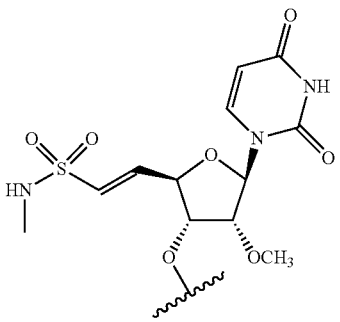
Formula (3A)



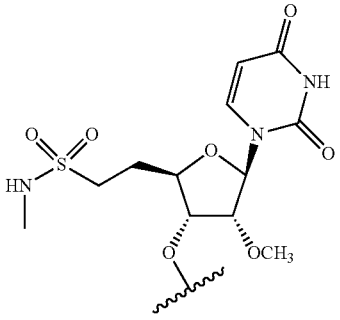
Formula (4A)



Formula (5A)

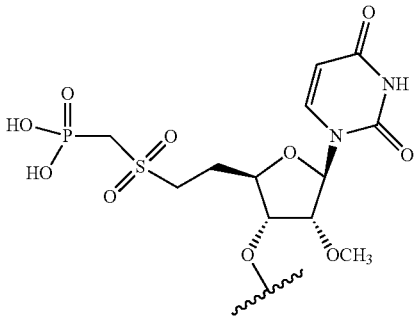


Formula (6A)

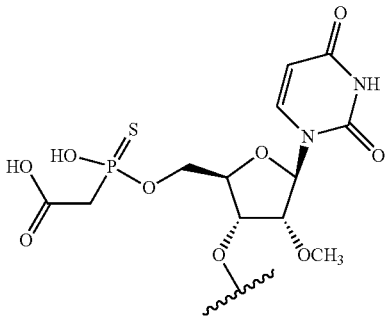


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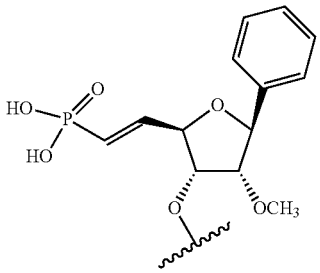
Formula (7A)



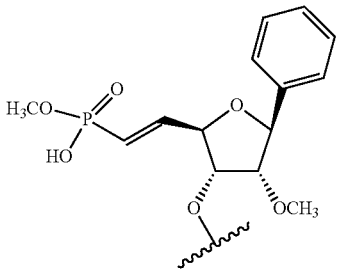
Formula (8A)



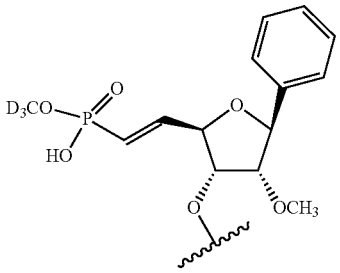
Formula (9A)



Formula (9AX)

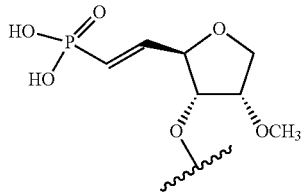


Formula (9AY)

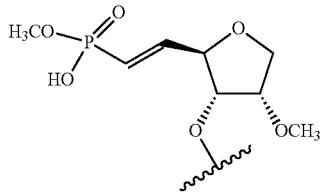


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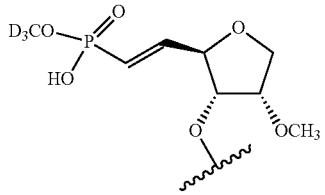
Formula (9B)



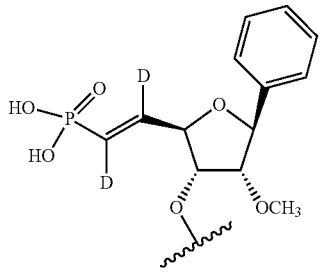
Formula (9BX)



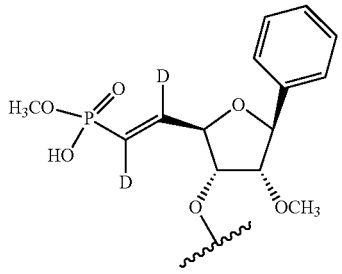
Formula (9BY)



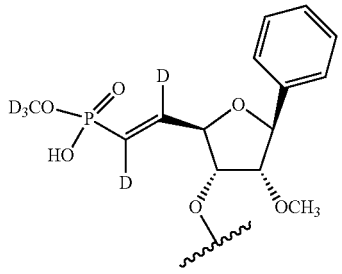
Formula (10A)



Formula (10AX)

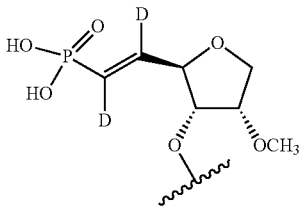


Formula (10AY)

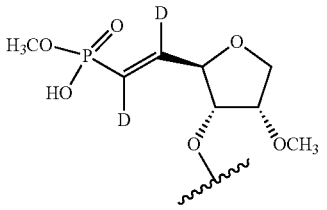


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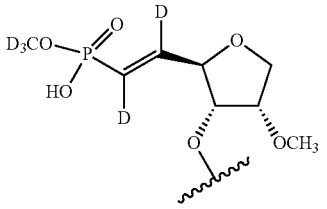
Formula (10B)



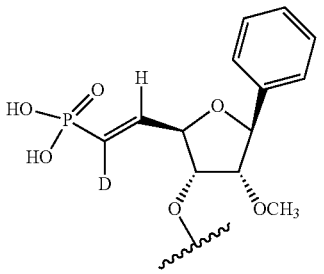
Formula (10BX)



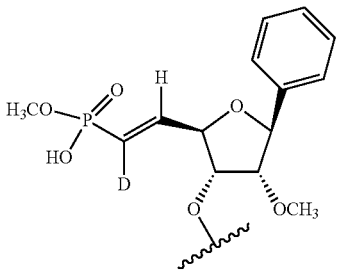
Formula (10BY)



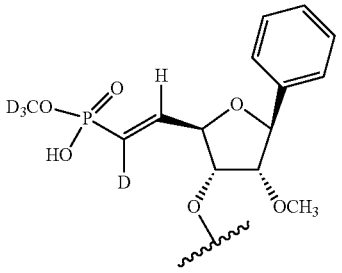
Formula (11A)



Formula (11AX)

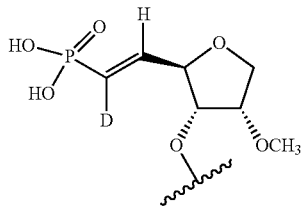


Formula (11AY)

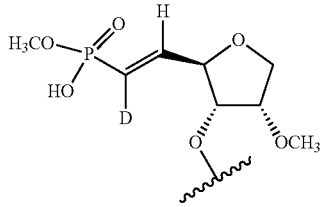


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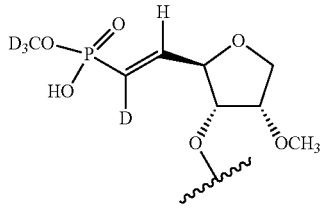
Formula (11B)



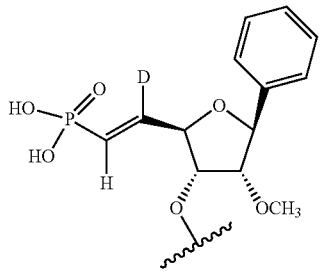
Formula (11BX)



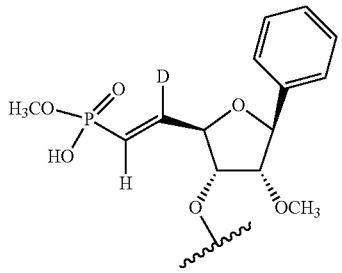
Formula (11BY)



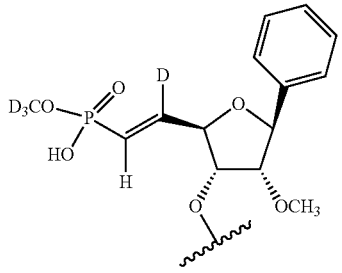
Formula (12A)



Formula (12AX)

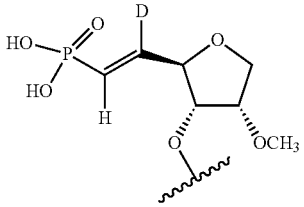


Formula (12AY)

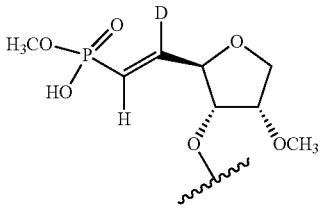


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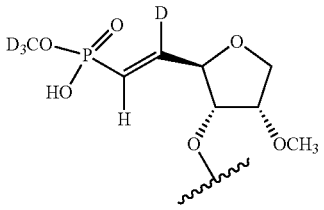
Formula (12B)



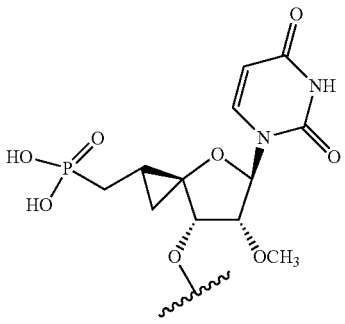
Formula (12BX)



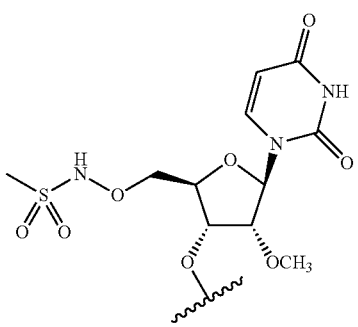
Formula (12BY)



Formula (13A)

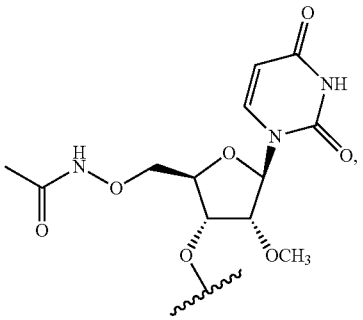


Formula (14A)



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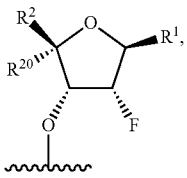
Formula (15A)



and (b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0039] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising:

(a) a 5'-stabilized end cap of Formula (Ic):

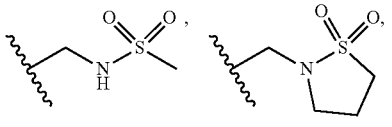


wherein

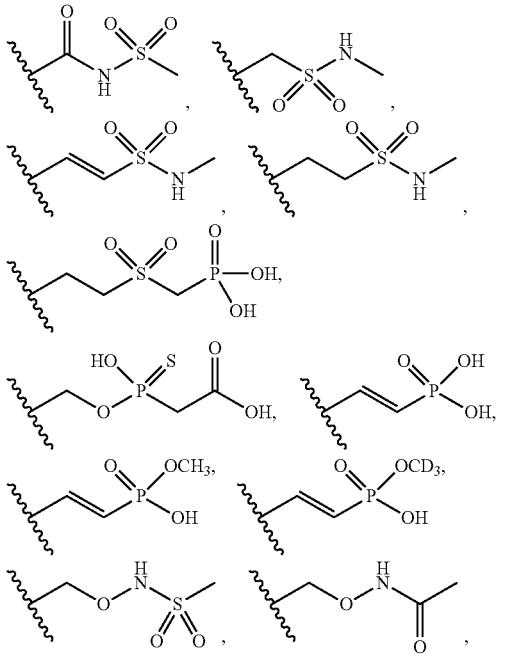
R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0040]



-continued



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$, R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4; and

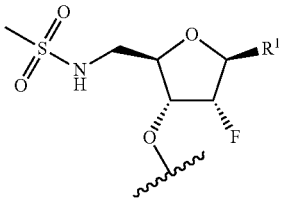
(b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated

moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

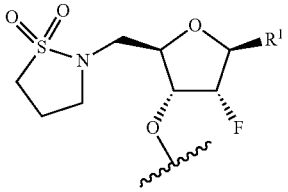
[0041] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising:

(a) a 5'-stabilized end cap selected from the group consisting of Formula (21) to Formula (35):

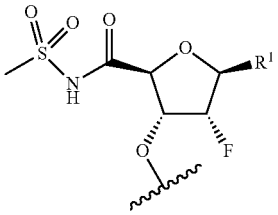
Formula (21)



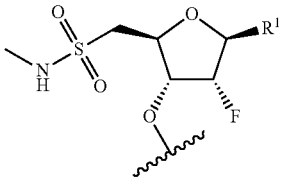
Formula (22)



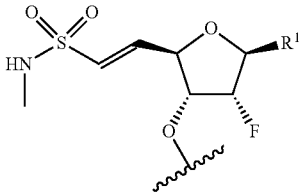
Formula (23)



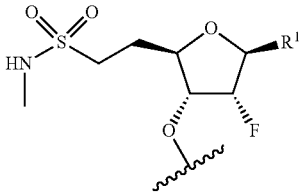
Formula (24)



Formula (25)

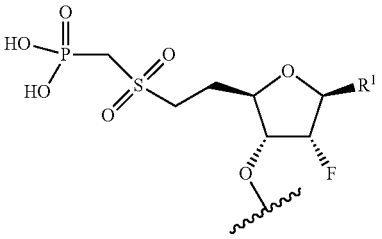


Formula (26)

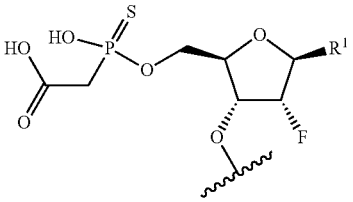


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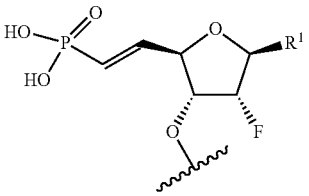
Formula (27)



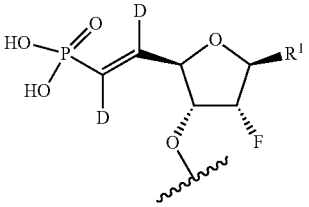
Formula (28)



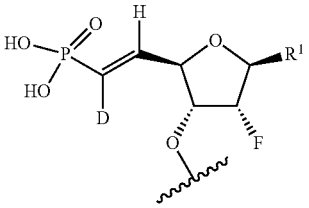
Formula (29)



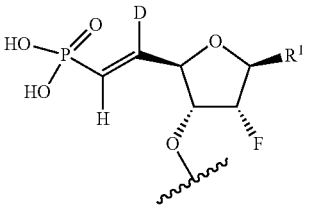
Formula (30)



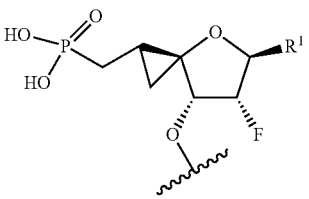
Formula (31)



Formula (32)

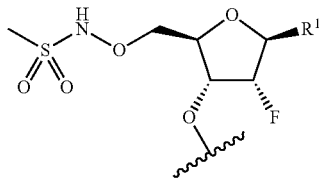


Formula (33)

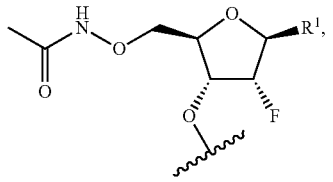


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Formula (34)



Formula (35)

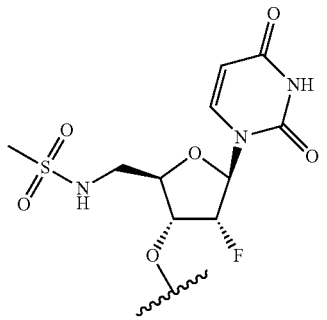


wherein R^1 is a nucleobase, aryl, heteroaryl, or H; and (b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0042] Disclosed herein is a short-interfering nucleic acid (siNA) molecule comprising:

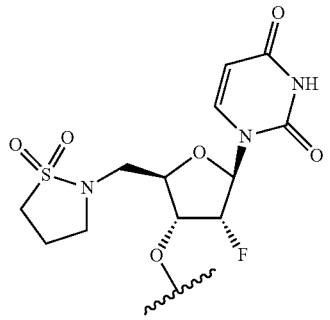
(a) a 5'-stabilized end cap selected from the group consisting of Formulas (21A)-(35A), Formulas (29B)-(32B), Formulas (29AX)-(32AX), Formulas (29AY)-(32AY), Formulas (29BX)-(32BX), and Formulas (29BY)-(32BY):

Formula (21A)

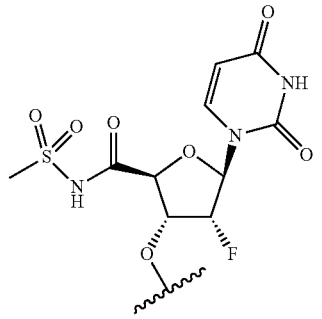


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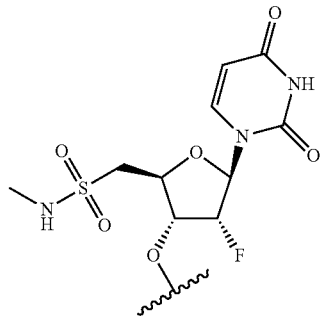
Formula (22A)



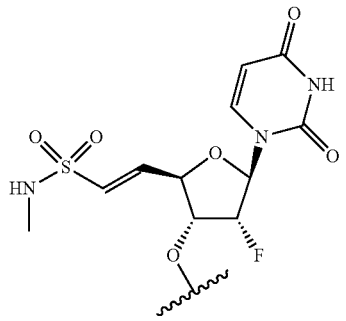
Formula (23A)



Formula (24A)

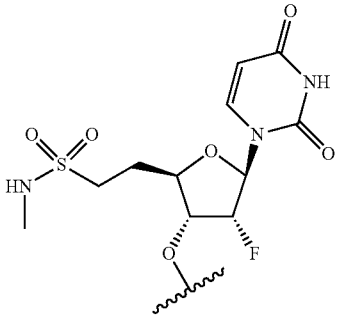


Formula (25A)

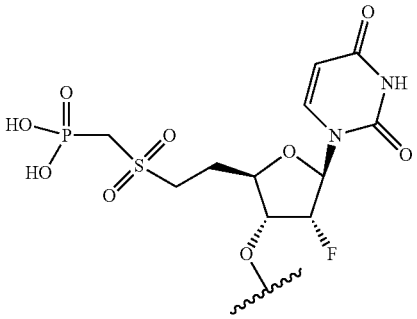


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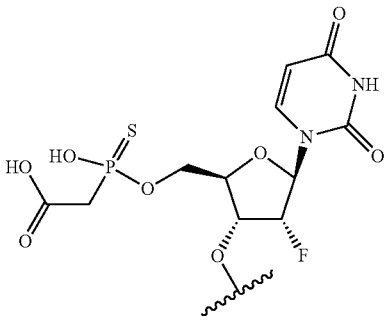
Formula (26A)



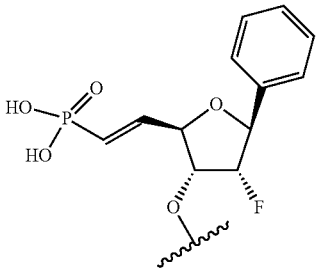
Formula (27A)



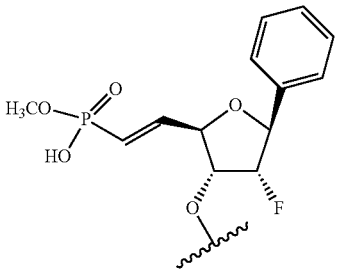
Formula (28A)



Formula (29A)

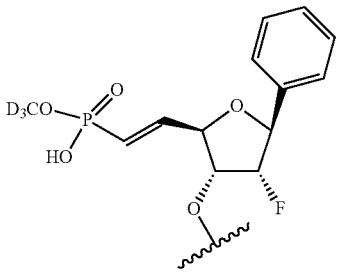


Formula (29AX)

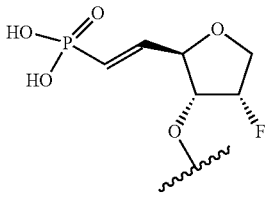


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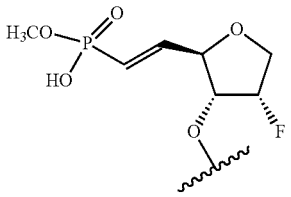
Formula (29AY)



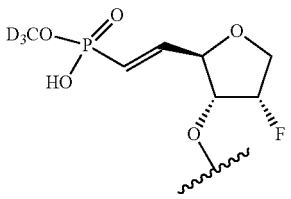
Formula (29B)



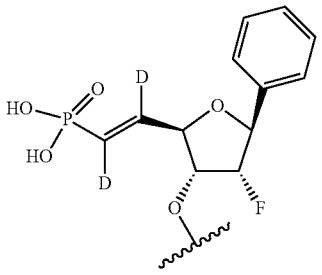
Formula (29BX)



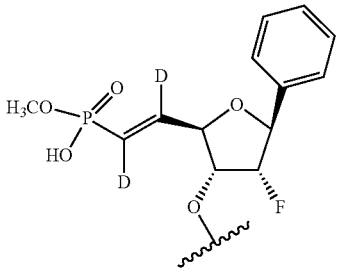
Formula (29BY)



Formula (30A)

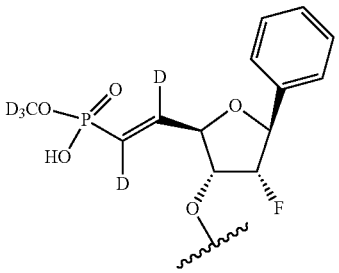


Formula (30AX)

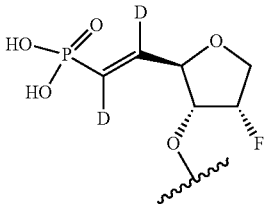


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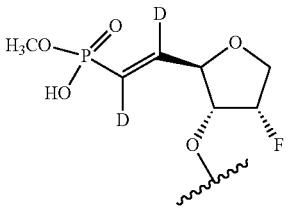
Formula (30AY)



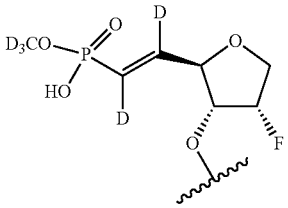
Formula (30B)



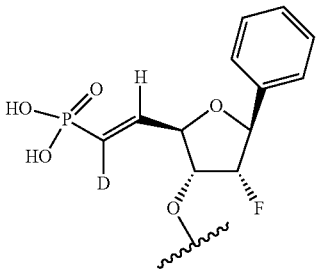
Formula (30BX)



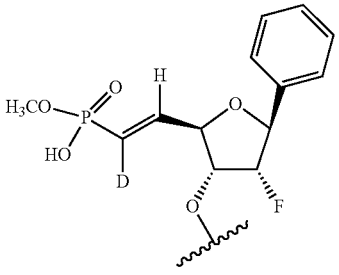
Formula (30BY)



Formula (31A)

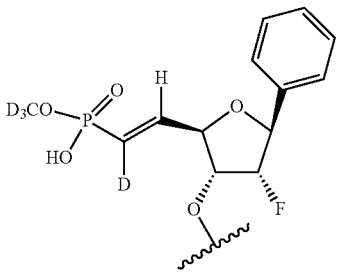


Formula (31AX)

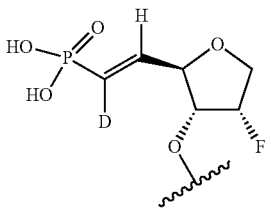


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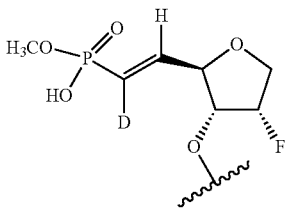
Formula (31AY)



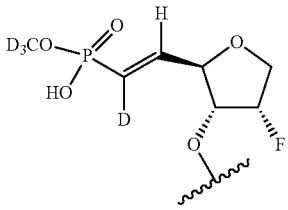
Formula (31B)



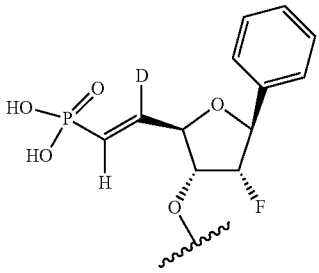
Formula (31BX)



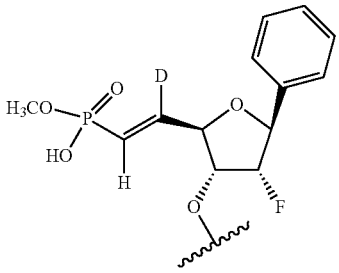
Formula (31BY)



Formula (32A)

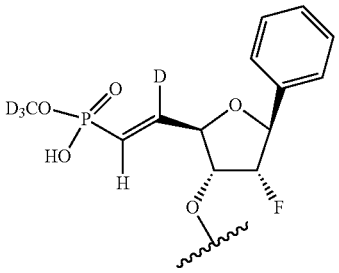


Formula (32AX)

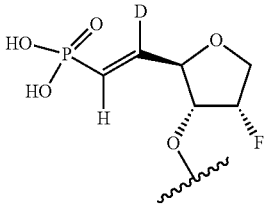


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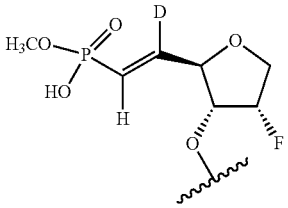
Formula (32AY)



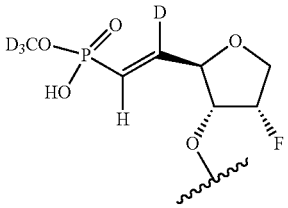
Formula (32B)



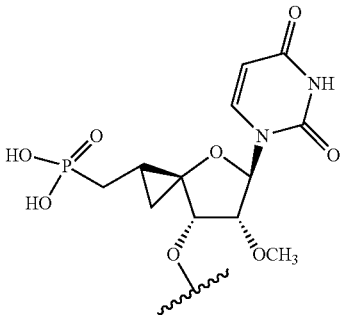
Formula (32BX)



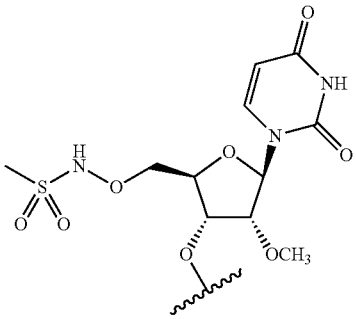
Formula (32BY)



Formula (33A)

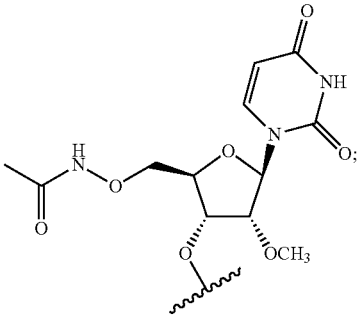


Formula (34A)



-continued

Formula (35A)



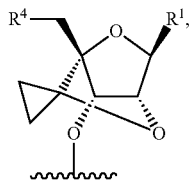
and (b) a short interfering nucleic acid (siNA). In some embodiments, the siNA comprises any of the sense strands disclosed herein. In some embodiments, the siNA comprises any of the antisense strand disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence selected from any one of SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence selected from any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense sequence selected from any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense sequence selected from any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA comprises a ds-siNA sequence selected from any one of ds-siNA-001 to ds-siNA-0178. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0043] Disclosed herein is a short interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilizing nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0044] Disclosed herein is a interfering nucleic acid (siNA) molecule comprising: (a) a sense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444; and (b) an antisense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

[0045] In some embodiments, any of the siNA disclosed herein further comprise a phosphorylation blocker.

[0046] In some embodiments, the phosphorylation blocker has the structure of Formula (IV):



wherein

R^1 is a nucleobase,

R^4 is —O—R^{30} or —$NR^{31}R^{32}$, R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and

R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring.

[0047] In some embodiments, R^4 is —OCH_3 or —$N(CH_2CH_2)_2O$.

[0048] In some embodiments, the phosphorylation blocker is attached to the 5' end of the sense strand.

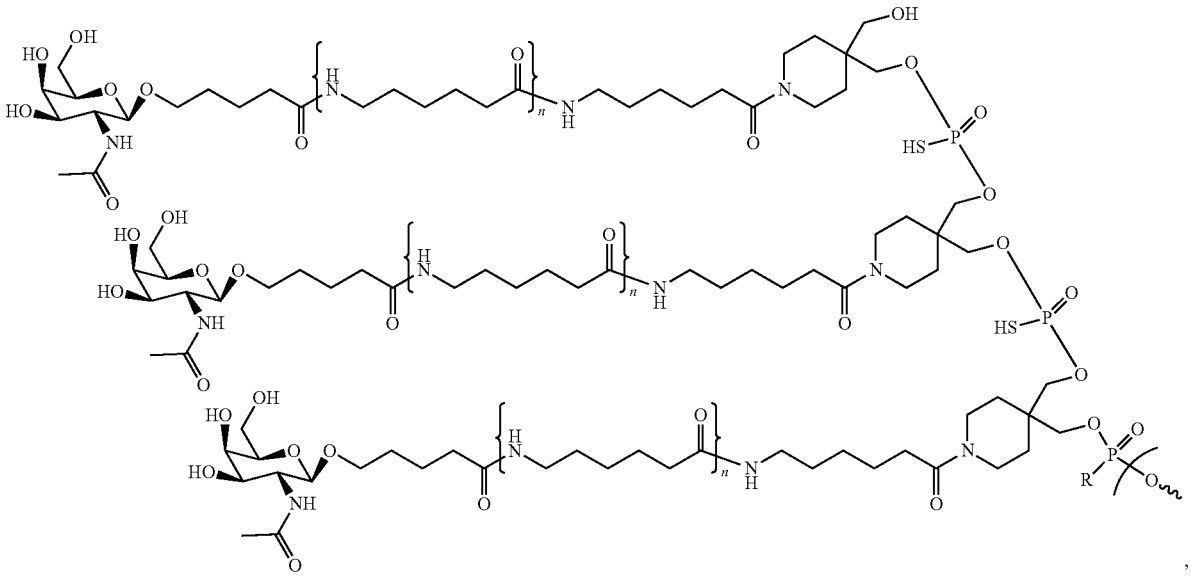
[0049] In some embodiments, the phosphorylation blocker is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

[0050] In some embodiments, the phosphorylation blocker is attached to the 3' end of the sense strand.

[0051] In some embodiments, the phosphorylation blocker is attached to the 3' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

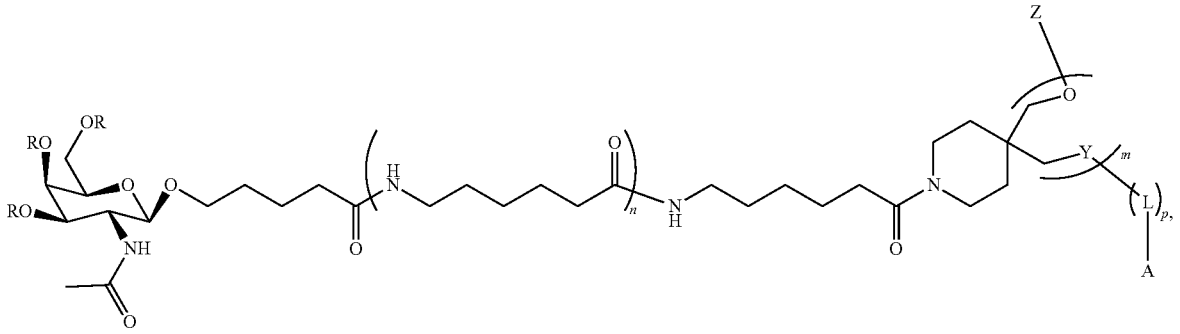
[0052] In some embodiments, the phosphorylation blocker is attached to the 5' end of the antisense strand. In some embodiments, the phosphorylation blocker is attached to the 5' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker. In some embodiments, the phosphorylation blocker is attached to the 3' end of the antisense strand. In some embodiments, the phosphorylation blocker is attached to the 3' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

[0053] In some embodiments, any of the siNAs disclosed herein further comprise a conjugated moiety. In some embodiments, the conjugated moiety comprises a galactosamine. In some embodiments, the galactosamine is N-acetylgalactosamine (GalNAc) of Formula (VII):



R = OH or SH

wherein each n is independently 1 or 2. In some embodiments, the galactosamine is N-acetylgalactosamine (GaNAc) of Formula (VI):



wherein

m is 1, 2, 3, 4, or 5;

each n is independently 1 or 2;

p is 0 or 1;

each R is independently H;

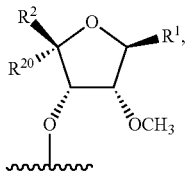
each Y is independently selected from —O—P(═O)(SH)—, —O—P(═O)(O)—, —O—P(═O)(OH)—, and —O—P(S)S—;

Z is H or a second protecting group;

either L is a linker or L and Y in combination are a linker; and

A is H, OH, a third protecting group, an activated group, or an oligonucleotide. In some embodiments, wherein A is an oligonucleotide. In some embodiments, A is 1-2 oligonucleotides. In some embodiments, the oligonucleotide is dTdT. In some embodiments, the galactosamine is attached to the 3' end of the sense strand. In some embodiments, the galactosamine is attached to the 3' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker. In some embodiments, the galactosamine is attached to the 5' end of the sense strand. In some embodiments, the galactosamine is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker. In some embodiments, the galactosamine is attached to the 3' end of the antisense strand. In some embodiments, the galactosamine is attached to the 3' end of the atnisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker. In some embodiments, the galactosamine is attached to the 5' end of the antisense strand. In some embodiments, the galactosamine is attached to the 5' end of the atnisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

[0054] In some embodiments, any of the siNAs disclosed herein further comprise a 5'-stabilized end cap. In some embodiments, the 5'-stabilized end cap is a 5' vinyl phosphonate or deuterated 5' vinyl phosphonate. In some embodiments, the 5'-stabilized end cap has the structure of Formula (Ia):

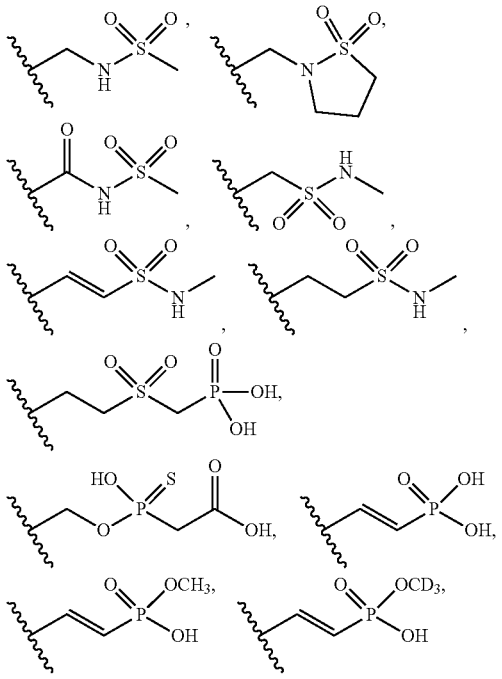


wherein

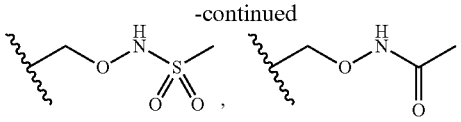
R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0055]



-continued



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$;

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

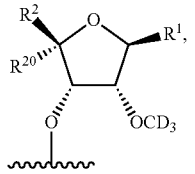
R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4. In some embodiments, the 5'-stabilized end cap has the structure of Formula (Ib):

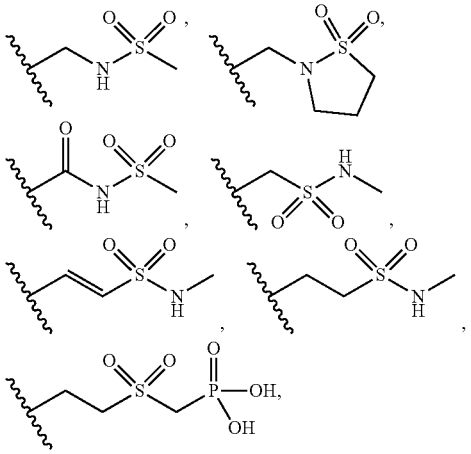


wherein

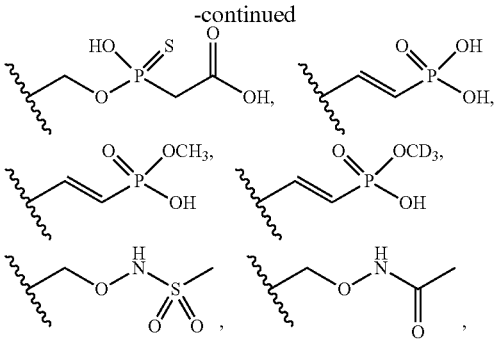
R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0056]



-continued



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$;

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

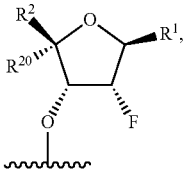
R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4. In some embodiments, the 5'-stabilized end cap has the structure of Formula (Ic):

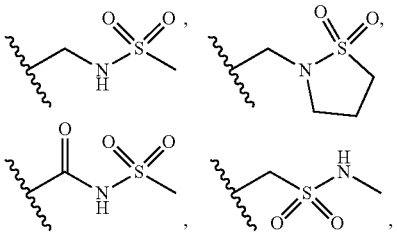


wherein

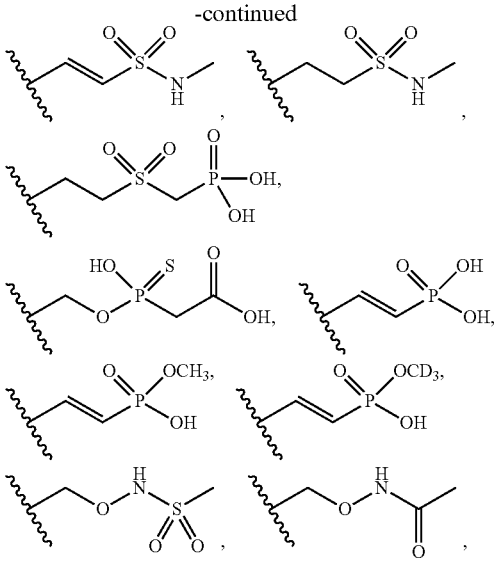
R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0057]



-continued



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$;

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

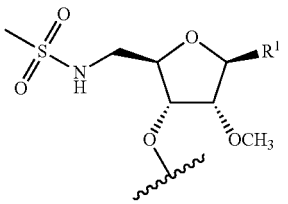
R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

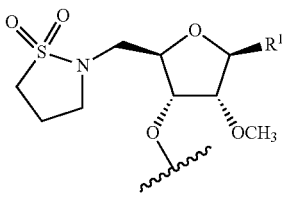
R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl. In some embodiments, the 5'-stabilized end cap is selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

Formula (1)

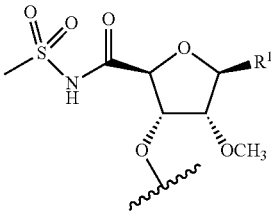


Formula (2)

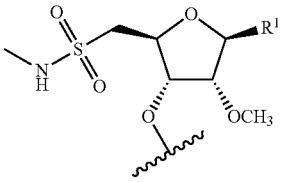


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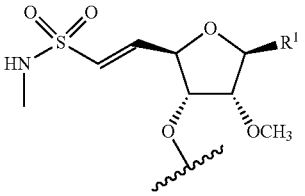
Formula (3)



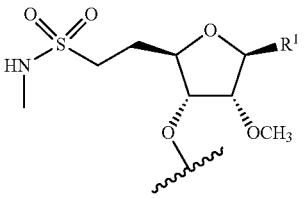
Formula (4)



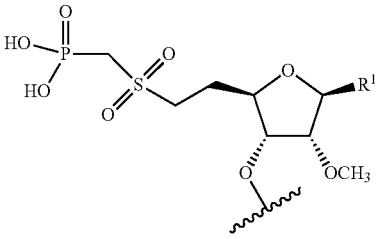
Formula (5)



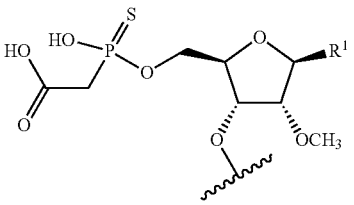
Formula (6)



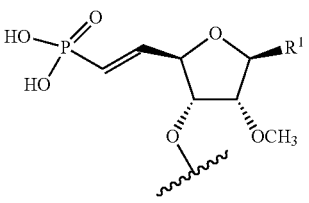
Formula (7)



Formula (8)

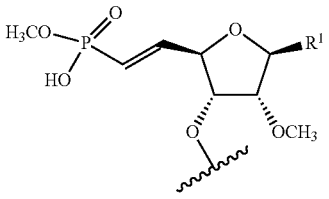


Formula (9)

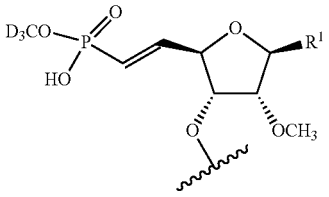


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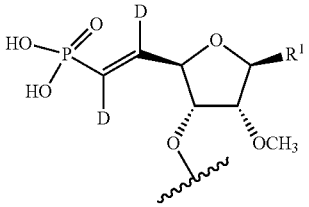
Formula (9X)



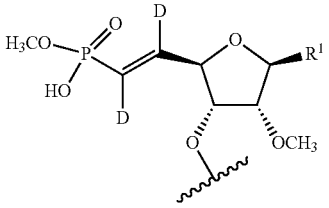
Formula (9Y)



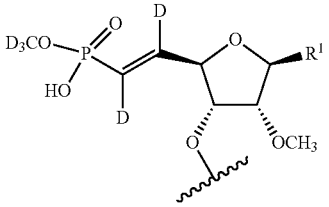
Formula (10)



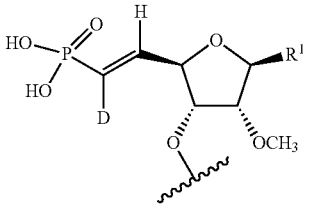
Formula (10X)



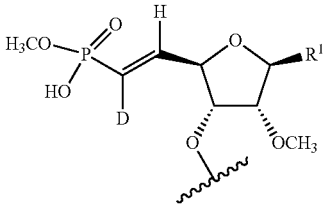
Formula (10Y)



Formula (11)

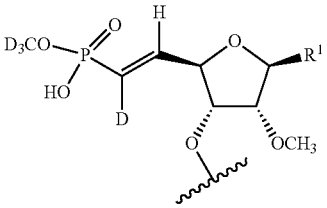


Formula (11X)

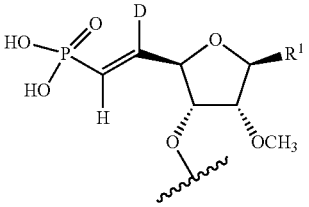


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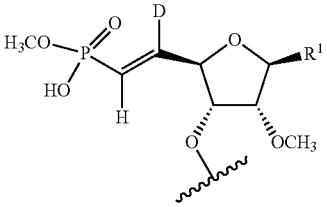
Formula (11Y)



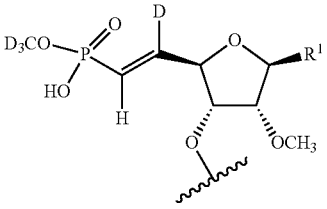
Formula (12)



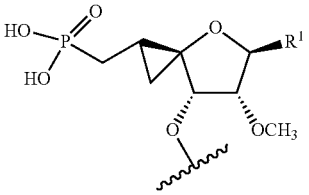
Formula (12X)



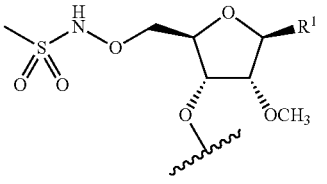
Formula (12Y)



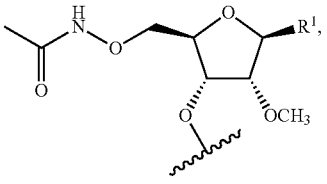
Formula (13)



Formula (14)



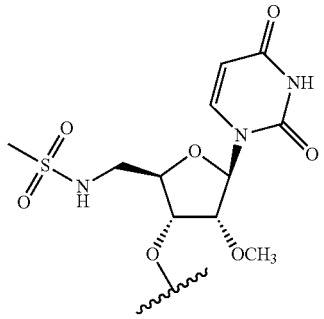
Formula (15)



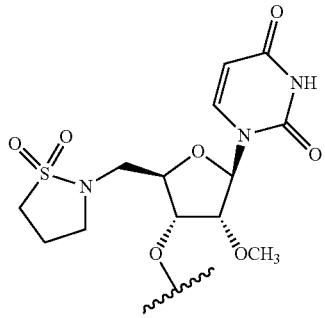
wherein R^1 independently is a nucleobase, aryl, heteroaryl, or H. In some embodiments, the 5'-stabilized end cap is selected from the group consisting of Formulas (1A)-(15A),

Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

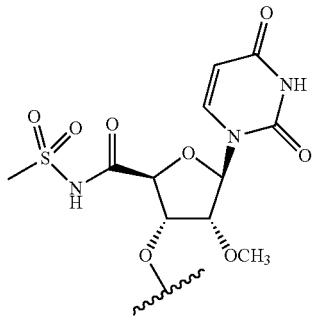
Formula (1A)



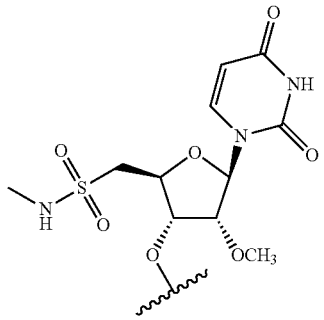
Formula (2A)



Formula (3A)

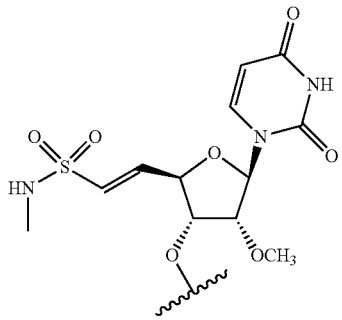


Formula (4A)

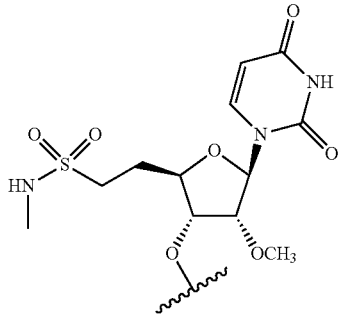


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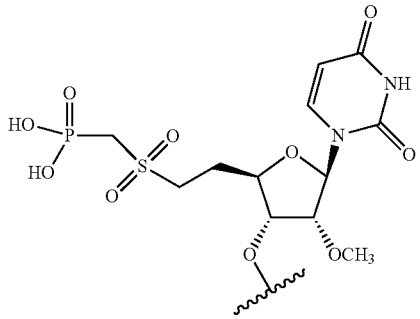
Formula (5A)



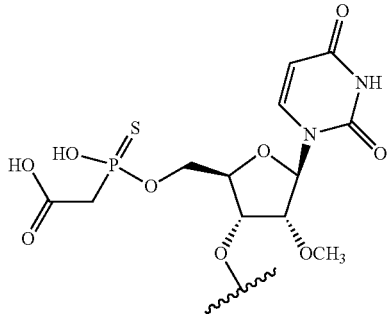
Formula (6A)



Formula (7A)

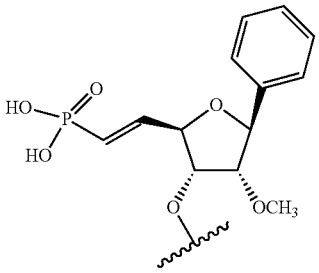


Formula (8A)

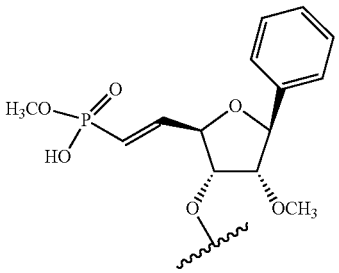


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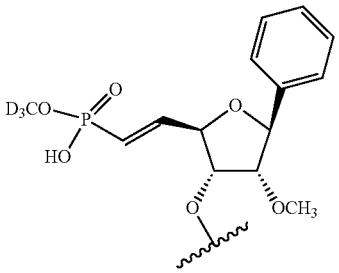
Formula (9A)



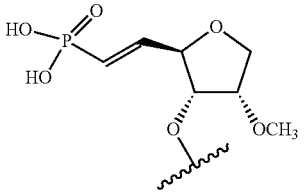
Formula (9AX)



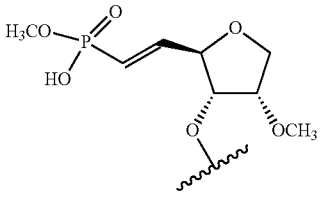
Formula (9AY)



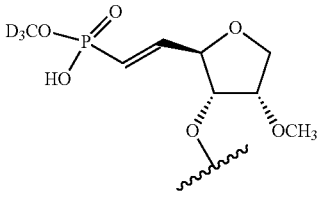
Formula (9B)



Formula (9BX)

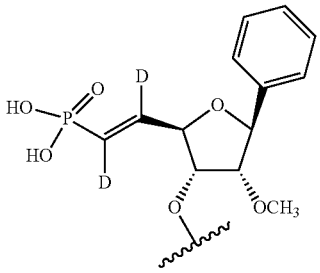


Formula (9BY)

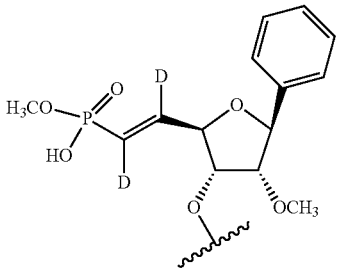


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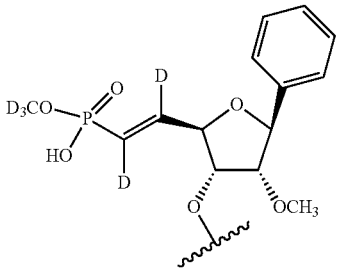
Formula (10A)



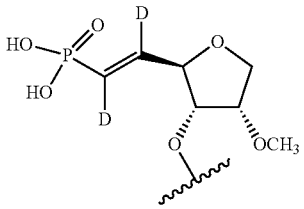
Formula (10AX)



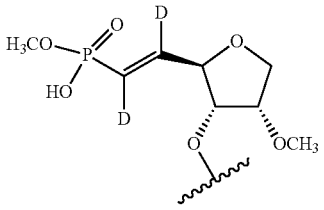
Formula (10AY)



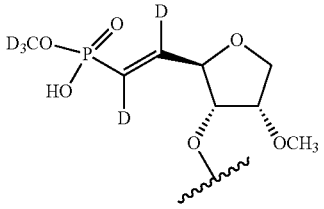
Formula (10B)



Formula (10BX)

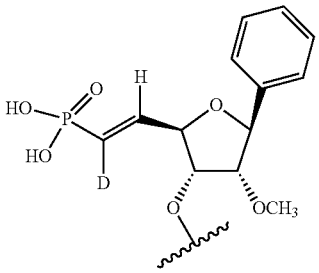


Formula (10BY)

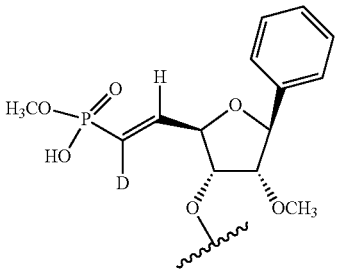


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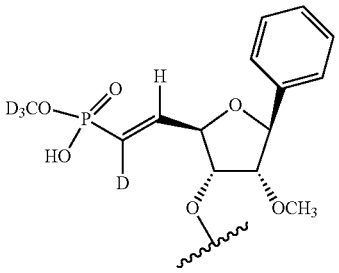
Formula (11A)



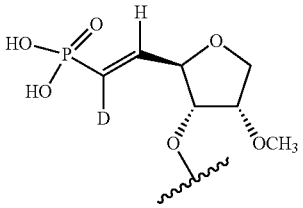
Formula (11AX)



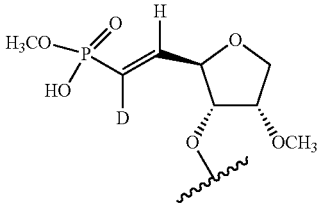
Formula (11AY)



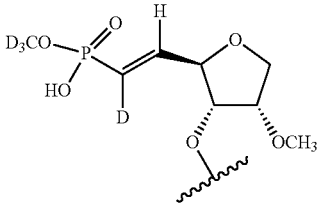
Formula (11B)



Formula (11BX)

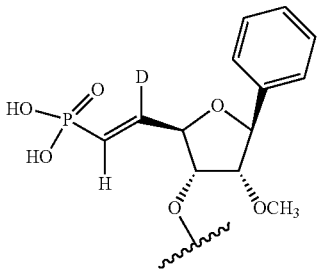


Formula (11BY)

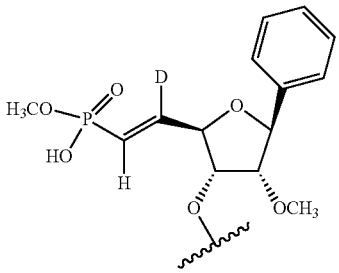


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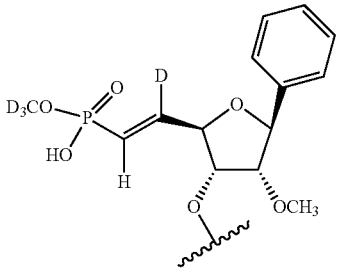
Formula (12A)



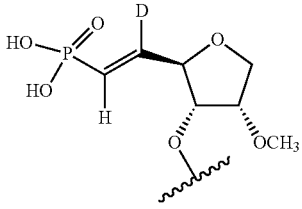
Formula (12AX)



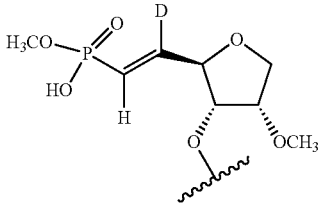
Formula (12AY)



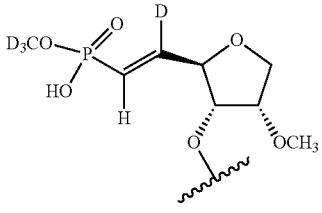
Formula (12B)



Formula (12BX)

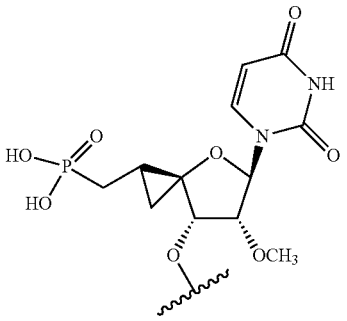


Formula (12BY)

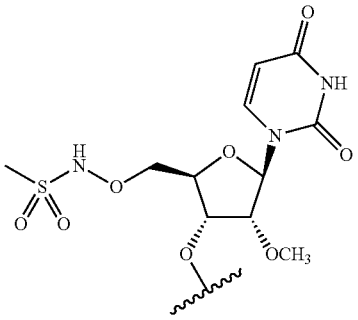


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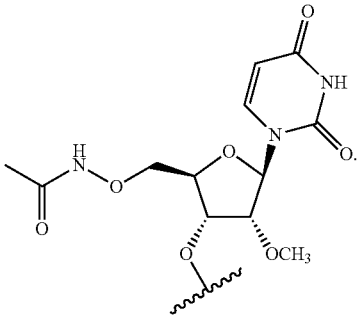
Formula (13A)



Formula (14A)

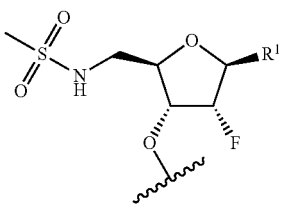


Formula (15A)

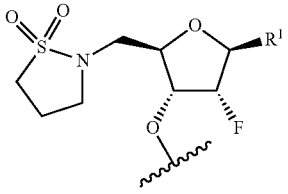


In some embodiments, the 5'-stabilized end cap is selected from the group consisting of Formula (21) to Formula (35):

Formula (21)

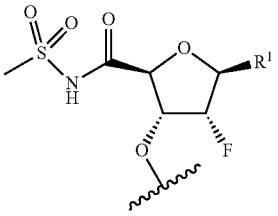


Formula (22)

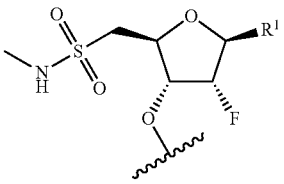


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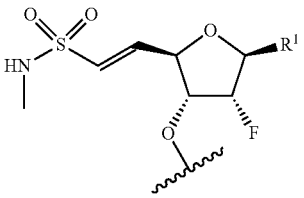
Formula (23)



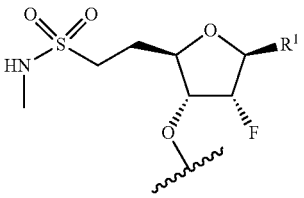
Formula (24)



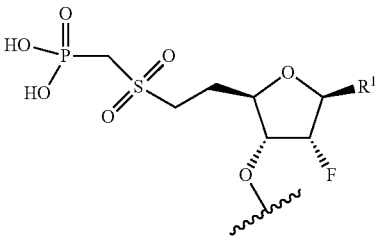
Formula (25)



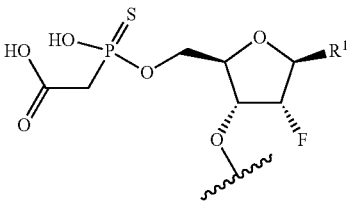
Formula (26)



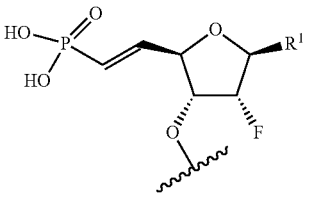
Formula (27)



Formula (28)

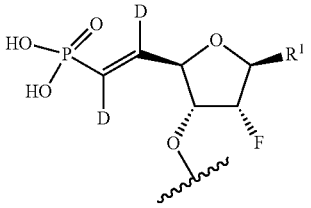


Formula (29)

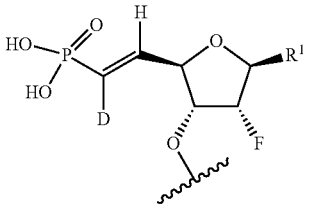


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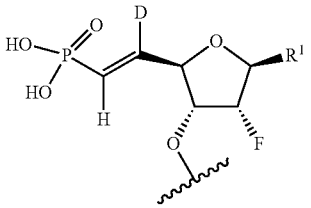
Formula (30)



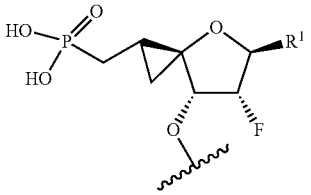
Formula (31)



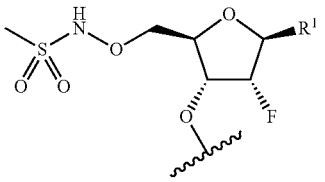
Formula (32)



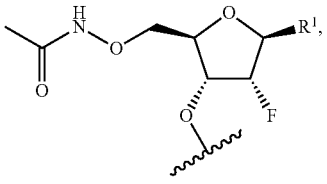
Formula (33)



Formula (34)

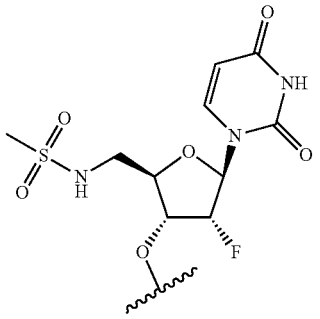


Formula (35)

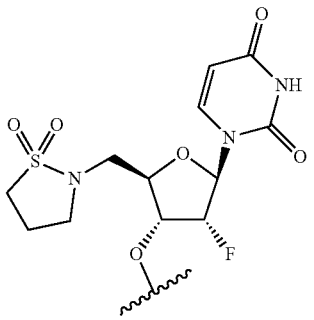


wherein R^1 is a nucleobase, aryl, heteroaryl, or H. In some embodiments, the 5'-stabilized end cap is selected from the group consisting of Formulas (21A)-(35A), Formulas (29B)-(32B), Formulas (29AX)-(32AX), Formulas (29AY)-(32AY), Formulas (29BX)-(32BX), and Formulas (29BY)-(32BY):

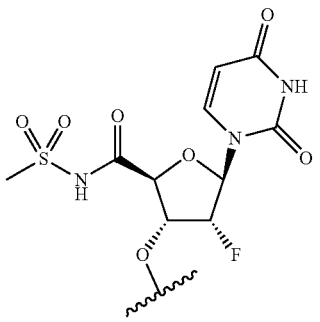
Formula (21A)



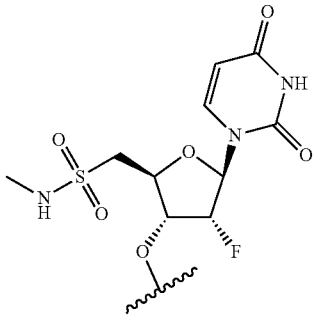
Formula (22A)



Formula (23A)

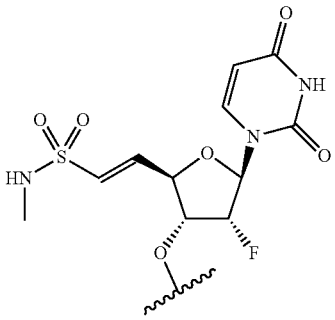


Formula (24A)

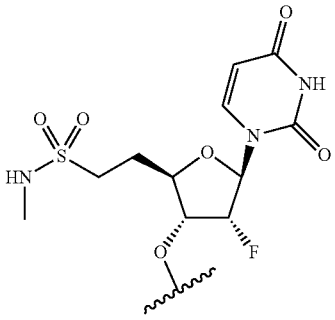


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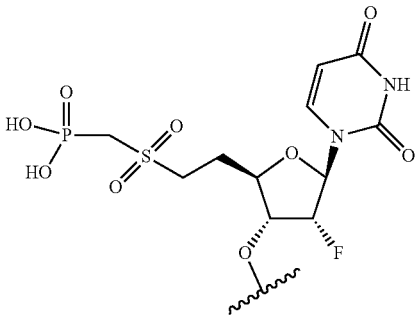
Formula (25A)



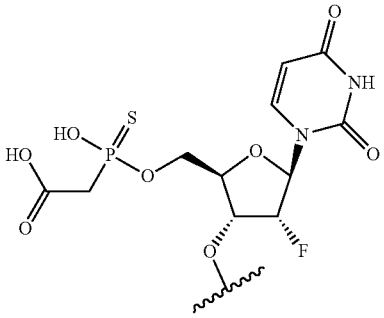
Formula (26A)



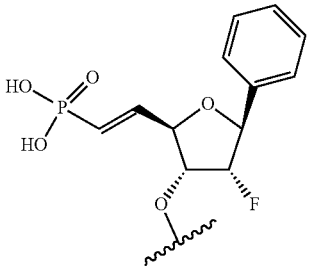
Formula (27A)



Formula (28A)

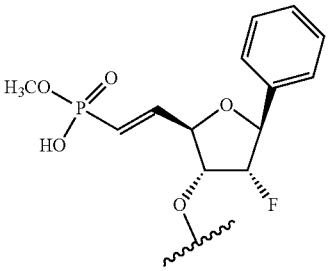


Formula (29A)

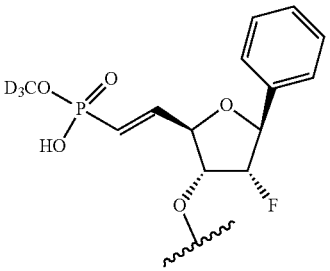


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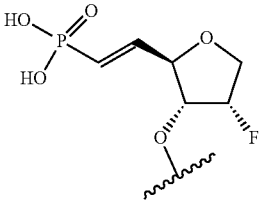
Formula (29AX)



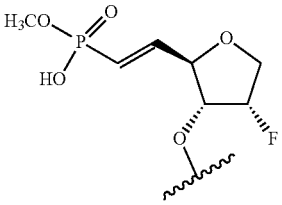
Formula (29AY)



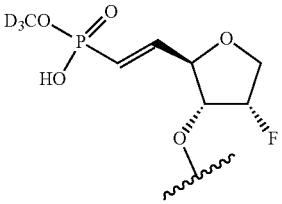
Formula (29B)



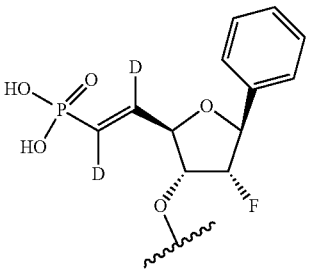
Formula (29BX)



Formula (29BY)

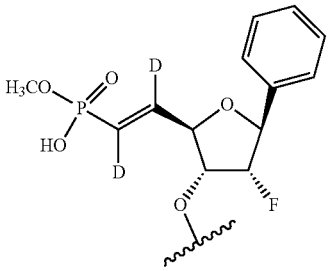


Formula (30A)

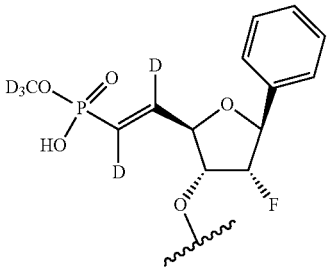


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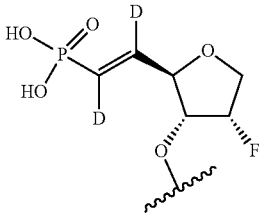
Formula (30AX)



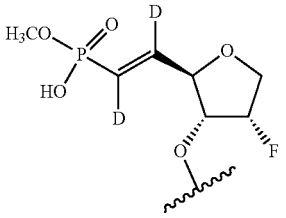
Formula (30AY)



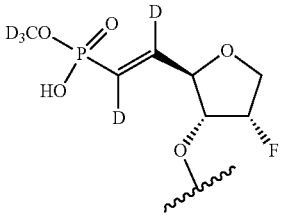
Formula (30B)



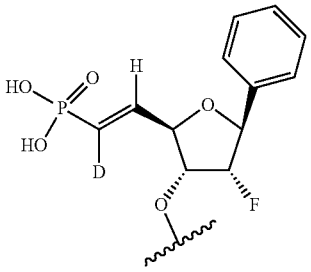
Formula (30BX)



Formula (30BY)

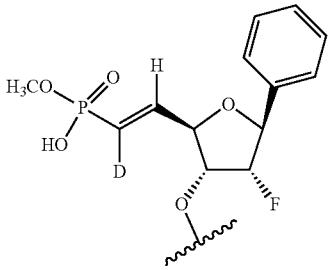


Formula (31A)

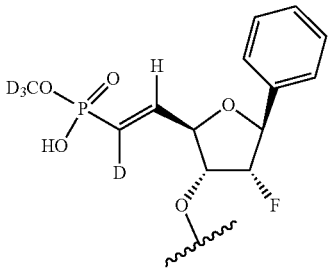


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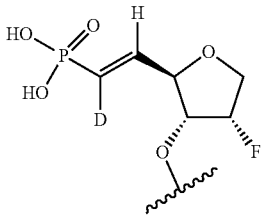
Formula (31AX)



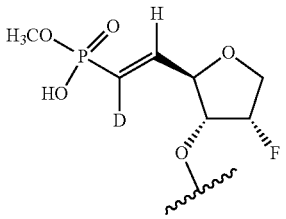
Formula (31AY)



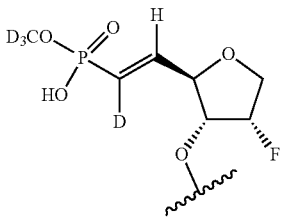
Formula (31B)



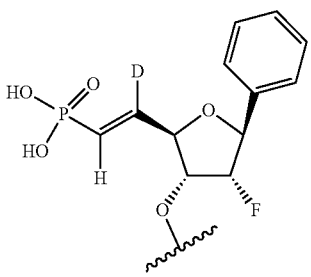
Formula (31BX)



Formula (31BY)

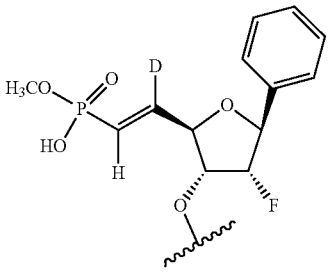


Formula (32A)

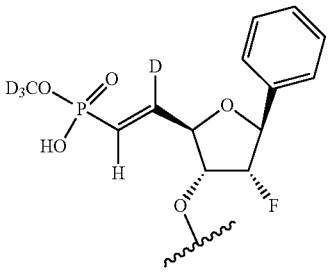


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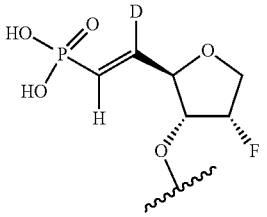
Formula (32AX)



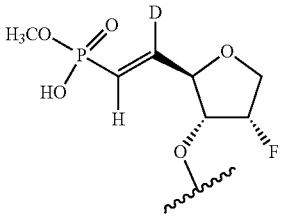
Formula (32AY)



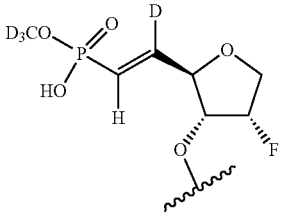
Formula (32B)



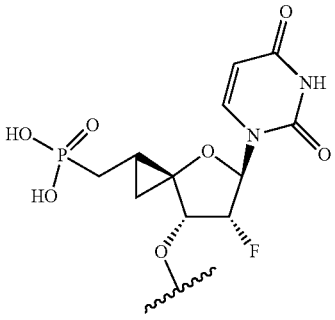
Formula (32BX)



Formula (32BY)

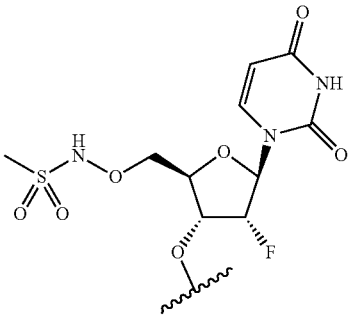


Formula (33A)

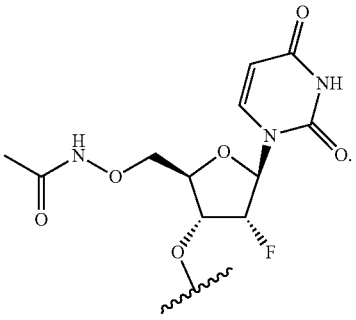


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Formula (34A)

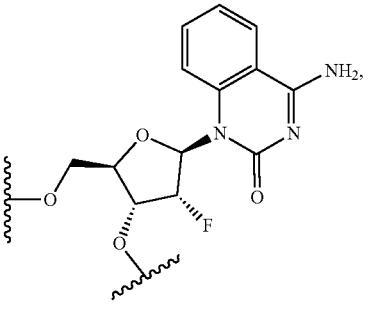


Formula (35A)

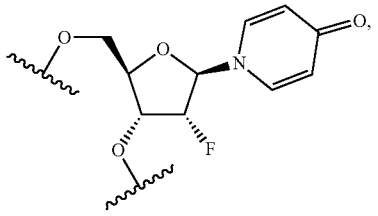


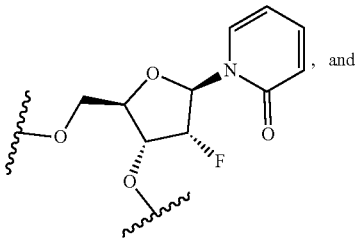
In some embodiments, the 5'-stabilized end cap is attached to the 5' end of the antisense strand. In some embodiments, the 5'-stabilized end cap is attached to the 5' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker. In some embodiments, the 5'-stabilized end cap is attached to the 5' end of the sense strand. In some embodiments, the 5'-stabilized end cap is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

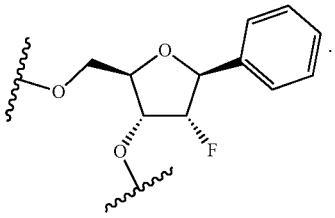
[0058] In some embodiments, any of the siNAs, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein further comprise at least one thermally destabilizing nucleotides. In some embodiments, any of the antisense strands disclosed herein further comprise at least one thermally destabilizing nucleotide selected from:



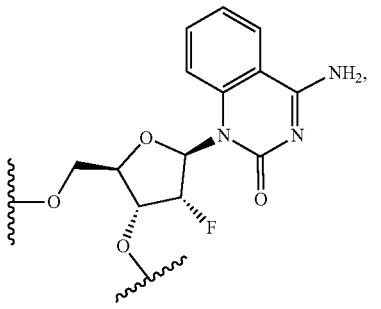
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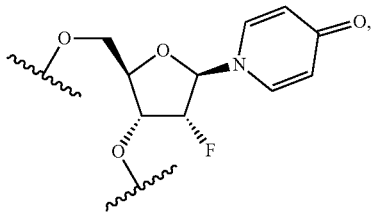


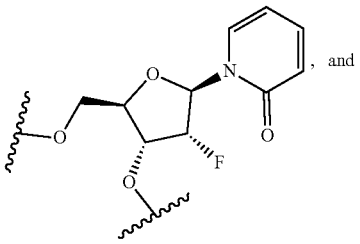




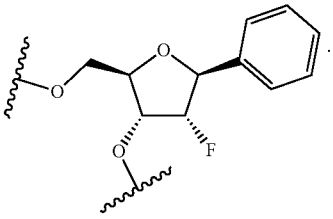
In some embodiments, any of the sense strands disclosed herein comprise at least one thermally destabilizing nucleotide selected from:



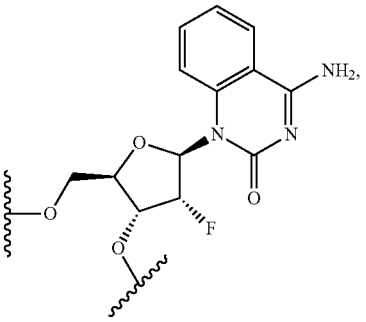


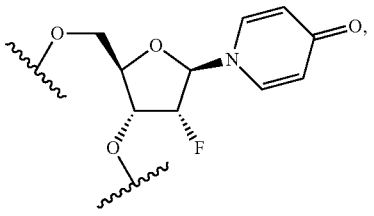


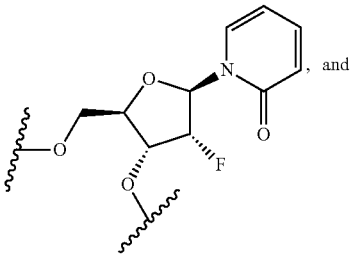
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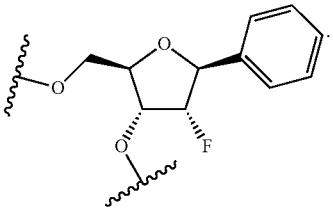


In some embodiments, any of the first nucleotide sequences disclosed herein further comprise at least one thermally destabilizing nucleotide selected from:

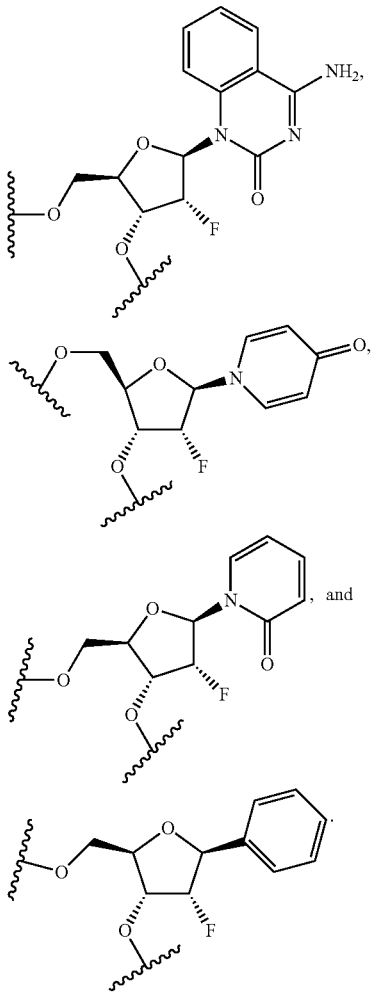








In some embodiments, any of the second nucleotide sequences disclosed herein further comprise at least one thermally destabilizing nucleotide selected from:



In some embodiments, any of the modified nucleotides disclosed herein is a thermally destabilizing nucleotide.

[0059] In some embodiments, any of the siNAs disclosed herein specifically downregulate or reduce expression of a target gene. In some embodiments, the target gene is a viral gene. In some embodiments, the viral gene is from a DNA virus. In some embodiments, the DNA virus is a double-stranded DNA (dsDNA) virus. In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV). In some embodiments, the HBV is selected from HBV genotypes A-J. In some embodiments, the target gene is selected from the S gene or X gene of the HBV.

[0060] In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410. In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410. In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410. In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

[0061] In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410. In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410. In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410. In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

[0062] In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260.

[0063] In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306.

[0064] In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444.

[0065] In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

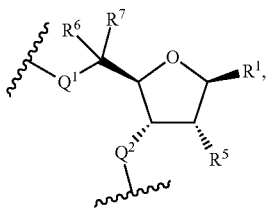
[0066] In some embodiments, at least one end of the siNA is a blunt end.

[0067] In some embodiments, at least one end of the siNA comprises an overhang, wherein the overhang comprises at least one nucleotide.

[0068] In some embodiments, both ends of the siNA comprise an overhang, wherein the overhang comprises at least one nucleotide.

[0069] In some embodiments, the siNA is selected from ds-siNA-001 to ds-siNA-0178.

[0070] In some embodiments, at least one 2'-fluoro nucleotide or 2'-O-methyl nucleotide is a 2'-fluoro or 2-O-methyl nucleotide mimic of Formula (V):



wherein

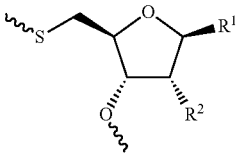
R^1 is independently a nucleobase, aryl, heteroaryl, or H, Q^1 and Q^2 are independently S or O,

R^5 is independently-OCD_3, —F, or —OCH_3, and

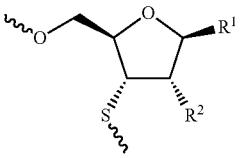
R^6 and R^7 are independently H, D, or CD3.

[0071] In some embodiments, the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (16)-Formula (20):

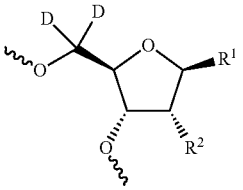
Formula (16)



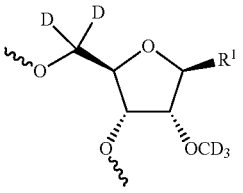
Formula (17)



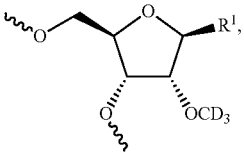
Formula (18)



Formula (19)



Formula (20)



wherein R^1 is a nucleobase and R^2 is independently F or —OCH_3.

[0072] Further disclosed herein are compositions comprising any of the siNAs disclosed herein. In some embodiments, the siNA targets an S gene of HBV. In some embodiments, the siNA specifically downregulates or reduces expression of the S gene of HBV. In some embodiments, the siNA targets an X gene of HBV. In some embodiments, the siNA specifically downregulates or reduces expression of the X gene of HBV. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0073] Further disclosed herein are compositions comprising 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of any of the siNAs disclosed herein. In some embodiments, at least 1, 2, 3, 4, 5, or more siNAs target an S gene of HBV. In some embodiments, at least 1, 2, 3, 4, 5, or more siNAs specifically downregulate or reduce expression of the S gene of HBV. In some embodiments, at least 1, 2, 3, 4, 5, or more siNAs target an X gene of HBV. In some embodiments, at least 1, 2, 3, 4, 5, or more siNAs specifically downregulate or reduce expression of the X gene of HBV. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0074] In some embodiments, any of the compositions disclosed herein further comprise an additional HBV treatment agent. In some embodiments, the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy. In some embodiments, the oligonucleotide therapy is an additional siNA. In some embodiments, the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178. In some embodiments, the oligonucleotide therapy is an antisense oligonucleotide (ASO), NAPs, or STOPs. In some embodiments, the ASO is ASO 1 or ASO 2. In some embodiments, the ASO specifically targets the S gene of HBV. In some embodiments, the ASO specifically targets the X gene of HBV. In

some embodiments, the additional HBV treatment agent is selected from HBV STOPS' ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H2158.

[0075] In some embodiments, any of the compositions disclosed herein further comprise a liver disease treatment agent. In some embodiments, the liver disease treatment agent is selected from a peroxisome proliferator-activator receptor (PPAR) agonist, farnesoid X receptor (FXR) agonist, lipid-altering agent, and incretin-based therapy. In some embodiments, the PPAR agonist is selected from a PPARα agonist, dual PPARα/δ agonist, PPARγ agonist, and dual PPARα/γ agonist. In some embodiments, the dual PPARα agonist is a fibrate. In some embodiments, the PPARα/δ agonist is elafibranor. In some embodiments, the PPARγ agonist is a thiazolidinedione (TZD). In some embodiments, TZD is pioglitazone. In some embodiments, the dual PPARα/γ agonist is saroglitazar. In some embodiments, the FXR agonist is obeticholic acis (OCA). In some embodiments, the lipid-altering agent is aramchol. In some embodiments, the incretin-based therapy is a glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor. In some embodiments, the GLP-1 receptor agonist is exenatide or liraglutide. In some embodiments, the DPP-4 inhibitor is sitagliptin or vildapliptin.

[0076] Further disclosed herein are methods of treating a disease in a subject in need thereof, comprising administering to the subject any of the siNAs disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0077] Further disclosed herein are methods of treating a disease in a subject in need thereof, comprising administering to the subject any of the compositions disclosed herein. In some embodiments, the composition comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of any of the siNAs disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein. In some embodiments, the composition further comprises any of the additional HBV treatment agents disclosed herein. In some embodiments, the disease is a viral disease. In some embodiments, the viral disease is caused by a DNA virus. In some embodiments, the DNA virus is a double stranded DNA (dsDNA) virus. In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV). In some embodiments, the HBV is selected from HBV genotypes A-J. In some embodiments, the method further comprises administering an additional HBV treatment agent. In some embodiments, the siNA or the composition and the additional HBV treatment agent are administered concurrently. In some embodiments, the siNA or the composition and the additional HBV treatment agent are administered sequentially. In some embodiments, the siNA or the composition is administered prior to administering the additional HBV treatment agent. In some embodiments, the siNA or the composition is administered after administering the additional HBV treatment agent. In some embodiments, the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy. In some embodiments, the oligonucleotide therapy is an additional siNA. In some embodiments, the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178. In some embodiments, the oligonucleotide therapy is an antisense oligonucleotide (ASO), NAPs, or STOPs. In some embodiments, the ASO is ASO 1 or ASO 2. In some embodiments, the additional HBV treatment agent is selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H2158.

[0078] In some embodiments, the disease is a liver disease. In some embodiments, the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC). In some embodiments, the NAFLD is

nonalcoholic steatohepatitis (NASH). In some embodiments, the method further comprises administering to the subject a liver disease treatment agent. In some embodiments, the liver disease treatment agent is selected from a peroxisome proliferator-activator receptor (PPAR) agonist, farnesoid X receptor (FXR) agonist, lipid-altering agent, and incretin-based therapy. In some embodiments, the PPAR agonist is selected from a PPARα agonist, dual PPARα/δ agonist, PPARγ agonist, and dual PPARα/γ agonist. In some embodiments, the dual PPARα agonist is a fibrate. In some embodiments, the PPARα/δ agonist is elafibranor. In some embodiments, the PPARγ agonist is a thiazolidinedione (TZD). In some embodiments, TZD is pioglitazone. In some embodiments, the dual PPARα/γ agonist is saroglitazar. In some embodiments, the FXR agonist is obeticholic acis (OCA). In some embodiments, the lipid-altering agent is aramchol. In some embodiments, the incretin-based therapy is a glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor. In some embodiments, the GLP-1 receptor agonist is exenatide or liraglutide. In some embodiments, the DPP-4 inhibitor is sitagliptin or vildapliptin. In some embodiments, the siNA or composition and the liver disease treatment agent are administered concurrently. In some embodiments, the siNA or composition and the liver disease treatment agent are administered sequentially. In some embodiments, the siNA or composition is administered prior to administering the liver disease treatment agent. In some embodiments, the siNA or composition is administered after administering the liver disease treatment agent.

[0079] In some embodiments, the siNA or the composition is administered at a dose of at least 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg 14 mg/kg, or 15 mg/kg. In some embodiments, the siNA or the composition is administered at a dose of between 0.5 mg/kg to 50 mg/kg, 0.5 mg/kg to 40 mg/kg 0.5 mg/kg to 30 mg/kg, 1 mg/kg to 50 mg/kg, 1 mg/kg to 40 mg/kg, 1 mg/kg to 30 mg/kg, 1 mg/kg to 20 mg/kg, 3 mg/kg to 50 mg/kg, 3 mg/kg to 40 mg/kg, 3 mg/kg to 30 mg/kg, 3 mg/kg to 20 mg/kg, 3 mg/kg to 15 mg/kg, 3 mg/kg to 10 mg/kg, 4 mg/kg to 50 mg/kg, 4 mg/kg to 40 mg/kg, 4 mg/kg to 30 mg/kg, 4 mg/kg to 20 mg/kg, 4 mg/kg to 15 mg/kg, 4 mg/kg to 10 mg/kg, 5 mg/kg to 50 mg/kg, 5 mg/kg to 40 mg/kg, 5 mg/kg to 30 mg/kg, 5 mg/kg to 20 mg/kg, 5 mg/kg to 15 mg/kg, or 5 mg/kg to 10 mg/kg.

[0080] In some embodiments, the siNA or the composition is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times. In some embodiments, the siNA or the composition is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a day, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a week, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a month. In some embodiments, the siNA or the composition are administered at least once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days. In some embodiments, the siNA or the composition is administered for a period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days, 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, 35, 40, 45, 50, 51, 52, 53, 54, or 55 weeks.

[0081] In some embodiments, the siNA or the composition is administered at a single dose of 5 mg/kg. In some embodiments, the siNA or the composition is administered at a single dose of 10 mg/kg. In some embodiments, the siNA or the composition is administered at three doses of 10 mg/kg once a week. In some embodiments, the siNA or the composition is administered at three doses of 10 mg/kg once every three days. In some embodiments, the siNA or the composition is administered at five doses of 10 mg/kg once every three days. In some embodiments, the siNA or the composition is administered at six doses of ranging from 1 mg/kg to 15 mg/kg, 1 mg/kg to 10 mg/kg, 2 mg/kg to 15 mg/kg, 2 mg/kg to 10 mg/kg, 3 mg/kg to 15 mg/kg, or 3 mg/kg to 10 mg/kg. In some embodiments, the first dose and second dose are administered at least 3 days apart. In some embodiments, the second dose and third dose are administered at least 4 days apart. In some embodiments, the third dose and fourth dose, fourth dose and fifth dose, or fifth dose and sixth dose are administered at least 7 days apart.

[0082] In some embodiments, any of the siNAs or the compositions disclosed herein are formulated as a particle or viral vector. In some embodiments, the siNA or the composition are administered in a particle or viral vector. In some embodiments, the viral vector is a vector of adenovirus, adeno-associated virus (AAV), alphavirus, flavivirus, herpes simplex virus, lentivirus, measles virus, picornavirus, poxvirus, retrovirus, or rhabdovirus. In some embodiments, the viral vector is a recombinant viral vector. In some embodiments, the viral vector is selected from AAVrh.74, AAVrh.10, AAVrh.20, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11, AAV-12 and AAV-13. In some embodiments, the siNA or the composition is administered systemically. In some embodiments, the siNA or the composition is administered locally. In some embodiments, the siNA or the composition is administered intravenously, subcutaneously, or intramuscularly.

[0083] In some embodiments, any of the siRNAs or compositions disclosed herein are used in the manufacture of a medicament for treating a disease. In some embodiments, the disease is a viral disease. In some embodiments, the viral disease is caused by a DNA virus. In some embodiments, the DNA virus is a double stranded DNA (dsDNA virus). In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV). In some embodiments, the HBV is selected from HBV genotypes A-J. In some embodiments, an additional HBV treatment agent is further used in the manufacture of the medicament. In some embodiments, the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy. In some embodiments, the oligonucleotide therapy is an additional siNA. In some embodiments, the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178. In some embodiments, the oligonucleotide therapy is an antisense oligonucleotide (ASO), NAPs, or STOPs. In some embodiments, the ASO is ASO 1 or ASO 2. In some embodiments, the additional HBV treatment agent is selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-

HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H2158.

[0084] In some embodiments, any of the siRNAs or compositions disclosed herein are used in the manufacture of a medicament for treating a disease. In some embodiments, the disease is a liver disease. In some embodiments, the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC). In some embodiments, the NAFLD is nonalcoholic steatohepatitis (NASH). In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein. In some embodiments, a liver disease treatment agent is further used in the manufacture of the medicament. In some embodiments, the liver disease treatment agent is selected from a peroxisome proliferator-activator receptor (PPAR) agonist, farnesoid X receptor (FXR) agonist, lipid-altering agent, and incretin-based therapy. In some embodiments, the PPAR agonist is selected from a PPARα agonist, dual PPARα/δ agonist, PPARγ agonist, and dual PPARα/γ agonist. In some embodiments, the dual PPARα agonist is a fibrate. In some embodiments, the PPARα/δ agonist is elafibranor. In some embodiments, the PPARγ agonist is a thiazolidinedione (TZD). In some embodiments, TZD is pioglitazone. In some embodiments, the dual PPARα/γ agonist is saroglitazar. In some embodiments, the FXR agonist is obeticholic acis (OCA). In some embodiments, the lipid-altering agent is aramchol. In some embodiments, the incretin-based therapy is a glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor. In some embodiments, the GLP-1 receptor agonist is exenatide or liraglutide. In some embodiments, the DPP-4 inhibitor is sitagliptin or vildapliptin.

[0085] In some embodiments, any of the siNAs disclosed herein is used as a medicament. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0086] In some embodiments, any of the compositions disclosed herein are used as a medicament. In some embodiments, the composition comprises any of the siNAs disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein.

[0087] In some embodiments, any of the siNAs disclosed herein are used in the treatment of a disease. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified

nucleotides disclosed herein. In some embodiments, the disease is a viral disease. In some embodiments, the viral disease is caused by a DNA virus. In some embodiments, the DNA virus is a double stranded DNA (dsDNA virus). In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV). In some embodiments, the HBV is selected from HBV genotypes A-J. In some embodiments, the disease is a liver disease. In some embodiments, the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC). In some embodiments, the NAFLD is nonalcoholic steatohepatitis (NASH).

[0088] In some embodiments, any of the compositions disclosed herein are used in the treatment of a disease. In some embodiments, the composition comprises any of the siNAs disclosed herein. In some embodiments, the siNA comprises a first nucleotide sequence. In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the siNA comprises a second nucleotide sequence. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the siNA comprises a sense strand. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the siNA comprises an antisense strand. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the siNA further comprises any of the 5' end caps disclosed herein. In some embodiments, the siNA further comprises any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA further comprises any of the conjugated moieties disclosed herein. In some embodiments, the siNA further comprises any of the destabilized nucleotides disclosed herein. In some embodiments, the siNA further comprises any of the modified nucleotides disclosed herein. In some embodiments, the disease is a viral disease. In some embodiments, the viral disease is caused by a DNA virus. In some embodiments, the DNA virus is a double stranded DNA (dsDNA virus). In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV). In some embodiments, the HBV is selected from HBV genotypes A-J. In some embodiments, the disease is a liver disease. In some embodiments, the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC). In some embodiments, the NAFLD is nonalcoholic steatohepatitis (NASH).

BRIEF DESCRIPTION OF THE DRAWINGS

[0089] FIG. **1** illustrates an exemplary siNA molecule.

[0090] FIG. **2** illustrates an exemplary siNA molecule.

[0091] FIGS. **3**A-**3**G illustrate exemplary double-stranded siNA molecules.

[0092] FIG. **4** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with ds-siNA-0160, ds-siNA-0165, ds-siNA-0163, or ds-siNA-0166.

[0093] FIG. **5**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0160 (G03).

[0094] FIG. **5**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0160 (G15).

[0095] FIG. **5**C shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0160 (G03).

[0096] FIG. **5**D shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G03), or ds-siNA-0109 (G09).

[0097] FIGS. **5**E-**5**F show a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0169 (G18).

[0098] FIG. **5**G shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0169 (G04).

[0099] FIG. **5**H shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0169 (G04).

[0100] FIG. **5**I shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0169 (G04), or ds-siNA-0147 (G08).

[0101] FIG. **5**J shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0166 (G06), or ds-siNA-0153 (G14).

[0102] FIG. **5**K shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0163 (G05), or ds-siNA-0119 (G13).

[0103] FIG. **6**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G15), or ds-siNA-080 (G14).

[0104] FIG. **6**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0169 (G16), or ds-siNA-081 (G13).

[0105] FIG. **7**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0165 (G18), or ds-siNA-0127 (G17).

[0106] FIG. **7**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0168 (G20), or ds-siNA-0150 (G19).

[0107] FIG. **8**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G06), ASO 1 (G18), or a combination of ds-siNA-0160 and ASO 1 (G20).

[0108] FIG. **8**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G06), ASO 1 (G18), or a combination of ds-siNA-0160 and ASO 1 (G20).

[0109] FIG. **8**C shows a graph of a synergy analysis of a combination therapy with unconjugated forms of ds-siNA-0164 and ASO 2 (e.g., ds-siNA-0160 and ASO 1 without GalNac).

[0110] FIG. **9** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0166 (G03), ds-siNA-0155 (G08), or ds-siNA-0157.

[0111] FIG. **10** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0165 (G10), ds-siNA-0160 (G06), or a combination therapy with ds-siNA-0160 and ds-siNA-0165 (G14).

[0112] FIG. **11** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0165 (G05), or ds-siNA-0144 (G11).

[0113] FIG. **12** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0163 (G04), ds-siNA-0122 (G09), or ds-siNA-0123 (G13).

[0114] FIG. **13** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 15) or ds-siNA-0147 (G 19).

[0115] FIG. **14** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 15, square), ds-siNA-0109 (G 21, circle), or ds-siNA-0172 (G 27, diamond).

[0116] FIG. **15** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 01, circle), ds-siNA-0109 (G 07, square), ds-siNA-0119 (G 11, triangle), or ds-siNA-0153 (G 13, diamond).

[0117] FIG. **16** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 01, circle), ASO 1 (G 20, square), ds-siNA-0147 (G 24, diamond), or a combination of ASO 1 and ds-siNA-0147 (G 25, triangle).

[0118] FIG. **17** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 01, circle), ASO 1 (G 20, square), ds-siNA-0109 (G 26, diamond), or a combination of ASO 1 and ds-siNA-0109 (G 27, triangle).

DETAILED DESCRIPTION OF THE INVENTION

[0119] Disclosed herein are short interfering nucleic acid (siNA) molecules comprising modified nucleotides. The siNA molecules described herein may be double-stranded siNA (ds-siNA) molecules. The siNA molecules described herein may comprise modified nucleotides selected from 2'-O-methyl nucleotides and 2'-fluoro nucleotides. The siNA molecules described herein may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more phosphorothioate internucleoside linkages. The siNA molecules described herein may comprise a phosphorylation blocker. The siNA molecules described herein may comprise a 5'-stabilized end cap. The siNA molecules described herein may comprise a galactosamine. The siNA molecules described herein may comprise one or more blunt ends. The siNA molecules described herein may comprise one or more overhangs.

[0120] Further disclosed herein are short interfering nucleic acid (siNA) molecules comprising (a) a phosphorylation blocker; and (b) a short interfering nucleic acid (siNA). The siNA may comprise at least 5 nucleotides. The nucleotides may be modified nucleotides, non-modified nucleotides, or any combination thereof. The nucleotides may be ribonucleotides, deoxyribonucleotides, or any combination thereof. The siNA may be single-stranded. Alternatively, the siNA is double-stranded. The double-stranded siNA may comprise one or more blunt ends. The double-stranded siNA may comprise one or more overhangs. The double-stranded siNA may comprise a blunt end and an overhang.

[0121] Further disclosed herein are short interfering nucleic acid (siNA) molecules comprising (a) a conjugated moiety; and (b) a short interfering nucleic acid (siNA). The siNA may comprise at least 5 nucleotides. The nucleotides may be modified nucleotides, non-modified nucleotides, or any combination thereof. The nucleotides may be ribonucleotides, deoxyribonucleotides, or any combination thereof. The siNA may be single-stranded. Alternatively, the siNA is double-stranded. The double-stranded siNA may comprise one or more blunt ends. The double-stranded siNA may comprise one or more overhangs. The double-stranded siNA may comprise a blunt end and an overhang.

[0122] Further disclosed herein are short interfering nucleic acid (siNA) molecules comprising (a) a 5'-stabilized end cap; and (b) a short interfering nucleic acid (siNA). The siNA may comprise at least 5 nucleotides. The nucleotides may be modified nucleotides, non-modified nucleotides, or any combination thereof. The nucleotides may be ribonucleotides, deoxyribonucleotides, or any combination thereof. The siNA may be single-stranded. Alternatively, the siNA is double-stranded. The double-stranded siNA may comprise one or more blunt ends. The double-stranded siNA may comprise one or more overhangs. The double-stranded siNA may comprise a blunt end and an overhang.

[0123] Further disclosed herein are short interfering nucleic acid (siNA) molecules comprising (a) at least one phosphorylation blocker, conjugated moiety, or 5'-stabilized end cap; and (b) a short interfering nucleic acid (siNA). The siNA may comprise at least 5 nucleotides. The nucleotides may be modified nucleotides, non-modified nucleotides, or any combination thereof. The nucleotides may be ribonucleotides, deoxyribonucleotides, or any combination thereof. The siNA may be single-stranded. Alternatively, the siNA is double-stranded. The double-stranded siNA may comprise one or more blunt ends. The double-stranded siNA may comprise one or more overhangs. The double-stranded siNA may comprise a blunt end and an overhang.

[0124] An exemplary siNA molecule of the present disclosure is shown in FIG. **1**. As shown in FIG. **1**, an exemplary siNA molecule comprises a sense strand (**101**) and an antisense strand (**102**). The sense strand (**101**) may comprise a first oligonucleotide sequence (**103**). The first oligonucleotide sequence (**103**) may comprise one or more phosphorothioate internucleoside linkages (**109**). The phosphorothioate internucleoside linkage (**109**) may be between the nucleotides at the 5' or 3' terminal end of the first oligonucleotide sequence (**103**). The phosphorothioate internucleoside linkage (**109**) may be between the first three nucleotides from the 5' end of the first oligonucleotide sequence (**103**). The first oligonucleotide sequence (**103**) may comprise one or more 2'-fluoro nucleotides (**110**). The first oligonucleotide sequence (**103**) may comprise one or more 2'-O-methyl nucleotides (**111**). The first oligonucleotide sequence (**103**) may comprise 15 or more modified nucleotides independently selected from 2'-fluoro nucleotides (**110**) and 2'-O-methyl nucleotides (**111**). The sense strand (**101**) may further comprise a phosphorylation blocker (**105**). The sense strand (**101**) may further comprise a galactosamine (**106**). The antisense strand (**102**) may comprise a second oligonucleotide sequence (**104**). The second oligonucleotide sequence (**104**) may comprise one or more phophorothioate internucleoside linkages (**109**). The phosphorothioate internucleoside linkage (**109**) may be between the nucleotides at the 5' or 3' terminal end of the second oligonucleotide sequence (**104**). The phosphorothioate internucleoside linkage (**109**) may be between the first three nucleotides from the 5' end of the second oligonucleotide sequence (**104**). The phosphorothioate internucleoside linkage (**109**) may be between the first three nucleotides from the 3' end of the second oligonucleotide sequence (**104**). The second oligonucleotide sequence (**104**) may comprise one or more 2'-fluoro nucleotides (**110**). The

second oligonucleotide sequence (**104**) may comprise one or more 2'-O-methyl nucleotides (**111**). The second oligonucleotide sequence (**104**) may comprise 15 or more modified nucleotides independently selected from 2'-fluoro nucleotides (**110**) and 2'-O-methyl nucleotides (**111**). The antisense strand (**102**) may further comprise a 5'-stabilized end cap (**107**). The siNA may further comprise one or more blunt ends. Alternatively, or additionally, one end of the siNA may comprise an overhang (**108**). The overhang (**108**) may be part of the sense strand (**101**). The overhang (**108**) may be part of the antisense strand (**102**). The overhang (**108**) may be distinct from the first nucleotide sequence (**103**). The overhang (**108**) may be distinct from the second nucleotide sequence (**104**). The overhang (**108**) may be part of the first nucleotide sequence (**103**). The overhang (**108**) may be part of the second nucleotide sequence (**104**). The overhang (**108**) may comprise 1 or more nucleotides. The overhang (**108**) may comprise 1 or more deoxyribonucleotides. The overhang (**108**) may comprise 1 or more modified nucleotides. The overhang (**108**) may comprise 1 or more modified ribonucleotides. The sense strand (**101**) may be shorter than the antisense strand (**102**). The sense strand (**101**) may be the same length as the antisense strand (**102**). The sense strand (**101**) may be longer than the antisense strand (**102**).

[0125] An exemplary siNA molecule of the present disclosure is shown in FIG. **2**. As shown in FIG. **2**, an exemplary siNA molecule comprises a sense strand (**201**) and an antisense strand (**202**). The sense strand (**201**) may comprise a first oligonucleotide sequence (**203**). The first oligonucleotide sequence (**203**) may comprise one or more phophorothioate internucleoside linkages (**209**). The phosphorothioate internucleoside linkage (**209**) may be between the nucleotides at the 5' or 3' terminal end of the first oligonucleotide sequence (**203**). The phosphorothioate internucleoside linkage (**209**) may be between the first three nucleotides from the 5' end of the first oligonucleotide sequence (**203**). The first oligonucleotide sequence (**203**) may comprise one or more 2'-fluoro nucleotides (**210**). The first oligonucleotide sequence (**203**) may comprise one or more 2'-O-methyl nucleotides (**211**). The first oligonucleotide sequence (**203**) may comprise 15 or more modified nucleotides independently selected from 2'-fluoro nucleotides (**210**) and 2'-O-methyl nucleotides (**211**). The sense strand (**201**) may further comprise a phosphorylation blocker (**205**). The sense strand (**201**) may further comprise a galactosamine (**206**). The antisense strand (**202**) may comprise a second oligonucleotide sequence (**204**). The second oligonucleotide sequence (**204**) may comprise one or more phophorothioate internucleoside linkages (**209**). The phosphorothioate internucleoside linkage (**209**) may be between the nucleotides at the 5' or 3' terminal end of the second oligonucleotide sequence (**204**). The phosphorothioate internucleoside linkage (**209**) may be between the first three nucleotides from the 5' end of the second oligonucleotide sequence (**204**). The phosphorothioate internucleoside linkage (**209**) may be between the first three nucleotides from the 3' end of the second oligonucleotide sequence (**204**). The second oligonucleotide sequence (**204**) may comprise one or more 2'-fluoro nucleotides (**210**). The second oligonucleotide sequence (**204**) may comprise one or more 2'-O-methyl nucleotides (**211**). The second oligonucleotide sequence (**204**) may comprise 15 or more modified nucleotides independently selected from 2'-fluoro nucleotides (**210**) and 2'-O-methyl nucleotides (**211**). The antisense strand (**202**) may further comprise a 5'-stabilized end cap (**207**). The siNA may further comprise one or more overhangs (**208**). The overhang (**208**) may be part of the sense strand (**201**). The overhang (**208**) may be part of the antisense strand. (**202**). The overhang (**208**) may be distinct from the first nucleotide sequence (**203**). The overhang (**208**) may be distinct from the second nucleotide sequence (**204**). The overhang (**208**) may be part of the first nucleotide sequence (**203**). The overhang (**208**) may be part of the second nucleotide sequence (**204**). The overhang (**208**) may be adjacent to the 3' end of the first nucleotide sequence (**203**). The overhang (**208**) may be adjacent to the 5' end of the first nucleotide sequence (**203**). The overhang (**208**) may be adjacent to the 3' end of the second nucleotide sequence (**204**). The overhang (**208**) may be adjacent to the 5' end of the second nucleotide sequence (**204**). The overhang (**208**) may comprise 1 or more nucleotides. The overhang (**208**) may comprise 1 or more deoxyribonucleotides. The overhang (**208**) may comprise a TT sequence. The overhang (**208**) may comprise 1 or more modified nucleotides. The overhang (**208**) may comprise 1 or more modified nucleotides disclosed herein (e.g., 2-fluoro nucleotide, 2'-O-methyl nucleotide, 2'-fluoro nucleotide mimic, 2'-O-methyl nucleotide mimic, or a nucleotide comprising a modified nucleobase). The overhang (**208**) may comprise 1 or more modified ribonucleotides. The sense strand (**201**) may be shorter than the antisense strand (**202**). The sense strand (**201**) may be the same length as the antisense strand (**202**). The sense strand (**201**) may be longer than the antisense strand (**202**).

[0126] FIGS. **3**A-**3**G depict exemplary ds-siNA modification patterns. As shown in FIGS. **3**A-**3**G, an exemplary ds-siNA molecule may have the following formula:

$$5'\text{-}A_n{}^{1}B_n{}^{2}A_n{}^{3}B_n{}^{4}A_n{}^{5}B_n{}^{6}A_n{}^{7}B_n{}^{8}A_n{}^{9}\text{-}3'$$

$$3'\text{-}C_q{}^{1}A_q{}^{2}B_q{}^{3}A_q{}^{4}B_q{}^{5}A_q{}^{6}B_q{}^{7}A_q{}^{8}B_q{}^{9}A_q{}^{10}B_q{}^{11}A_q{}^{12}\text{-}5'$$

wherein:

[0127] the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

[0128] the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

[0129] each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5' stabilized end cap or phosphorylation blocker;

[0130] B is a 2'-fluoro nucleotide;

[0131] C represents overhanging nucleotides and is a 2'-O-methyl nucleotide;

[0132] n^1=1-4 nucleotides in length;

[0133] each n^2, n^6, n^8, q^3, q^5, q^7, q^9, q^{11}, and q^{12} is independently 0-1 nucleotides in length;

[0134] each n^3 and n^4 is independently 1-3 nucleotides in length;

[0135] n^5 is 1-10 nucleotides in length;

[0136] n^7 is 0-4 nucleotides in length;

[0137] each n^9, q^1, and q^2 is independently 0-2 nucleotides in length;

[0138] q^4 is 0-3 nucleotides in length;

[0139] q^6 is 0-5 nucleotides in length;

[0140] q^8 is 2-7 nucleotides in length; and

[0141] q^{10} is 2-11 nucleotides in length.

The ds-siNA may further comprise a conjugated moiety. The conjugated moiety may comprise any of the galactosamines disclosed herein. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. The ds-siNA may further comprise a 5'-stabilizing end cap. The 5'-stabilizing end cap may be a vinyl phosphonate. The 5'-stabilizing end cap may be attached to the 5' end of the antisense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. An exemplary ds-siNA molecule may have the following formula:

$$5'\text{-}A_{2-4}B_1A_{1-3}B_{2-3}A_{2-10}B_{0-1}A_{0-4}B_{0-1}A_{0-2}\text{-}3'$$

$$3'\text{-}C_2A_{0-2}B_{0-1}A_{0-3}B_{0-1}A_{0-5}B_{0-1}A_{2-7}B_1A_{2-11}B_1A_1\text{-}5'$$

wherein:

[0142] the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

[0143] the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

[0144] each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5' stabilized end cap or phosphorylation blocker;

[0145] B is a 2'-fluoro nucleotide;

[0146] C represents overhanging nucleotides and is a 2'-O-methyl nucleotide.

The ds-siNA may further comprise a conjugated moiety. The conjugated moiety may comprise any of the galactosamines disclosed herein. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. The ds-siNA may further comprise a 5'-stabilizing end cap. The 5'-stabilizing end cap may be a vinyl phosphonate. The vinyl phosphonate may be a deuterated vinyl phosphonate. The deuterated vinyl phosphonate may be a mono-deuterated vinyl phosphonate. The deuterated vinyl phosphonate may be a mono-di-deuterated vinyl phosphonate. The 5'-stabilizing end cap may be attached to the 5' end of the antisense strand. The 5'-stabilizing end cap may be attached to the 3' end of the antisense strand. The 5'-stabilizing end cap may be attached to the 5' end of the sense strand. The 5'-stabilizing end cap may be attached to the 3' end of the sense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker.

[0147] The exemplary ds-siNA shown in FIGS. **3**A-**3**G comprise (i) a sense strand comprising 19-21 nucleotides; and (ii) an antisense strand comprising 21-23 nucleotides. The ds-siNA may further comprise (iii) a conjugated moiety, wherein the conjugated moiety is attached to the 3' end of the antisense strand. The ds-siNA may comprise a 2 nucleotide overhang consisting of nucleotides at positions 20 and 21 from the 5' end of the antisense strand. The ds-siNA may comprise a 2 nucleotide overhang consisting of nucleotides at positions 22 and 23 from the 5' end of the antisense strand. The ds-siNA may further comprise 1, 2, 3, 4, 5, 6 or more phosphorothioate (ps) internucleoside linkages. At least one phosphorothioate internucleoside linkage may be between the nucleotides at positions 1 and 2 or positions 2 and 3 from the 5' end of the sense strand. At least one phosphorothioate internucleoside linkage may be between the nucleotides at positions 1 and 2 or positions 2 and 3 from the 5' end of the antisense strand. At least one phosphorothioate internucleoside linkage may be between the nucleotides at positions 19 and 20, positions 20 and 21, positions 21 and 22, or positions 22 and 23 from the 5' end of the antisense strand. As shown in FIGS. **3**A-**3**G, 4-6 nucleotides in the sense strand may be 2'-fluoro nucleotides. As shown in FIGS. **3**A-**3**G, 2-5 nucleotides in the antisense strand may be 2'-fluoro nucleotides. As shown in FIGS. **3**A-**3**G, 13-15 nucleotides in the sense strand may be 2'-O-methyl nucleotides. As shown in FIGS. **3**A-**3**G, 14-19 nucleotides in the antisense strand may be 2'-O-methyl nucleotides. As shown in FIGS. **3**A-**3**G, the ds-siNA does not contain a base pair between 2'-fluoro nucleotides on the sense and antisense strands. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the

antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker.

[0148] As shown in FIG. **3**A, a ds-siNA may comprise (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12, and 17 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, 13-16, 18, and 19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein nucleotides at positions 2 and 14 from the 5' end of the antisense strand are 2'-fluoro nucleotides; and wherein nucleotides at positions 1, 3-13, and 15-21 are 2'-O-methyl nucleotides. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0149] As shown in FIG. **3**B, a ds-siNA may comprise (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7, 8, and 17 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 9-16, 18, and 19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein nucleotides at positions 2 and 14 from the 5' end of the antisense strand are 2'-fluoro nucleotides; and wherein nucleotides at positions 1, 3-13, and 15-21 are 2'-O-methyl nucleotides. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0150] As shown in FIG. **3**C, a ds-siNA may comprise (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12 and 17 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, 13-16, 18, and 19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein the nucleotides in the antisense strand comprise an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5'

end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. The ds-siNA may comprise 2-5 alternating 1:3 modification patterns on the antisense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0151] As shown in FIG. **3**D, a ds-siNA may comprise (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein the nucleotides in the antisense strand comprise an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. The ds-siNA may comprise 2-5 alternating 1:3 modification patterns on the antisense strand. The alternating 1:3 modification pattern may start at the nucleotide at any of positions 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0152] As shown in FIG. **3**E, a ds-siNA may comprise (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein the nucleotides in the antisense strand comprise an alternating 1:2 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. The ds-siNA may comprise 2-5 alternating 1:2 modification patterns on the antisense strand. The alternating 1:2 modification pattern may start at the nucleotide at any of positions 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand. In some embodiments, the ds-siNA comprises (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein 2'-fluoro nucleotides are at positions 2, 5, 8, 14, and 17 from the 5' end of the antisense strand, and wherein 2'-O-methyl nucleotides are at positions 1, 3, 4, 6, 7, 9-13, 15, 16, and 18-21 from the 5' end of the sense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In

some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0153] As shown in FIG. **3**F, a ds-siNA may comprise (a) a sense strand consisting of 19 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-19 from the 5' end of the sense strand; (b) an antisense strand consisting of 21 nucleotides, wherein 2'-fluoro nucleotides are at positions 2, 6, 14, and 16 from the 5' end of the antisense strand, and wherein 2'-O-methyl nucleotides are at positions 1, 3-5, 7-13, 15, and 17-21 from the 5' end of the antisense strand. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a f4P nucleotide. In some embodiments, at least 1, 2, 3, or 4 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, at least one of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, at least two of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, less than or equal to 3 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, less than or equal to 2 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 2 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 6 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 14 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 16 from the 5' end of the antisense strand is a f4P nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a f2P nucleotide. In some embodiments, at least 1, 2, 3, or 4 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, at least one of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, at least two of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, less than or equal to 3 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, less than or equal to 2 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 2 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 6 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 14 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 16 from the 5' end of the antisense strand is a f2P nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a fX nucleotide. In some embodiments, at least 1, 2, 3, or 4 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, at least one of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, at least two of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, less than or equal to 3 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, less than or equal to 2 of the 2'-fluoro-nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 2 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 6 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 14 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, the 2'-fluoro-nucleotide at position 16 from the 5' end of the antisense strand is a fX nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodi-

ments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0154] As shown in FIG. **3**G, a ds-siNA may comprise (a) a sense strand consisting of 21 nucleotides, wherein 2'-fluoro nucleotides are at positions 5, 9-11, 14, and 19 from the 5' end of the sense strand, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6-8, 12, 13, 15-18, 20, and 21 from the 5' end of the sense strand; and (b) an antisense strand consisting of 23 nucleotides, wherein 2'-flouro nucleodies are at positions 2 and 14 from the 5' end of the antisense strand, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-23 from the 5' end of the antisense strand. The ds-siNA may further comprise a conjugated moiety attached to the 3' end of the sense strand. The ds-siNA may further comprise (i) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2 and positions 2 and 3 from the 5' end of the sense strand; and (ii) phosphorothioate internucleoside linkages between the nucleotides at positions 1 and 2; positions 2 and 3; positions 19 and 20; and positions 20 and 21 from the 5' end of the antisense strand. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a 5' stabilizing end cap. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is further modified to contain a phosphorylation blocker. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 5' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the sense strand is a d2vd3 nucleotide. In some embodiments, the 2'-O-methyl nucleotide at position 1 from the 3' end of the antisense strand is a d2vd3 nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand or antisense strand is a 2'-fluoro nucleotide mimic. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the sense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-fluoro nucleotides on the antisense strand is a f4P, f2P, or fX nucleotide. In some embodiments, at least 1, 2, 3, 4 or more 2'-O-methyl nucleotide on the sense or antisense strand is a 2'-O-methyl nucleotide mimic.

[0155] Any of the siNAs disclosed herein may comprise a sense strand and an antisense strand. The sense strand may comprise a first nucleotide sequence that is 15 to 30 nucleotides in length. The antisense strand may comprise a second nucleotide sequence that is 15 to 30 nucleotides in length.

[0156] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

[0157] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one

modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

[0158] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 7 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

[0159] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 7, 9, 10, and/or 11 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

[0160] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

[0161] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 2 of the second nucleotide sequence is a 2'-fluoro nucleotide.

[0162] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (iii) comprises 1 or more phosphorothioate internucleoside linkage; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (iii) comprises 1 or more phosphorothioate internucleoside linkage.

[0163] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a

2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide, wherein the ds-siNA may further comprise a phosphorylation blocker, a galactosamine, or 5'-stabilized end cap.

[0164] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (I) a sense strand comprising (A) a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (B) a phosphorylation blocker or a galactosamine; and (II) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (a) is 15 to 30 nucleotides in length; and (b) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

[0165] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (I) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (a) is 15 to 30 nucleotides in length; and (b) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (II) an antisense strand comprising (A) a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (B) a 5'-stabilized end cap.

[0166] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (I) a sense strand comprising (A) a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (B) a phosphorylation blocker or a galactosamine; and (II) an antisense strand comprising (A) a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence: (i) is 15 to 30 nucleotides in length; and (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and (B) a 5'-stabilized end cap.

[0167] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises a nucleotide sequence as shown in Tables 1-3; and (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises a nucleotide sequence as shown in Tables 1-3.

[0168] In some embodiments, the double-stranded short interfering nucleic acid (ds-siNA) molecule comprises: (a) a sense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444; and (b) an antisense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539. In some embodiments, the ds-siNA molecule comprises a double-stranded molecule as identified by the duplex ID (e.g., ds-siNA-001 to ds-siNA-0178) shown in Tables 6 and 10.

[0169] Further disclosed herein are compositions comprising two or more of the siNA molecules described herein.

[0170] Further disclosed herein are compositions comprising any of the siNA molecule described and a pharmaceutically acceptable carrier or diluent.

[0171] Further disclosed herein are compositions comprising two or more of the siNA molecules described herein for use as a medicament.

[0172] Further disclosed herein are compositions comprising any of the siNA molecule described and a pharmaceutically acceptable carrier or diluent for use as a medicament.

[0173] Further disclosed herein are methods of treating a disease in a subject in need thereof, the method comprising administering to the subject any of the siNA molecules described herein.

[0174] Further disclosed herein are uses of any of the siNA molecules described herein in the manufacture of a medicament for treating a disease.

Short Interfering Nucleic Acid (siNA) Molecules

[0175] As indicated above, the present disclosure provides siNA molecules comprising modified nucleotides. Any of the siNA molecules described herein may be double-stranded siNA (ds-siNA) molecules. The terms "siNA molecules" and "ds-siNA molecules" may be used interchange-

ably. In some embodiments, the ds-siNA molecules comprise a sense strand and an antisense strand.

[0176] Further disclosed herein are siNA molecules comprising (a) at least one phosphorylation blocker, conjugated moiety, or 5'-stabilized end cap; and (b) a short interfering nucleic acid (siNA). In some embodiments, the phosphorylation blocker is a phosphorylation blocker disclosed herein. In some embodiments, the conjugated moiety is a galactosamine disclosed herein. In some embodiments, the 5'-stabilized end cap is a 5'-stabilized end cap disclosed herein. The siNA may comprise any of the first nucleotide, second nucleotide, sense strand, or antisense strand sequences disclosed herein. The siNA may comprise 5 to 100, 5 to 90, 10 to 100, 10 to 90, 10 to 80, 10 to 70, 10 to 60, 10 to 50, 10 to 30, 10 to 25, 15 to 100, 15 to 90, 15 to 80, 15 to 70, 15 to 60, 15 to 50, 15 to 30, or 15 to 25 nucleotides. The siNA may comprise at least 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides. The siNA may comprise less than or equal to 50, 45, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, or 19 nucleotides. The nucleotides may be modified nucleotides. The siNA may be single stranded. The siNA may be double stranded. The siNA may comprise (a) a sense strand comprising 15 to 30, 15 to 25, 15 to 24, 15 to 23, 15 to 22, 15 to 21, 17 to 30, 17 to 25, 17 to 24, 17 to 23, 17 to 22, 17 to 21, 18 to 30, 18 to 25, 18 to 24, 18 to 23, 18 to 22, 18 to 21, 19 to 30, 19 to 25, 19 to 24, 19 to 23, 19 to 22, 19 to 21, 20 to 25, 20 to 24, 20 to 23, 21 to 25, 21 to 24, or 21 to 23 nucleotides; and (b) an antisense strand comprising 15 to 30, 15 to 25, 15 to 24, 15 to 23, 15 to 22, 15 to 21, 17 to 30, 17 to 25, 17 to 24, 17 to 23, 17 to 22, 17 to 21, 18 to 30, 18 to 25, 18 to 24, 18 to 23, 18 to 22, 18 to 21, 19 to 30, 19 to 25, 19 to 24, 19 to 23, 19 to 22, 19 to 21, 20 to 25, 20 to 24, 20 to 23, 21 to 25, 21 to 24, or 21 to 23 nucleotides. The siNA may comprise (a) a sense strand comprising about 15, 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides; and (b) an antisense strand comprising about 15, 16, 17, 18, 19, 20, 21, 22, or 23 nucleotides. The siNA may comprise (a) a sense strand comprising about 19 nucleotides; and (b) an antisense strand comprising about 21 nucleotides. The siNA may comprise (a) a sense strand comprising about 21 nucleotides; and (b) an antisense strand comprising about 23 nucleotides.

[0177] In some embodiments, any of the siNA molecules disclosed herein further comprise one or more linkers independently selected from a phosphodiester (PO) linker, phosphorothioate (PS) linker, phosphorodithioate linker, and PS-mimic linker. In some embodiments, the PS-mimic linker is a sulfur linker. In some embodiments, the linkers are internucleoside linkers. Alternatively, or additionally, the linkers connect a nucleotide of the siNA molecule to at least one phosphorylation blocker, conjugated moiety, or 5'-stabilized end cap. In some embodiments, the linkers connect a conjugated moiety to a phosphorylation blocker or 5'-stabilized end cap.

siNA Sense Strand

[0178] Any of the siNA molecules described herein may comprise a sense strand. The sense strand may comprise a first nucleotide sequence. The first nucleotide sequence may be 15 to 30, 15 to 25, 15 to 23, 17 to 23, 19 to 23, or 19 to 21 nucleotides in length. In some embodiments, the first nucleotide sequence is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the first nucleotide sequence is at least 19 nucleotides in length. In some embodiments, the first nucleotide sequence is at least 21 nucleotides in length.

[0179] In some embodiments, the sense strand is the same length as the first nucleotide sequence. In some embodiments, the sense strand is longer than the first nucleotide sequence. In some embodiments, the sense strand may further comprise 1, 2, 3, 4, or 5 or more nucleotides than the first nucleotide sequence. In some embodiments, the sense strand may further comprise a deoxyribonucleic acid (DNA). In some embodiments, the DNA is thymine (T). In some embodiments, the sense strand may further comprise a TT sequence. In some embodiments, the sense strand may further comprise one or more modified nucleotides that are adjacent to the first nucleotide sequence. In some embodiments, the one or more modified nucleotides are independently selected from any of the modified nucleotides disclosed herein (e.g., 2'-fluoro nucleotide, 2'-O-methyl nucleotide, 2'-fluoro nucleotide mimic, 2'-O-methyl nucleotide mimic, or a nucleotide comprising a modified nucleobase).

[0180] In some embodiments, the first nucleotide sequence comprises 15, 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the first nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, 100% of the nucleotides in the first nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, the 2'-O-methyl nucleotide is a 2'-O-methyl nucleotide mimic. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0181] In some embodiments, between about 15 to 30, 15 to 25, 15 to 24, 15 to 23, 15 to 22, 15 to 21, 17 to 30, 17 to 25, 17 to 24, 17 to 23, 17 to 22, 17 to 21, 18 to 30, 18 to 25, 18 to 24, 18 to 23, 18 to 22, 18 to 21, 19 to 30, 19 to 25, 19 to 24, 19 to 23, 19 to 22, 19 to 21, 20 to 25, 20 to 24, 20 to 23, 21 to 25, 21 to 24, or 21 to 23 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 2 to 20 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 5 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 10 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 12 to 25 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 12 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 13 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 14 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 15 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 16 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 17 modi-

fied nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 18 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 19 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 21 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 20 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 19 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 18 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 17 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 16 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 15 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 14 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 13 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least one modified nucleotide of the first nucleotide sequence is a 2'-O-methyl pyrimidine. In some embodiments, at least 5, 6, 7, 8, 9, or 10 modified nucleotides of the first nucleotide sequence are 2'-O-methyl pyrimidines. In some embodiments, at least one modified nucleotide of the first nucleotide sequence is a 2'-O-methyl purine. In some embodiments, at least 5, 6, 7, 8, 9, or 10 modified nucleotides of the first nucleotide sequence are 2'-O-methyl purines. In some embodiments, the 2'-O-methyl nucleotide is a 2'-O-methyl nucleotide mimic.

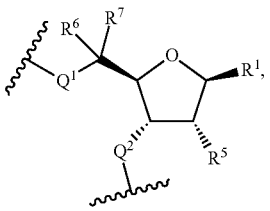
[0182] In some embodiments, between 2 to 15 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 10 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 1 to 6, 1 to 5, 1 to 4, or 1 to 3 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 1, 2, 3, 4, 5, or 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 1 modified nucleotide of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, at least 2 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 3 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 4 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 5 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 10, 9, 8, 7, 6, 5, 4, 3 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 10 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 7 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 6 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 5 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 4 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 3 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 2 or fewer modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least one modified nucleotide of the first nucleotide sequence is a 2'-fluoro pyrimidine. In some embodiments, 1, 2, 3, 4, 5, or 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro pyrimidines. In some embodiments, at least one modified nucleotide of the first nucleotide sequence is a 2'-fluoro purine. In some embodiments, 1, 2, 3, 4, 5, or 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro purines. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0183] In some embodiments, the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, at least two nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least three nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least four nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least five nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotide at position 3 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 7 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 8 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 9 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 12 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0184] In some embodiments, at least 1, 2, 3, 4, 5, 6, or 7 nucleotides at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, at least two nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the

5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least three nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotide at position 3 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 5 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 7 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 8 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 9 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 10 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 11 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 12 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 14 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 3, 7, 8, 9, 12, and/or 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 3, 7, 8, and/or 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 3, 7, 8, 9, 12, and/or 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 5, 7, 8, and/or 9 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 5, 9, 10, 11, 12, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

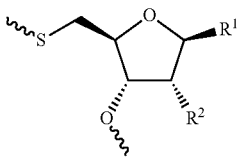
[0185] In some embodiments, the 2'-fluoro nucleotide or 2'-O-methyl nucleotide is a 2'-fluoro or 2'-O-methyl nucleotide mimic. In some embodiments, the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (V):



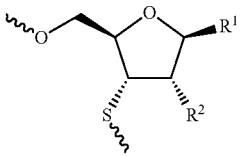
wherein R^1 is independently a nucleobase, aryl, heteroaryl, or H, Q^1 and Q^2 are independently S or O, R^5 is independently-OCD_3, —F, or —OCH_3, and R^6 and R^7 are independently H, D, or CD3. In some embodiments, the nucleobase is selected from cytosine, guanine, adenine, uracil, aryl, heteroaryl, and an analogue or derivative thereof.

[0186] In some embodiments, the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (16)-Formula (20):

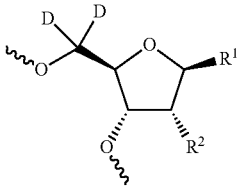
Formula (16)



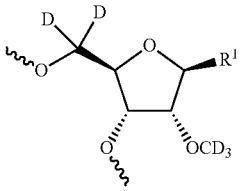
Formula (17)



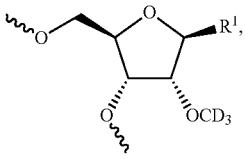
Formula (18)



Formula (19)



Formula (20)



wherein R^1 is independently a nucleobase and R^2 is F or —OCH_3. In some embodiments, the nucleobase is selected from cytosine, guanine, adenine, uracil, aryl, heteroaryl, and an analogue or derivative thereof.

[0187] In some embodiments, the first nucleotide sequence comprises, consists of, or consists essentially of ribonucleic acids (RNAs). In some embodiments, the first nucleotide sequence comprises, consists of, or consists essentially of modified RNAs. In some embodiments, the modified RNAs are selected from a 2'-O-methyl RNA and 2'-fluoro RNA. In some embodiments, 15, 16, 17, 18, 19, 20, 21, 22, or 23 modified nucleotides of the first nucleotide sequence are independently selected from 2'-O-methyl RNA and 2'-fluoro RNA.

[0188] In some embodiments, the sense strand may further comprise one or more internucleoside linkages independently selected from a phosphodiester (PO) internucleoside linkage, phosphorothioate (PS) internucleoside linkage, phosphorodithioate internucleoside linkage, and PS-mimic

internucleoside linkage. In some embodiments, the PS-mimic internucleoside linkage is a sulfo internucleoside linkage.

[0189] In some embodiments, the sense strand may further comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand comprises 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, or 3 or fewer phosphorothioate internucleoside linkages. In some embodiments, the sense strand comprises 2 to 10, 2 to 8, 2 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2 phosphorothioate internucleoside linkages. In some embodiments, the sense strand comprises 1 to 2 phosphorothioate internucleoside linkages. In some embodiments, the sense strand comprises 2 to 4 phosphorothioate internucleoside linkages. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the first nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the first nucleotide sequence. In some embodiments, the sense strand comprises two phosphorothioate internucleoside linkages between the nucleotides at positions 1 to 3 from the 5' end of the first nucleotide sequence.

[0190] In some embodiments, any of the sense strands disclosed herein further comprise a monomer selected from Examples 21-32, 36, 37, 40-42, and 44-46 monomers. In some embodiments, any of the sense strands disclosed herein further comprise a 5' end cap monomer. In some embodiments, the 5' end cap monomer is selected from Examples 5-11, 33-35, 38, 39, 43, and 49-53 5' end cap monomers.

[0191] In some embodiments, any of the first nucleotide sequences disclosed herein further comprise a monomer selected from Examples 21-32, 36, 37, 40-42, and 44-46 monomers. In some embodiments, any of the first nucleotide sequences disclosed herein further comprise a 5' end cap monomer. In some embodiments, the 5' end cap monomer is selected from Examples 5-11, 33-35, 38, 39, 43, and 49-53 5' end cap monomers.

siNA Antisense Strand

[0192] Any of the siNA molecules described herein may comprise an antisense strand. The antisense strand may comprise a second nucleotide sequence. The second nucleotide sequence may be 15 to 30, 15 to 25, 15 to 23, 17 to 23, 19 to 23, or 19 to 21 nucleotides in length. In some embodiments, the second nucleotide sequence is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In some embodiments, the second nucleotide sequence is at least 19 nucleotides in length. In some embodiments, the second nucleotide sequence is at least 21 nucleotides in length.

[0193] In some embodiments, the antisense strand is the same length as the second nucleotide sequence. In some embodiments, the antisense strand is longer than the second nucleotide sequence. In some embodiments, the antisense strand may further comprise 1, 2, 3, 4, or 5 or more nucleotides than the second nucleotide sequence. In some embodiments, the antisense strand is the same length as the sense strand. In some embodiments, the antisense strand is longer than the sense strand. In some embodiments, the antisense strand may further comprise 1, 2, 3, 4, or 5 or more nucleotides than the sense strand. In some embodiments, the antisense strand may further comprise a deoxyribonucleic acid (DNA). In some embodiments, the DNA is thymine (T). In some embodiments, the antisense strand may further comprise a TT sequence. In some embodiments, the antisense strand may further comprise one or more modified nucleotides that are adjacent to the second nucleotide sequence. In some embodiments, the one or more modified nucleotides are independently selected from any of the modified nucleotides disclosed herein (e.g., 2'-fluoro nucleotide, 2'-O-methyl nucleotide, 2'-fluoro nucleotide mimic, 2'-O-methyl nucleotide mimic, or a nucleotide comprising a modified nucleobase).

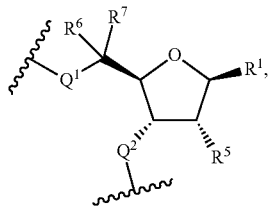
[0194] In some embodiments, the second nucleotide sequence comprises 15, 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the second nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide. In some embodiments, 100% of the nucleotides in the second nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

[0195] In some embodiments, between about 15 to 30, 15 to 25, 15 to 24, 15 to 23, 15 to 22, 15 to 21, 17 to 30, 17 to 25, 17 to 24, 17 to 23, 17 to 22, 17 to 21, 18 to 30, 18 to 25, 18 to 24, 18 to 23, 18 to 22, 18 to 21, 19 to 30, 19 to 25, 19 to 24, 19 to 23, 19 to 22, 19 to 21, 20 to 25, 20 to 24, 20 to 23, 21 to 25, 21 to 24, or 21 to 23 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 2 to 20 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 5 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 10 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, between about 12 to 25 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 12 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 13 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 14 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 15 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 16 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 17 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 18 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least about 19 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 21 modified nucleotides of the second nucleotide

sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 20 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 19 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 18 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 17 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 16 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 15 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 14 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, less than or equal to 13 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides. In some embodiments, at least one modified nucleotide of the second nucleotide sequence is a 2'-O-methyl pyrimidine. In some embodiments, at least 5, 6, 7, 8, 9, or 10 modified nucleotides of the second nucleotide sequence are 2'-O-methyl pyrimidines. In some embodiments, at least one modified nucleotide of the second nucleotide sequence is a 2'-O-methyl purine. In some embodiments, at least 5, 6, 7, 8, 9, or 10 modified nucleotides of the second nucleotide sequence are 2'-O-methyl purines. In some embodiments, the 2'-O-methyl nucleotide is a 2'-O-methyl nucleotide mimic.

[0196] In some embodiments, between 2 to 15 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 10 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, between 2 to 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 1 to 6, 1 to 5, 1 to 4, or 1 to 3 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 1, 2, 3, 4, 5, or 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 1 modified nucleotide of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, at least 2 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 3 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 4 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least 5 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 10, 9, 8, 7, 6, 5, 4, 3 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 10 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 7 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 6 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 5 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 4 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 3 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, 2 or fewer modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least one modified nucleotide of the second nucleotide sequence is a 2'-fluoro pyrimidine. In some embodiments, 1, 2, 3, 4, 5, or 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro pyrimidines. In some embodiments, at least one modified nucleotide of the second nucleotide sequence is a 2'-fluoro purine. In some embodiments, 1, 2, 3, 4, 5, or 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro purines. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

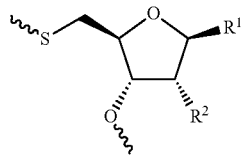
[0197] In some embodiments, the 2'-fluoro nucleotide or 2'-O-methyl nucleotide is a 2'-fluoro or 2'-O-methyl nucleotide mimic. In some embodiments, the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (V):



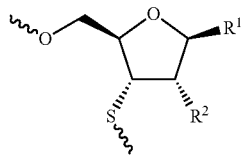
wherein R^1 is independently a nucleobase, aryl, heteroaryl, or H, Q^1 and Q^2 are independently S or O, R^5 is independently-OCD_3, —F, or —OCH_3, and R^6 and R^7 are independently H, D, or CD3. In some embodiments, the nucleobase is selected from cytosine, guanine, adenine, uracil, aryl, heteroaryl, and an analogue or derivative thereof.

[0198] In some embodiments, the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (16)-Formula (20):

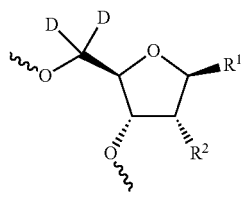
Formula (16)



Formula (17)

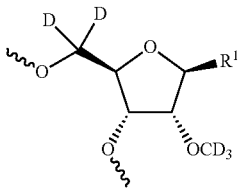


Formula (18)

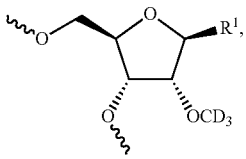


-continued

Formula (19)



Formula (20)



wherein R^1 is a nucleobase and R^2 is independently F or —OCH_3. In some embodiments, the nucleobase is selected from cytosine, guanine, adenine, uracil, aryl, heteroaryl, and an analogue or derivative thereof.

[0199] In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 nucleotides at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, at least two nucleotides at positions 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least three nucleotides at positions 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least four nucleotides at positions 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, at least five nucleotides at positions 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 2 and/or 14 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 2, 6, and/or 16 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 2, 6, 14, and/or 16 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 2, 6, 10, 14, and/or 18 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotides at positions 2, 5, 8, 14, and/or 17 from the 5' end of the second nucleotide sequence are 2'-fluoro nucleotides. In some embodiments, the nucleotide at position 2 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 5 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 6 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 8 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 10 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 14 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 16 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 17 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the nucleotide at position 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0200] In some embodiments, the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides, and wherein the alternating 1:3 modification pattern occurs at least 2 times. In some embodiments, the alternating 1:3 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:3 modification pattern occur consecutively. In some embodiments, at least two of the alternating 1:3 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0201] In some embodiments, the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides, and wherein the alternating 1:2 modification pattern occurs at least 2 times. In some embodiments, the alternating 1:2 modification pattern occurs 2-5 times. In some embodiments, at least two of the alternating 1:2 modification pattern occurs consecutively. In some embodiments, at least two of the alternating 1:2 modification pattern occurs nonconsecutively. In some embodiments, at least 1, 2, 3, 4, or 5 alternating 1:2 modification pattern begins at nucleotide position 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 5 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 8 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand. In some embodiments, at least one alternating 1:2 modification pattern begins at nucleotide position 17 from the 5' end of the antisense strand. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0202] In some embodiments, the second nucleotide sequence comprises, consists of, or consists essentially of ribonucleic acids (RNAs). In some embodiments, the second nucleotide sequence comprises, consists of, or consists essentially of modified RNAs. In some embodiments, the modified RNAs are selected from a 2'-O-methyl RNA and 2'-fluoro RNA. In some embodiments, 15, 16, 17, 18, 19, 20, 21, 22, or 23 modified nucleotides of the second nucleotide sequence are independently selected from 2'-O-methyl RNA and 2'-fluoro RNA. In some embodiments, the 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

[0203] In some embodiments, the sense strand may further comprise one or more internucleoside linkages independently selected from a phosphodiester (PO) internucleoside linkage, phosphorothioate (PS) internucleoside linkage, phosphorodithioate internucleoside linkage, and PS-mimic internucleoside linkage. In some embodiments, the PS-mimic internucleoside linkage is a sulfo internucleoside linkage.

[0204] In some embodiments, the antisense strand may further comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 or more phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, or 3 or fewer phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 to 10, 2 to 8, 2 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 to 10, 2 to 8, 2 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 to 8 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 3 to 8 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 4 to 8 phosphorothioate internucleoside linkages. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the second nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the second nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 3' end of the second nucleotide sequence. In some embodiments, at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 3' end of the second nucleotide sequence. In some embodiments, the antisense strand comprises two phosphorothioate internucleoside linkages between the nucleotides at positions 1 to 3 from the 5' end of the first nucleotide sequence. In some embodiments, the antisense strand comprises two phosphorothioate internucleoside linkages between the nucleotides at positions 1 to 3 from the 3' end of the first nucleotide sequence. In some embodiments, the antisense strand comprises (a) two phosphorothioate internucleoside linkages between the nucleotides at positions 1 to 3 from the 5' end of the first nucleotide sequence; and (b) two phosphorothioate internucleoside linkages between the nucleotides at positions 1 to 3 from the 3' end of the first nucleotide sequence.

[0205] In some embodiments, at least one end of the ds-siNA is a blunt end. In some embodiments, at least one end of the ds-siNA comprises an overhang, wherein the overhang comprises at least one nucleotide. In some embodiments, both ends of the ds-siNA comprise an overhang, wherein the overhang comprises at least one nucleotide. In some embodiments, the overhang comprises 1 to 5 nucleotides, 1 to 4 nucleotides, 1 to 3 nucleotides, or 1 to 2 nucleotides. In some embodiments, the overhang consists of 1 to 2 nucleotides.

[0206] In some embodiments, the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

[0207] In some embodiments, any of the antisense strands disclosed herein further comprise a monomer selected from Examples 21-32, 36, 37, 40-42, and 44-46 monomers. In some embodiments, any of the antisense strands disclosed herein further comprise a 5' end cap monomer. In some embodiments, the 5' end cap monomer is selected from Examples 5-11, 33-35, 38, 39, 43, and 49-53 5' end cap monomers.

[0208] In some embodiments, any of the second nucleotide sequences disclosed herein further comprise a monomer selected from Examples 21-32, 36, 37, 40-42, and 44-46 monomers. In some embodiments, any of the second nucleotide sequences disclosed herein further comprise a 5' end cap monomer. In some embodiments, the 5' end cap monomer is selected from Examples 5-11, 33-35, 38, 39, 43, and 49-53 5' end cap monomers.

Modified Nucleotides

[0209] Further disclosed herein are siNA molecules comprising one or more modified nucleotides. In some embodiments, any of the siNAs disclosed herein comprise one or more modified nucleotides. In some embodiments, any of the sense strands disclosed herein comprise one or more modified nucleotides. In some embodiments, any of the first nucleotide sequences disclosed herein comprise one or more modified nucleotides. In some embodiments, any of the antisense strands disclosed herein comprise one or more modified nucleotides. In some embodiments, any of the second nucleotide sequences disclosed herein comprise one or more modified nucleotides. In some embodiments, the one or more modified nucleotides is adjacent to the first nucleotide sequence. In some embodiments, at least one modified nucleotide is adjacent to the 5' end of the first nucleotide sequence. In some embodiments, at least one modified nucleotide is adjacent to the 3' end of the first nucleotide sequence. In some embodiments, at least one modified nucleotide is adjacent to the 5' end of the first nucleotide sequence and at least one modified nucleotide is adjacent to the 3' end of the first nucleotide sequence. In some embodiments, the one or more modified nucleotides is adjacent to the second nucleotide sequence. In some embodiments, at least one modified nucleotide is adjacent to the 5' end of the second nucleotide sequence. In some embodiments, at least one modified nucleotide is adjacent to the 3' end of the second nucleotide sequence. In some embodiments, at least one modified nucleotide is adjacent to the 5' end of the second nucleotide sequence and at least one

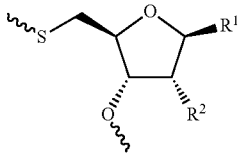
modified nucleotide is adjacent to the 3' end of the second nucleotide sequence. In some embodiments, a 2'-O-methyl nucleotide in any of sense strands or first nucleotide sequences disclosed herein is replaced with a modified nucleotide. In some embodiments, a 2'-O-methyl nucleotide in any of antisense strands or second nucleotide sequences disclosed herein is replaced with a modified nucleotide.

[0210] In some embodiments, any of the siNA molecules, siNAs, sense strands, first nucleotide sequences, antisense strands, and second nucleotide sequences disclosed herein comprise 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, or 30 or more modified nucleotides. In some embodiments, 1%, 2%, 3%, 4%, 5%0, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%0, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% of the nucleotides in the siNA molecule, siNA, sense strand, first nucleotide sequence, antisense strand, or second nucleotide sequence are modified nucleotides.

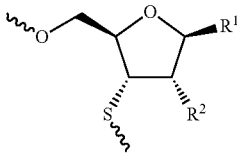
[0211] In some embodiments, a modified nucleotide is selected from the group consisting of 2'-fluoro nucleotide, 2'-O-methyl nucleotide, 2'-fluoro nucleotide mimic, 2'-O-methyl nucleotide mimic, a locked nucleic acid, and a nucleotide comprising a modified nucleobase.

[0212] In some embodiments, any of the siRNAs disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more 2'-fluoro or 2'-O-methyl nucleotide mimics. In some embodiments, any of the sense strands disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more 2'-fluoro or 2'-O-methyl nucleotide mimics. In some embodiments, any of the first nucleotide sequences disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more 2'-fluoro or 2'-O-methyl nucleotide mimics. In some embodiments, any of the antisense strand disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more 2'-fluoro or 2'-O-methyl nucleotide mimics. In some embodiments, any of the second nucleotide sequences disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more 2'-fluoro or 2'-O-methyl nucleotide mimics. In some embodiments, the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (16)-Formula (20):

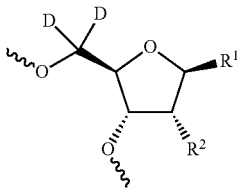
Formula (16)



Formula (17)

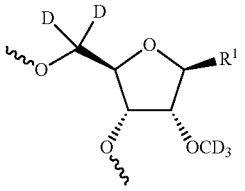


Formula (18)

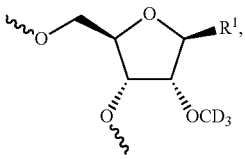


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Formula (19)

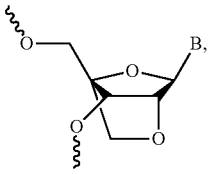


Formula (20)

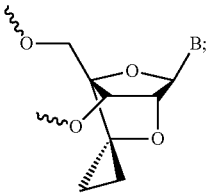


wherein R^1 is a nucleobase and R^2 is independently F or —OCH_3. In some embodiments, the nucleobase is selected from cytosine, guanine, adenine, uracil, aryl, heteroaryl, and an analogue or derivative thereof. In some embodiments, the siNA molecules disclosed herein comprise at least one 2'-fluoro nucleotide, at least one 2'-O-methyl nucleotide, and at least one 2'-fluoro or 2'-O-methyl nucleotide mimic. In some embodiments, the at least one 2'-fluoro or 2'-O-methyl nucleotide mimic is adjacent to the first nucleotide sequence. In some embodiments, the at least one 2'-fluoro or 2'-O-methyl nucleotide mimic is adjacent to the 5' end of first nucleotide sequence. In some embodiments, the at least one 2'-fluoro or 2'-O-methyl nucleotide mimic is adjacent to the 3' end of first nucleotide sequence. In some embodiments, the at least one 2'-fluoro or 2'-O-methyl nucleotide mimic is adjacent to the second nucleotide sequence. In some embodiments, the at least one 2'-fluoro or 2'-O-methyl nucleotide mimic is adjacent to the 5' end of second nucleotide sequence. In some embodiments, the at least one 2'-fluoro or 2'-O-methyl nucleotide mimic is adjacent to the 3' end of second nucleotide sequence. In some embodiments, the first nucleotide sequence does not comprise a 2'-fluoro nucleotide mimic. In some embodiments, the first nucleotide sequence does not comprise a 2'-O-methyl nucleotide mimic. In some embodiments, the second nucleotide sequence does not comprise a 2'-fluoro nucleotide mimic. In some embodiments, the second nucleotide sequence does not comprise a 2'-O-methyl nucleotide mimic.

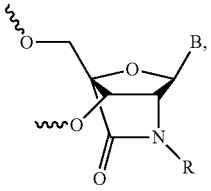
[0213] In some embodiments, any of the siRNAs disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more locked nucleic acids. In some embodiments, any of the sense strands disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more locked nucleic acids. In some embodiments, any of the first nucleotide sequences disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more locked nucleic acids. In some embodiments, any of the antisense strand disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more locked nucleic acids. In some embodiments, any of the second nucleotide sequences disclosed herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more locked nucleic acids. In some embodiments, the locked nucleic acid is selected from



(LNA)



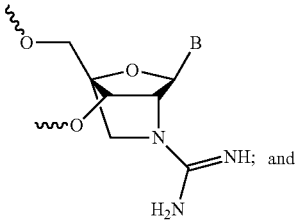
(ScpBNA or "cp")



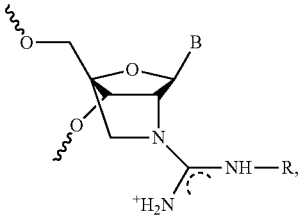
(AmNA)

where

R is H or alkyl (or AmNA(N-Me)) when R is alkyl);

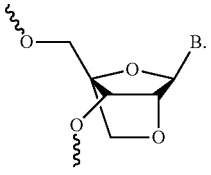


(GuNA)



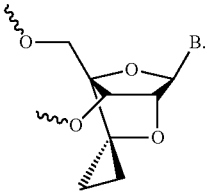
GuNA(N—R), R = Me, Et, iPr, tBu

wherein B is a nucleobase. In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise at least modified nucleotide that is



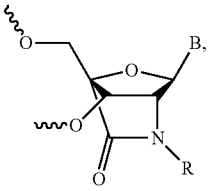
(LNA)

In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise at least modified nucleotide that is



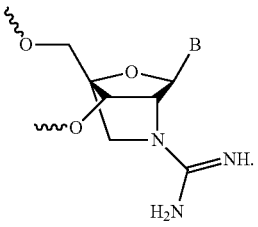
(ScpBNA or "cp")

In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise at least modified nucleotide that is



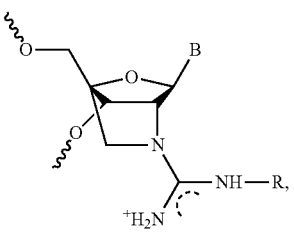
(AmNA)

where R is H or alkyl (or AmNA(N-Me)) when R is alkyl). In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise at least modified nucleotide that is



(GuNA)

In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise at least modified nucleotide that is



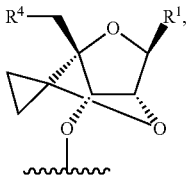
GuNA(N—R), R = Me, Et, iPr, tBu

wherein B is a nucleobase.

Phosphorylation Blocker

[0214] Further disclosed herein are siNA molecules comprising a phosphorylation blocker. In some embodiments, a 2'-O-methyl nucleotide in any of sense strands or first nucleotide sequences disclosed herein is replaced with a nucleotide containing a phosphorylation blocker. In some embodiments, a 2'-O-methyl nucleotide in any of antisense strands or second nucleotide sequences disclosed herein is replaced with a nucleotide containing a phosphorylation blocker. In some embodiments, a 2'-O-methyl nucleotide in any of sense strands or first nucleotide sequences disclosed herein is further modified to contain a phosphorylation blocker. In some embodiments, a 2'-O-methyl nucleotide in any of antisense strands or second nucleotide sequences disclosed herein is further modified to contain a phosphorylation blocker.

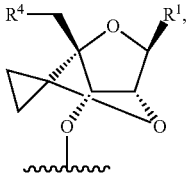
[0215] In some embodiments, any of the siNA molecules disclosed herein comprise a phosphorylation blocker of Formula (IV):



wherein R^1 is a nucleobase, R^4 is —O—R^{30} or —$NR^{31}R^{32}$, R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring.

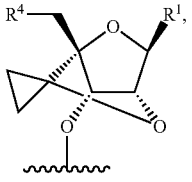
[0216] In some embodiments, any of the siNA molecules disclosed herein comprise a phosphorylation blocker of Formula (IV):

Formula (IV)



wherein R^1 is a nucleobase, and R^4 is —OCH_3 or —$N(CH_2CH_2)_2O$.

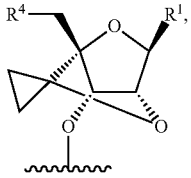
[0217] In some embodiments, a siNA molecule comprises (a) a phosphorylation blocker of Formula (IV):



wherein R^1 is a nucleobase, R^4 is —O—R^{30} or —$NR^{31}R^{32}$, R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; and (b) a short interfering nucleic acid (siNA), wherein the phosphorylation blocker is conjugated to the siNA.

[0218] In some embodiments, a siNA molecule comprises (a) a phosphorylation blocker of Formula (IV):

Formula (IV)



wherein R^1 is a nucleobase, and R^4 is —OCH_3 or —$N(CH_2CH_2)_2O$; and (b) a short interfering nucleic acid (siNA), wherein the phosphorylation blocker is conjugated to the siNA.

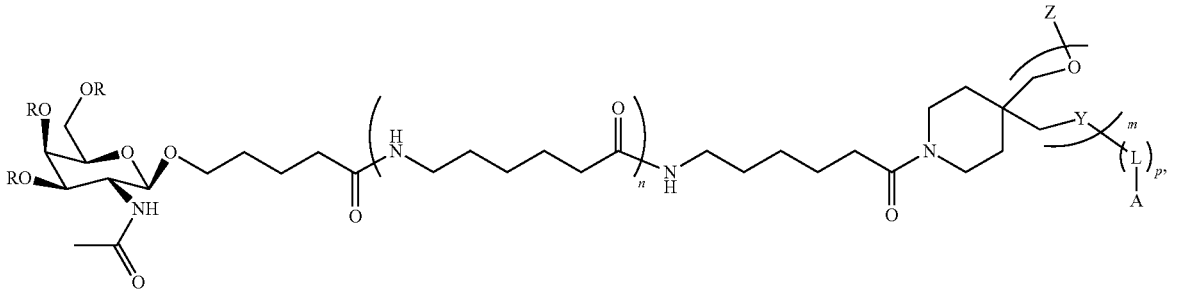
[0219] In some embodiments, the phosphorylation blocker is attached to the 3' end of the sense strand or first nucleotide sequence. In some embodiments, the phosphorylation blocker is attached to the 3' end of the sense strand or first nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the phosphorylation blocker is attached to the 5' end of the sense strand or first nucleotide sequence. In some embodiments, the phosphorylation blocker is attached to the 5' end of the sense strand or first nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the phosphorylation blocker is attached to the 3' end of the antisense strand or second nucleotide sequence. In some embodiments, the phosphorylation blocker is attached to the 3' end of the antisense strand or second nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the phosphorylation blocker is attached to the 5' end of the antisense strand or second nucleotide sequence. In some embodiments, the phosphorylation blocker is attached to the 5' end of the antisense strand or second nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the one or more linkers are independently selected from the group consisting of a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

Conjugated Moiety

[0220] Further disclosed herein are siNA molecules comprising a conjugated moiety. In some embodiments, the conjugated moiety is selected from galactosamine, peptides, proteins, sterols, lipids, phosphohipids, biotin, phenoxazines, active drug substance, cholesterols, phenanthridine, anthraquinone, acridine, fluoresceins, rhodarnines, coumarins, and dyes. In some embodiments, the conjugated moiety is attached to the 3' end of the sense strand or first nucleotide sequence. In some embodiments, the conjugated moiety is attached to the 3' end of the sense strand or first nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the conjugated moiety is attached to the 5' end of the sense strand or first nucleotide sequence. In some embodiments, the conjugated moiety is attached to the 5' end of the sense strand or first nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the conjugated moiety is attached to the 3' end of the antisense strand or second nucleotide sequence. In some embodiments, the conjugated moiety is attached to the 3' end of the antisense strand or second nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the conjugated moiety is attached to the 5' end of the antisense strand or second nucleotide sequence. In some embodiments, the

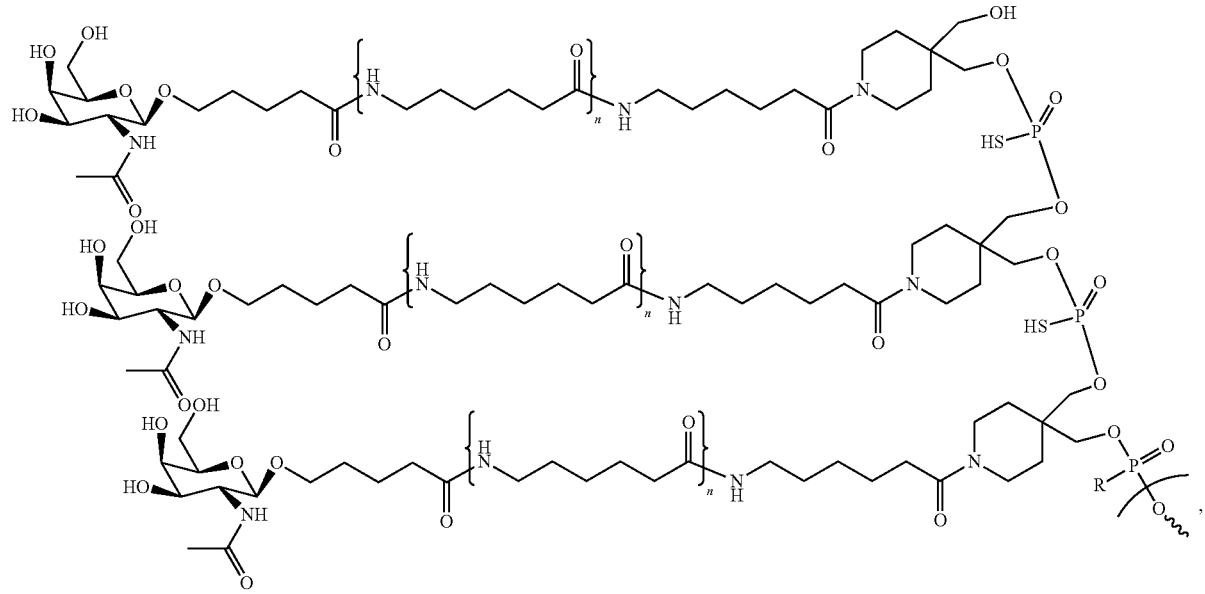
conjugated moiety is attached to the 5' end of the antisense strand or second nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the one or more linkers are independently selected from the group consisting of a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

[0221] In some embodiments, the conjugated moiety is galactosamine. In some embodiments, any of the siNAs disclosed herein are attached to a conjugated moiety that is galactosamine. In some embodiments, the galactosamine is N-acetylgalactosamine (GalNAc). In some embodiments, any of the siNA molecules disclosed herein comprise GalNAc. In some embodiments, the GalNAc is of Formula (VI):



wherein m is 1, 2, 3, 4, or 5; each n is independently 1 or 2; p is 0 or 1; each R is independently H or a first protecting group; each Y is independently selected from —O—P(═O)(SH)—, —O—P(═O)(O)—, —O—P(═O)(OH)—, —O—P(S)S—, and —O—; Z is H or a second protecting group; either L is a linker or L and Y in combination are a linker; and A is H, OH, a third protecting group, an activated group, or an oligonucleotide. In some embodiments, the first protecting group is acetyl. In some embodiments, the second protecting group is trimethoxytrityl (TMT). In some embodiments, the activated group is a phosphoramidite group. In some embodiments, the phosphoramidite group is a cyanoethoxy N,N-diisopropylphosphoramidite group. In some embodiments, the linker is a C6-NH_2 group. In some embodiments, A is a short interfering nucleic acid (siNA) or siNA molecule. In some embodiments, m is 3. In some embodiments, R is H, Z is H, and n is 1. In some embodiments, R is H, Z is H, and n is 2.

[0222] In some embodiments, the GalNAc is of Formula (VII):



R = OH or SH

wherein each n is independently 1 or 2.

[0223] In some embodiments, the galactosamine is attached to the 3' end of the sense strand or first nucleotide sequence. In some embodiments, the galactosamine is attached to the 3' end of the sense strand or first nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the galactosamine is attached to the 5' end of the sense strand or first nucleotide sequence. In some embodiments, the galactosamine is attached to the 5' end of the sense strand or first nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the galactosamine is attached to the 3' end of the antisense strand or second nucleotide sequence. In some embodiments, the galactosamine is attached to the 3' end of the antisense strand or second nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the galactosamine is attached to the 5' end of the antisense strand or second nucleotide sequence. In some embodiments, the galactosamine is attached to the 5' end of the antisense strand or second nucleotide sequence via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the one or more linkers are independently selected from the group consisting of a phosphodiester (p or po) linker, phosphorothioate (ps) linker, phosphoramidite (HEG) linker, triethylene glycol (TEG) linker, and/or phosphorodithioate linker. In some embodiments, the one or more linkers are independently selected from the group consisting of p-$(PS)_2$, $(PS)_2$-p-TEG-p, $(PS)_2$-p-HEG-p, and $(PS)_2$-p-$(HEG\text{-}p)_2$.

[0224] In some embodiments, the conjugated moiety is a lipid moiety. In some embodiments, any of the siNAs disclosed herein are attached to a conjugated moiety that is a lipid moiety. Examples of lipid moieties include, but are not limited to, a cholesterol moiety, a thioether, e.g., hexyl-S-tritylthiol a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylanmrmoniumr 1-di-O-hexadecyl-rac-glycero-S—H-phosphonate, a polyamine or a polyethylene glycol chain, adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

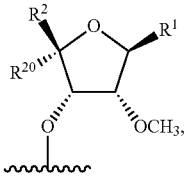
[0225] In some embodiments, the conjugated moiety is an active drug substance. In some embodiments, any of the siNAs disclosed herein are attached to a conjugated moiety that is an active drug substance, Examples of active drug substances include, but are not limited to, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (5)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethicin, a barbiturate, a cephalosporir, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

5'-Stabilized End Cap

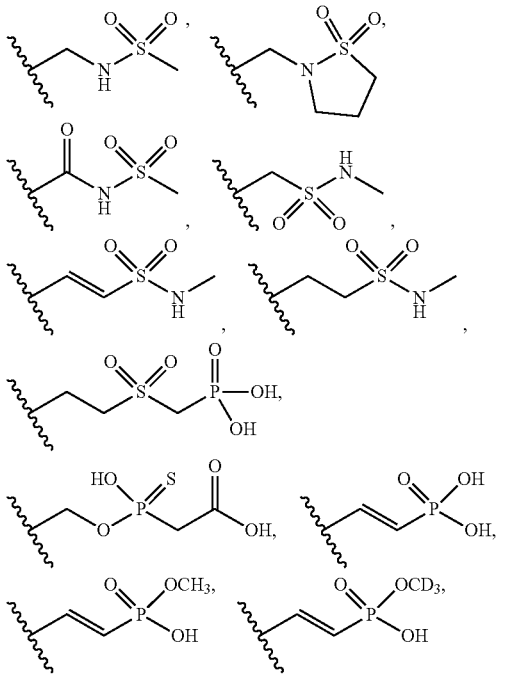
[0226] Further disclosed herein are siNA molecules comprising a 5'-stabilized end cap. As used herein the terms "5'-stabilized end cap" and "5' end cap" are used interchangeably. In some embodiments, a 2'-O-methyl nucleotide in any of sense strands or first nucleotide sequences disclosed herein is replaced with a nucleotide containing a 5'-stabilized end cap. In some embodiments, a 2'-O-methyl nucleotide in any of antisense strands or second nucleotide sequences disclosed herein is replaced with a nucleotide containing a 5'-stabilized end cap. In some embodiments, a 2'-O-methyl nucleotide in any of sense strands or first nucleotide sequences disclosed herein is further modified to contain a 5'-stabilized end cap. In some embodiments, a 2'-O-methyl nucleotide in any of antisense strands or second nucleotide sequences disclosed herein is further modified to contain a 5'-stabilized end cap.

[0227] In some embodiments, the 5'-stabilized end cap is a 5' phosphate mimic. In some embodiments, the 5'-stabilized end cap is a modified 5' phosphate mimic. In some embodiments, the modified 5' phosphate is a chemically modified 5' phosphate. In some embodiments, the 5'-stabilized end cap is a 5'-vinyl phosphonate. In some embodiments, the 5'-vinyl phosphonate is a 5'-(E)-vinyl phosphonate or 5'-(Z)-vinyl phosphonate. In some embodiments, the 5'-vinyl phosphonate is a deuterated vinyl phosphonate. In some embodiments, the deuterated vinyl phosphonate is a mono-deuterated vinyl phosphonate. In some embodiments, the deuterated vinyl phosphonate is a di-deuterated vinyl phosphonate. In some embodiments, the 5'-stabilized end cap is a phosphate mimic. Examples of phosphate mimics are disclosed in Parmar et al., 2018, *J Med Chem,* 61(3): 734-744, International Publication Nos. WO2018/045317 and WO2018/044350, and U.S. Pat. No. 10,087,210, each of which is incorporated by reference in its entirety.

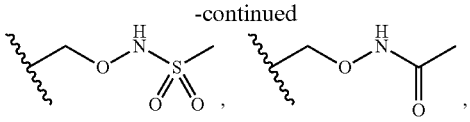
[0228] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap of Formula (Ia):



wherein R^1 is H, a nucleobase, aryl, or heteroaryl; R^2 is

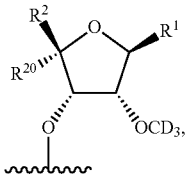


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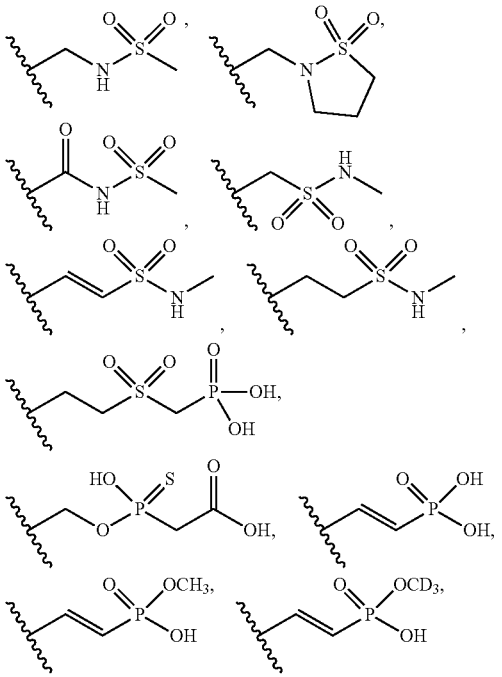


—CH═CD-Z,-CD═CH—Z, —CD═CD-Z, —($CR^{21}R^{22}$)$_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is H; or R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —($CR^{21}R^{22}$)$_n$—Z or —(C_2-C_6alkenylene)-Z; n is 1, 2, 3, or 4; Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, —$NR^{23}SO_2R^{24}$; either R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group; R^{23} is hydrogen or C_1-C_6 alkyl; R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; R^{25} is C_1-C_6 alkyl; and m is 1, 2, 3, or 4. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

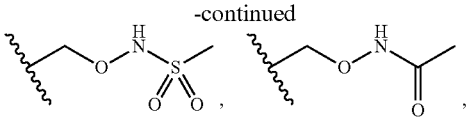
[0229] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap of Formula (Ib):



wherein R^1 is H, a nucleobase, aryl, or heteroaryl; R^2 is

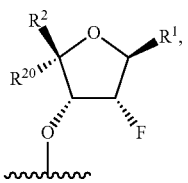


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—CH═CD-Z,-CD═CH—Z, —CD═CD-Z, —($CR^{21}R^{22}$)$_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is H; or R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —($CR^{21}R^{22}$)$_n$—Z or —(C_2-C_6alkenylene)-Z; n is 1, 2, 3, or 4; Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, —$NR^{23}SO_2R^{24}$; either R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group; R^{23} is hydrogen or C_1-C_6 alkyl; R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; R^{25} is C_1-C_6 alkyl; and m is 1, 2, 3, or 4. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

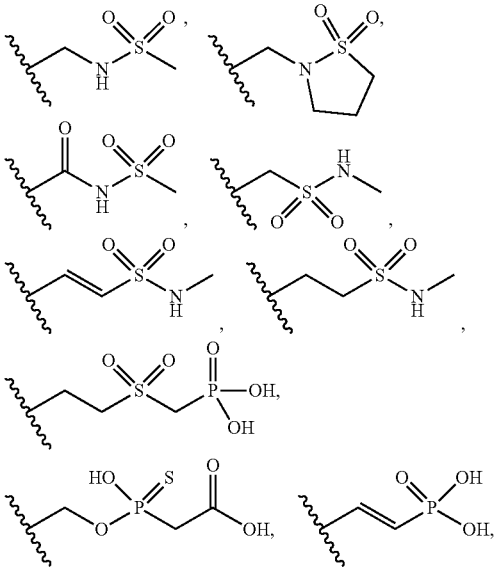
[0230] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap of Formula (Ic):



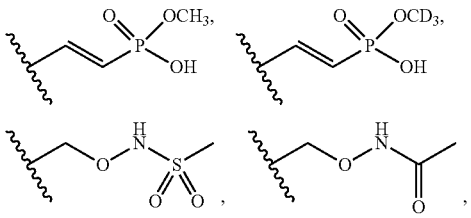
wherein R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0231]

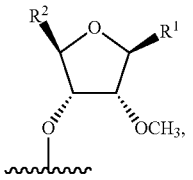


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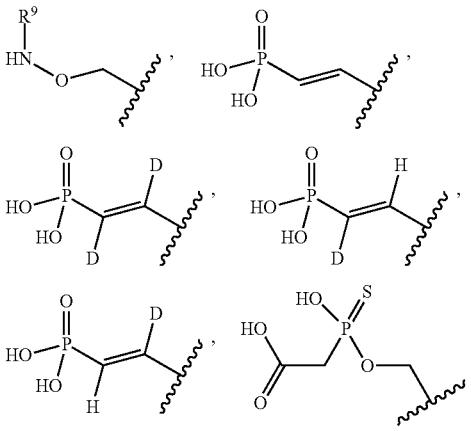


—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z; n is 1, 2, 3, or 4; Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$; R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group; R^{23} is hydrogen or C_1-C_6 alkyl; R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; R^{25} is C_1-C_6 alkyl; and m is 1, 2, 3, or 4. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

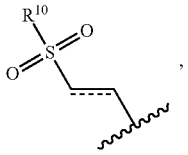
[0232] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap of Formula (IIa):



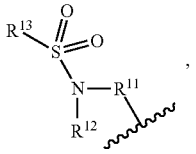
wherein R^1 is a nucleobase, aryl, heteroaryl, or H, R^2 is



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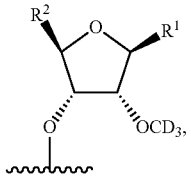


—$CH_2SO_2NHCH_3$, or

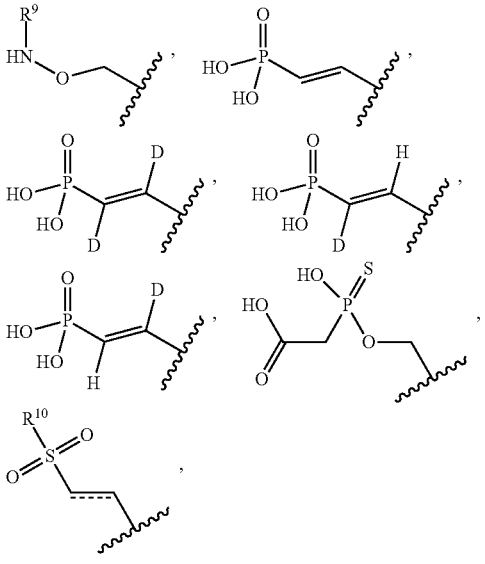


R^9 is —SO_2CH_3 or —$COCH_3$, ⎓ is a double or single bond, R^{10}=—CH_2PO_3H or —$NHCH_3$, R^{11} is —CH_2— or —CO—, and R^{12} is H and R^{13} is CH_3 or R^{12} and R^{13} together form —$CH_2CH_2CH_2$—. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

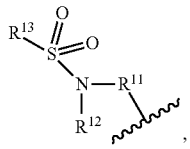
[0233] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap of Formula (IIb):



wherein R^1 is a nucleobase, aryl, heteroaryl, or H, R^2 is

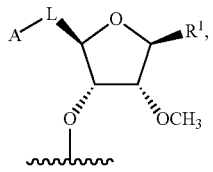


—$CH_2SO_2NHCH_3$, or



R^9 is —SO_2CH_3 or —$COCH_3$, ⎓ is a double or single bond, R^{10}=—CH_2PO_3H or —$NHCH_3$, R^{11} is —CH_2— or —CO—, and R^{12} is H and R^{15} is CH_3 or R^{12} and R^{13} together form —$CH_2CH_2CH_2$—. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

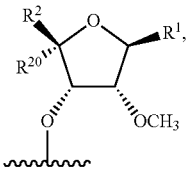
[0234] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap of Formula (III):



wherein R^1 is a nucleobase, aryl, heteroaryl, or H, L is —CH_2—, —CH=CH—, —CO—, or —CH_2CH_2—, and A is —$ONHCOCH_3$, —$ONHSO_2CH_3$, —PO_3H, —$OP(SOH)CH_2CO_2H$, —$SO_2CH_2PO_3H$, —SO_2NHCH_3, —$NHSO_2CH_3$, or —$N(SO_2CH_2CH_2CH_2)$. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

[0235] In some embodiments, any of the siNA molecules, sense strands, first nucleotide sequences, antisense strands, or second nucleotide sequences disclosed herein comprise a 5'-stabilized end cap selected from Examples 5-11, 33-35, 38, 39, 43, and 49-53 5' end cap monomers.

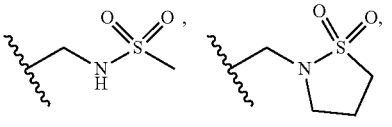
[0236] Further disclosed herein are siNA molecules comprising (a) a 5'-stabilized end cap of Formula (Ia):



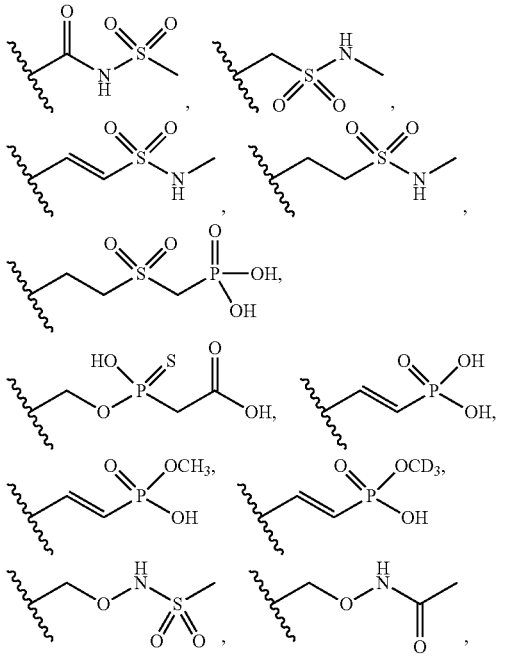
wherein R^1 is a nucleobase, aryl, heteroaryl, or H;

R^2 is

[0237]

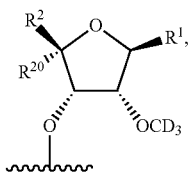


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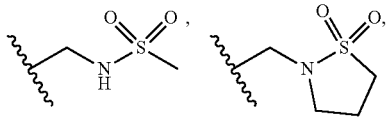


—CH=CD-Z,-CD=CH—Z,-CD=CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is H; or R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z; n is 1, 2, 3, or 4; Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, —$NR^{23}SO_2R^{24}$; either R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group; R^{23} is hydrogen or C_1-C_6 alkyl; R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; R^{25} is C_1-C_6 alkyl; and m is 1, 2, 3, or 4; and (b) a short interfering nucleic acid (siNA), wherein the 5'-stabilized end cap is conjugated to the siNA. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

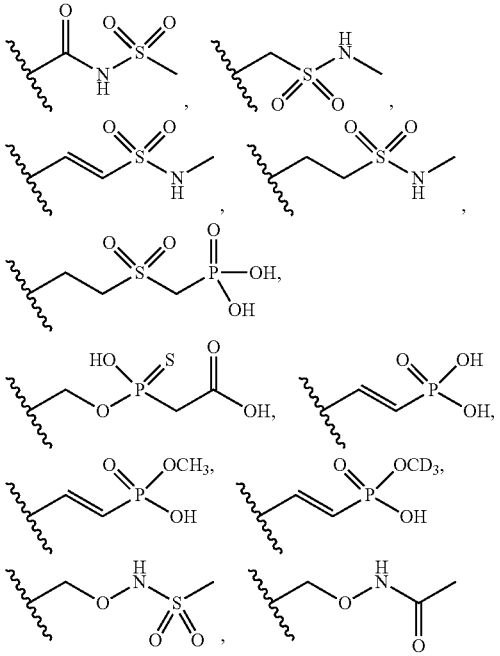
[0238] Further disclosed herein are siNA molecules comprising (a) a 5'-stabilized end cap of Formula (Ib):



wherein R^1 is a nucleobase, aryl, heteroaryl, or H; R^2 is

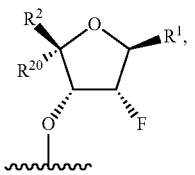


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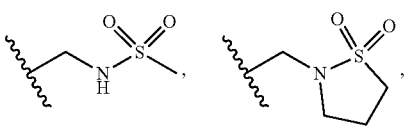


—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is H; or R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z; n is 1, 2, 3, or 4; Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, —$NR^{23}SO_2R^{24}$; either R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group; R^{23} is hydrogen or C_1-C_6 alkyl; R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; R^{25} is C_1-C_6 alkyl; and m is 1, 2, 3, or 4; and (b) a short interfering nucleic acid (siNA), wherein the 5'-stabilized end cap is conjugated to the siNA. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

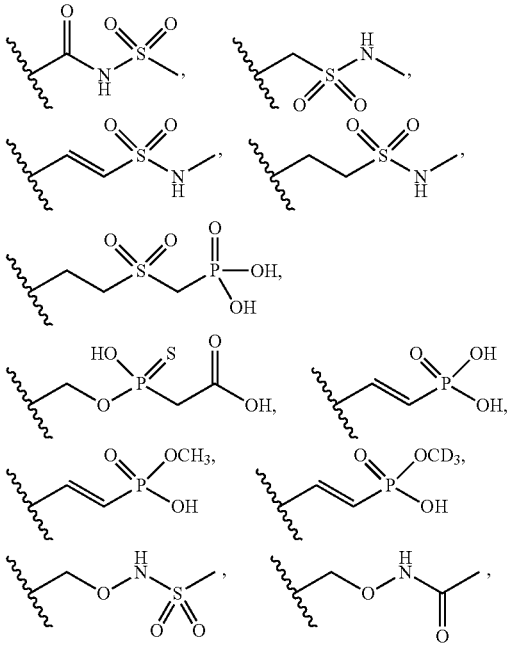
[0239] Further disclosed herein are siNA molecules comprising (a) a 5'-stabilized end cap of Formula (Ic):



wherein R^1 is a nucleobase, aryl, heteroaryl, or H, R^2 is

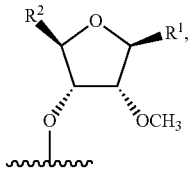


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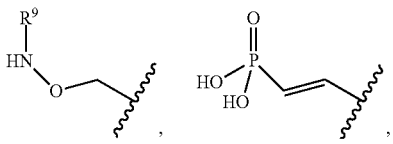


—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z; n is 1, 2, 3, or 4; Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$; R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group; R^{23} is hydrogen or C_1-C_6 alkyl; R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; R^{25} is C_1-C_6 alkyl; and m is 1, 2, 3, or 4; and (b) a short interfering nucleic acid (siNA), wherein the 5'-stabilized end cap is conjugated to the siNA. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

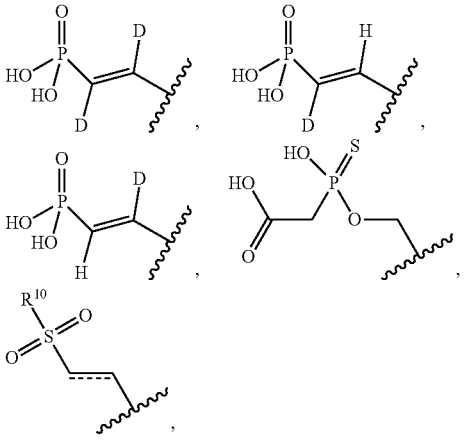
[0240] In some embodiments, a siNA molecule comprises (a) a 5'-stabilized end cap of Formula (IIa):



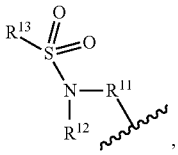
wherein R^1 is a nucleobase, aryl, heteroaryl, or H, R^2 is



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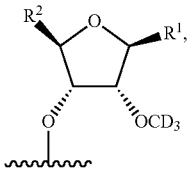


—$CH_2SO_2NHCH_3$ or

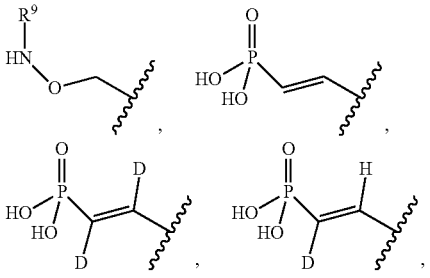


R^9 is —SO_2CH_3 or —$COCH_3$, wherein ⋯ is a double or single bond, R^{10}=—CH_2PO_3H or —$NHCH_3$, R^{11} is —CH_2— or —CO—, and R^{12} is H and R^{13} is CH_3 or R^{12} and R^{13} together form —$CH_2CH_2CH_2$—; and (b) a short interfering nucleic acid (siNA), wherein the 5'-stabilized end cap is conjugated to the siNA. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

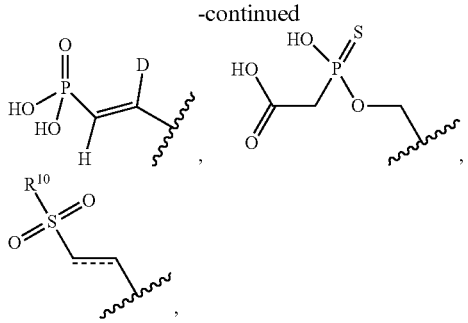
[0241] In some embodiments, a siNA molecule comprises (a) a 5'-stabilized end cap of Formula (IIb):



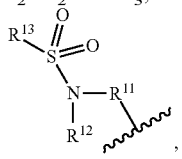
wherein R^1 is a nucleobase, aryl, heteroaryl, or H, R^2 is



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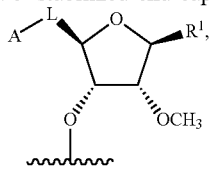


—$CH_2SO_2NHCH_3$, or



R^9 is —SO_2CH_3 or —$COCH_3$, wherein ⋯ is a double or single bond, R^{10}=—CH_2PO_3H or —$NHCH_3$, R^{11} is —CH_2— or —CO—, and R^{12} is H and R^{13} is CH_3 or R^{12} and R^{13} together form —$CH_2CH_2CH_2$—; and (b) a short interfering nucleic acid (siNA), wherein the 5'-stabilized end cap is conjugated to the siNA. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

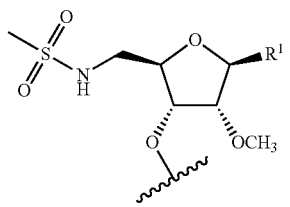
[0242] In some embodiments, a siNA molecule comprises (a) a 5'-stabilized end cap of Formula (III):



wherein R^1 is a nucleobase, aryl, heteroaryl, or H, L is —CH_2—, —CH=CH—, —CO—, or —CH_2CH_2—, and A is —$ONHCOCH_3$, —$ONHSO_2CH_3$, —PO_3H, —OP(SOH)CH_2CO_2H, —$SO_2CH_2PO_3H$, —SO_2NHCH_3, —$NHSO_2CH_3$, or —$N(SO_2CH_2CH_2CH_2)$; and (b) a short interfering nucleic acid (siNA), wherein the 5'-stabilized end cap is conjugated to the siNA. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is phenyl.

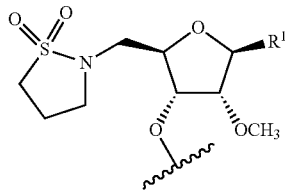
[0243] In some embodiments, any of the siNA molecules disclosed herein comprise a 5'-stabilized end cap selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

Formula (1)

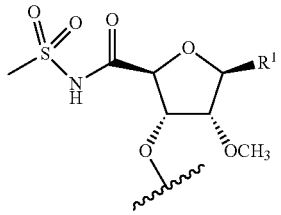


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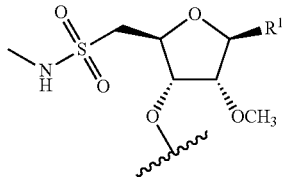
Formula (2)



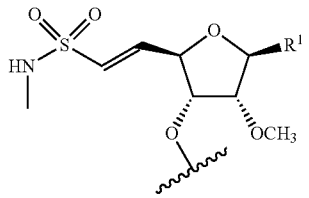
Formula (3)



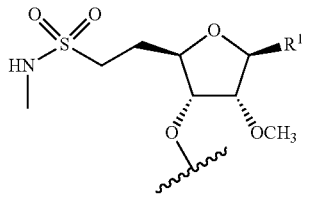
Formula (4)



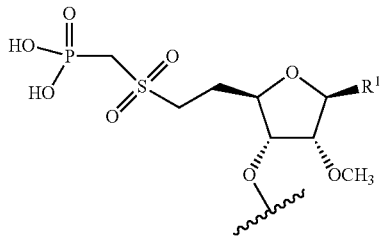
Formula (5)



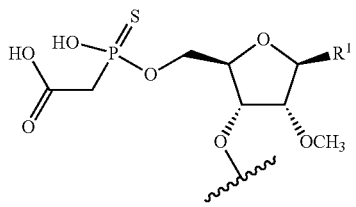
Formula (6)



Formula (7)

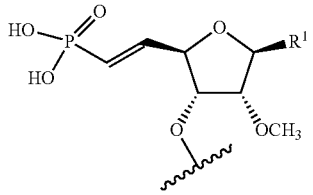


Formula (8)

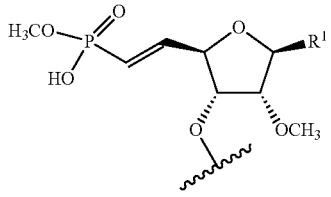


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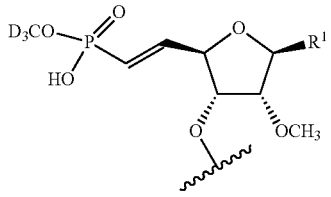
Formula (9)



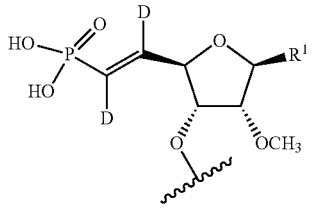
Formula (9X)



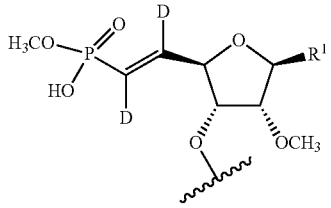
Formula (9Y)



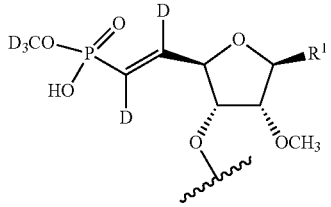
Formula (10)



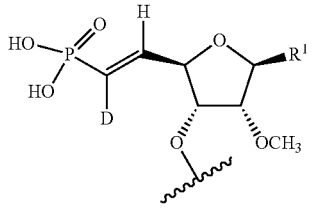
Formula (10X)



Formula (10Y)

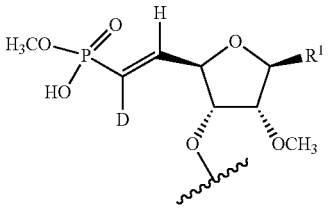


Formula (11)

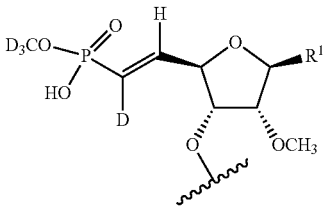


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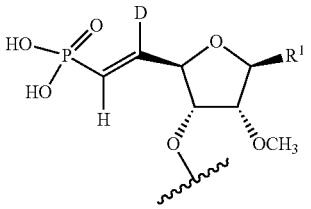
Formula (11X)



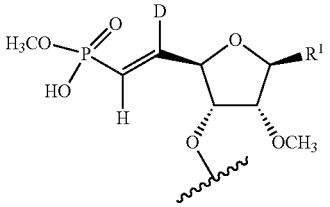
Formula (11Y)



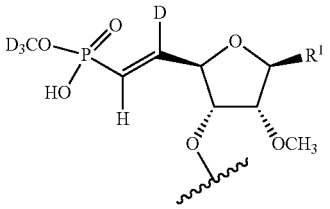
Formula (12)



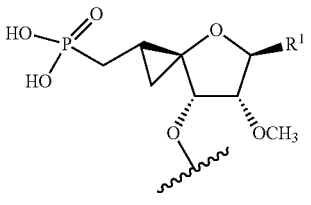
Formula (12X)



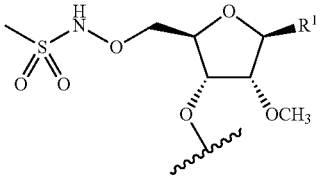
Formula (12Y)



Formula (13)

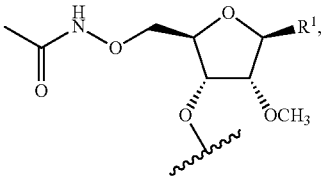


Formula (14)



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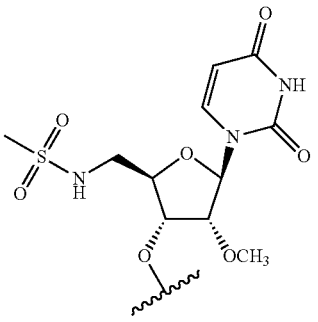
Formula (15)



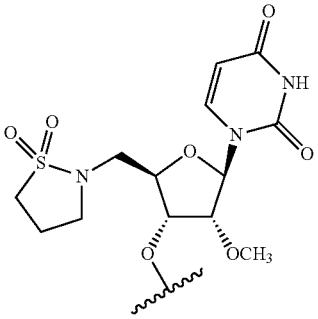
wherein R^1 is a nucleobase, aryl, heteroaryl, or H. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

[0244] In some embodiments, any of the siNA molecules disclosed herein comprise a 5'-stabilized end cap selected from the group consisting of Formulas (1A)-(15A), Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

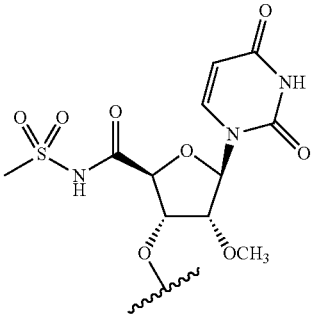
Formula (1A)



Formula (2A)

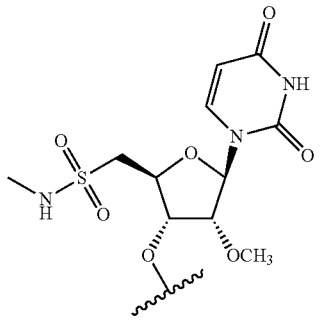


Formula (3A)

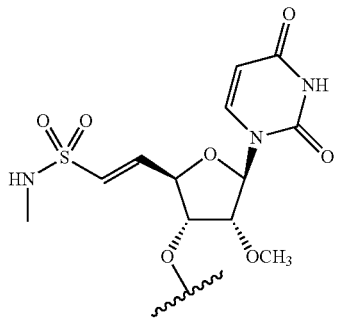


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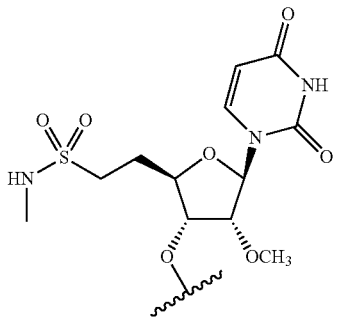
Formula (4A)



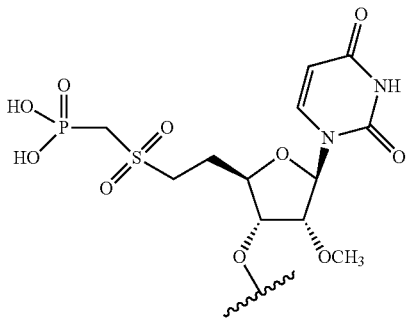
Formula (5A)



Formula (6A)

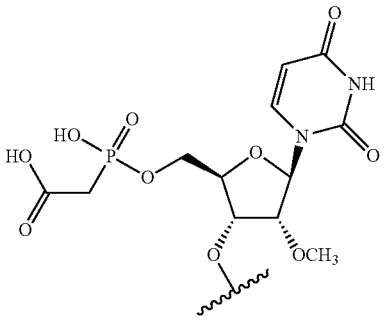


Formula (7A)

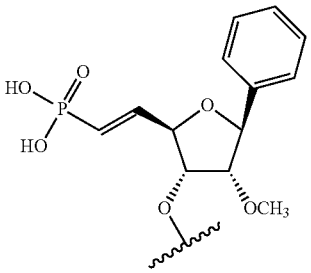


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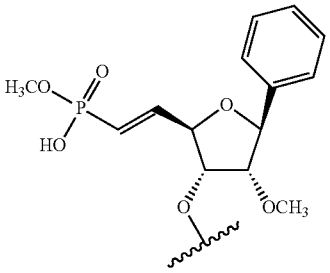
Formula (8A)



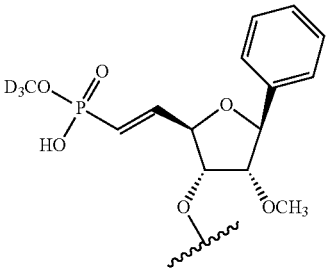
Formula (9A)



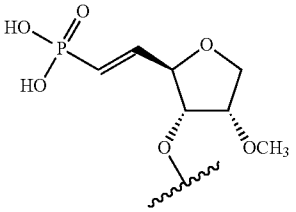
Formula (9AX)



Formula (9AY)

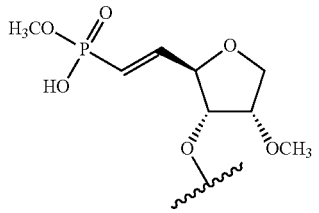


Formula (9B)

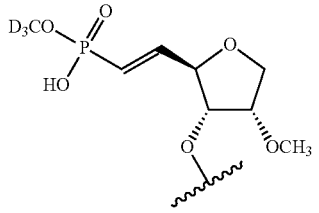


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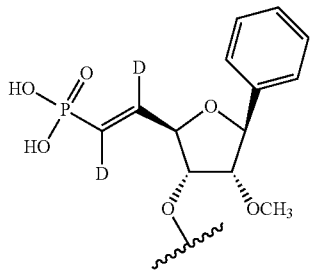
Formula (9BX)



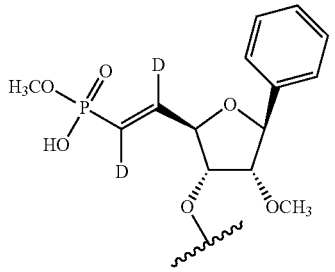
Formula (9BY)



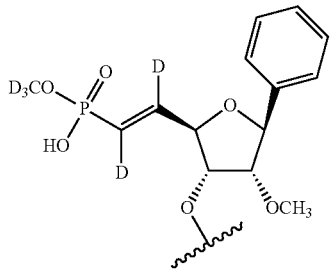
Formula (10A)



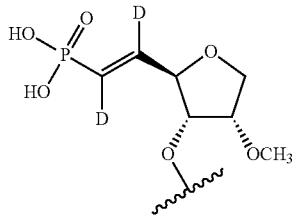
Formula (10AX)



Formula (10AY)

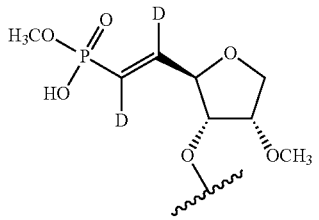


Formula (10B)

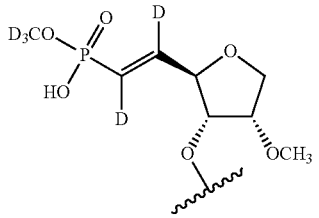


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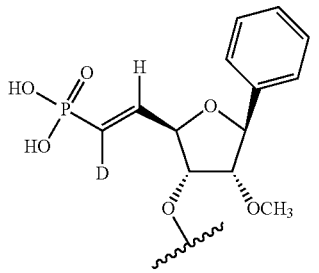
Formula (10BX)



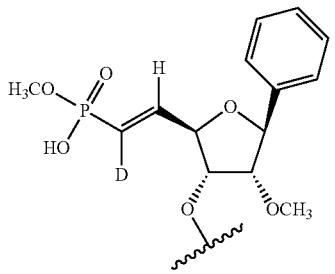
Formula (10BY)



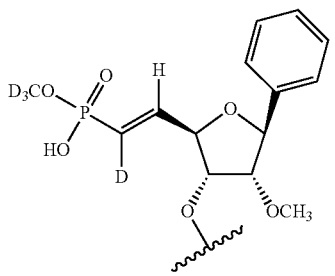
Formula (11A)



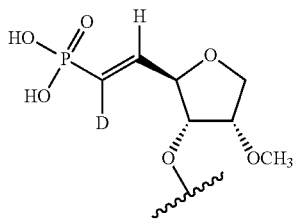
Formula (11AX)



(Formula (11AY)

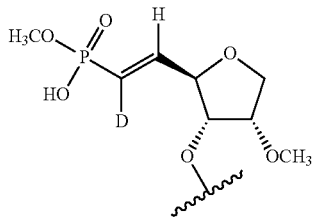


Formula (11B)

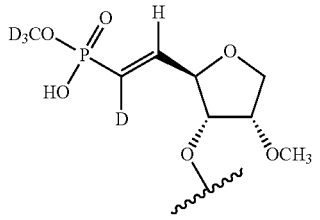


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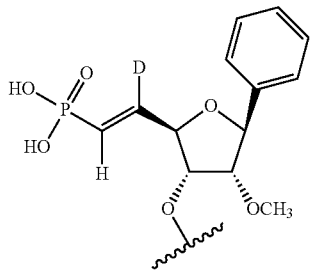
Formula (11BX)



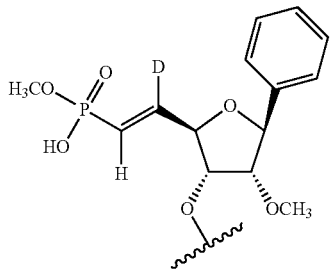
Formula (11BY)



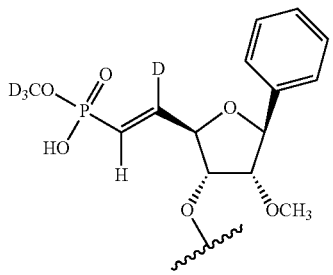
Formula (12A)



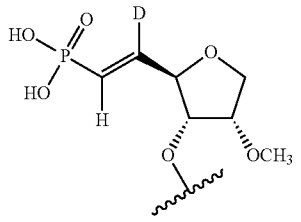
Formula (12AX)



Formula (12AY)

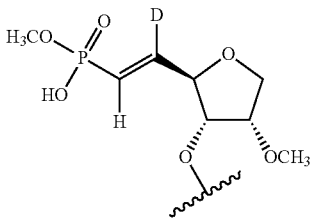


Formula (12B)

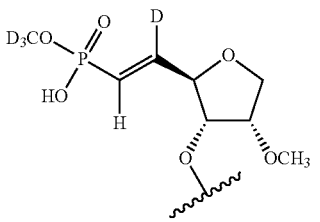


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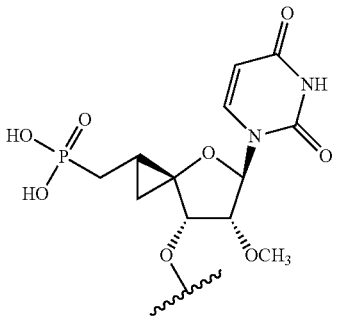
Formula (12BX)



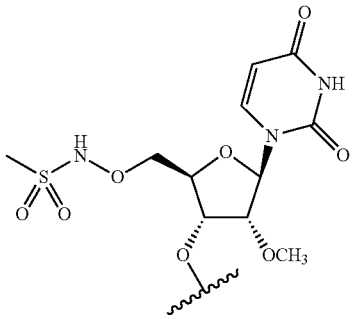
Formula (12BY)



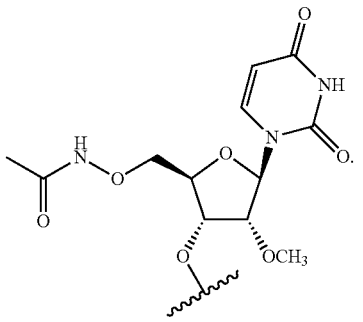
Formula (13A)



Formula (14A)

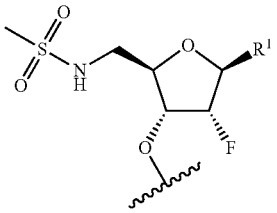


Formula (15A)

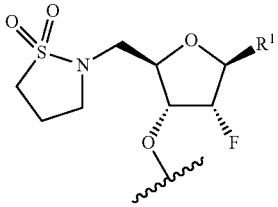


[0245] In some embodiments, any of the siNA molecules disclosed herein comprise a 5'-stabilized end cap selected from the group consisting of Formula (21) to Formula (35):

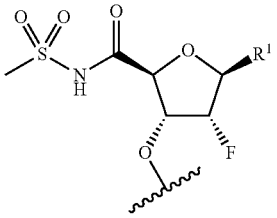
Formula (21)



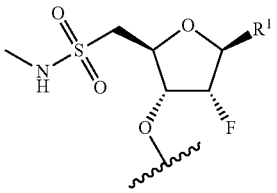
Formula (22)



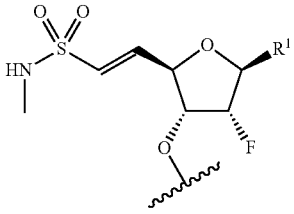
Formula (23)



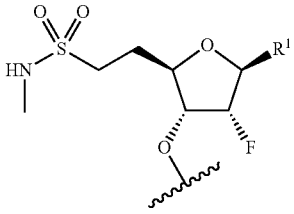
Formula (24)



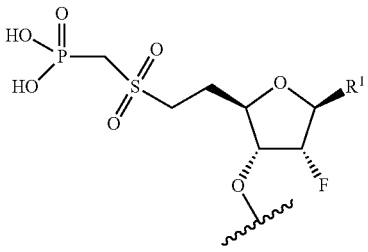
Formula (25)



Formula (26)

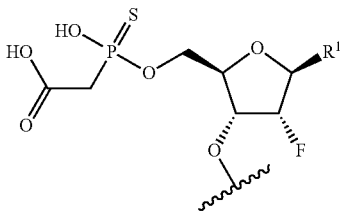


Formula (27)

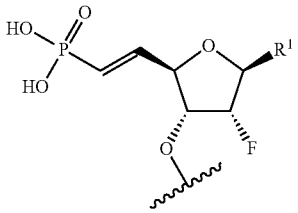


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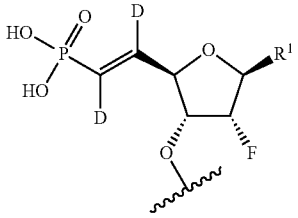
Formula (28)



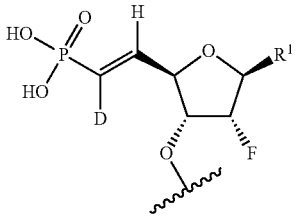
Formula (29)



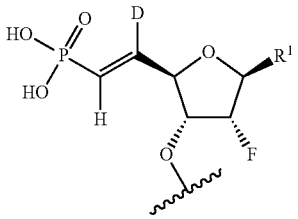
Formula (30)



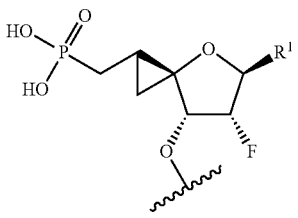
Formula (31)



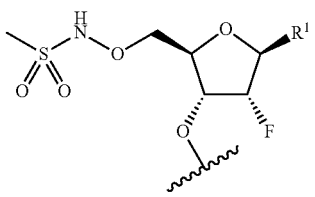
Formula (32)



Formula (33)

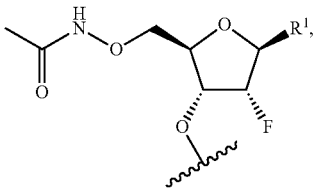


Formula (34)



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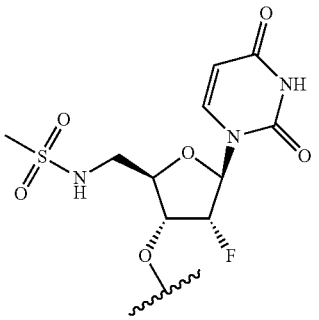
Formula (35)



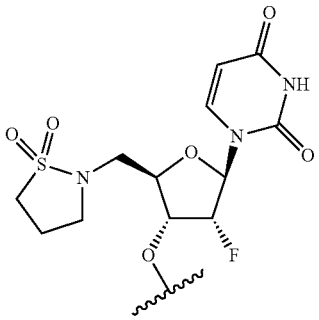
wherein R^1 is a nucleobase, aryl, heteroaryl, or H. In some embodiments, R^1 is an aryl. In some embodiments, the aryl is a phenyl.

[0246] In some embodiments, any of the siNA molecules disclosed herein comprise a 5'-stabilized end cap selected from the group consisting of Formulas (21A)-(35A), Formulas (29B)-(32B), Formulas (29AX)-(32AX), Formulas (29AY)-(32AY), Formulas (29BX)-(32BX), and Formulas (29BY)-(32BY):

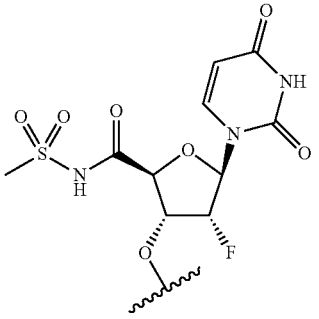
Formula (21A)



Formula (22A)

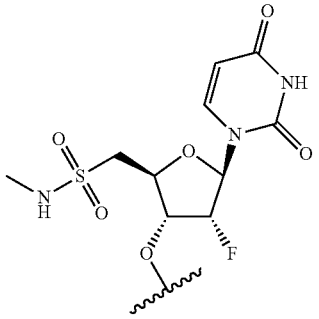


Formula (23A)

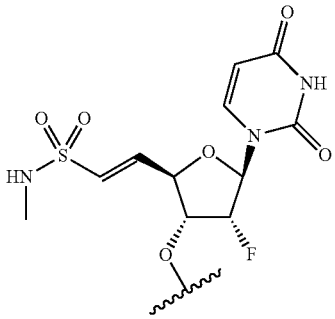


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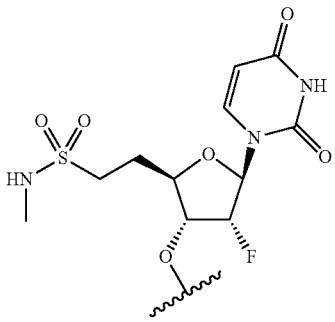
Formula (24A)



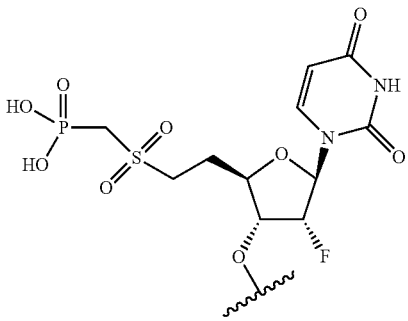
Formula (25A)



Formula (26A)

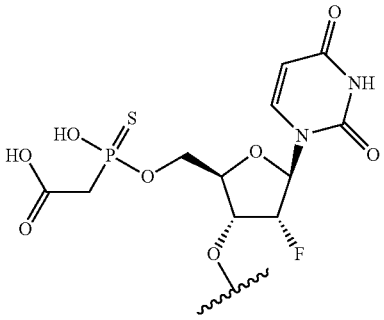


Formula (27A)

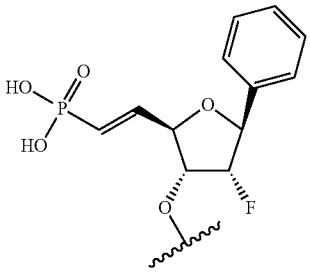


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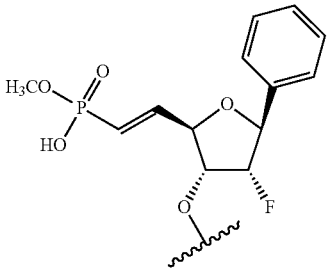
Formula (28A)



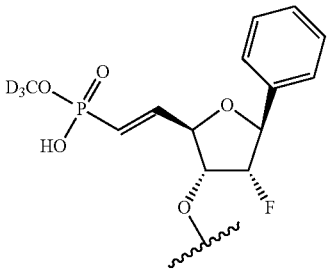
Formula (29A)



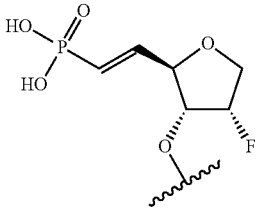
Formula (29AX)



Formula (29AY)

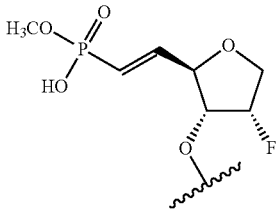


Formula (29B)

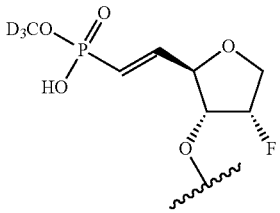


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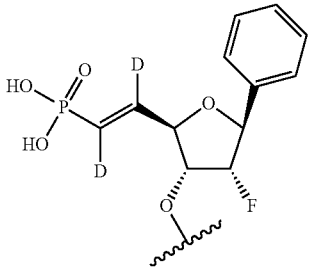
Formula (29BX)



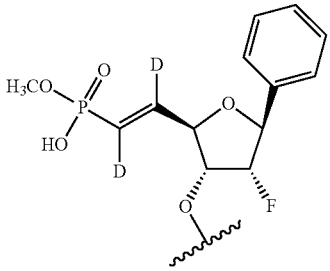
Formula (29BY)



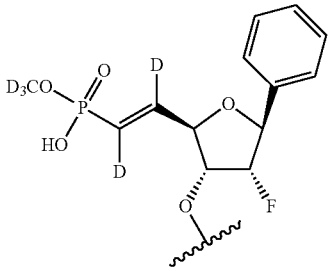
Formula (30A)



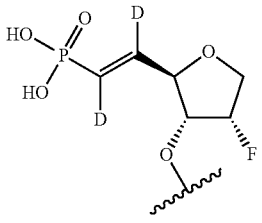
Formula (30AX)



Formula (30AY)

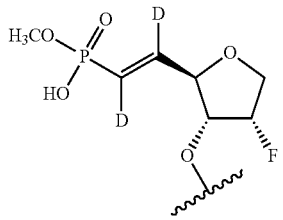


Formula (30B)

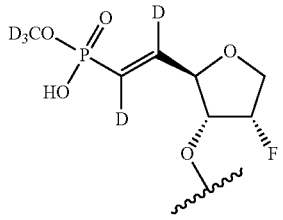


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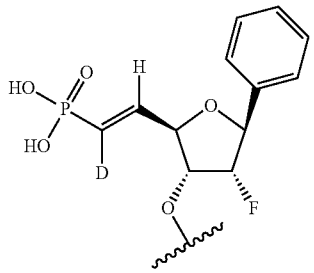
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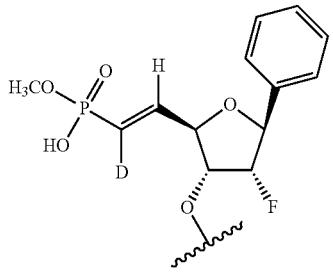
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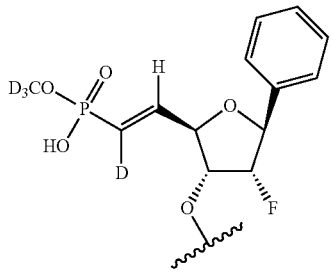
Formula (31A)



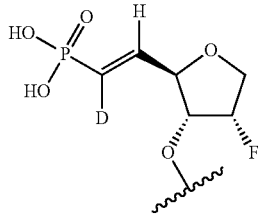
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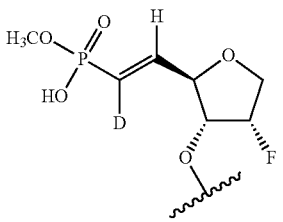


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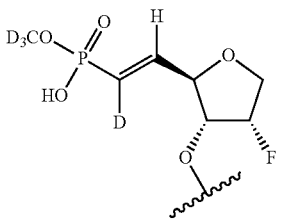


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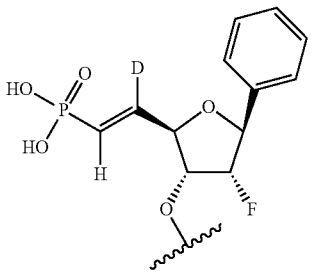
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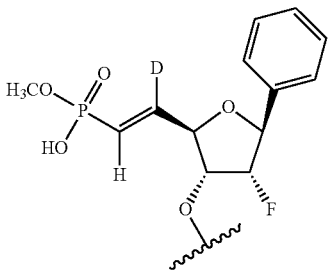
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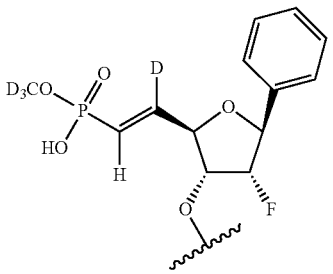
Formula (32A)



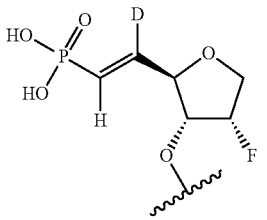
Formula (32AX)



Formula (32AY)

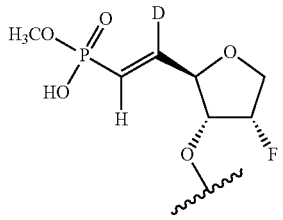


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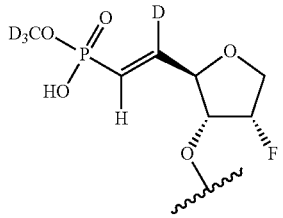


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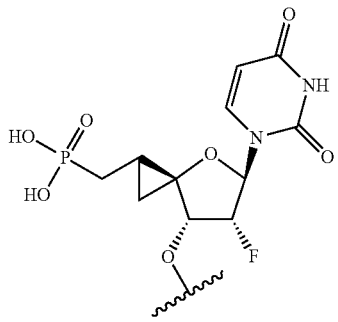
Formula (32BX)



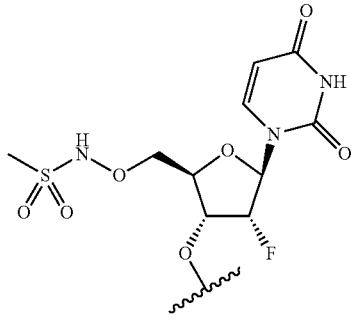
Formula (32BY)



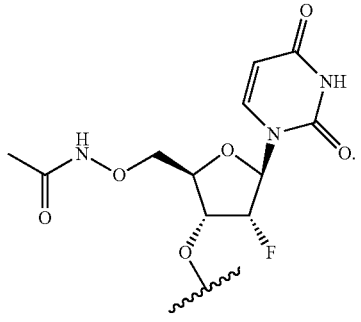
Formula (33A)



Formula (34A)



Formula (35A)



[0247] In some embodiments, the 5'-stabilized end cap is attached to the 5' end of the antisense strand. In some embodiments, the 5'-stabilized end cap is attached to the 5' end of the antisense strand via 1, 2, 3, 4, or 5 or more linkers. In some embodiments, the one or more linkers are independently selected from the group consisting of a phosphodiester (p or po) linker, phosphorothioate (ps) linker (ps), phosphoramidite (HEG) linker, triethylene glycol (TEG) linker, and/or phosphorodithioate linker. In some embodiments, the one or more linkers are independently selected from the group consisting of p-(PS)2, (PS)2-p-TEG-p, (PS) 2-p-HEG-p, and (PS)2-p-(HEG-p)$_2$.

Linker

[0248] In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, and/or second nucleotide sequences disclosed herein comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or more internucleoside linkers. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more internucleoside linkers are independently selected from the group consisting of a phosphodiester (p or po) linker, phosphorothioate (ps) linker, or phosphorodithioate linker.

[0249] In some embodiments, any of the siRNAs, sense strands, first nucleotide sequences, antisense strands, and/or second nucleotide sequences disclosed herein further comprise 1, 2, 3, 4 or more linkers that attach a conjugated moiety, phosphorylation blocker, and/or 5' end cap to the siRNA, sense strand, first nucleotide sequence, antisense strand, and/or second nucleotide sequences. In some embodiments, the 1, 2, 3, 4 or more linkers are independently selected from the group consisting of a phosphodiester (p or po) linker, phosphorothioate (ps) linker, phosphoramidite (HEG) linker, triethylene glycol (TEG) linker, and/or phosphorodithioate linker. In some embodiments, the one or more linkers are independently selected from the group consisting of p-(PS)2, (PS)2-p-TEG-p, (PS)2-p-HEG-p, and (PS)2-p-(HEG-p)$_2$.

Target Gene

[0250] Without wishing to be bound by theory, upon entry into a cell, any of the ds-siNA molecules disclosed herein may interact with proteins in the cell to form a RNA-Induced Silencing Complex (RISC). Once the ds-siNA is part of the RISC, the ds-siNA may be unwound to form a single-stranded siNA (ss-siNA). The ss-siNA may comprise the antisense strand of the ds-siNA. The antisense strand may bind to a complementary messenger RNA (mRNA), which results in silencing of the gene that encodes the mRNA.

[0251] The target gene may be any gene in a cell. In some embodiments, the target gene is a viral gene. In some embodiments, the viral gene is from a DNA virus. In some embodiments, the DNA virus is a double-stranded DNA (dsDNA) virus. In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV). In some embodiments, the HBV is selected from HBV genotypes A-J.

[0252] In some embodiments, the target gene is selected from the S gene or X gene of the HBV. In some embodiments, the HBV has a genome sequence shown in the nucleotide sequence of SEQ ID NO: 410, which corresponds to the nucleotide sequence of GenBank Accession No. U95551.1, which is incorporated by reference in its entirety.

[0253] An exemplary HBV genome sequence is shown in SEQ ID NO: 415, corresponding to Genbank Accession No. KC315400.1, which is incorporated by reference in its entirety. Nucleotides 2307 . . . 3215, 1 . . . 1623 of SEQ ID NO: 415 correspond to the polymerase/RT gene sequence, which encodes for the polymerase protein. Nucleotides 2848

. . . 3215, 1 . . . 835 of SEQ ID NO: 415 correspond to the PreS1/S2/S gene sequence, which encodes for the large S protein. Nucleotides 3205 . . . 3215, 1 . . . 835 of SEQ ID NO: 415 correspond to the PreS2/S gene sequence, which encodes for the middle S protein. Nucleotides 155 . . . 835 of SEQ ID NO: 415 correspond to the S gene sequence, which encodes the small S protein. Nucleotides 1374 . . . 1838 of SEQ ID NO: 415 correspond to the X gene sequence, which encodes the X protein. Nucleotides 1814 . . . 2452 of SEQ ID NO: 415 correspond to the PreC/C gene sequence, which encodes the precore/core protein. Nucleotides 1901.2452 of SEQ ID NO: 415 correspond to the C gene sequence, which encodes the core protein. The HBV genome further comprises viral regulatory elements, such as viral promoters (preS2, preS1, Core, and X) and enhancer elements (ENH1 and ENH2). Nucleotides 1624 . . . 1771 of SEQ ID NO: 415 correspond to ENH2. Nucleotides 1742 . . . 1849 of SEQ ID NO: 415 correspond to the Core promoter. Nucleotides 1818 . . . 3215, 1 . . . 1930 of SEQ ID NO: 415 correspond to the pregenomic RNA (pgRNA), which encodes the core and polymerase proteins.

[0254] In some embodiments, the ASO is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary or hybridizes to a viral target RNA sequence that begins in an X region of HBV or in an S region of HBV. The viral target may, e.g., begin at the 5'-end of target-site in acc. KC315400.1 (genotype B, "gt B"), or in any one of genotypes A, C, or D. The skilled person would understand the HBV position, e.g., as described in Wing-Kin Sung, et al., *Nature Genetics* 44:765 (2012). In some embodiments, the S region is defined as from the beginning of small S protein (in genotype B KC315400.1 isolate, position #155) to before beginning of X protein (in genotype B KC315400.1 isolate, position #1373). In some embodiments, the X region is defined as from the beginning X protein (in genotype B KC315400.1 isolate, position #1374) to end of DR2 site (in genotype B KC315400.1 isolate, position #1603).

[0255] In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21, or 19 to 21 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410. In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21, or 19 to 21 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410. In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21, or 19 to 21 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410. In some embodiments, the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21,or 19 to 21 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

[0256] In some embodiments, the first nucleotide is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to a nucleotide region within SEQ ID NO: 410, with the exception that the thymines (Ts) in SEQ ID NO: 410 are replaced with uracil (U). In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21, or 19 to 21 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410. In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21,or 19 to 21 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410. In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21,or 19 to 21 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410. In some embodiments, the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30, 15 to 25, 15 to 23, 15 to 22, 15 to 21, 17 to 25, 17 to 23, 17 to 22, 17 to 21, or 19 to 21 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

[0257] In some embodiments, the target gene is involved in liver metabolism. In some embodiments, the target gene is an inhibitor of the electron transport chain. In some embodiments, the target gene encodes the MCJ protein (MCJ/DnaJC15 or Methylation-Controlled J protein). In some embodiments, the MCJ protein is encoded by the mRNA sequence of SEQ ID NO: 411, which corresponds to the nucleotide sequence of GenBank Accession No. NM_013238.3, which is incorporated by reference in its entirety.

[0258] In some embodiments, the target gene is TAZ. In some embodiments, TAZ comprises the nucleotide sequence of SEQ ID NO: 412, which corresponds to the nucleotide sequence of GenBank Accession No. NM_000116.5, which is incorporated by reference in its entirety.

[0259] In some embodiments, the target gene is angiopoietin like 3 (ANGPTL3). In some embodiments, ANGPTL3 comprises the nucleotide sequence of SEQ ID NO: 413, which corresponds to the nucleotide sequence of GenBank Accession No. NM_014495.4, which is incorporated by reference in its entirety.

[0260] In some embodiments, the target gene is diacylglycerol acyltransferase 2 (DGAT2). In some embodiments, DGAT2 comprises the nucleotide sequence of SEQ ID NO: 414, which corresponds to the nucleotide sequence of GenBank Accession No. NM_001253891.1, which is incorporated by reference in its entirety.

Compositions

[0261] As indicated above, the present disclosure provides compositions comprising any of the siNA molecules, sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. The compositions may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more siNA molecules described herein. The compositions may comprise a first nucleotide sequence comprising a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260. In some embodiments, the composition comprises a second nucleotide sequence comprising a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306. In some embodiments, the composition comprises a sense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444. In some embodiments, the composition comprises an antisense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

[0262] Alternatively, the compositions may comprise (a) a phosphorylation blocker; and (b) a short interfering nucleic acid (siNA). In some embodiments, the phosphorylation blocker is any of the phosphorylation blockers disclosed herein. In some embodiments, the siNA is any of the siNAs disclosed herein. In some embodiments, the siNA comprises any of the sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. In some embodiments, the siNA comprises any of the sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. In some embodiments, the siNA comprises one or more modified nucleotides. In some embodiments, the one or more modified nucleotides are independently selected from a 2'-fluoro nucleotide and a 2'-O-methyl nucleotide. In some embodiments, the 2'-fluoro nucleotide or the 2'-O-methyl nucleotide is independently selected from any of the 2'-fluoro or 2'-O-methyl nucleotide mimics disclosed herein. In some embodiments, the siNA comprises a nucleotide sequence comprising any of the modification patterns disclosed herein.

[0263] In some embodiments, the composition comprises (a) a conjugated moiety; and (b) a short interfering nucleic acid (siNA). In some embodiments, the conjugated moiety is any of the galactosamines disclosed herein. In some embodiments, the siNA is any of the siNAs disclosed herein. In some embodiments, the siNA comprises any of the sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. In some embodiments, the siNA comprises any of the sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. In some embodiments, the siNA comprises one or more modified nucleotides. In some embodiments, the one or more modified nucleotides are independently selected from a 2'-fluoro nucleotide and a 2'-O-methyl nucleotide. In some embodiments, the 2'-fluoro nucleotide or the 2'-O-methyl nucleotide is independently selected from any of the 2'-fluoro or 2'-O-methyl nucleotide mimics disclosed herein. In some embodiments, the siNA comprises a nucleotide sequence comprising any of the modification patterns disclosed herein.

[0264] In some embodiments, the composition comprises (a) a 5'-stabilized end cap; and (b) a short interfering nucleic acid (siNA). In some embodiments, the 5'-stabilized end cap is any of the 5-stabilized end caps disclosed herein. In some embodiments, the siNA is any of the siNAs disclosed herein. In some embodiments, the siNA comprises any of the sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. In some embodiments, the siNA comprises one or more modified nucleotides. In some embodiments, the one or more modified nucleotides are independently selected from a 2'-fluoro nucleotide and a 2'-O-methyl nucleotide. In some embodiments, the 2'-fluoro nucleotide or the 2'-O-methyl nucleotide is independently selected from any of the 2'-fluoro or 2'-O-methyl nucleotide mimics disclosed herein. In some embodiments, the siNA comprises a nucleotide sequence comprising any of the modification patterns disclosed herein.

[0265] In some embodiments, the composition comprises (a) at least one phosphorylation blocker, conjugated moiety, or 5'-stabilized end cap; and (b) a short interfering nucleic acid (siNA). In some embodiments, the phosphorylation blocker is any of the phosphorylation blockers disclosed herein. In some embodiments, the conjugated moiety is any of the galactosamines disclosed herein. In some embodiments, the 5'-stabilized end cap is any of the 5-stabilized end caps disclosed herein. In some embodiments, the siNA is any of the siNAs disclosed herein. In some embodiments, the siNA comprises any of the sense strands, antisense strands, first nucleotide sequences, or second nucleotide sequences described herein. In some embodiments, the siNA comprises one or more modified nucleotides. In some embodiments, the one or more modified nucleotides are independently selected from a 2'-fluoro nucleotide and a 2'-O-methyl nucleotide. In some embodiments, the 2'-fluoro nucleotide or the 2'-O-methyl nucleotide is independently selected from any of the 2'-fluoro or 2'-O-methyl nucleotide mimics disclosed herein. In some embodiments, the siNA comprises a nucleotide sequence comprising any of the modification patterns disclosed herein.

[0266] The composition may be a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an amount of one or more of the siNA molecules described herein formulated with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

[0267] The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a siNA of the present disclosure which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[0268] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0269] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0270] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0271] Formulations of the present disclosure include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound (e.g., siNA molecule) which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0272] In certain embodiments, a formulation of the present disclosure comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound (e.g., siNA molecule) of the present disclosure. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound (e.g., siNA molecule) of the present disclosure.

[0273] Methods of preparing these formulations or compositions include the step of bringing into association a compound (e.g., siNA molecule) of the present disclosure with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound (e.g., siNA molecule) of the present disclosure with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0274] Formulations of the disclosure suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound (e.g., siNA molecule) of the present disclosure as an active ingredient. A compound (e.g., siNA molecule) of the present disclosure may also be administered as a bolus, electuary or paste.

[0275] In solid dosage forms of the disclosure for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose.

[0276] In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0277] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0278] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present disclosure, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried.

[0279] They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and

may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0280] Liquid dosage forms for oral administration of the compounds (e.g., siNA molecules) of the disclosure include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (I particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0281] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0282] Suspensions, in addition to the active compounds (e.g., siNA molecules), may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0283] Formulations of the pharmaceutical compositions of the disclosure for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds (e.g., siNA molecules) of the disclosure with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound (e.g., siNA molecule).

[0284] Formulations of the present disclosure which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0285] Dosage forms for the topical or transdermal administration of a compound (e.g., siNA molecule) of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound (e.g., siNA molecule) may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0286] The ointments, pastes, creams and gels may contain, in addition to an active compound (e.g., siNA molecule) of this disclosure, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0287] Powders and sprays can contain, in addition to a compound (e.g., siNA molecule) of this disclosure, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0288] Transdermal patches have the added advantage of providing controlled delivery of a compound (e.g., siNA molecule) of the present disclosure to the body. Such dosage forms can be made by dissolving or dispersing the compound (e.g., siNA molecule) in the proper medium. Absorption enhancers can also be used to increase the flux of the compound (e.g., siNA molecule) across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound (e.g., siNA molecule) in a polymer matrix or gel.

[0289] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0290] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise one or more compounds (e.g., siNA molecules) of the disclosure in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0291] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0292] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0293] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0294] Injectable depot forms are made by forming microencapsule matrices of the subject compounds (e.g., siNA molecules) in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate

of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0295] When the compounds (e.g., siNA molecules) of the present disclosure are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of Treatment and Administration

[0296] The siNA molecules of the present disclosure may be used to treat a disease in a subject in need thereof. In some embodiments, a method of treating a disease in a subject in need thereof comprises administering to the subject any of the siNA molecules disclosed herein. In some embodiments, a method of treating a disease in a subject in need thereof comprises administering to the subject any of the compositions disclosed herein.

[0297] The preparations (e.g., siNA molecules or compositions) of the present disclosure may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[0298] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0299] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0300] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0301] Regardless of the route of administration selected, the compounds (e.g., siNA molecules) of the present disclosure, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present disclosure, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0302] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this disclosure may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0303] The selected dosage level will depend upon a variety of factors including the activity of the particular compound (e.g., siNA molecule) of the present disclosure employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0304] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds (e.g., siNA molecules) of the disclosure employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0305] In general, a suitable daily dose of a compound (e.g., siNA molecule) of the disclosure is the amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose generally depends upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. In some embodiments, the compound is administered at a dose equal to or greater than 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or 1 mg/kg. In some embodiments, the compound is administered at a dose equal to or less than 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, or 15 mg/kg. In some embodiments, the total daily dose of the compound is equal to or greater than 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 100 mg.

[0306] When the compounds (e.g., siNA molecules) described herein are co-administered with another, the effective amount may be less than when the compound is used alone.

[0307] If desired, the effective daily dose of the active compound (e.g., siNA molecule) may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day. In some embodiments, the compound is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 times a week. In some embodiments, the compound is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 times a month. In some embodiments, the compound is administered once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days. In some embodiments, the compound is administered once every 1, 2, 3, 4, 5, 6, 7, or 8 weeks.

Diseases

[0308] The siNA molecules and compositions described herein may be administered to a subject to treat a disease. Further disclosed herein are uses of any of the siNA molecules or compositions disclosed herein in the manufacture of a medicament for treating a disease.

[0309] In some embodiments, the disease is a viral disease. In some embodiments, the viral disease is caused by a DNA virus. In some embodiments, the DNA virus is a double stranded DNA (dsDNA virus). In some embodiments, the dsDNA virus is a hepadnavirus. In some embodiments, the hepadnavirus is a hepatitis B virus (HBV).

[0310] In some embodiments, the disease is a liver disease. In some embodiments, the liver disease is nonalcoholic fatty liver disease (NAFLD). In some embodiments, the NAFLD is nonalcoholic steatohepatitis (NASH). In some embodiments, the liver disease is hepatocellular carcinoma (HCC).

Administration of siNA

[0311] Administration of any of the siNAs disclosed herein may be conducted by methods known in the art. In some embodiments, the siNA is administered by subcutaneous (SC) or intravenous (IV) delivery. The preparations (e.g., siNAs or compositions) of the present disclosure may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. In some embodiments, subcutaneous administration is preferred.

[0312] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0313] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0314] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0315] Regardless of the route of administration selected, the compounds (e.g., siNAs) of the present disclosure, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present disclosure, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0316] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this disclosure may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0317] The selected dosage level will depend upon a variety of factors including the activity of the particular compound (e.g., siNA) of the present disclosure employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0318] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds (e.g., siNAs) of the disclosure employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0319] In general, a suitable daily dose of a compound (e.g., siNA) of the disclosure is the amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose generally depends upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. In some embodiments, the compound is administered at about 1 mg/kg to about 40 mg/kg, about 1 mg/kg to about 30 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, or 1 mg/kg to about 10 mg/kg. In some embodiments, the compound is administered at a dose equal to or greater than 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.29, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, or 1 mg/kg. In some embodiments, the compound is administered at a dose equal to or greater than 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, or 30 mg/kg. In some embodiments, the compound is administered at a dose equal to or less than 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, or 15 mg/kg. In some embodiments, the total daily dose of the compound is equal to or greater than 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 100 mg.

[0320] If desired, the effective daily dose of the active compound (e.g., siNA) may be administered as two, three, four, five, six, seven, eight, nine, ten or more doses or sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In some embodiments, the compound is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 times. Preferred dosing is one administration per day. In some embodiments, the compound is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 times a week. In some embodiments, the compound is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,

18, 19, 20, or 21 times a month. In some embodiments, the compound is administered once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days. In some embodiments, the compound is administered every 3 days. In some embodiments, the compound is administered once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 weeks. In some embodiments, the compound is administered every month. In some embodiments, the compound is administered once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 months. In some embodiments, the compound is administered 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, or 53 times over a period of 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, or 70 days. In some embodiments, the compound is administered 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, or 53 times over a period of 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, or 53 weeks. In some embodiments, the compound is administered 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, or 53 times over a period of 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, or 53 months. In some embodiments, the compound is administered at least once a week for a period of 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, or 70 weeks. In some embodiments, the compound is administered at least once a week for a period of 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, or 70 months. In some embodiments, the compound is administered at least twice a week for a period of 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, or 70 weeks. In some embodiments, the compound is administered at least twice a week for a period of 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, or 70 months. In some embodiments, the compound is administered at least once every two weeks for a period of 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, 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, or 70 weeks. In some embodiments, the compound is administered at least once every two weeks for a period of 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, 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, or 70 months. In some embodiments, the compound is administered at least once every four weeks for a period of at least 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, or 70 weeks. In some embodiments, the compound is administered at least once every four weeks for a period of at least 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, or 70 months.

[0321] In some embodiments, any one of the siNAs or compositions disclosed herein is administered in a particle or viral vector. In some embodiments, the viral vector is a vector of adenovirus, adeno-associated virus (AAV), alphavirus, flavivirus, herpes simplex virus, lentivirus, measles virus, picornavirus, poxvirus, retrovirus, or rhabdovirus. In some embodiments, the viral vector is a recombinant viral vector. In some embodiments, the viral vector is selected from AAVrh.74, AAVrh.10, AAVrh.20, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11, AAV-12 and AAV-13.

[0322] The subject of the described methods may be a mammal, and it includes humans and non-human mammals. In some embodiments, the subject is a human, such as an adult human.

[0323] Some embodiments include a method for treating an HBV virus in a subject infected with the virus comprising administering a therapeutically effective amount of one or more siNA of the present disclosure or a composition of the present disclosure to the subject in need thereof thereby reducing the viral load of the virus in the subject and/or reducing a level of a virus antigen in the subject. The siNA may be complementary or hybridize to a portion of the target RNA in the virus, e.g., an X region and/or an S region of HBV.

Combination Therapies

[0324] Any of the methods disclosed herein may further comprise administering to the subject an additional HBV treatment agent. Any of the compositions disclosed herein may further comprise an additional HBV treatment agent. In some embodiments, the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy. In some embodiments, the additional HBV treatment agent is selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423,

AB-506, ABI-H03733 and ABI-H2158. In some embodiments, the oligonucleotide therapy is selected from Nucleic Acid Polymers or S-Antigen Transport-inhibiting Oligonucleotide Polymers (NAPs or STOPS), siRNA, and ASO. In some embodiments, the oligonucleotide therapy is an additional siNA. In some embodiments, the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178. In some embodiments, the oligonucleotide therapy is an antisense oligonucleotide (ASO). In some embodiments, the ASO is ASO 1. In some embodiments, any of the siNAs disclosed herein are co-administered with STOPS. Exemplary STOPS are described in International Publication No. WO2020/097342 and U.S. Publication No. 2020/0147124, both of which are incorporated by reference in their entirety. In some embodiments, the STOPS is ALG-010133. In some embodiments, any of the siNAs disclosed herein are co-administered with tenofovir. In some embodiments, any of the siNAs disclosed herein are co-administered with a CAM. Exemplary CAMs are described in Berke et al., *Antimicrob Agents Chemother,* 2017, 61(8):e00560-17, Klumpp, et al., Gastroenterology, 2018, 154(3):652-662.e8, International Application Nos. PCT/US2020/017974, PCT/US2020/026116, and PCT/US2020/028349 and U.S. application Ser. Nos. 16/789,298, 16/837,515, and 16/849,851, each which is incorporated by reference in its entirety. In some embodiments, the CAM is ALG-000184, ALG-001075, ALG-001024, JNJ-632, BAY41-4109, or NVR3-778. In some embodiments, the siNA and the HBV treatment agent are administered simultaneously. In some embodiments, the siNA and the HBV treatment agent are administered concurrently. In some embodiments, the siNA and the HBV treatment agent are administered sequentially. In some embodiments, the siNA is administered prior to administering the HBV treatment agent. In some embodiments, the siNA is administered after administering the HBV treatment agent. In some embodiments, the siNA and the HBV treatment agent are in separate containers. In some embodiments, the siNA and the HBV treatment agent are in the same container.

[0325] Any of the methods disclosed herein may further comprise administering to the subject a liver disease treatment agent. Any of the compositions disclosed herein may further comprise a liver disease treatment agent. In some embodiments, the liver disease treatment agent is selected from a peroxisome proliferator-activator receptor (PPAR) agonist, farnesoid X receptor (FXR) agonist, lipid-altering agent, and incretin-based therapy. In some embodiments, the PPAR agonist is selected from a PPARα agonist, dual PPARα/δ agonist, PPARγ agonist, and dual PPARα/γ agonist. In some embodiments, the dual PPARα agonist is a fibrate. In some embodiments, the PPARα/δ agonist is elafibranor. In some embodiments, the PPARγ agonist is a thiazolidinedione (TZD). In some embodiments, TZD is pioglitazone. In some embodiments, the dual PPARα/γ agonist is saroglitazar. In some embodiments, the FXR agonist is obeticholic acis (OCA). In some embodiments, the lipid-altering agent is aramchol. In some embodiments, the incretin-based therapy is a glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor. In some embodiments, the GLP-1 receptor agonist is exenatide or liraglutide. In some embodiments, the DPP-4 inhibitor is sitagliptin or vildapliptin. In some embodiments, the siNA and the liver disease treatment agent are administered concurrently. In some embodiments, the siNA and the liver disease treatment agent are administered sequentially. In some embodiments, the siNA is administered prior to administering the liver disease treatment agent. In some embodiments, the siNA is administered after administering the liver disease treatment agent. In some embodiments, the siNA and the liver disease treatment agent are in separate containers. In some embodiments, the siNA and the liver disease treatment agent are in the same container.

Definitions

[0326] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al., (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise. The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the disclosure.

[0327] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0328] As used herein, the terms "patient" and "subject" refer to organisms to be treated by the methods of the present disclosure. Such organisms are preferably mammals (e.g., marines, simians, equines, bovines, porcinis, canines, felines, and the like), and more preferably humans.

[0329] As used herein, the term "effective amount" refers to the amount of a compound (e.g., a siNA of the present disclosure) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0330] As used herein, the term "treating" includes any effect, e.g., lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0331] As used herein, the terms "alleviate" and "alleviating" refer to reducing the severity of the condition, such as reducing the severity by, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%.

[0332] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

[0333] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see, for example, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, Pa. [1975].

[0334] The term "about" as used herein when referring to a measurable value (e.g., weight, time, and dose) is meant to encompass variations, such as ±10%, 5%, ±1%, or ±0.1% of the specified value.

[0335] As used herein, the term "nucleobase" refers to a nitrogen-containing biological compound that forms a nucleoside. Examples of nucleobases include, but are not limited to, thymine, uracil, adenine, cytosine, guanine, aryl, heteroaryl, and an analogue or derivative thereof.

[0336] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present disclosure that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present disclosure that consist essentially of, or consist of, the recited processing steps.

[0337] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

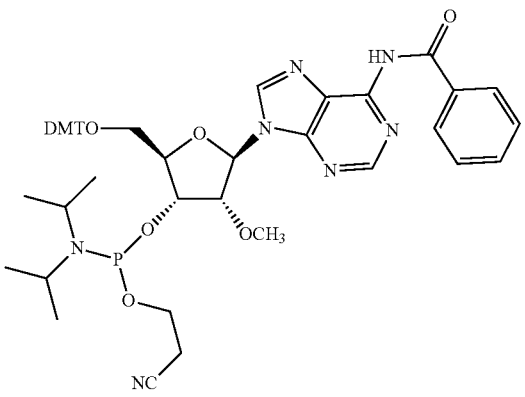
[0338] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates that may need to be independently confirmed.

EXAMPLES

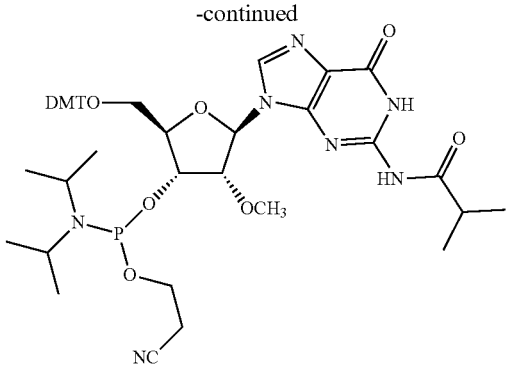
Example 1. siNA Synthesis

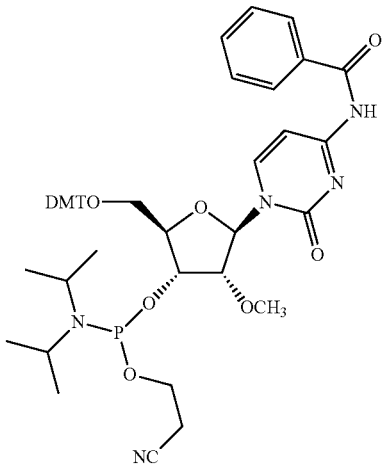
[0339] This example describes an exemplary method for synthesizing ds-siNAs, such as the siNAs disclosed in Table 6 (as identified by the ds-siNA ID).

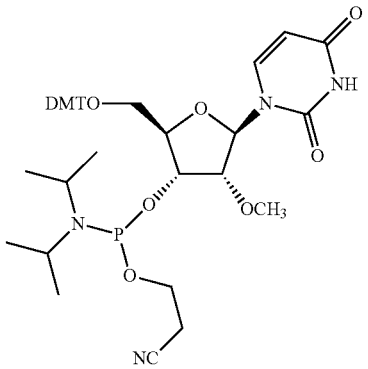
[0340] The 2'-OMe phosphoramidite 5'-O-DMT-deoxy Adenosine (NH-Bz), 3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite, 5'-O-DMT-deoxy Guanosine (NH-ibu), 3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite, 5'-O-DMT-deoxy Cytosine (NH-Bz), 3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite, 5'-O-DMT-Uridine 3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite and solid supports were purchased from Chemgenes Corp. MA.



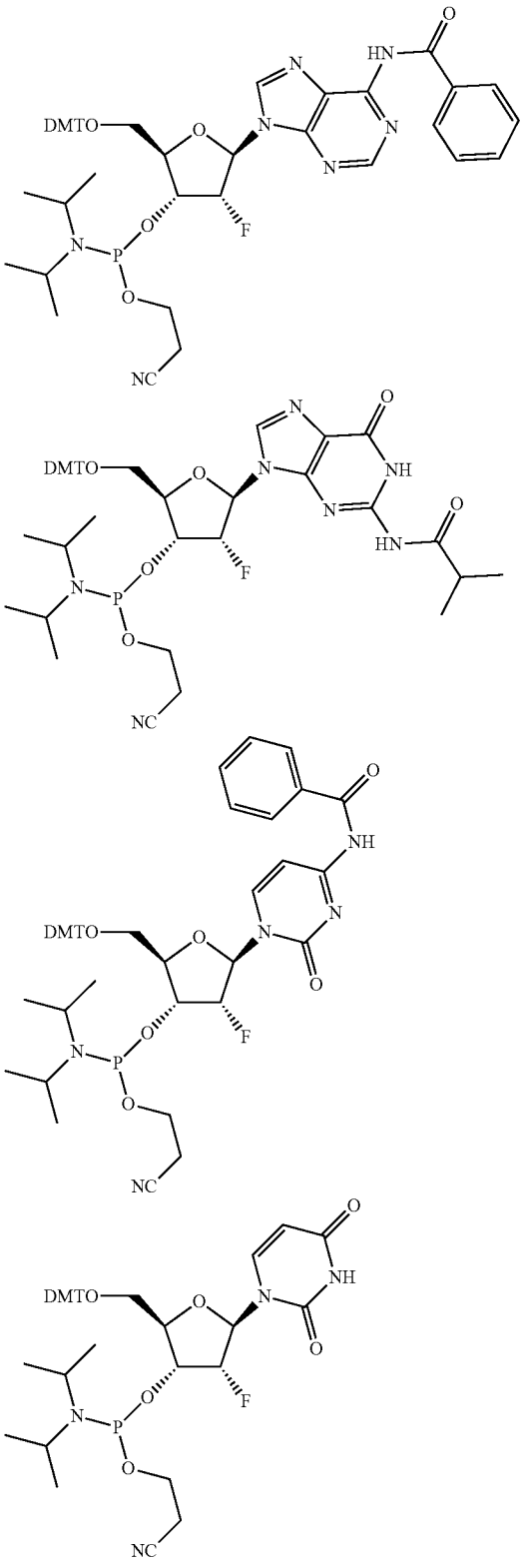
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[0341] The 2'-F-5'-O-DMT-(NH-Bz) Adenosine-3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite, 2'-F-5'-O-DMT-(NH-ibu)-Guanosine, 3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite, 5'-O-DMT-(NH-Bz)-Cytosine, 2'-F-3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite, 5'-O-DMT-Uridine, 2'-F-3'-O-(2-cyanoethyl-N,N-diisopropyl phosphoramidite and solid supports were purchased from Thermo Fischer Milwaukee Wis., USA.



[0342] All the monomers were dried in vacuum desiccator with desiccants (P205, RT 24h). The solid supports (CPG) attached to the nucleosides and universal supports was obtained from LGC and Chemgenes. The chemicals and solvents for post synthesis workflow were purchased from commercially available sources like VWR/Sigma and used without any purification or treatment. Solvent (Acetonitrile) and solutions (amidite and activator) were stored over molecular sieves during synthesis.

[0343] The oligonucleotides were synthesized on a DNA/RNA Synthesizers (Expedite 8909 or ABI-394) using standard oligonucleotide phosphoramidite chemistry starting from the 3' residue of the oligonucleotide preloaded on CPG support. An extended coupling of 0.1M solution of phosphoramidite in CH_3CN in the presence of 5-(ethylthio)-1H-tetrazole activator to a solid bound oligonucleotide followed by standard capping, oxidation and deprotection afforded modified oligonucleotides. The 0.1M I_2, THF:Pyridine; Water-7:2:1 was used as oxidizing agent while DDTT ((dimethylamino-methylidene) amino)-3H-1,2,4-dithiazaoline-3-thione was used as the sulfur-transfer agent for the synthesis of oligoribonucleotide phosphorothioates. The stepwise coupling efficiency of all modified phosphoramidites was more than 98%.

Reagents	Detailed Description
Deblock Solution	3% Dichloroacetic acid (DCA) in Dichloromethane (DCM)
Amidite Concentration	0.1M in Anhydrous Acetonitrile
Activator	0.25M Ethyl-thio-Tetrazole (ETT)
Cap-A solution	Acetic anhydride in Pyridine/THF
Cap-B Solution	16% 1-Methylimidazole in THF
Oxidizing Solution	0.02M I_2, THF:Pyridine; Water-7:2:1
Sulfurizing Solution	0.2M DDTT in Pyridine/Acetonitrile 1:1

[0344] Cleavage and Deprotection:

[0345] Deprotection and cleavage from the solid support was achieved with mixture of ammonia methylamine (1:1, AMA) for 15 min at 65° C., when the universal linker was used, the deprotection was left for 90 min at 65° C. or solid supports were heated with aqueous ammonia (28%) solution at 55° C. for 16 h to deprotect the base labile protecting groups.

[0346] Quantitation of Crude SiNA or Raw Analysis

[0347] Samples were dissolved in deionized water (1.0 mL) and quantitated as follows: Blanking was first performed with water alone (2 ul) on Nanodrop then Oligo sample reading obtained at 260 nm. The crude material is dried down and stored at −20° C.

[0348] Crude HPLC/LC-MS Analysis

[0349] The 0.1 OD of the crude samples were analyzed for crude HPLC and LC-MS analysis. After Confirming the crude LC-MS data then purification step was performed.

[0350] HPLC Purification

[0351] The unconjugated and GalNac modified oligonucleotides were purified by anion-exchange HPLC. The buffers were 20 mM sodium phosphate in 10% CH_3CN, pH 8.5 (buffer A) and 20 mM sodium phosphate in 10% CH_3CN, 1.0 M NaBr, pH 8.5 (buffer B). Fractions containing full-length oligonucleotides were pooled.

[0352] Desalting of Purified SiNA

[0353] The purified dry siNA was then desalted using Sephadex G-25 M (Amersham Biosciences). The cartridge was conditioned with 10 mL of deionized water thrice. Finally, the purified siNA dissolved thoroughly in 2.5 mL RNAse free water was applied to the cartridge with very

slow drop wise elution. The salt free siNA was eluted with 3.5 ml deionized water directly into a screw cap vial.

[0354] IEX HPLC and Electrospray LC/MS Analysis

[0355] Approximately 0.10 OD of siNA is dissolved in water and then pipetted in special vials for IEX-HPLC and LC/MS analysis. Analytical HPLC and ES LC-MS established the integrity of the compounds.

[0356] Duplex Preparation:

[0357] Single strand oligonucleotides (Sense and Antisense strands) were annealed (1:1 by molar equivalents, heat 90° C. for 3 min followed by room temperature, 20 min) to give the duplex ds-siNA. The final compounds were analyzed on size exclusion chromatography (SEC).

Example 2. Ds-siNA Activity

[0358] This example investigates the activity of the ds-siNAs synthesized in Example 1.

[0359] *Homo sapiens* HepG2.2.15 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (ATCC 30-2002) supplemented to also contain 10% fetal calf serum (FCS). Cells were incubated at 37° C. in an atmosphere with 5% CO_2 in a humidified incubator. For transfection of HepG2.2.15 cells with HBV targeting siRNAs, cells were seeded at a density of 15000 cells/well in 96-well regular tissue culture plates. Transfection of cells was carried out using RNAiMAX (Invitrogen/Life Technologies) according to the manufacturer's instructions. Dose-response experiments were done with oligo concentrations of 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625 and 0.07813 nM. For each HBV targeting siRNA treatment (e.g., ds-siRNA, as identified by the ds-siNA ID in Table 6), four wells were transfected in parallel, and individual data points were collected from each well. After 24h of incubation with siRNA, media was removed, and cells were lysed and analyzed with a QuantiGene2.0 branched DNA (bDNA) probe set specific for HBV genotype D (also called Hepatitis B virus subtype ayw, complete genome of 3182 base-pairs) as present in cell line HepG2.2.15.

[0360] For each well, the HBV on-target mRNA levels were normalized to the GAPDH mRNA level. As shown in Table 6, the activity of the HBV targeting ds-siRNAs was expressed as EC50, 50% reduction of normalized HBV RNA level from no drug control. As shown in Table 6, the cytotoxicity of the HBV targeting ds-siRNAs was expressed by CC50 of 50% reduction of GAPDH mRNA from no drug control.

Example 3. Use of Ds-siNAs to Treat Hepatitis B Virus Infection

[0361] In this example, the ds-siNAs synthesized in Example 1 are used to treat a hepatitis B virus infection in a subject. Generally, a composition comprising a ds-siNA from Table 6 (as identified by the ds-siNA ID) and a pharmaceutically acceptable carrier is administered to the subject suffering from hepatitis B virus. The ds-siNA from Table 6 is conjugated to N-acetylgalactosamine. The ds-siNA is administered at a dose of 0.3 to 5 mg/kg every three weeks by subcutaneous injection or intravenous infusion.

Example 4. Ds-siNA Hepatitis B Clinical Trial

[0362] In this example, the ds-siNAs from Tables 6A and 6B (as identified by the ds-siNA ID) will be evaluated for safety and efficacy in healthy volunteers and chronic hepatitis B patients.

[0363] ds-siNAs are being developed for the treatment of chronic hepatitis B (CHB) in adults. The study will be conducted in 3 parts, a single ascending-dose (SAD) phase in healthy volunteers (Group A), a single-dose (SD) phase in patients with CHB (Group B), and a multiple ascending-dose (MAD) phase in patients with CHB (Group C).

Study Design

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	50 participants
Allocation:	Randomized
Intervention Model:	Sequential Assignment
Intervention Model Description:	Progression from the SAD phase to the first cohort in the MAD phase is contingent upon the Safety Review Committee (SRC) review of a minimum of 14 days post-dose safety and tolerability data from all HV in at least the first 2 SAD cohorts. The SRC will select one (or more) well-tolerated dose(s) from the SAD phase for administration in the SD and MAD phases. In all study phases, dosing will be staggered with the use of sentinel participants to allow time for the assessment of safety before additional subjects are exposed to study drug.
Masking:	Triple (Participant, Care Provider, Investigator)
Masking Description:	This is a double-blind placebo-controlled study in which the study site team, the Sponsor, and the participants will be blinded to treatment assignment. The unblinded pharmacist will cover each syringe, prior to transport to the bedside, to ensure blinding. Participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS).
Primary Purpose:	Treatment

Arms and Interventions

Arm	Intervention/treatment
Experimental: Cohort A1 ds-siNA Single dose, Subcutaneous injection of 0.1 mg/kg of ds-siNA (HV)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort A1 Placebo Single dose, Subcutaneous injection of 0.1 mg/kg of Placebo for ds-siNA (HV)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort A2 ds-siNA Single dose, Subcutaneous injection of 1.5 mg/kg of ds-siNA (HV)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort A2 Placebo Single dose, Subcutaneous injection of 1.5 mg/kg of Placebo for ds-siNA (HV)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo

-continued

Arms and Interventions	
Arm	Intervention/treatment
Experimental: Cohort A3 ds-siNA Single dose, Subcutaneous injection of 3 mg/kg of ds-siNA (HV)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort A3 Placebo Single dose, Subcutaneous injection of 3 mg/kg of Placebo for ds-siNA (HV)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort A4 ds-siNA Single dose, Subcutaneous injection of 6 mg/kg of ds-siNA (HV)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort A4 Placebo Single dose, Subcutaneous injection of 6 mg/kg of Placebo for ds-siNA (HV)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort A5 ds-siNA Single dose, Subcutaneous injection of 12 mg/kg of ds-siNA (HV)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort A5 Placebo Single dose, Subcutaneous injection of 12 mg/kg of Placebo for ds-siNA (HV)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort B ds-siNA Single dose, Subcutaneous injection of 3 mg/kg of for ds-siNA (NUC naïve, CHB)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort B Placebo Single dose, Subcutaneous injection of 3 mg/kg of Placebo for ds-siNA (NUC naïve, CHB)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort C1 ds-siNA 4 doses- Subcutaneous injection of 1.5 mg/kg of ds-siNA administered every 28 days (NUC experienced, CHB)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).

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Arms and Interventions	
Arm	Intervention/treatment
Placebo Comparator: Cohort C1 Placebo 4 doses- Subcutaneous injection of 1.5 mg/kg of Placebo for ds-siNA administered every 28 days (NUC experienced, CHB)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort C2 ds-siNA 4 doses- Subcutaneous injection of 3 mg/kg of ds-siNA administered every 28 days (NUC experienced, CHB)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort C2 Placebo 4 doses- Subcutaneous injection of 3 mg/kg of Placebo for ds-siNA administered every 28 days (NUC experienced, CHB)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo
Experimental: Cohort C3 ds-siNA 4 doses- Subcutaneous injection of 6 mg/kg of ds-siNA administered every 28 days (NUC experienced, CHB)	Drug: ds-siNA ds-siNA is a synthetic ribonucleic acid interference (RNAi) drug that consists of double-stranded oligonucleotides conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. ds-siNA, sterile solution of the ds-siNA at a concentration of 185 mg/mL in water for injection (WFI).
Placebo Comparator: Cohort C3 Placebo 4 doses- Subcutaneous injection of 6 mg/kg of Placebo for ds-siNA administered every 28 days (NUC experienced, CHB)	Drug: Placebo for ds-siNA Sterile 9% saline for injection. Other Name: Placebo

[0364] Outcome Measures

[0365] Primary Outcome Measures:

[0366] Number of healthy volunteers with Adverse Events as assessed by CTCAE v5.0 [Time Frame: 4 weeks]

[0367] Number of participants with abnormalities in vital signs, electrocardiogram (ECG), and clinically significant laboratory findings

[0368] Number participants with non-cirrhotic chronic Hepatitis B with Adverse Events as assessed by CTCAE v5.0 [Time Frame: 16 weeks]

[0369] Number of participants with abnormalities in vital signs, electrocardiogram (ECG), and clinically significant laboratory findings.

[0370] Secondary Outcome Measures:

[0371] To characterize the pharmacokinetics of ds-siNA in healthy volunteers by monitoring plasma pharmacokinetics profiles of [Time Frame: 4 weeks] Measure the amount of ds-siNA excreted in urine

[0372] To characterize the pharmacokinetics of ds-siNA in healthy volunteers by monitoring through concentrations of [Time Frame: 4 weeks]

[0373] Measure the Amount of Ds-siNA Renal Clearance (CLR).

[0374] To characterize the pharmacokinetics of ds-siNA in participants with non-cirrhotic CHB by monitoring plasma pharmacokinetics profiles of ds-siNA. [Time Frame: 12 weeks]

[0375] Measure the Amount of Ds-siNA Excreted in Urine

[0376] To characterize the pharmacokinetics of ds-siNA in participants with non-cirrhotic CHB by monitoring through concentrations of ds-siNA. [Time Frame: 12 weeks]

[0377] Measure Ds-siNA Renal Clearance (CLR).

[0378] Other Outcome Measures:

[0379] To evaluate the preliminary antiviral efficacy of ds-siNA in participants with CHB by monitoring changes in serum HBsAg levels (all Group B and C participants) during and after single dose and 12 weeks of treatment with DCR HBVS. [Time Frame: 12 weeks]

[0380] Proportion of participants achieving at least a 1-log reduction in HBsAg and achieving a HBsAg level <100 IU/mL at last scheduled visit Time to HBsAg loss (Kaplan-Mayer) Time to anti-HBs seroconversion

[0381] To evaluate the preliminary antiviral efficacy of ds-siNA in participants with CHB by monitoring HBeAg levels (HBeAg+ participants only) during and after single dose and 12 weeks of treatment with DCR HBVS. [Time Frame: 12 weeks]

[0382] % of participants with HBeAg loss and anti HBe at last scheduled visit (if HBeAg positive at study entry)

[0383] To evaluate the preliminary antiviral efficacy of ds-siNA in participants with CHB by monitoring HBV DNA levels (all Group B and C participants) during and after single dose and 12 weeks of treatment with DCR HBVS. [Time Frame: 12 weeks]

[0384] Proportion of participants achieving HBV DNA <2000 IU/mL (if >2,000 IU/mL at Baseline); and proportion of participants achieving PCR-nondetectable HBV DNA (if HBV DNA was detectable at Baseline).

[0385] To characterize the pharmacodynamics (PD) of ds-siNA on plasma levels of HBsAg and HBV in blood. [Time Frame: 12 weeks]

[0386] Track post-treatment duration of any observed efficacy effects.

Eligibility Criteria	
Ages Eligible for Study:	18 Years to 65 Years (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes

[0387] Inclusion Criteria:

[0388] Healthy at the time of screening as determined by medical evaluation.

[0389] Capable of giving informed consent.

[0390] 12-lead ECG within normal limits or with no clinically significant abnormalities.

[0391] Negative screen for alcohol or drugs of abuse.

[0392] Non-smokers for at least 3 months with a negative urinary cotinine concentration at screening.

[0393] BMI within range 18.0-32.0 kg/m2 (inclusive).

[0394] Female participants not pregnant, not breastfeeding, and not of childbearing potential or willing to follow contraceptive guidance.

[0395] Chronic hepatitis B infection (Group B and C only).

[0396] Clinical history compatible with compensated liver disease with no evidence of cirrhosis (Group B and C only).

[0397] Continuously on nucleotides (NUC) therapy for at least 12 weeks prior to screening (Group C only).

[0398] Exclusion Criteria:

[0399] History of any medical condition that may interfere with the absorption, distribution, or elimination of study drug.

[0400] Poorly controlled or unstable hypertension.

[0401] History of diabetes mellitus treated with insulin or hypoglycemic agents.

[0402] History of asthma requiring hospital admission within the preceding 12 months.

[0403] Evidence of G-6-PD deficiency.

[0404] Currently poorly controlled endocrine conditions, excluding thyroid conditions.

[0405] History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.

[0406] Clinically relevant surgical history.

[0407] Use of prescription medications (excluding contraception for women) within 4 weeks prior to the administration of study intervention.

[0408] Use of clinically relevant over-the-counter medication or supplements (excluding routine vitamins) within 7 days of first dosing.

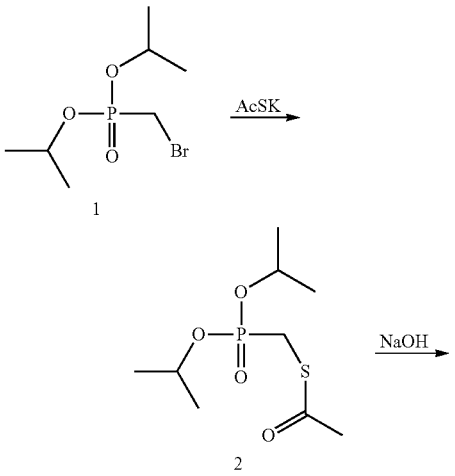
[0409] Has received an investigational agent within the 3 months prior to dosing or is in follow-up of another study.

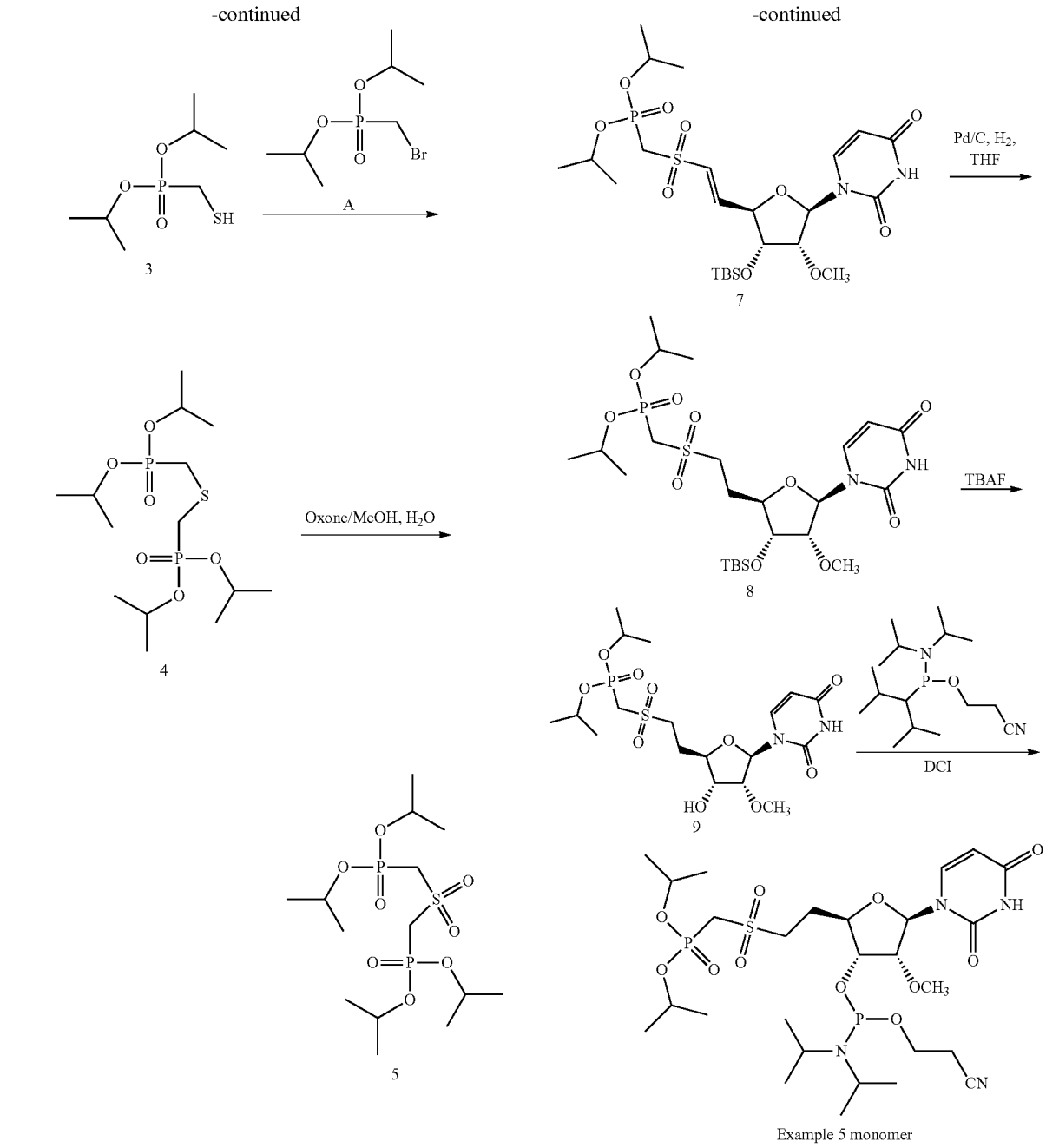
[0410] Antiviral therapy (other than entecavir or tenofovir) within 3 months of screening or treatment with interferon in the last 3 years (Group B and C only).

[0411] Use within the last 6 months of anticoagulants or systemically administered corticosteroids, immunomodulators, or immunosuppressants (Group B and C only).

Example 5: Synthesis of 5' End Cap Monomer

[0412]





Example 5 Monomer Synthesis Scheme

[0413] Preparation of (2): To a solution of 1 (15 g, 57.90 mmol) in DMF (150 mL) were added AcSK (11.24 g, 98.43 mmol) and TBAI (1.07 g, 2.89 mmol), and the mixture was stirred at 25° C. for 12 h. Upon completion as monitored by LCMS, the mixture was diluted with H_2O (10 mL) and extracted with EA (200 mL*3). The combined organic layers were washed with brine (200 mL*3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 2 (14.5 g, 96.52% yield, 98% purity) as a colorless oil. ESI-LCMS: 254.28 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$)

δ=4.78-4.65 (m, 2H), 3.19 (d, J=14.1 Hz, 2H), 2.38 (s, 3H), 1.32 (t, J=6.7 Hz, 12H); 31P NMR (162 MHz, $CDCl_3$) δ=20.59.

[0414] Preparation of (3): To a solution of 2 (14.5 g, 57.02 mmol) in CH_3CN (50 mL) and MeOH (25 mL) was added NaOH (3 M, 28.51 mL), and the mixture was stirred at 25° C. for 12 h under Ar. Upon completion as monitored by TLC, the reaction mixture was concentrated under reduced pressure to remove CH_3CN and $CH_{30}H$. The residue was diluted with water (50 mL) and adjust pH=7 by 6M HCl, and the mixture was extracted with EA (50 mL*3). The combined organic layers were washed with brine (50 mL*3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 3 (12.1 g, crude) as a colorless oil.

[0415] Preparation of (4): To a solution of 3 (12.1 g, 57.01 mmol) in CH_3CN (25 mL) and MeOH (25 mL) was added A (14.77 g, 57.01 mmol) dropwise at 25° C., and the mixture was stirred at 25° C. under Ar for 12 h. Upon completion as monitored by LCMS, the reaction mixture was concentrated under reduced pressure to give 4 (19.5 g, 78.85% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ=4.80-4.66 (m, 4H), 2.93 (d, J=11.3 Hz, 4H), 1.31 (dd, J=3.9, 6.1 Hz, 24H); ^{31}P NMR (162 MHz, $CDCl_3$) δ=22.18.

[0416] Preparation of (5): To a solution of 4 (19.5 g, 49.95 mmol) in MeOH (100 mL) and H_2O (100 mL) was added Oxone (61.41 g, 99.89 mmol) at 25° C. in portions, and the mixture was stirred at 25° C. for 12 h under Ar. Upon completion as monitored by LCMS, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to remove MeOH. The residue was extracted with EA (50 mL*3). The combined organic layers were washed with brine (50 mL*3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with i-Pr_2O and n-Hexane (1:2, 100 mL) at 25° C. for 30 min to give 5 (15.6 g, 73.94% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ=4.92-4.76 (m, 4H), 4.09 (d, J=16.1 Hz, 4H), 1.37 (dd, J=3.5, 6.3 Hz, 24H); ^{31}P NMR (162 MHz, $CDCl_3$) δ=10.17.

[0417] Preparation of (7): To a mixture of 5 (6.84 g, 16.20 mmol) in THE (20 mL) was added LiBr (937.67 mg, 10.80 mmol) until dissolved, followed by DIEA (1.40 g, 10.80 mmol, 1.88 mL) under argon at 15° C. The mixture was stirred at 15° C. for 15 min. 6 (4 g, 10.80 mmol) were added. The mixture was stirred at 15° C. for 3 h. Upon completion as monitored by LCMS, the reaction mixture was quenched by addition of H_2O (40 mL) and extracted with EA (40 mL*3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash reverse-phase chromatography (120 g C-18 Column, Eluent of 0~60% ACN/H_2O gradient @ 80 mL/min) to give 7 (5.7 g, 61.95% yield) as a colorless oil. ESI-LCMS: 611.2 [M+H]; ^1H NMR (400 MHz, $CDCl_3$); δ=9.26 (s, 1H), 7.50 (d, J=8.1 Hz, 1H), 7.01 (s, 2H), 5.95 (d, J=2.7 Hz, 1H), 5.80 (dd, J=2.1, 8.2 Hz, 1H), 4.89-4.72 (m, 2H), 4.66 (d, J=7.2 Hz, 1H), 4.09-4.04 (m, 1H), 3.77 (dd, J=2.7, 4.9 Hz, 1H), 3.62 (d, J=3.1 Hz, 1H), 3.58 (d, J=3.1 Hz, 1H), 3.52 (s, 3H), 1.36 (td, J=1.7, 6.1 Hz, 12H), 0.92 (s, 9H), 0.12 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ=9.02

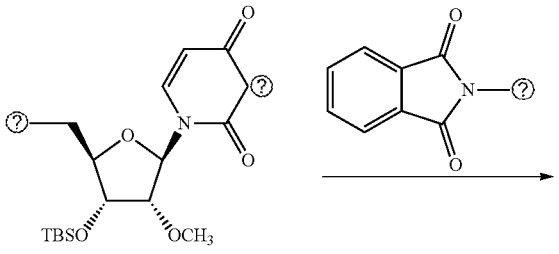
[0418] Preparation of (8): To a mixture of 7 (5.4 g, 8.84 mmol) in THE (80 mL) was added Pd/C (5.4 g, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H2 several times. The mixture was stirred under H2 (15 psi) at 20° C. for 1 hr. Upon completion as monitored by LCMS, the reaction mixture was filtered, and the filtrate was concentrated to give 8 (5.12 g, 94.5% yield) as a white solid. ESI-LCMS: 613.3 $[M+H]^+$; H NMR (400 MHz, CD3CN) 6=9.31 (s, 1H), 7.37 (d, J=8.0 Hz, 1H), 5.80-5.69 (m, 2H), 4.87-4.75 (m, 2H), 4.11-4.00 (m, 1H), 3.93-3.85 (m, 1H), 3.80-3.74 (m, 1H), 3.66-3.60 (m, 1H), 3.57-3.52 (m, 1H), 3.49 (s, 3H), 3.46-3.38 (m, 1H), 2.35-2.24 (m, 1H), 2.16-2.03 (m, 1H), 1.89-1.80 (m, 1H), 1.37-1.34 (m, 12H), 0.90 (s, 9H), 0.09 (s, 6H); ^{31}P NMR (162 MHz, CD_3CN) δ=9.41.

[0419] Preparation of (9): To a solution of 8 (4.4 g, 7.18 mmol) in THE (7.2 mL) was added TBAF (1 M, 7.18 mL), and the mixture was stirred at 20° C. for 1 hr. Upon completion as monitored by LCMS, the reaction mixture was diluted with H_2O (50 mL) and extracted with EA (50 mL*4). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5%, MeOH/DCM gradient @ 40 mL/min) to give 9 (3.2 g, 88.50% yield) as a white solid. ESI-LCMS: 499.2 $[M+H]^{+1}$; ^1H NMR (400 MHz, CD_3CN) δ=9.21 (s, 1H), 7.36 (d, J=8.3 Hz, 1H), 5.81-5.72 (m, 2H), 4.88-4.74 (m, 2H), 3.99-3.87 (m, 2H), 3.84 (dd, J=1.9, 5.4 Hz, 1H), 3.66-3.47 (m, 7H), 2.98 (s, 1H), 2.44-2.15 (m, 2H), 1.36 (d, J=6.0 Hz, 12H); ^{31}P NMR (162 MHz, CD_3CN) δ=9.48.

[0420] Preparation of (Example 5 monomer): To a mixture of 9 (3.4 g, 6.82 mmol, 1 eq) and 4A MS (3.4 g) in MeCN (50 mL) was added P1 (2.67 g, 8.87 mmol, 2.82 mL, 1.3 eq) at 0° C., followed by addition of 1H-imidazole-4,5-dicarbonitrile (886.05 mg, 7.50 mmol) at 0° C. The mixture was stirred at 20° C. for 2 h. Upon completion as monitored by LCMS, the reaction mixture was quenched by addition of saturated aq. $NaHCO_3$(50 mL) and diluted with DCM (100 mL). The organic layer was washed with saturated aq. $NaHCO_3$ (50 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC: column: YMC-Triart Prep C18 250*50 mm*10 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B %: 15% to give a impure product. The impure product was further purified by a flash silica gel column (0% to 5% i-PrOH in DCM with 0.5% TEA) to give Example 5 monomer (2.1 g, 43.18% yield) as a white solid. ESI-LCMS: 721.2 $[M+Na]^+$; H NMR (400 MHz, CD_3CN) δ=9.29 (s, 1H), 7.45 (d, J=8.1 Hz, 1H), 5.81 (d, J=4.2 Hz, 1H), 5.65 (d, J=8.1 Hz, 1H), 4.79-4.67 (m, 2H), 4.26-4.05 (m, 2H), 4.00-3.94 (m, 1H), 3.89-3.63 (m, 6H), 3.53-3.33 (m, 5H), 2.77-2.61 (m, 2H), 2.31-2.21 (m, 1H), 2.16-2.07 (m, 1H), 1.33-1.28 (m, 12H), 1.22-1.16 (m, 1H), 1.22-1.16 (m, 11H); ^{31}P NMR (162 MHz, CD_3CN) δ=149.89, 149.78, 10.07, 10.02.

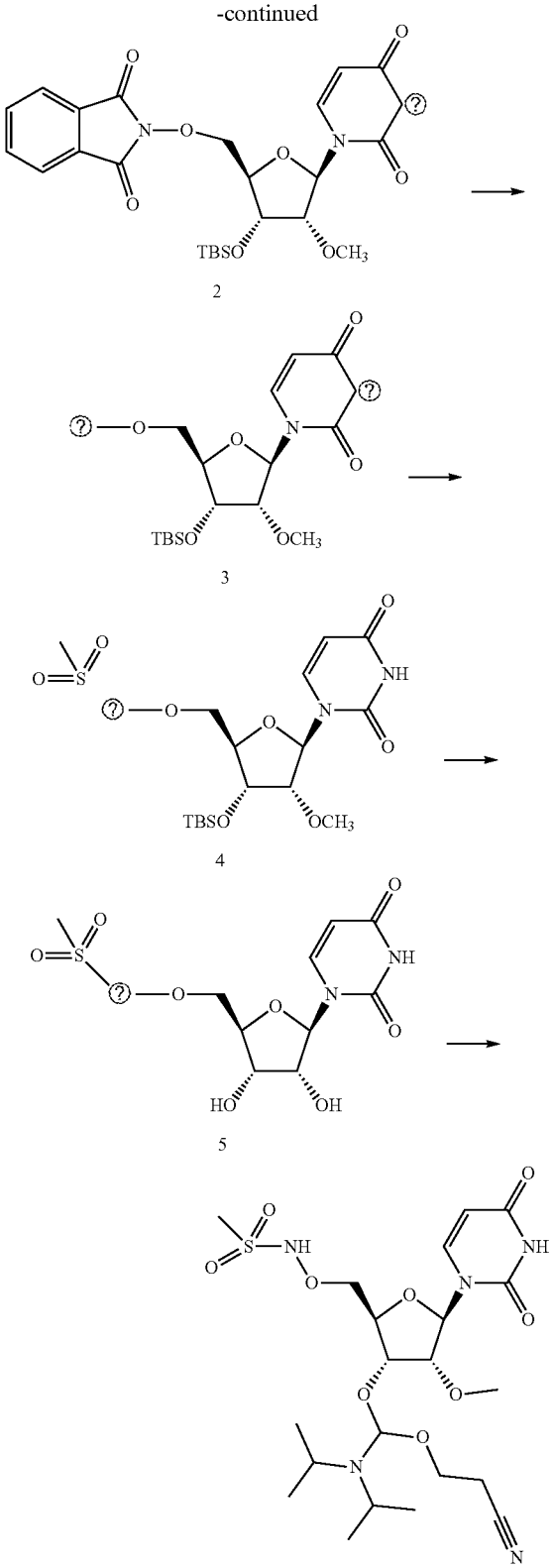
Example 6. Synthesis of 5' End Cap Monomer

[0421]



1

-continued



Example 6 Monomer

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Example 6 Monomer Synthesis Scheme

[0422] Preparation of (2): To a solution of 1 (5 g, 13.42 mmol) in DMF (50 mL) were added PPh_3 (4.58 g, 17.45 mmol) and 2-hydroxyisoindoline-1,3-dione (2.85 g, 17.45 mmol), followed by a solution of DIAD (4.07 g, 20.13 mmol, 3.91 mL) in DMF (10 mL) dropwise at 15° C. The resulting solution was stirred at 15° C. for 18 hr. The reaction mixture was then diluted with DCM (50 mL), washed with H_2O (60 mL*3) and brine (30 mL), dried over Na_2SO_4, filtered and evaporated to give a residue. The residue was then triturated with EtOH (55 mL) for 30 min, and the collected white powder was washed with EtOH (10 mL*2) and dried to give 2 (12.2 g, 85.16% yield) as a white powder (the reaction was set up in two batches and combined) ESI-LCMS: 518.1 $[M+H]^+$.

[0423] Preparation of (3): 2 (6 g, 11.59 mmol) was suspended in MeOH (50 mL), and then $NH_2NH_2.H_2O$ (3.48 g, 34.74 mmol, 3.38 mL, 50% purity) was added dropwise at 20° C. The reaction mixture was stirred at 20° C. for 4 hr. Upon completion, the reaction mixture was diluted with EA (20 mL) and washed with $NaHCO_3$(10 mL*2) and brine (10 mL). The combined organic layers were then dried over Na_2SO_4, filtered and evaporated to give 3 (8.3 g, 92.5% yield) as a white powder. (The reaction was set up in two batches and combined). ESI-LCMS: 388.0 [M+H]; ^{1}H NMR (400 MHz, DMSO-d6) δ=11.39 (br s, 1H), 7.72 (d, J=8.1 Hz, 1H), 6.24-6.09 (m, 2H), 5.80 (d, J=4.9 Hz, 1H), 5.67 (d, J=8.1 Hz, 1H), 4.26 (t, J=4.9 Hz, 1H), 4.03-3.89 (m, 1H), 3.87-3.66 (m, 3H), 3.33 (s, 3H), 0.88 (s, 9H), 0.09 (d, J=1.3 Hz, 6H)

[0424] Preparation of (4): To a solution of 3 (7 g, 18.06 mmol) and Py (1.43 g, 18.06 mmol, 1.46 mL) in DCM (130 mL) was added a solution of MsCl (2.48 g, 21.68 mmol, 1.68 mL) in DCM (50 mL) dropwise at −78° C. under N_2. The reaction mixture was allowed to warm to 15° C. in 30 min and stirred at 15° C. for 3 h. The reaction mixture was quenched by addition of ice-water (70 mL) at 0° C., and then extracted with DCM (50 mL*3). The combined organic layers were washed with saturated aq. $NaHCO_3$(50 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 30 g SepaFlash® Silica Flash Column, Eluent of 0~20% i-PrOH/DCM gradient @ 30 mL/min to give 4 (6.9 g, 77.94% yield) as a white solid. ESI-LCMS: 466.1 [M+H]; ^{1}H NMR (400 MHz, DMSO-d6) δ=11.41 (br s, 1H), 10.15 (s, 1H), 7.69 (d, J=8.1 Hz, 1H), 5.80 (d, J=4.4 Hz, 1H), 5.65 (d, J=8.1 Hz, 1H), 4.24 (t, J=5.2 Hz, 1H), 4.16-3.98 (m, 3H), 3.87 (t, J=4.8 Hz, 1H), 3.00 (s, 3H), 2.07 (s, 3H), 0.88 (s, 9H), 0.10 (d, J=1.5 Hz, 6H)

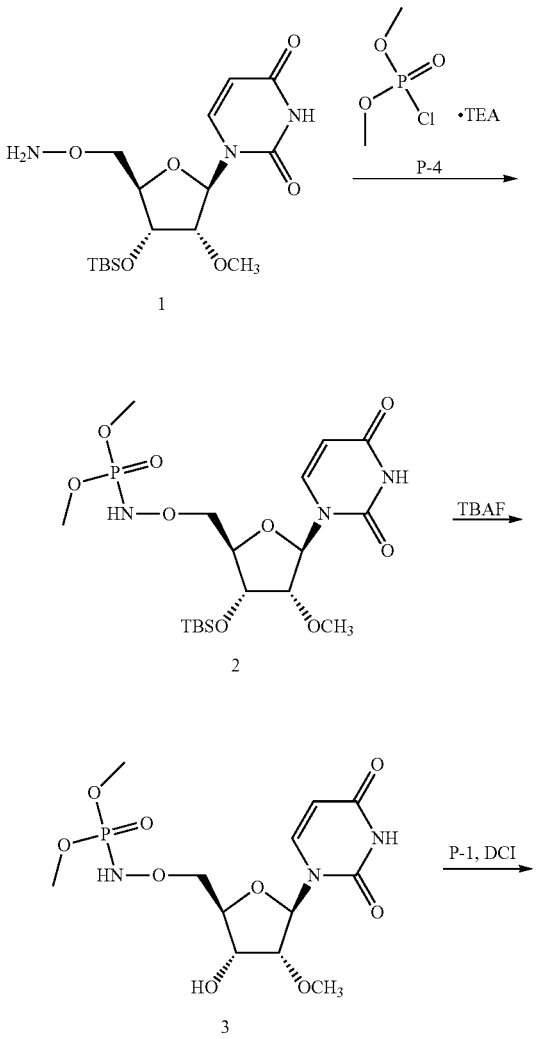
[0425] Preparation of (5): To a solution of 4 (6.9 g, 14.82 mmol) in THE (70 mL) was added TBAF (1 M, 16.30 mL) at 15° C. The reaction mixture was stirred at 15° C. for 18 hr, and then evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~9% MeOH/Ethyl acetate gradient @ 30 mL/min) to give 5 (1.8 g, 50.8% yield) as a white solid. ESI-LCMS: 352.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ=11.40 (s, 1H), 10.13 (s, 1H), 7.66 (d, J=8.1 Hz, 1H), 5.83 (d, J=4.9 Hz, 1H), 5.65 (dd, J=1.8, 8.1 Hz, 1H), 5.36 (d, J=6.2 Hz, 1H), 4.13-4.00 (m, 4H), 3.82 (t, J=5.1 Hz, 1H), 3.36 (s, 3H), 3.00 (s, 3H)

[0426] Preparation of (Example 6 monomer): To a mixture of 5 (3 g, 8.54 mmol) and DIEA (2.21 g, 17.08 mmol, 2.97

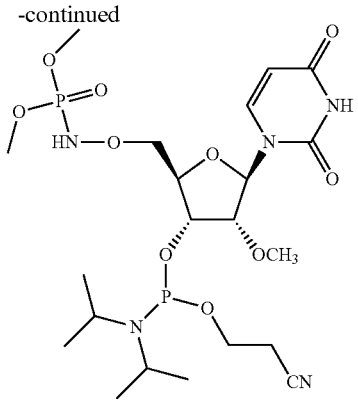
mL) in ACN (90 mL) was added P2 (3.03 g, 12.81 mmol) dropwise at 15° C. The reaction mixture was stirred at 15° C. for 5 h. Upon completion, the reaction mixture was diluted with EA (40 mL) and quenched with 5% $NaHCO_3$ (20 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0-15% i-PrOH/(DCM with 2% TEA) gradient @ 20 mL/min) to Example 6 monomer (2.1 g, 43.93% yield) as a white solid. ESI-LCMS: 552.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ=8.78 (br s, 1H), 7.57 (dd, J=4.6, 8.2 Hz, 1H), 5.97-5.80 (m, 1H), 5.67 (d, J=8.3 Hz, 1H), 4.46-4.11 (m, 4H), 3.95-3.58 (m, 5H), 3.44 (d, J=16.3 Hz, 3H), 3.02 (d, J=7.5 Hz, 3H), 2.73-2.59 (m, 2H), 1.23-1.15 (m, 12H); ^{31}P NMR (162 MHz, CD_3CN) δ=150.30, 150.10

Example 7: Synthesis of 5' End Cap Monomer

[0427]



-continued



Example 7 Monomer

Example 7 Monomer Synthesis Scheme

[0428] Preparation of (2): To the solution of 1 (5 g, 12.90 mmol) and TEA (1.57 g, 15.48 mmol, 2.16 mL) in DCM (50 mL) was added P-4 (2.24 g, 15.48 mmol, 1.67 mL) in DCM (10 mL) dropwise at 15° C. under N_2. The reaction mixture was stirred at 15° C. for 3 h. Upon completion as monitored by LCMS and TLC (PE:EtOAc=0:1), the reaction mixture was concentrated to dryness, diluted with H_2O (20 mL), and extracted with EA (50 mL*3). The combined organic layers were washed with brine (30 mL*3), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa-Flash® Silica Flash Column, Eluent of 0~95% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 2 (5.3 g, 71.3% yield) as a white solid. ESI-LCMS: 496.1 $[M+H]^+$; H NMR (400 MHz, $CDCl_3$) δ=0.10 (d, J=4.02 Hz, 6H) 0.91 (s, 9H) 3.42-3.54 (m, 3H) 3.65-3.70 (m, 1H) 3.76-3.89 (m, 6H) 4.00 (dd, J=10.92, 2.89 Hz, 1H) 4.08-4.13 (m, 1H) 4.15-4.23 (m, 2H) 5.73 (dd, J=8.28, 2.01 Hz, 1H) 5.84 (d, J=2.76 Hz, 1H) 6.86 (d, J=15.81 Hz, 1H) 7.72 (d, J=8.03 Hz, 1H) 9.10 (s, 1H); ^{31}P NMR (162 MHz, CD_3CN) δ=9.65

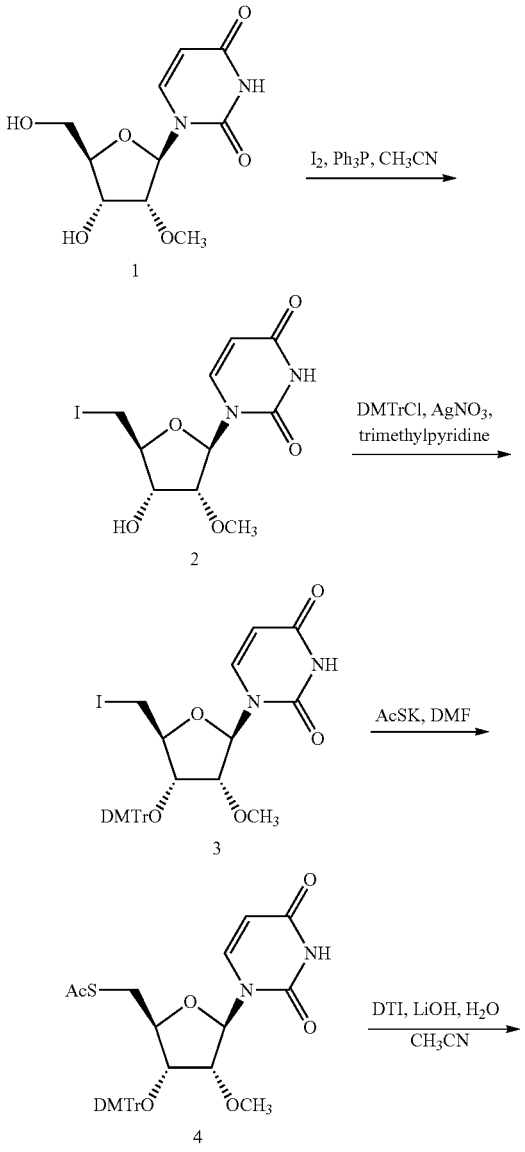
[0429] Preparation of (3): To a solution of 2 (8.3 g, 16.75 mmol) in THE (50 mL) were added TBAF (1 M, 16.75 mL) and CH_3COOH (1.01 g, 16.75 mmol, 957.95 uL). The mixture was stirred at 20° C. for 12 hr. Upon completion as monitored by LCMS, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, PE:EA=0-100%; MeOH/EA=0-10%) to give 3 (5 g, 77.51% yield) as a white solid. ESI-LCMS: 382.1 [M+H]; ^1H NMR (400 MHz, $CDCl_3$) δ=3.35 (s, 3H) 3.65 (br d, J=2.76 Hz, 3H) 3.68 (d, J=2.76 Hz, 3H) 3.77 (t, J=5.08 Hz, 1H) 3.84-4.10 (m, 4H) 5.33 (br d, J=5.52 Hz, 1H) 5.62 (d, J=7.77 Hz, 1H) 5.83 (d, J=4.94 Hz, 1H) 7.69 (d, J=7.71 Hz, 1H) 9.08 (d, J=16.81 Hz, 1H) 11.39 (br s, 1H); ^{31}P NMR (162 MHz, CD_3CN) δ=15.41

[0430] Preparation of (Example 7 monomer): To a solution of 3 (2 g, 5.25 mmol) and DIPEA (2.03 g, 15.74 mmol, 2.74 mL, 3 eq) in MeCN (21 mL) and pyridine (7 mL) was added P2 (1.86 g, 7.87 mmol) dropwise at 20° C., and the mixture was stirred at 20° C. for 3 hr. Upon completion as monitored by LCMS, the reaction mixture was diluted with water (20 mL) and extracted with EA (50 mL). The combined organic layers were washed with brine (30 mL), dried

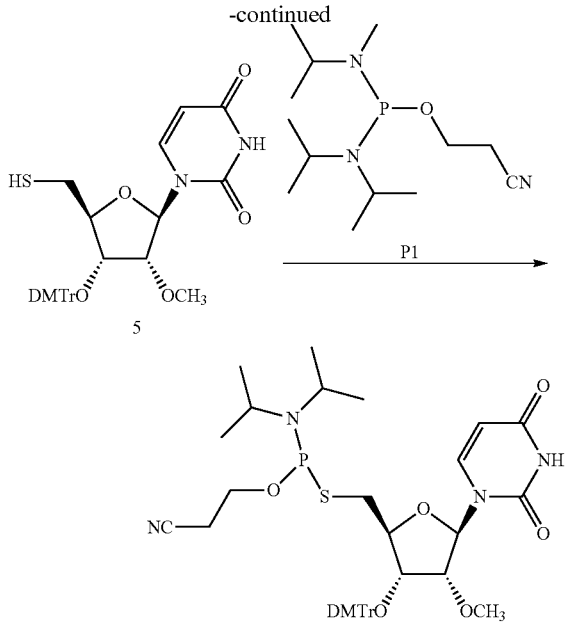
over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~45% (Ethyl acetate:EtOH=4:1)/Petroleum ether gradient) to give Example 7 monomer (1.2 g, 38.2% yield) as a white solid. ESI-LCMS: 604.1 [M+H]; ^{1}H NMR (400 MHz, CD_3CN) δ=1.12-1.24 (m, 12H) 2.61-2.77 (m, 2H) 3.43 (d, J=17.64 Hz, 3H) 3.59-3.69 (m, 2H) 3.71-3.78 (m, 6H) 3.79-4.14 (m, 5H) 4.16-4.28 (m, 1H) 4.29-4.42 (m, 1H) 5.59-5.72 (m, 1H) 5.89 (t, J=4.53 Hz, 1H) 7.48 (br d, J=12.76 Hz, 1H) 7.62-7.74 (m, 1H) 9.26 (br s, 1H); ^{31}P NMR (162 MHz, CD_3CN) δ=150.57, 149.96, 9.87

Example 8: Synthesis of 5' End Cap Monomer

[0431]



-continued



Example 8 Monomer

Example 8 Monomer Synthesis Scheme

[0432] Preparation of (2): To a solution of 1 (30 g, 101.07 mmol, 87% purity) in CH_3CN (1.2 L) and Py (60 mL) were added I2 (33.35 g, 131.40 mmol, 26.47 mL) and PPh_3 (37.11 g, 141.50 mmol) in one portion at 10° C. The reaction was stirred at 25° C. for 48 h. Upon completion, the mixture was diluted with saturated aq.$Na_2S_2O_3$ (300 mL) and saturated aq.$NaHCO_3$(300 mL), concentrated to remove CH_3CN, and extracted with EtOAc (300 mL*3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~60% Methanol/Dichloromethane gradient @ 100 mL/min) to give 2 (28.2 g, 72% yield) as a brown solid. ESI-LCMS: 369.1 $[M+H]^+$; H NMR (400 MHz, DMSO-d_6) δ=11.43 (s, 1H), 7.68 (d, J=8.1 Hz, 1H), 5.86 (d, J=5.5 Hz, 1H), 5.69 (d, J=8.1 Hz, 1H), 5.46 (d, J=6.0 Hz, 1H), 4.08-3.96 (m, 2H), 3.90-3.81 (m, 1H), 3.60-3.51 (m, 1H), 3.40 (dd, J=6.9, 10.6 Hz, 1H), 3.34 (s, 3H).

[0433] Preparation of (3): To the solution of 2 (12 g, 32.6 mmol) in DCM (150 mL) were added $AgNO_3$ (11.07 g, 65.20 mmol), 2,4,6-trimethylpyridine (11.85 g, 97.79 mmol, 12.92 mL), and DMTCl (22.09 g, 65.20 mmol) at 10° C., and the reaction mixture was stirred at 10° C. for 16 hr. Upon completion, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 60 mL/min) to give 3 (17 g, 70.78% yield) as a yellow solid. ESI-LCMS: 693.1 [M+Na]*^{1}; H NMR (400 MHz, DMSO-d_6) δ=11.46 (s, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.49 (d, J=7.2 Hz, 2H), 7.40-7.30 (m, 6H), 7.29-7.23 (m, 1H), 6.93 (d, J=8.8 Hz, 4H), 5.97 (d, J=6.0 Hz, 1H), 5.69 (d, J=8.0 Hz, 1H), 4.05-4.02 (m, 1H), 3.75 (d, J=1.2 Hz, 6H), 3.57 (t, J=5.6 Hz, 1H), 3.27 (s, 4H), 3.06 (t, J=10.4 Hz, 1H), 2.98-2.89 (m, 1H).

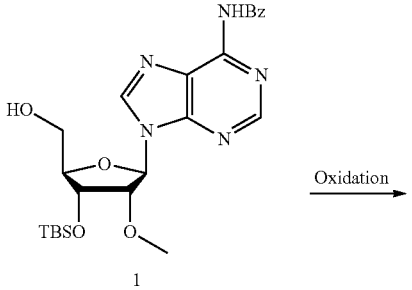
[0434] Preparation of (4): To a solution of 3 (17 g, 25.35 mmol) in DMF (200 mL) was added AcSK (11.58 g, 101.42 mmol) at 25° C., and the reaction was stirred at 60° C. for 2 hr. The mixture was diluted with H_2O (600 mL) and extracted with EtOAc (300 mL*4). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 4 (15.6 g, crude) as a brown solid, which was used directly without further purification. ESI-LCMS: 641.3 $[M+H]^+$.

[0435] Preparation of (5): To a solution of 4 (15.6 g, 25.21 mmol) in CH_3CN (200 mL) were added DTT (11.67 g, 75.64 mmol, 11.22 mL) and $LiOH.H_2O$ (1.06 g, 25.21 mmol) at 10° C. under Ar. The reaction was stirred at 10° C. for 1 hr. The mixture was concentrated under reduced pressure to remove CH_3CN, and the residue was diluted with H_2O (400 mL) and extracted with EtOAc (200 mL*3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of $0\sim_{60}$% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give 5 (8.6 g, 56.78% yield) as a white solid. ESI-LCMS: 599.3 $[M+Na]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=8.79 (s, 1H), 7.61 (d, J=8.0 Hz, 1H), 7.56-7.46 (m, 2H), 7.45-7.37 (m, 4H), 7.36-7.27 (m, 3H), 6.85 (dd, J=2.8, 8.8 Hz, 4H), 5.85 (d, J=1.3 Hz, 1H), 5.68 (dd, J=2.0, 8.2 Hz, 1H), 4.33-4.29 (m, 1H), 3.91 (dd, J=4.8, 8.2 Hz, 1H), 3.81 (d, J=1.6 Hz, 6H), 3.33 (s, 3H), 2.85-2.80 (m, 1H), 2.67-2.55 (m, 2H), 1.11 (t, J=8.8 Hz, 1H).

[0436] Preparation of (Example 8 monomer): To a solution of 5 (6 g, 10.40 mmol) in DCM (120 mL) were added P1 (4.08 g, 13.53 mmol, 4.30 mL) and DCI (1.35 g, 11.45 mmol) in one portion at 10° C. under Ar. The reaction was stirred at 10° C. for 2 hr. The reaction mixture was diluted with saturated aq.$NaHCO_3$(50 mL) and extracted with DCM (20 mL*3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Triart Prep C18 250*50 mm*10 um; mobile phase: [water(10 mM NH_4HCO_3)-ACN]; B %: 35%-81%,20 min) to give Example 8 monomer (3.54 g, 43.36% yield) as a yellow solid. ESI-LCMS: 776.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=7.65-7.38 (m, 7H), 7.37-7.22 (m, 3H), 6.90 (d, J=8.4 Hz, 4H), 5.92 (s, 1H), 5.66 (t, J=8.2 Hz, 1H), 4.13 (d, J=4.0 Hz, 1H), 4.00-3.88 (m, 1H), 3.87-3.59 (m, 10H), 3.33 (d, J=5.8 Hz, 3H), 3.12-2.94 (m, 1H), 2.78-2.60 (m, 3H), 2.55-2.48 (m, 1H), 1.36-0.98 (m, 12H); ^{31}P NMR (162 MHz, DMSO-d_6) δ=162.69.

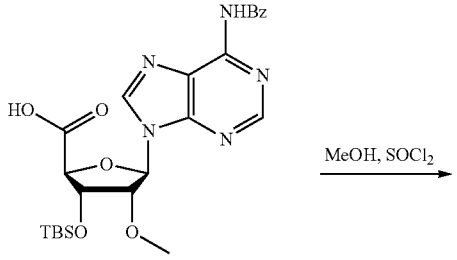
Example 9: Synthesis of 5' End Cap Monomer

[0437]

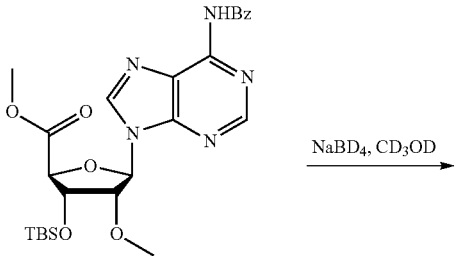


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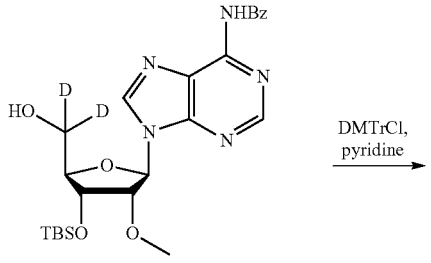
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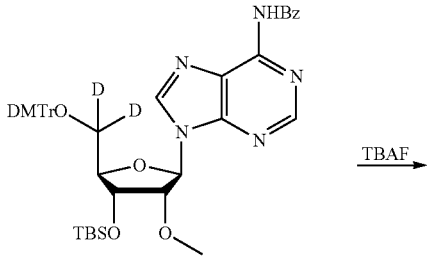
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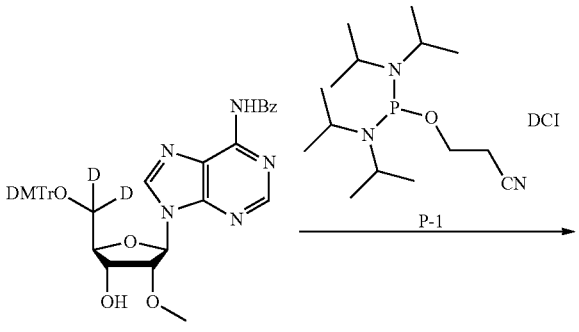
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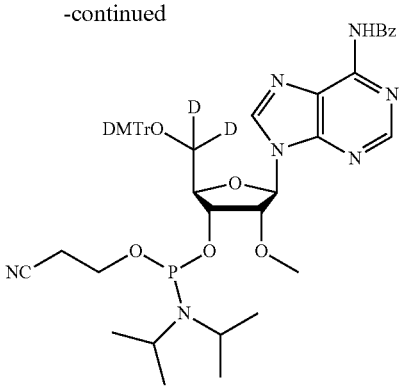


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Example 9 Monomer

Example 9 Monomer Synthesis Scheme

[0438] Preparation of (2): To a solution of 1 (22.6 g, 45.23 mmol) in DCM (500 mL) and H_2O (125 mL) were added TEMPO (6.40 g, 40.71 mmol) and DIB (29.14 g, 90.47 mmol) at 0° C. The mixture was stirred at 20° C. for 20 h. Upon completion as monitored by LCMS, saturated aq. $NaHCO_3$ was added to the mixture to adjust pH >8. The mixture was diluted with H_2O (200 mL) and washed with DCM (100 mL*3). The aqueous layer was collected, adjusted to pH<5 by HCl (4M), and extracted with DCM (200 mL*3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 2 (17.5 g, 68.55% yield) as a yellow solid. ESI-LCMS: 514.2 [M+H]; ^{1}H NMR (400 MHz, DMSO-d_6) δ=11.27 (s, 1H), 8.86 (s, 1H), 8.78 (s, 1H), 8.06 (d, J=7.5 Hz, 2H), 7.68-7.62 (m, 1H), 7.59-7.52 (m, 2H), 6.28 (d, J=6.8 Hz, 1H), 4.82-4.76 (m, 1H), 4.54 (dd, J=4.1, 6.7 Hz, 1H), 4.48 (d, J=1.8 Hz, 1H), 3.32 (s, 3H), 0.94 (s, 9H), 0.18 (d, J=4.8 Hz, 6H).

[0439] Preparation of (3): To a solution of 2 (9.3 g, 18.11 mmol) in MeOH (20 mL) was added $SOCl_2$ (3.23 g, 27.16 mmol, 1.97 mL) dropwise at 0° C. The mixture was stirred at 20° C. for 0.5 hr. Upon completion as monitored by LCMS, the reaction mixture was quenched by addition of saturated aq. $NaHCO_3$(80 mL) and concentrated under reduced pressure to remove MeOH. The aqueous layer was extracted with DCM (80 mL*3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~5%, MeOH/DCM gradient @ 85 mL/min) to give 3 (5.8 g, 60% yield) as a yellow solid. ESI-LCMS: 528.3 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ=11.28 (s, 1H), 8.79 (d, J=7.3 Hz, 2H), 8.06 (d, J=7.5 Hz, 2H), 7.68-7.62 (m, 1H), 7.60-7.53 (m, 2H), 6.28 (d, J=6.6 Hz, 1H), 4.87 (dd, J=2.4, 4.0 Hz, 1H), 4.61 (dd, J=4.3, 6.5 Hz, 1H), 4.57 (d, J=2.2 Hz, 1H), 3.75 (s, 3H), 3.32 (s, 3H), 0.94 (s, 9H), 0.17 (d, J=2.2 Hz, 6H).

[0440] Preparation of (4): To a mixture of 3 (5.7 g, 10.80 mmol) in CD_3OD (120 mL) was added $NaBD_4$ (1.63 g, 43.21 mmol) in portions at 0° C., and the mixture was stirred at 20° C. for 1 hr. Upon completion as monitored by LCMS, the reaction mixture was neutralized by AcOH (~10 mL) and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5%, MeOH/DCM gradient @ 40 mL/min) to give 4 (4.15 g, 7.61 mmol, 70.45% yield) as a yellow solid. ESI-LCMS: 502.2 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ=11.23 (s, 1H), 8.76 (s, 2H), 8.04 (d, J=7.3 Hz, 2H), 7.69-7.62 (m, 1H), 7.60-7.52 (m, 2H), 6.14 (d, J=6.0 Hz, 1H), 5.18 (s, 1H), 4.60-4.51 (m, 2H), 3.98 (d, J=3.0 Hz, 1H), 3.32 (s, 3H), 0.92 (s, 9H), 0.13 (d, J=1.5 Hz, 6H).

[0441] Preparation of (5): To a solution of 4 (4.85 g, 9.67 mmol) in pyridine (50 mL) was added DMTrCl (5.90 g, 17.40 mmol) at 25° C. and the mixture was stirred for 2 hr. Upon completion as monitored by LCMS, the reaction mixture was concentrated under reduced pressure to remove pyridine. The residue was diluted with EtOAc (150 mL) and washed with H_2O (50 mL*3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~70%, EA/PE gradient @ 60 mL/min) to give 5 (6.6 g, 84.06% yield) as a yellow solid. ESI-LCMS: 804.3[M+H]$^+$, iH NMR (400 MHz, DMSO-d_6) δ=11.22 (s, 1H), 8.68 (d, J=11.0 Hz, 2H), 8.03 (d, J=7.3 Hz, 2H), 7.68-7.60 (m, 1H), 7.58-7.49 (m, 2H), 7.37-7.30 (m, 2H), 7.27-7.16 (m, 7H), 6.88-6.79 (m, 4H), 6.17 (d, J=4.2 Hz, 1H), 4.72 (t, J=5.0 Hz, 1H), 4.60 (t, J=4.5 Hz, 1H), 4.03-3.98 (m, 1H), 3.71 (s, 6H), 0.83 (s, 9H), 0.12-0.03 (m, 6H).

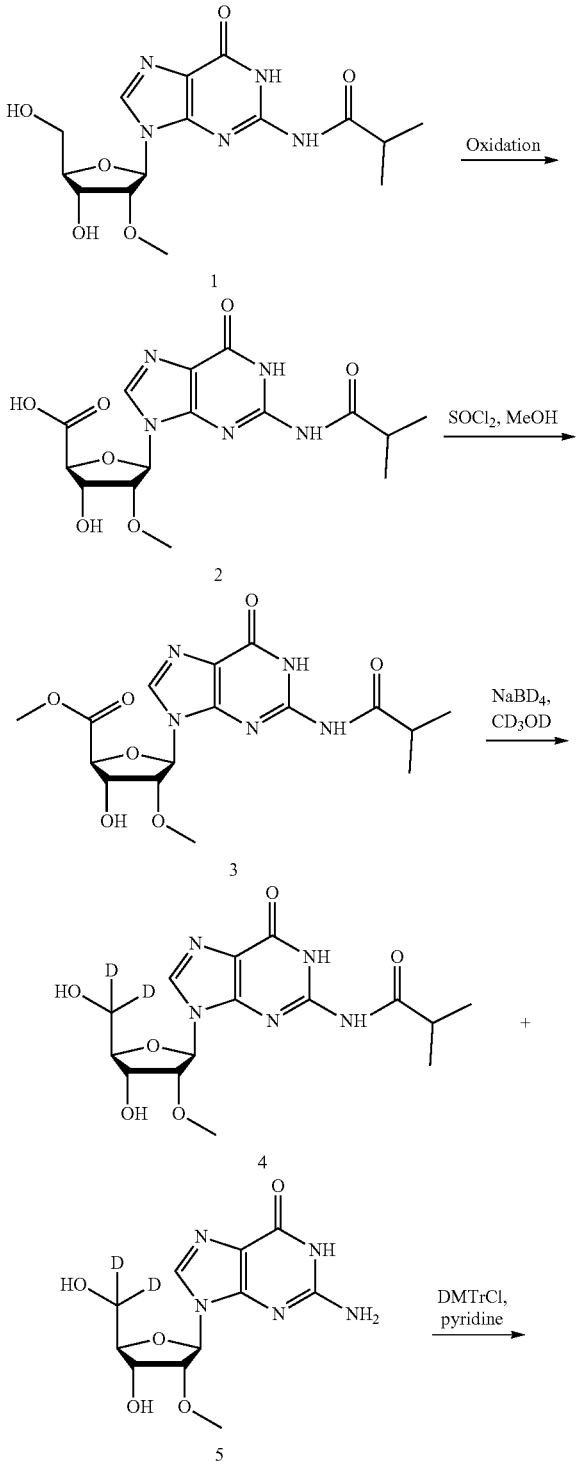
[0442] Preparation of (6): To a solution of 5 (6.6 g, 8.21 mmol) in THE (16 mL) was added TBAF (1 M, 8.21 mL), and the mixture was stirred at 20° C. for 2 hr. Upon completion as monitored by LCMS, the reaction mixture was diluted with EA (150 mL) and washed with H_2O (50 mL*3). The organic layer was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 10-100%, EA/PE gradient @ 30 mL/min) to give 6 (5.4 g, 94.4% yield) as a yellow solid. ESI-LCMS: 690.3 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ=11.24 (s, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 8.05 (d, J=7.3 Hz, 2H), 7.69-7.62 (m, 1H), 7.60-7.52 (m, 2H), 7.40-7.33 (m, 2H), 7.30-7.18 (m, 7H), 6.84 (dd, J=5.9, 8.9 Hz, 4H), 6.19 (d, J=4.8 Hz, 1H), 5.36 (d, J=6.0 Hz, 1H), 4.59-4.52 (m, 1H), 4.48 (q, J=5.1 Hz, 1H), 4.11 (d, J=4.8 Hz, 1H), 3.72 (d, J=1.0 Hz, 6H), 3.40 (s, 3H).

[0443] Preparation of (Example 9 monomer): To a solution of 6 (8.0 g, 11.60 mmol) in MeCN (150 mL) was added P-1 (4.54 g, 15.08 mmol, 4.79 mL) at 0° C., followed by DCI (1.51 g, 12.76 mmol) in one portion. The mixture was warmed to 20° C. and stirred for 2 h. Upon completion as monitored by LCMS, the reaction mixture was quenched by addition of saturated aq. $NaHCO_3$(50 mL) and diluted with DCM (250 mL). The organic layer was washed with saturated aq.$NaHCO_3$(50 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by a flash silica gel column (0% to 60% EA in PE contain 0.5% TEA) to give Example 9 monomer (5.75 g, 55.37% yield, 99.4% purity) as a white solid. ESI-LCMS: 890.4 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3CN) δ=9.55 (s, 1H), 8.63-8.51 (m, 1H), 8.34-8.24 (m, 1H), 7.98 (br d, J=7.5 Hz, 2H), 7.65-7.55 (m, 1H), 7.53-7.46 (m, 2H), 7.44-7.37 (m, 2H), 7.32-7.17 (m, 7H), 6.84-6.77 (m, 4H), 6.14 (d, J=4.3 Hz, 1H), 4.84-4.73 (m, 1H), 4.72-4.65 (m, 1H), 4.34-4.27 (m, 1H), 3.91-3.61 (m, 9H), 3.50-3.43 (m, 3H),

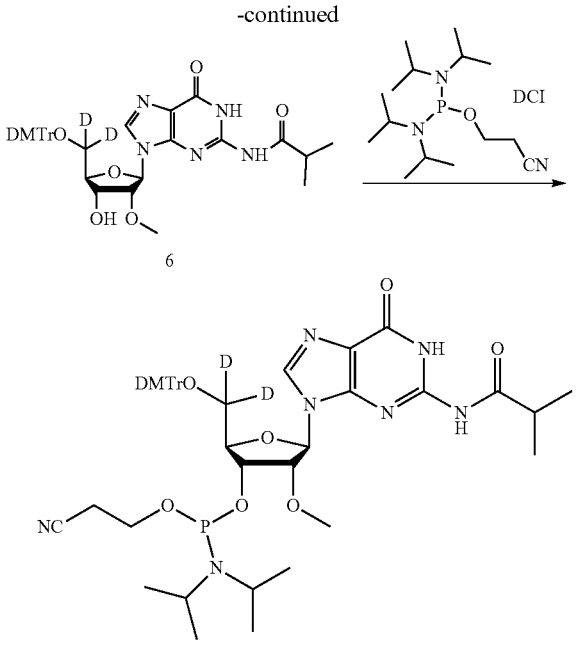
2.72-2.61 (m, 1H), 2.50 (t, J=6.0 Hz, 1H), 1.21-1.15 (m, 10H), 1.09 (d, J=6.8 Hz, 2H); ^{31}P NMR (162 MHz, CD_3CN) δ=150.01, 149.65

Example 10: Synthesis of 5' End Cap Monomer

[0444]



-continued



Example 10 Monomer

Example 10 Monomer Synthesis Scheme

[0445] Preparation of (2): To a solution of 1 (10 g, 27.22 mmol) in CH_3CN (200 mL) and H_2O (50 mL) were added TEMPO (3.85 g, 24.50 mmol) and DIB (17.54 g, 54.44 mmol). The mixture was stirred at 25° C. for 12 h. Upon completion as monitored by LCMS, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was triturated with EtOAc (600 mL) for 30 min. The resulting suspension was filtered and the collected solid was washed with EtOAc (300 mL*2) to give 2 (20.09 g, 91.5% yield) as a white solid. ESI-LCMS: 382.0 $[M+H]^+$.

[0446] Preparation of (3): To a solution of 2 (6 g, 15.73 mmol) in MeOH (100 mL) was added $SOCl_2$ (2.81 g, 23.60 mmol, 1.71 mL) dropwise at 0° C. The mixture was stirred at 25° C. for 12 h. Upon completion as monitored by LCMS, the reaction mixture was quenched by addition of $NaHCO_3$(4 g) and stirred at 25° C. for 30 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give 3 (18.8 g, 95.6% yield) as a white solid. The crude product was used for the next step without further purification. (The reaction was set up in parallel 3 batches and combined). ESI-LCMS: 396.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ=12.26-11.57 (m, 2H), 8.42-8.06 (m, 1H), 6.14-5.68 (m, 2H), 4.56 (s, 2H), 4.33 (dd, J=4.0, 7.3 Hz, 1H), 3.77 (m, 3H), 3.30 (s, 3H), 2.81-2.69 (m, 1H), 1.11 (s, 6H)

[0447] Preparation of (4 & 5): To a mixture of 3 (10.1 g, 25.55 mmol) in CD_3OD (120 mL) was added $NaBD_4$ (3.29 g, 86.86 mmol, 3.4 eq) in portions at 0° C. The mixture was stirred at 25° C. for 1 h. Upon completion as monitored by LCMS, the reaction mixture was neutralized with AcOH (~15 mL) and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~7.4%, MeOH/DCM gradient @ 80

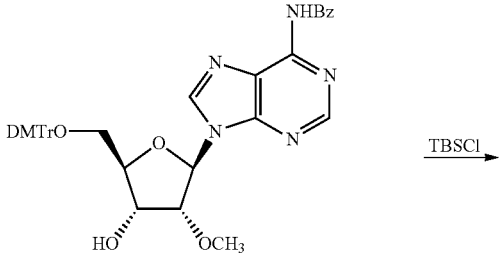
mL/min) to give 4 (2.98 g, 6.88 mmol, 27% yield) as a yellow solid. ESI-LCMS: 370.1[M+H]$^+$ and 5 (10.9 g, crude) as a yellow solid. ESI-LCMS: 300.1[M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ=7.85 (s, 1H), 5.87 (d, J=6.0 Hz, 1H), 4.46-4.39 (m, 1H), 4.34 (t, J=5.4 Hz, 1H), 4.08 (d, J=3.1 Hz, 1H), 3.49-3.38 (m, 4H)

[0448] Preparation of 6: To a solution of 4 (1.9 g, 4.58 mmol, 85.7% purity) in pyridine (19 mL) was added DMTrCl (2.02 g, 5.96 mmol). The mixture was stirred at 25° C. for 2 h under N_2. Upon completion as monitored by LCMS, the reaction mixture was quenched by MeOH (10 mL) and concentrated under reduce pressure to give a residue. The residue was diluted with H_2O (10 mL*3) and extracted with EA (20 mL*3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~77%, PE: (EA with 10% EtOH): 1% TEA@ 35 mL/min) to give 6 (2.6 g, 81.71% yield, 96.71% purity) as a white foam. ESI-LCMS: 672.2 [M+H]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ=12.02 (s, 1H), 7.96 (s, 1H), 7.83 (s, 1H), 7.51 (d, J=7.4 Hz, 2H), 7.37 (d, J=8.6 Hz, 4H), 7.25-7.17 (m, 2H), 6.80 (t, J=8.4 Hz, 4H), 5.88 (d, J=6.3 Hz, 1H), 4.69 (t, J=5.7 Hz, 1H), 4.64 (s, 1H), 4.54 (s, 1H), 4.19 (d, J=2.9 Hz, 1H), 3.77 (d, J=4.5 Hz, 6H), 3.60-3.38 (m, 3H), 2.81 (s, 1H), 1.81 (td, J=6.9, 13.7 Hz, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.80 (d, J=6.9 Hz, 3H)

[0449] Preparation of Example 10 monomer: To a solution of 6 (8.4 g, 12.5 mmol) in MeCN (80 mL) was added P-1 (4.9 g, 16.26 mmol, 5.16 mL) at 0° C., followed by addition of DCI (1.624 g, 13.76 mmol) in one portion at 0° C. under Ar. The mixture was stirred at 25° C. for 2 h. Upon completion as monitored by LCMS, the reaction mixture was quenched with saturated aq.$NaHCO_3$(20 mL) and extracted with DCM (50 mL*2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~52% PE:EA (10% EtOH): 5% TEA, @ 80 mL/min) to give Example 10 monomer (3.4 g, 72.1% yield) as a white foam. ESI-LCMS: 872.4 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3CN) δ=12.46-11.07 (m, 1H), 9.29 (s, 1H), 7.84 (d, J=14.6 Hz, 1H), 7.42 (t, J=6.9 Hz, 2H), 7.34-7.17 (m, 7H), 6.85-6.77 (m, 4H), 5.95-5.77 (m, 1H), 4.56-4.40 (m, 2H), 4.24 (dd, J=4.0, 13.3 Hz, 1H), 3.72 (d, J=2.0 Hz, 7H), 3.66-3.53 (m, 3H), 3.42 (d, J=11.8 Hz, 3H), 2.69-2.61 (m, 1H), 2.60-2.42 (m, 2H), 1.16-1.00 (m, 18H); ^{31}P NMR (162 MHz, CD_3CN) δ=149.975, 149.9

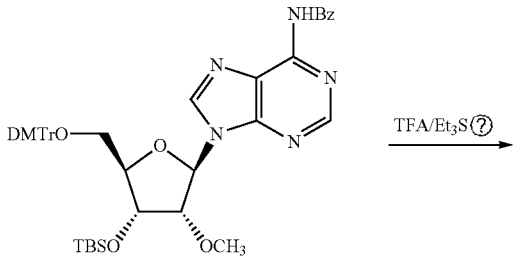
Example 11: Synthesis of 5' End Cap Monomer

[0450]

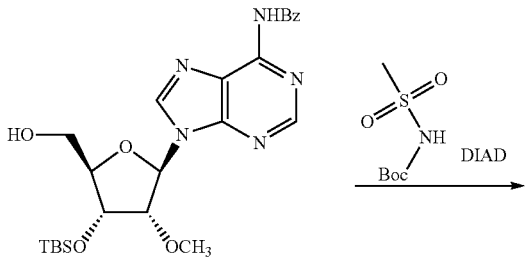


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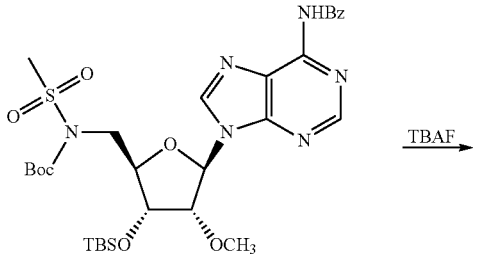
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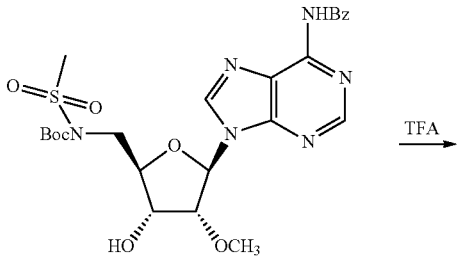
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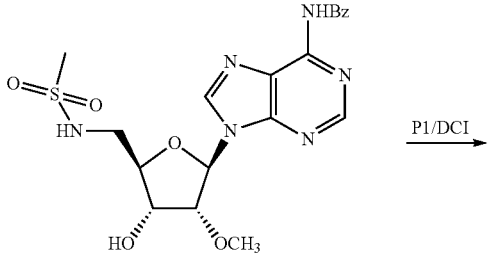
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4

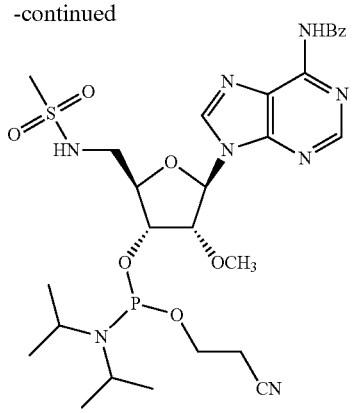


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6

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Example 11 Monomer

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Example 11 Monomer Synthesis Scheme

[0451] Preparation of (2): To a solution of 1 (40 g, 58.16 mmol) in DMF (60 mL) were added imidazole (11.88 g, 174.48 mmol), NaI (13.08 g, 87.24 mmol), and TBSCl (17.52 g, 116.32 mmol) at 20° C. in one portion. The reaction mixture was stirred at 20° C. for 12 h. Upon completion, the mixture was diluted with EA (200 mL). The organic layer was washed with brine/water (80 mL/80 mL*4), dried over Na_2SO_4, filtered and evaporated to give 2 (50.8 g, crude) as yellow solid. ESI-LCMS: 802.3 $[M+H]^+$

[0452] Preparation of (3): To a solution of 2 (8.4 g, 10.47 mmol) in DCM (120 mL) were added Et_3SiH (3.06 g, 26.3 mmol, 4.2 mL) and TFA (1.29 g, 0.84 mL) dropwise at 0° C. The reaction mixture was stirred at 20° C. for 2 h. The reaction mixture was washed with saturated aq.$NaHCO_3$(15 mL) and brine (80 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~83% EA/PE gradient @ 80 mL/min) to give 3 (2.92 g, 55.8% yield) as a white solid. ESI-LCMS: 500.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=8.79 (s, 1H), 8.14 (s, 1H), 8.02 (d, J=7.6 Hz, 2H), 7.64-7.58 (m, 1H), 7.56-7.49 (m, 2H), 5.98-5.93 (m, 1H), 4.63-4.56 (m, 2H), 4.23 (s, 1H), 3.98 (dd, J=1.5, 13.1 Hz, 1H), 3.75 (dd, J=1.5, 13.1 Hz, 1H), 3.28 (s, 3H), 2.06-1.99 (m, 1H), 1.00-0.90 (m, 9H), 0.15 (d, J=7.0 Hz, 6H).

[0453] Preparation of (4): 3 (6 g, 12.01 mmol) and tert-butyl N-methylsulfonylcarbamate (3.52 g, 18.01 mmol) were co-evaporated with toluene (50 mL), dissolved in dry THE (100 mL), and cooled to 0° C. PPh_3 (9.45 g, 36.03 mmol) was then added, followed by dropwise addition of DIAD (7.28 g, 36.03 mmol, 7.00 mL) in dry THF (30 mL). The reaction mixture was stirred at 20° C. for 18 h. Upon completion, the reaction mixture was then diluted with DCM (100 mL) and washed with water (70 mL) and brine (70 mL), dried over Na_2SO_4, filtered and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) followed by reverse-phase HPLC (0.1% $NH_3.H_2O$ condition, eluent at 74%) to give 4 (2.88 g, 25% yield) as a white solid. ESI-LCMS: 677.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=9.24 (s, 1H), 8.84 (s, 1H), 8.36 (s, 1H), 8.05 (br d, J=7.3 Hz, 2H), 7.66-7.42 (m, 4H), 6.16 (d, J=5.0 Hz, 1H), 4.52 (br t, J=4.5 Hz, 1H), 4.25-4.10 (m, 1H), 3.97 (br dd, J=8.0, 14.8 Hz, 1H), 3.48 (s, 3H), 3.27 (s, 3H), 1.54 (s, 9H), 0.95 (s, 9H), 0.14 (d, J=0.8 Hz, 6H).

[0454] Preparation of (5): To a solution of 4 (2.8 g, 4.14 mmol) in THE (20 mL) was added TBAF (4 M, 1.03 mL) and the mixture was stirred at 20° C. for 12 h. The reaction mixture was then evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~6% MeOH/ethyl acetate gradient @ 20 mL/min) to give 5 (2.1 g, 83.92% yield) as a white solid. ESI-LCMS: 563.1$[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=8.85-8.77 (m, 1H), 8.38 (s, 1H), 8.11-7.99 (m, 2H), 7.64-7.50 (m, 4H), 6.19 (d, J=2.8 Hz, 1H), 4.36-4.33 (m, 1H), 4.29 (br d, J=4.3 Hz, 1H), 4.22-4.02 (m, 2H), 3.65-3.59 (m, 3H), 3.28 (s, 3H), 1.54 (s, 9H).

[0455] Preparation of (6): To a solution of 5 (2.1 g, 3.73 mmol) in DCM (20 mL) was added TFA (7.70 g, 67.53 mmol, 5 mL) at 0° C. The reaction mixture was stirred at 20° C. for 24 h. Upon completion, the reaction was quenched with saturated aq. $NaHCO_3$ to reach pH 7. The organic layer was dried over Na_2SO_4, filtered, and evaporated at low pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~7% DCM/MeOH gradient @ 20 mL/min) to give 1.6 g (impure, 75% LCMS purity), followed by prep-HPLC [FA condition, column: Boston Uni C18 40*150*5 um; mobile phase: [water (0.225% FA)-ACN]; B %: 8%-38%,7.7 min.] to give 6 (1.04 g, 63.7% yield) as a white solid. ESI-LCMS: 485.0 $[M+Na]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.27-11.21 (m, 1H), 8.77 (s, 1H), 8.74 (s, 1H), 8.05 (d, J=7.3 Hz, 2H), 7.68-7.62 (m, 1H), 7.59-7.53 (m, 2H), 7.39 (t, J=6.3 Hz, 1H), 6.16 (d, J=6.0 Hz, 1H), 5.48 (d, J=5.5 Hz, 1H), 4.55 (t, J=5.5 Hz, 1H), 4.43-4.37 (m, 1H), 4.08-4.02 (m, 1H), 3.41-3.36 (m, 1H), 3.35 (s, 3H), 3.31-3.22 (m, 1H), 2.91 (s, 3H).

[0456] Preparation of (Example 11 monomer): To a solution of 6 (1 g, 2.16 mmol) in DCM (30 mL) was added P1 (977.58 mg, 3.24 mmol, 1.03 mL), followed by DCI (306.43 mg, 2.59 mmol) at 0° C. in one portion under Ar atmosphere. The mixture was degassed and purged with Ar for 3 times, warmed to 20° C., and stirred for 2 hr under Ar atmosphere. Upon completion as monitored by LCMS and TLC (PE: EtOAc=4:1), the reaction mixture was diluted with sat.aq. $NaHCO_3$(30 mL) and extracted with DCM (50 mL*2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (40 g C18 column: neutral condition, Eluent of 0~57% of 0.3% NH_4HCO_3 in H_2O/CH_3CN ether gradient @ 35 mL/min) to give Example 11 monomer (0.49 g, 33.7% yield) as a white solid. ESI-LCMS: 663.1$[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ=1.19-1.29 (m, 12H) 2.71 (q, J=5.77 Hz, 2H) 2.94 (d, J=6.27 Hz, 3H) 3.35 (d, J=15.56 Hz, 3H) 3.40-3.52 (m, 2H) 3.61-3.97 (m, 4H) 4.23-4.45 (m, 1H) 4.55-4.74 (m, 2H) 6.02 (dd, J=10.67, 6.40 Hz, 1H) 7.25 (br s, 1H) 7.47-7.57 (m, 2H) 7.59-7.68 (m, 1H) 8.01 (d, J=7.78 Hz, 2H) 8.28 (s, 1H) 8.66 (s, 1H) 9.69 (br s, 1H); ^{31}P NMR (162 MHz, CD_3CN) δ=150.92, 149.78.

Example 12. Synthesis of 5'-Stabilized End Cap Modified Oligonucleotides

[0457] This example provides an exemplary method for synthesizing the siNAs comprising a 5'-stabilized end caps disclosed herein. The 5'-stabilized end cap and/or deuterated phosphoramidites were dissolved in anhydrous acetonitrile and oligonucleotide synthesis was performed on a Expedite 8909 Synthesizer using standard phosphoramidite chemistry. An extended coupling (12 minutes) of 0.12 M solution of phosphoramidite in anhydrous CH_3CN in the presence of Benzyl-thio-tetrazole (BTT) activator to a solid bound oligonucleotide followed by standard capping, oxidation and sulfurization produced modified oligonucleotides. The 0.02 M 12, THF: Pyridine; Water 7:2:1 was used as an oxidizing agent, while DDTT (dimethylamino-methylidene) amino)-3H-1,2,4-dithiazaoline-3-thione was used as the sulfur-transfer agent for the synthesis of oligoribonucleotide with a phosphorothioate backbone. The stepwise coupling efficiency of all modified phosphoramidites was achieved around 98%. After synthesis the solid support was heated with aqueous ammonia (28%) solution at 45° C. for 16h or 0.05 M K_2CO_3 in methanol was used to deprotect the base labile protecting groups. The crude oligonucleotides were precipitated with isopropanol and centrifuged (Eppendorf 5810R, 3000 g, 4° C., 15 min) to obtain a pellet. The crude product was then purified using ion exchange chromatography (TSK gel column, 20 mM NaH_2PO_4, 10% CH_3CN, 1 M NaBr, gradient 20-60% B over 20 column volumes) and fractions were analyzed by ion change chromatography on an HPLC. Pure fractions were pooled and desalted by Sephadex G-25 column and evaporated to dryness. The purity and molecular weight were determined by HPLC analysis and ESI-MS analysis. Single strand RNA oligonucleotides (sense and antisense strand) were annealed (1:1 by molar equivalents) at 90° C. for 3 min followed by RT 40 min) to produce the duplexes.

Example 13. siNA Activity Assays

[0458] This example provides exemplary methods for testing the activity of the siNAs disclosed herein.

[0459] In Vitro Assay:

[0460] *Homo sapiens* HepG2.2.15 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (ATCC 30-2002) supplemented to also contain 10% fetal calf serum (FCS). Cells were incubated at 37° C. in an atmosphere with 5% CO_2 in a humidified incubator. For transfection of HepG2.2.15 cells with HBV targeting siRNAs, cells were seeded at a density of 15000 cells/well in 96-well regular tissue culture plates. Transfection of cells was carried out using RNAiMAX (Invitrogen/Life Technologies) according to the manufacturer's instructions. Dose-response experiments were done with oligo concentrations of 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625 and 0.07813 nM. For each HBV targeting siRNA treatment (e.g., ds-siRNA, as identified by the ds-siNA ID in Table 6), four wells were transfected in parallel, and individual data points were collected from each well. After 24h of incubation with siRNA, media was removed, and cells were lysed and analyzed with a QuantiGene2.0 branched DNA (bDNA) probe set specific for HBV genotype D (also called Hepatitis B virus subtype ayw, complete genome of 3182 base-pairs) as present in cell line HepG2.2.15.

[0461] For each well, the HBV on-target mRNA levels were normalized to the GAPDH mRNA level. As shown in Table 6, the activity of the HBV targeting ds-siRNAs was expressed as EC50, 50% reduction of normalized HBV RNA level from no drug control. As shown in Table 6, the cytotoxicity of the HBV targeting ds-siRNAs was expressed by CC50 of 50% reduction of GAPDH mRNA from no drug control.

[0462] Unconjugated siRNA 1) with or without a phosphorylation blocker; and 2) with or without end caps (e.g., 5'-stabilized end cap) are transfected into in vitro disease models or in vitro toxicity models. After transfection, target reduction and/or cell viability is measured and compared after a period of incubation. For HBV, exemplary disease cell models include, but are not limited to, HepG2.2.15, HepG2.117 or live HBV infected HepG2-NTCP or Primary Human Hepatocytes.

[0463] In Vivo Assay:

[0464] GalNAc conjugated siRNA 1) with or without phosphorylation blocker; and 2) with or without 5'-end caps are dosed subcutaneously or intravenously in animal disease models. The target knockdown magnitude and duration is measured from serum or liver samples and compared to each other and/or control animals (e.g., non-treated diseased animals). In some instances, the toxicity of the siRNAs is compared through routine Clinpath or Histopath assays. For HBV, exemplary animal efficacy models include, but are not limited to, AAV-HBV mouse model, HBV transgenic mouse model, PXB or FRG mouse models.

Example 14. Ds-siNA Testing in AAV-HBV Mouse Model

[0465] In this example, the efficacy of ds-siNAs in treating HBV in an adeno-associated virus (AAV)-HBV mouse model was evaluated. AAV-HBV mice were subcutaneously injected with a single dose of (a) 5 mL/kg of vehicle; or (b) 5 mg/kg a ds-siNA at day 0. The sequences of the ds-siNA tested in this example are shown in Table 7.

[0466] FIG. **4** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G03), ds-siNA-0165 (G04), ds-siNA-0163 (G05), or ds-siNA-0166 (G06). These results demonstrate that the ds-siNAs containing various patterns of 2'-fluoro nucleotides and 2'-O-methyl nucleotides can effectively treated HBV.

TABLE 7

ds-siNA sequences tested in AAV-HBV mouse model

ds-siNA ID	Sense strand sequence (5'-3')	Antisense strand sequence (5'-3')
ds-siNA-0160	mCpsmCpsfGmUmGmUfGfCfAmCmUf UmCmGmCmUfUmCmA-p-(PS)2-GalNAc4	mUpsfGpsmAmAmGmCmGmAmAmGm UmGmCfAmCmAmCmGmGpsmUpsmC

TABLE 7-continued

ds-siNA sequences tested in AAV-HBV mouse model

ds-siNA ID	Sense strand sequence (5'-3')	Antisense strand sequence (5'-3')
ds-siNA-0165	mGpsmUpsfGmGmUmGfGfAfCmUmUfCmUmCmUmCfAmAmU-p-(PS)2-GalNAc4	mApsfUpsmUmGmAmGmAmGmAmAmGmUmCfCmAmCmCmAmCpsmGpsmA
ds-siNA-0163	mGpsmCpsmUmGmCmUfAmUfGfCfCmUmCmAmUmCmUmUmCmUmU-p-(PS)2-GalNAc4	mApsfApsmGmAmAfGmAmUmGmAmGmGmCfAmUfAmGmCmAmGmCpsmApsmG
ds-siNA-0166	mUpsmGpsfUmGmCmAfCfUmUmCmGmCmUmUmCmAfCmCmUFheg-p-(PS)2-GalNAc4	mApsfGpsmGmUmGmAmAmGmCmGmAmAmGfUmGmCmAmCmApsmCpsmG

Example 15. Ds-siNA Activity Assay and Testing in AAV-HBV Mouse Model

[0467] This example investigates the in vitro and in vivo activity of ds-siNAs. The sequences of the ds-siNAs tested in this example are shown in Table 8. As shown in Table 8, the ds-siNAs comprise a sense and antisense strand comprising a mixture of 2'-fluoro and 2'-O-methyl nucleotides. The total number of 2'-fluoro nucleotides in the ds-siNAs are between 6-8. The 2'-fluoro nucleotides may be at specific positions, such as nucleotide position 3, 5, 7, 8, 9, 10, 11, 12, and/or 17 from the 5' end of the sense strand or 2, 5, 6, 8, 10, 14, 16, 17, and/or 18. The 2'-fluoro nucleotides and 2'-O-methyl nucleotides might occur at specific patterns on the antisense strand, such as an alternating 1:2 or 1:3 pattern, wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 or 3 nucleotides are 2-O-methyl nucleotides.

[0468] In Vitro Activity Assay

[0469] *Homo sapiens* HepG2.2.15 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (ATCC 30-2002) supplemented to also contain 10% fetal calf serum (FCS). Cells were incubated at 37° C. in an atmosphere with 5% CO_2 in a humidified incubator. For transfection of HepG2.2.15 cells with HBV targeting siRNAs, cells were seeded at a density of 15000 cells/well in 96-well regular tissue culture plates. Transfection of cells was carried out using RNAiMAX (Invitrogen/Life Technologies) according to the manufacturer's instructions. Dose-response experiments were done with oligo concentrations of 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625 and 0.07813 nM. For each HBV targeting siRNA treatment (e.g., ds-siRNA, as identified by the ds-siNA ID in Table 8), four wells were transfected in parallel, and individual data points were collected from each well. After 24h of incubation with siRNA, media was removed, and cells were lysed and analyzed with a QuantiGene2.0 branched DNA (bDNA) probe set specific for HBV genotype D (also called Hepatitis B virus subtype ayw, complete genome of 3182 base-pairs) as present in cell line HepG2.2.15.

[0470] For each well, the HBV on-target mRNA levels were normalized to the GAPDH mRNA level. Table 8 shows the activity of the HBV targeting ds-siRNAs expressed as EC50, which is 50% reduction of normalized HBV RNA level from no drug control, where A=EC50<0.5 nM; B=0.5 nM<EC50<1; and C=EC50 >1.

[0471] In Vivo Testing in AAV-HBV Mouse Model:

[0472] AAV/HBV is a recombinant AAV carrying replicable HBV genome. Taking advantage of the highly hepatotropic feature of genotype 8 AAV, the HBV genome can be efficiently delivered to the mouse liver cells. Infection of immune competent mouse with AAV/HBV can result in long term HBV viremia, which mimics chronic HBV infection in patients. The AAV/HBV model can be used to evaluate the in vivo activity of various types of anti-HBV agents. Mice were infected with AAV-HBV on day −28 of the study. The test articles or negative control (PBS) were dosed subcutaneously (unless specified otherwise) as single dose on days 0 at 5 mg/kg. Serial blood collections were usually taken every 5 days on day 0, 5, 10 and 15 etc. until the termination of studies. Serum HBV S antigen (HBsAg) was assayed through ELISA.

[0473] GalNAc conjugated ds-siNAs were further tested at a single dose of 5 mg/kg at day 0 in the adeno-associated virus (AAV)-HBV mouse model. The resulting nadir $\log_{10}$ reduction in serum HBsAg is presented in Table 8, where X≥1 $\log_{10}$ reduction in HBsAg, Y is 0.5-1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

[0474] FIG. **5**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0160 (G03). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0160 on day 0.

[0475] FIG. **5**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0160 (G15). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0160 on day 0.

[0476] FIG. **5**C shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0160 (G03). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0.

[0477] FIG. **5**D shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G03), or ds-siNA-0109 (G09). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0.

[0478] FIGS. **5**E-**5**F show a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0169 (G18). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0169 on day 0.

[0479] FIG. **5**G shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0169 (G04). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0169 on day 0.

[0480] FIG. **5**H shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01) or ds-siNA-0169 (G04). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0.

[0481] FIG. **5**I shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0169 (G04) or ds-siNA-0147 (G08). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0.

[0482] FIG. **5**J shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0166 (G06), or ds-siNA-0153 (G14). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0.

[0483] FIG. **5**K shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0163 (G05), or ds-siNA-0119 (G13). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0.

[0484] These results demonstrate that ds-siNAs comprising combination of 2'-fluoro nucleotides and 2'-O-methyl nucleotides can be used to target HBV X and S gene sequences, which resulted in successful treatment of HBV.

[0485] As exemplified by ds-siNA-0160 and ds-siNA-0165, ds-siNAs comprising (a) a sense strand comprising 19 nucleotides, wherein 6 nucleotides are 2'-fluoro nucleotides and 13 nucleotides are 2'-O-methyl nucleotides; (b) an antisense strand comprising 21 nucleotides, wherein 2 nucleotides are 2'-fluoro nucleotides and 19 nucleotides are 2'-O-methyl nucleotides; and (c) a conjugated moiety, wherein the conjugated moiety is attached to the 3' end of the sense strand, resulted in successful treatment of HBV as evidenced by HBsAg reduction in serum. See FIGS. **4** and **5**A-**5**D, and Table 8. For ds-siNA-0160 and ds-siNA-0165, the 2'-fluoro nucleotides were located at positions 3, 7-9, 12, and 17 from the 5' end of the sense strand and at positions 2 and 14 from the 5' end of the antisense strand.

[0486] As exemplified by ds-siNA-0166, ds-siNAs comprising (a) a sense strand comprising 19 nucleotides, wherein 4 nucleotides are 2'-fluoro nucleotides and 15 nucleotides are 2'-O-methyl nucleotides; (b) an antisense strand comprising 21 nucleotides, wherein 2 nucleotides are 2'-fluoro nucleotides and 19 nucleotides are 2'-O-methyl nucleotides; and (c) a conjugated moiety, wherein the conjugated moiety is attached to the 3' end of the sense strand, resulted in successful treatment of HBV as evidenced by HBsAg reduction in serum. See FIGS. **4** and **5**J, and Table 8. For ds-siNA-0166, the 2'-fluoro nucleotides were located at positions 3, 7, 8, and 17 from the 5' end of the sense strand and at positions 2 and 14 from the 5' end of the antisense strand.

[0487] As exemplified by ds-siNA-0153, ds-siNAs comprising (a) a sense strand comprising 19 nucleotides; (b) an antisense strand comprising 21 nucleotides, wherein the nucleotides in the antisense strand comprise at least two alternating 1:3 modification pattern, and wherein approximate 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides in repeat pattern; and (c) a conjugated moiety, wherein the conjugated moiety is attached to the 3' end of the sense strand, resulted in successful treatment of HBV as evidenced by HBsAg reduction in serum. See FIG. **5**J. For ds-siNA-0153, the sense strand comprises 6 2'-fluoro nucleotides at positions 3, 7-9, 12, and 17 from the 5' end of the sense strand. In addition, the antisense strand comprises 5 repeats of the 1:3 modification pattern starting at position 2 from the 5' end of the antisense strand.

[0488] As exemplified by ds-siNA-0109, ds-siNAs comprising (a) a sense strand comprising 19 nucleotides wherein 4 nucleotides are 2'-fluoro nucleotides and 15 nucleotides are 2'-O-methyl nucleotides; (b) an antisense strand comprising 21 nucleotides, wherein 4 nucleotides are 2'-fluoro nucleotides and 17 nucleotides are 2'-O-methyl nucleotides; and (c) a conjugated moiety, wherein the conjugated moiety is attached to the 3' end of the sense strand, resulted in successful treatment of HBV as evidenced by HBsAg reduction in serum. See FIG. **5**D. For ds-siNA-0109 the sense strand comprises 4 2'-fluoro nucleotides at positions 5 and 7-9 from the 5' end of the sense strand. In addition, the antisense strand comprises 5 repeats of the 1:2 modification pattern starting at positions 2, 5, 8, 14, and 17 from the 5' end of the antisense strand.

[0489] As exemplified by ds-siNA-0147, ds-siNAs comprising (a) a sense strand comprising 19 nucleotides; (b) an antisense strand comprising 21 nucleotides, wherein the nucleotides in the antisense strand comprise at least two alternating 1:2 modification pattern, and wherein approximate 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides in repeat pattern; and (c) a conjugated moiety, wherein the conjugated moiety is attached to the 3' end of the sense strand, resulted in successful treatment of HBV as evidenced by HBsAg reduction in serum. See FIG. **5**I. For ds-siNA-0147, the 2'-fluoro nucleotides were located at positions 5 and 7-9 from the 5' end of the sense strand and at positions 2, 6, 14, and 16 from the 5' end of the antisense strand.

TABLE 8

ds-siNA tested in AAV-HBV Mouse Model

ds-siNA ID	Sense strand sequence (5'-3')	Antisense strand sequence (5'-3')	EC50 HepG2.2.15*	HBsAg Nadir (Log)**
ds-siNA-0109	mCpsmCpsmGmUfGmUfGfCf AmCmUmUmCmGmCmUmU mCmA-p-(PS)2-GalNac4	mUpsfGpsmAmAfGmCmGfA mAmGmUmGmCfAmCmAfC mGmGpsmUpsmC		

TABLE 8-continued

ds-siNA tested in AAV-HBV Mouse Model

ds-siNA ID	Sense strand sequence (5'-3')	Antisense strand sequence (5'-3')	EC50 HepG2.2.15*	HBsAg Nadir (Log)**
ds-siNA-0119	mGpsmCpsmUmGfCmUmAm UfGfCfCmUmCfAmUmCmU mUfCmUmU-p-(PS)2-GalNac4	mApsfApsmGmAmAmGmA mUmGmAmGmGmCfAmUm AmGmCmAmGmCpsmApsm G		
ds-siNA-0147	mGpsmUpsmGmGfUmGfGfAf CmUmUmCmUmCmUmCmA mAmU-p-(PS)2-GalNac4	mApsfUpsmUmGmAfGmAm GmAmAmGmUmCfCmAfCm CmAmCpsmGpsmA		
ds-siNA-0153	mUpsmGpsfUmGmCmAfCfUf UmCmGfCmUmUmCmAfCm CmU-p-(PS)2-GalNac4	mApsfGpsmGmUmGfAmAm GmCfGmAmAmGfUmGmC mAfCmApsmCpsmG		
ds-siNA-0167	mGpsmCpsfGmGmGmGfUfUf UmUmUfCmUmUmGmUfUm GmA-p-(PS)2-GalNac4	mUpsfCpsmAmAmCmAmA mGmAmAmAmAmAfCmCm CmCmGmCpsmCpsmU	A	X
ds-siNA-0162	mGpsmCpsfGmGmGmGfUfU mUmUmUmCmUmUmGmUf UmGmA-p-(PS)2-GalNac4	mUpsfCpsmAmAmCmAmA mGmAmAmAmAmAfCmCm CmCmGmCpsmCpsmU	C	X
ds-siNA-0165	mGpsmUpsfGmGmUmGfGfAf CmUmUfCmUmCmUmCfAm AmU-p-(PS)2-GalNac4	mApsfUpsmUmGmAmGmA mGmAmAmGmUmCfCmAm CmCmAmCpsmGpsmA	A	X
ds-siNA-0168	mUpsmCpsmGmUmGmGfUm GfGfAfCmUmUmCmUmCmU mCmAmAmU-p-(PS)2-GalNac4	mApsfUpsmUmGmAfGmAm GmAmAmGmUmCfCmAfCm CmAmCmGmApsmGpsmU	A	X
ds-siNA-0163	mGpsmCpsmUmGmCmUfAm UfGfCfCmUmCmAmUmCmU mUmCmUmU-p-(PS)2-GalNac4	mApsfApsmGmAmAfGmAm UmGmAmGmGmCfAmUfA mGmCmAmGmCpsmApsmG	A	Y
ds-siNA-0161	mCpsmUpsfGmCmUmAfUfGf CmCmUfCmAmUmCmUfUm CmU-p-(PS)2-GalNac4	mApsfGpsmAmAmGmAmU mGmAmGmGmCmAfUmAm GmCmAmGpsmCpsmA	A	Y
ds-siNA-0160	mCpsmCpsfGmUmGmUfGfCf AmCmUfUmCmGmCmUfUm CmA-p-(PS)2-GalNac4	mUpsfGpsmAmAmGmCmG mAmAmGmUmGmCfAmCm AmCmGmGpsmUpsmC	A	X
ds-siNA-0169	mCpsmCpsfGmUmGmUfGfCf AmCmUfUmCmGmCmUfUm CmA-p-(PS)2-GalNac4	mUpsfGpsmAmAmGmCmG mAmAmGmUmGmCfAmCm AmCmGmGpsTpsT	A	X
ds-siNA-0170	mUpsmGpsfUmGmCmAfCfUf UmCmGfCmUmUmCmAfCm CmU-p-(PS)2-GalNac4	mApsfGpsmGmUmGmAmA mGmCmGmAmAmGfUmGm CmAmCmApsmCpsmG	A	X
ds-siNA-0166	mUpsmGpsfUmGmCmAfCfU mUmCmGmCmUmUmCmAfC mCmU-p-(PS)2-GalNAc4	mApsfGpsmGmUmGmAmA mGmCmGmAmAmGfUmGm CmAmCmApsmCpsmG	A	X
ds-siNA-0171	mUpsmGpsfUmGmCmAfCfU mUmCmGmCmUmUmCmAfC mCmU-p-(PS)2-GalNac4	mApsfGpsmGmUmGmAmA mGmCmGmAmAmGfUmGm CmAmCmApsTpsT	A	X

mX = 2'-O-methyl nucleotide; fX = 2'-fluoro nucleotide; ps = phosphorothioate linkage

*For EC50, A = EC50 < 0.5 nM; B = 0.5 nM < EC50 < 1 ; and C = EC50 > 1.

**For HBsAg Nadir, X ≥ 1 $\log_{10}$ reduction in HBsAg, Y is 0.5 - 1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

Example 16. Testing of Ds-siNAs Having a 5'-Stabilized End Cap in AAV-HBV Mouse Model

[0490] This example investigates the in vivo activity of ds-siNAs having a 5'-stabilized end cap. The sequences of the ds-siNAs tested in this example are shown in Table 9.

[0491] FIG. **6**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G15) (ds-siNA without a 5'-stabilized end cap, e.g., vinyl phosphonate), or ds-siNA-080 (G14) (ds-siNA with a 5'-stabilized end cap, e.g., vinyl phosphonate). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0. The resulting nadir $\log_{10}$ reduction in serum HBsAg is presented in Table 9, where X ≥1 $\log_{10}$ reduction in HBsAg, Y is 0.5-1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

[0492] FIG. **6**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0169 (G16) (ds-siNA without a 5'-stabilized end cap, e.g., vinyl phosphonate), or ds-siNA-081 (G13) (ds-siNA with a 5'-stabilized end cap, e.g., vinyl phosphonate). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0. The resulting nadir $\log_{10}$ reduction in serum HBsAg is presented in Table 9, where X ≥1 $\log_{10}$ reduction in HBsAg, Y is 0.5-1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

[0493] FIG. **7**A shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0165 (G18) (ds-siNA without a 5'-stabilized end cap, e.g., vinyl phosphonate), or ds-siNA-0127 (G17) (ds-siNA with a 5'-stabilized end cap, e.g., vinyl phosphonate). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0. The resulting nadir $\log_{10}$ reduction in serum HBsAg is presented in Table 9, where X ≥1 $\log_{10}$ reduction in HBsAg, Y is 0.5-1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

[0494] FIG. **7**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0168 (G20) (ds-siNA without a 5'-stabilized end cap, e.g., vinyl phosphonate), or ds-siNA-0150 (G19) (ds-siNA with a 5'-stabilized end cap, e.g., vinyl phosphonate). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of each ds-siNA on day 0. The resulting nadir $\log_{10}$ reduction in serum HBsAg is presented in Table 9, where X ≥1 $\log_{10}$ reduction in HBsAg, Y is 0.5-1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

[0495] These results demonstrate that the addition of a 5'-stabilized end cap can improve the efficacy of ds-siNAs without a 5'-stabilized end cap.

TABLE 9

ds-siNA sequences and HBsAg Nadir

ds-siNA ID	Sense strand sequence (5'-3')	Antisense strand sequence (5'-3')	HBsAg Nadir (Log)*
ds-siNA-0160	mCpsmCpsfGmUmGmUfGfC fAmCmUfUmCmGmCmUfU mCmA-(PS)2-p-GalNAc4	mUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsm UpsmC	Y
ds-siNA-080	mCpsmCpsfGmUmGmUfGfC fAmCmUfUmCmGmCmUfU mCmA-(PS)2-p-GalNAc4	vmUpsfGpsmAmAmGmCmGmAmA mGmUmGmCfAmCmAmCmGmGps mUpsmC	X
ds-siNA-0169	mCpsmCpsfGmUmGmUfGfC fAmCmUfUmCmGmCmUfU mCmA-(PS)2-p-GalNAc4	mUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsTp sT	Y
ds-siNA-081	mCpsmCpsfGmUmGmUfGfC fAmCmUfUmCmGmCmUfU mCmA-(PS)2-p-GalNAc4	vmUpsfGpsmAmAmGmCmGmAmA mGmUmGmCfAmCmAmCmGmGpsT psT	X
ds-siNA-0165	mGpsmUpsfGmGmUmGfGfA fCmUmUfCmUmCmUmCfA mAmU-(PS)2-p-GalNAc4	mApsfUpsmUmGmAmGmAmGmAm AmGmUmCfCmAmCmCmAmCpsmG psmA	X
ds-siNA-0127	mGpsmUpsfGmGmUmGfGfA fCmUmUfCmUmCmUmCfA mAmU-(PS)2-p-GalNAc4	vmApsfUpsmUmGmAmGmAmGmA mAmGmUmCfCmAmCmCmAmCpsm GpsmA	X
ds-siNA-0168	mUpsmCpsmGmUmGmGfUm GfGfAfCmUmUmCmUmCm UmCmAmAmU-(PS)2-p-GalNAc4	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCmGmAp smGpsmU	Y
ds-siNA-0150	mUpsmCpsmGmUmGmGfUm GfGfAfCmUmUmCmUmCm UmCmAmAmU-(PS)2-p-GalNAc4	vmApsfUpsmUmGmAfGmAmGmAm AmGmUmCfCmAfCmCmAmCmGm ApsmGpsmU	X

mX = 2'-O-methyl nucleotide; fX = 2'-fluoro nucleotide; ps = phosphorothioate linkage; VP = vinyl phosphonate

*For HBsAg Nadir, X ≥ 1 $\log_{10}$ reduction in HBsAg, Y is 0.5 - 1 $\log_{10}$ reduction in HBsAg, and Z is <0.5 $\log_{10}$ reduction in HBsAg.

Example 17. Efficacy of a Combination Therapy in AAV-HBV Mouse Model

[0496] This example investigates the efficacy of a combination therapy comprising an antisense oligonucleotide (ASO 1, 5' GalNAc4-ps-GalNAc4-ps-GalNAc4-po-mA-po-lnGpslnApslnTpslnApslnApsApsAps(50H)CpsGps(5m) Cps(5m)CpsGps(5m)CpslnApslnG pslnApscp(5m)C-3' (SEQ ID NO: 534)) and a ds-siNA-0160 for treating HIBV in an AAV-HIBV mouse model.

[0497] FIG. **8**A shows a graph of the change in serum HBsAg from AAV-HIBV mice treated with vehicle (G01), ds-siNA-0160 (G06), ASO 1 (G18), or a combination of ds-siNA-0160 and ASO 1 (G20). AAV-HBV mice were subcutaneously injected with (a) 5 mL/kg of vehicle, three times a week, from days 0-42 (G01); (b) a single dose of 3 mg/kg of ds-siNA-0160 on day 0 (G06); (c) 3 mg/kg of ASO 1 on a weekly basis, from days 0-21 (G18); or (d) a combination of ASO 1 and ds-siNA-0160, wherein ASO 1 was administered at a dose of 3 mg/kg on a weekly basis, from days 0-21; and ds-siNA-0160 was administered as a single dose of 3 mg/kg at day 0.

[0498] FIG. **8**B shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G01), ds-siNA-0160 (G06), ASO 1 (G18), or a combination of ds-siNA-0160 and ASO 1 (G20). AAV-HBV mice were subcutaneously injected with (a) 5 mL/kg of vehicle, three times a week, from days 0-42 (G01); (b) a single dose of 10 mg/kg of ds-siNA-0160 on day 0 (G06); (c) 10 mg/kg of ASO 1 on a weekly basis, from days 0-21 (G18); or (d) a combination of ASO 1 and ds-siNA-0160, wherein ASO 1 was administered at a dose of 10 mg/kg on a weekly basis, from days 0-21; and ds-siNA-0160 was administered as a single dose of 3 mg/kg at day 0.

[0499] FIG. **8**C shows a graph of a synergy analysis of an in vitro combination therapy with the ASO 2 and ds-siNA-0164. For the ds-siNA-0164 combination studies with ASO 2, 35,000 cells per well were reverse transfected in a collagen I-coated 96-well plate (Corning, Biocoat; Catalog 356698). Test articles ds-siNA-0164 and ASO 2 were diluted in Opti-MEM™ I Reduced Serum Medium (Thermo Fisher Scientific; Catalog 31985088) to 40× the desired final test concentration then serially diluted (1:3) up to 5 or 9 distinct concentrations, respectively. A 3.25-L aliquot of each diluted compound was combined in a checkerboard fashion. This combination of compounds was mixed with 0.3 μL Lipofectamine© RNAiMAX Transfection Reagent (Thermo Fisher Scientific, Catalog 13778150) and 6.2 μL of Opti-MEM™ I Reduced Serum Medium. After incubating for 20 minutes, the mixture was added to the cells. Space was also allotted for titrations of each compound alone as reference controls. Cells were incubated with compounds for 3 days at 37° C. in a 5% CO_2 atmosphere. After that, HBsAg in the supernatant of cell culture was assayed by ELISA and cell viability was measured with Cell Titer Glow, the same procedures as in HepG2.2.15 in vitro assay section. The HBsAg reduction synergy between two test articles were analyzed using MacSynergy Software.

[0500] These results demonstrate that a combination therapy with ASO 1 and ds-siNA-0160 resulted in a greater reduction in serum HBsAg as compared to treatment with ASO 1 or ds-siNA-0160 alone.

Example 18. siNA Activity Assays

[0501] This example evaluates the activity of the siNAs disclosed in Table 10 (as identified by the ds-siNA ID). siRNAs were synthesized as described in Example 1. A conjugated moiety (e.g., ligand monomer) was further conjugated to the 3' end of the sense strand (note: for ds-siNA-067 and ds-siNA-083, the ligand monomer was conjugated to the 5' end of the sense strand). A 5'-stabilized end cap was further attached to the 5' end of the antisense strand of some siRNAs.

[0502] In Vitro Assay:

[0503] *Homo sapiens* HepG2.2.15 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (ATCC 30-2002) supplemented to also contain 10% fetal calf serum (FCS). Cells were incubated at 37° C. in an atmosphere with 5% CO_2 in a humidified incubator. For transfection of HepG2.2.15 cells with HBV targeting siRNAs, cells were seeded at a density of 15000 cells/well in 96-well regular tissue culture plates. Transfection of cells was carried out using RNAiMAX (Invitrogen/Life Technologies) according to the manufacturer's instructions. Dose-response experiments were done with oligo concentrations of 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625 and 0.07813 nM. For each HBV targeting siRNA treatment (e.g., ds-siRNA, as identified by the ds-siNA ID in Table 6), four wells were transfected in parallel, and individual data points were collected from each well. After 24h of incubation with siRNA, media was removed, and cells were lysed and analyzed with a QuantiGene2.0 branched DNA (bDNA) probe set specific for HBV genotype D (also called Hepatitis B virus subtype ayw, complete genome of 3182 base-pairs) as present in cell line HepG2.2.15.

[0504] For each well, the HBV on-target mRNA levels were normalized to the GAPDH mRNA level. As shown in Table 10, the activity of the HBV targeting ds-siRNAs was expressed as EC50, 50% reduction of normalized HBV RNA level from no drug control, where A=EC50<5 nM; B=5 nM<EC50<10; C=EC50≥10. As shown in Table 10, the cytotoxicity of the HBV targeting ds-siRNAs was expressed by CC50 of 50% reduction of GAPDH mRNA from no drug control.

[0505] In Vivo Assay:

[0506] GalNAc conjugated siRNA with or without 5'-stabilized end caps were subcutaneously injected at a single dose of 5 mg/kg into AAV-HBV mice. The target knockdown magnitude was measured from serum. The resulting max HBsAg knockdown (log_{10}) is presented in Table 10, where X ≥1 log_{10} reduction in HBsAg, Y is 0.5-1 log_{10} reduction in HBsAg, and Z is <0.5 log_{10} reduction in HBsAg.

Example 19: Analysis of 5'-Stabilized End Cap on the Efficacy of siNAs

[0507] In this example, the role of a 5'-stabilized end cap on the efficacy of siNAs was investigated. Specifically, the first nucleotide on the 5' end of the antisense strand was modified to contain a 5'-stabilized end cap. The ds-siNAs investigated in this example are shown in the table below:

ds-siNA ID	Sense Strand Sequence (5'→3')	Antisense Strand Sequence (5'→3')
ds-siNA-0166	mUpsmGpsfUmGmCmAfCfUmUmCmG mCmUmUmCmAfCmCmU-p-(PS)2-GalNAc4	mApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmApsm CpsmG
ds-siNA-0155	mUpsmGpsfUmGmCmAfCfUmUmCmG mCmUmUmCmAfCmCmU-p-(PS)2-GalNAc4	vmApsfGpsmGmUmGmAmAmGmC mGmAmAmGfUmGmCmAmCmAps mCpsmG
ds-siNA-0157	mUpsmGpsfUmGmCmAfCfUmUmCmG mCmUmUmCmAfCmCmU-p-(PS)2-GalNAc4	d2vmApsfGpsmGmUmGmAmAmG mCmGmAmAmGfUmGmCmAmCm ApsmCpsmG

mX = 2'-O-methyl nucleotide; fX = 2'-fluoro nucleotide; vmA = 5'-vinyl phosphonate 2'-O-methyl adenosine; d2vmA = deuterated 5' vinyl phosphonate adenosine; ps = phosphorothioate linkage

[0508] AAV-HBV mice were subcutaneously injected with vehicle or ds-siNAs. ds-siNA-0166, ds-siNA-0155, or ds-siNA-0157 were subcutaneously injected at a single dose of 5 mg/kg into AAV-HBV mice. The target knockdown magnitude is measured from serum. As shown in FIG. **9**, the presence of the 5' stabilized end cap in the first nucleotide from the 5' end of the antisense strand in ds-siNA-0155 (triangle) and ds-siNA-0157 (square) improved the efficacy of the siNA (squares and triangles) as compared to the siNA without the 5' stabilized end cap (ds-siNA-0166, diamond). In addition, the presence of the deuterated 5' vinyl phosphonate in ds-siNA-0157 resulted in a greater improvement in efficacy of a ds-siNA as compared to the presence of the 5' vinylphosphanate in ds-siNA-0155. These results demonstrate that a 5' stabilized end cap improves the efficacy of siNAs, with the greatest improvement seen in siNAs containing deuterated 5' vinyl phosphonate.

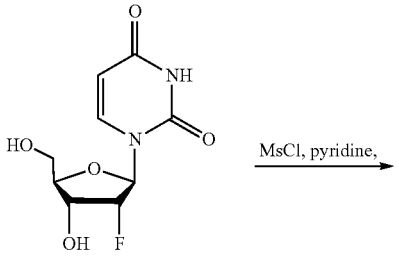
Example 20: Analysis of HBV siRNA S and X Combination Therapy

[0509] In this example, combination therapy using an siNA targeting the S gene of HBV and an siNA targeting the X gene of HBV was examined. AAV-HBV mice were treated with vehicle, a single siNA therapy, or a combination siNA therapy targeting the S gene and X gene of HBV. AAV-HBV mice were subcutaneously injected with a single dose of ds-siNA-0160 or ds-siNA-0165 on day 0. For the combination siNA therapy, AAV-HBV mice were subcutaneously injected with a single dose of 1.5 mg/kg of ds-siNA-0165 (S trigger) and 1.5 mg/kg of ds-siNA-0160 (X trigger) on day 0. As shown in FIG. **10**, the combination therapy with a siNA targeting the S gene and a siNA targeting the X gene was more potent than the single therapy with ds-siNA-0165 or ds-siNA-0160.

Example 21. Synthesis of Monomer

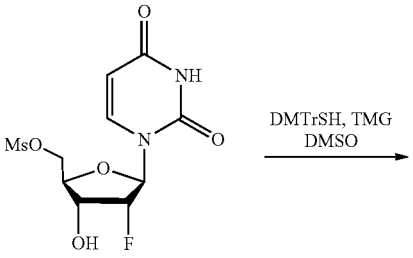
[0510]

Scheme 1

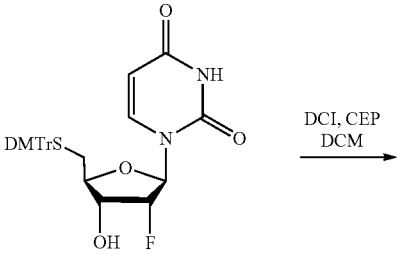


1

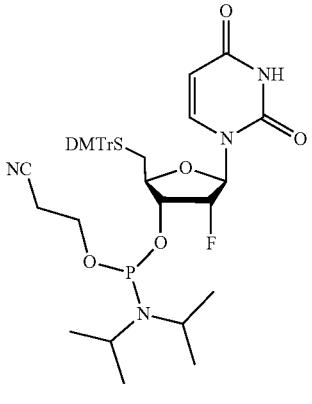
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2

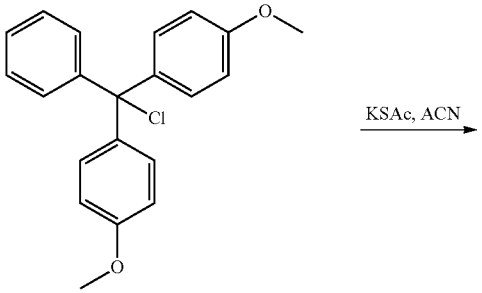


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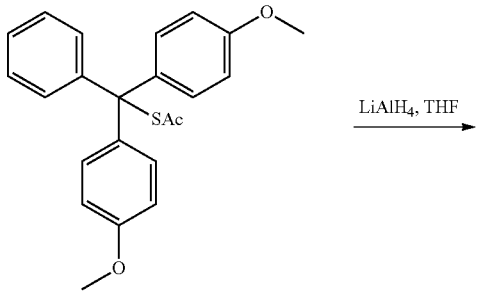


Example 21 monomer

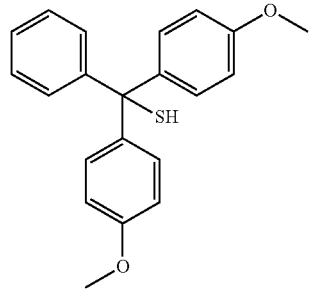
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1a



2a



3a

[0511] Preparation of (2a): To a solution of 1a (10.0 g, 29.5 mmol) in ACN (200.0 mL), KSAc (13.5 g, 118.6 mmol) was added at r.t., the mixture was stirred at r.t. for 15 h, TLC showed 1a was consumed completely. Mixture was filtered by silica gel and filter cake was washed with DCM (100.0 mL), the filtrate was concentrated to give crude 2a (11.1 g) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 5H), 7.16 (d, J=8.9 Hz, 4H), 6.82 (d, J=8.9 Hz, 4H), 3.82 (s, 6H), 2.28 (s, 3H).

[0512] Preparation of (3a): To a solution of crude 2a (11.1 g, 29.2 mmol) in THF (290.0 mL), $LiAlH_4$ (2.0 g, 52.6 mmol) was added at 0° C. and kept for 10 min, reaction was stirred at r.t. for 5 h under N_2, TLC showed 2a was consumed completely. Mixture was put into aqueous $NaHCO_3$ solution and extracted with EA (500.0 mL*2), organic phase was concentrated to give crude which was purified by column chromatography (SiO_2, PE/EA=30:1 to 10:1) to give 3a (8.1 g, 95% purity) as a white solid. ESI-LCMS: m/z 335.3 $[M-H]^-$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 7.19 (d, J=8.8 Hz, 4H), 6.82 (d, J=8.8 Hz, 4H), 3.83 (s, 6H), 3.09 (s, 1H).

[0513] Preparation of (2): To a solution of 1 (20.0 g, 81.3 mmol) in pyridine (400.0 mL), MsCl (10.23 g, 89.43 mmol) was added dropwise at −10° C., reaction was stirred at −10° C. for 1 h, LCMS showed 1 was consumed completely, 100.0 mL aqueous $NaHCO_3$ solution was added and extracted with DCM (100.0 mL*2), organic phase was concentrated to give crude which was purified by column chromatography (SiO_2, DCM/MeOH=30:1 to 10:1) to give 2 (9.5 g, 97% purity) as a white solid. ESI-LCMS: m/z 325.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 7.64-7.62 (d, J=8.0 Hz, 1H), 5.92-5.85 (m, 2H), 5.65-5.63 (d, J=8.0 Hz, 1H), 5.26-5.11 (m, 1H), 4.53-4.37 (m, 2H), 4.27-4.16 (m, 1H), 4.10-4.04 (m, 1H), 3.23 (s, 3H).

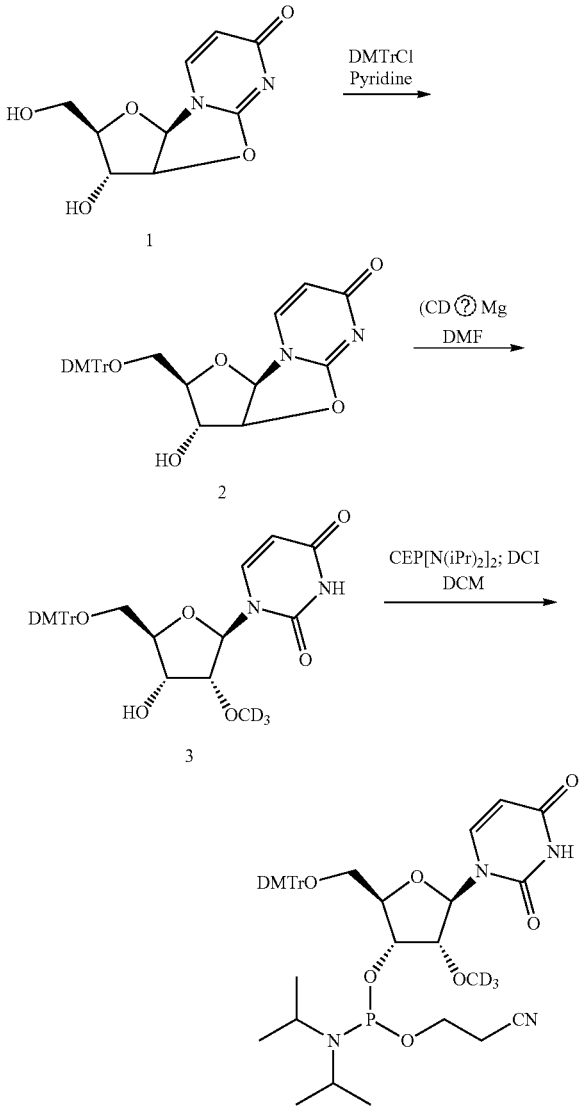
[0514] Preparation of (3): Intermediate 3 was prepared by prepared according to reaction condition described in reference *Helvetica Chimica Acta,* 2004, 87. 2812. To a solution of 2 (9.2 g, 28.3 mmol) in dry DMSO (130.0 mL). DMTrSH (14.31 g, 42.5 mmol) was added, followed by tetramethylguanidine (3.6 g, 31.2 mmol) was added under N_2, reaction was stirred at r.t. for 3 h, LCMS showed 2 was consumed completely. 100.0 mL H_2O was added and extracted with EA (100.0 mL*2), organic phase was concentrated to give crude which was purified by column chromatography (SiO_2, PE/EA=5:1 to 1:1) to give 3 (12.0 g, 97% purity) as a white solid. ESI-LCMS: m/z 563.2 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.43-11.42 (d, J=4.0 Hz, 1H), 7.57-7.55 (d, J=8.0 Hz, 1H), 7.33-7.17 (m, 9H), 6.89-6.86 (m, 4H), 5.80-5.74 (m, 1H), 5.65-5.62 (m, 1H), 5.58-5.57 (d, J=4.0 Hz, 1H), 5.16-5.01 (m, 1H), 3.98-3.90 (m, 1H), 3.73 (s, 6H), 3.73-3.67 (m, 1H), 2.50-2.37 (m, 2H).

[0515] Preparation of Example 21 monomer: To a solution of 3 (10.0 g, 17.7 mmol) in dichloromethane (120.0 mL) with an inert atmosphere of nitrogen was added CEOP[N(iPr)$_2$]$_2$ (6.4 g, 21.2 mmol) and DCI (1.8 g, 15.9 mmol) in order at room temperature. The resulting solution was stirred for 1.0 h at room temperature and diluted with 50 mL dichloromethane and washed with 2×50 mL of saturated aqueous sodium bicarbonate and 1×50 mL of saturated aqueous sodium chloride respectively. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated till no residual solvent left under reduced pressure. The residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=6/1; Detector, UV 254 nm. This resulted in to give Example 21 monomer (12.8 g, 98% purity, 93% yield) as an oil. ESI-LCMS: m/z 765.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.44 (s, 1H), 7.70-7.66 (m, 1H), 7.32-7.18 (m, 9H), 6.89-6.85 (m, 4H), 5.80-5.64 (m, 2H), 5.38-5.22 (m, 1H), 4.38-4.15 (m, 1H), 3.81-3.70 (m, 8H), 3.61-3.43 (m, 3H), 2.76-2.73 (m, 1H), 2.66-2.63 (m, 1H), 2.50-2.41 (m, 2H), 1.12-1.05 (m, 9H), 0.97-0.95 (m, 3H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.01, 148.97, 148.74, 148.67; ^{19}F-NMR (376 MHz, DMSO-d_6): δ 149.01, 148.97, 148.74, 148.67.

Example 22. Synthesis of Monomer

[0516]

Scheme-2



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[0517] Preparation of (2): To a stirred solution of 1 (2.0 g, 8.8 mmol) in pyridine (20 mL) were added DMTrCl (3.3 g, 9.7 mmol) at r.t. The reaction mixture was stirred at r.t. for 2.5 hrs. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (100 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by silica gel column chromatography (eluent, DCM:MeOH=50:1-20:1) to give 2 (3.7 g, 7.2 mmol, 80.1%) as a white solid. ESI-LCMS: m/z 527 $[M-H]^-$.

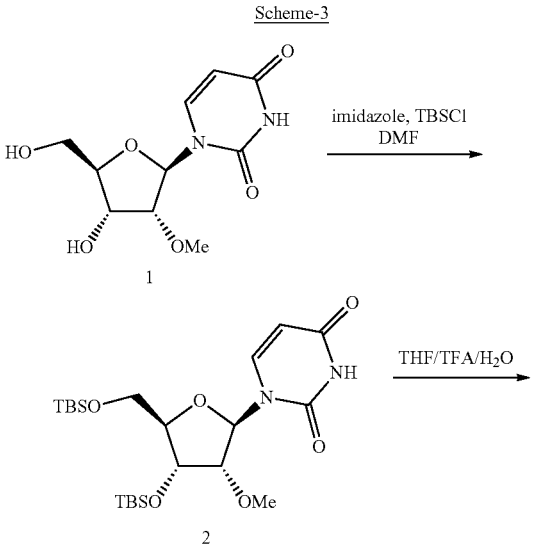
[0518] Preparation of (3): To the solution of 2 (2.8 g, 5.3 mmol) in dry DMF (56 mL) was added $(CD_{30})_2Mg$ (2.9 g, 31.8 mmol) at r.t. under N_2 atmosphere. The reaction mixture was stirred at 100° C. for 15 hrs. With ice-bath cooling, the reaction was quenched with saturated aq. NH_4Cl and extracted with EA (300 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 3 (2.0 g, 3.6 mmol, 67.9%) as a white solid. ESI-LCMS: m/z 562 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 7.73 (d, J=8 Hz, 1H), 7.46-7.19 (m, 9H), 6.91 (d, J=7.4 Hz, 4H), 5.81-5.76 (AB, J=20 Hz, 1H), 5.30 (d, J=8 Hz, 1H), 5.22 (s, 1H), 4.25-4.15 (m, 1H), 3.99-3.92 (m, 1H), 3.85-3.79 (m, 1H), 3.74 (s, 6H), 3.34-3.18 (m, 31H).

[0519] Preparation of Example 22 monomer: To a suspension of 3 (2.0 g, 3.5 mmol) in DCM (20 mL) was added DCI (357 mg, 3.0 mmol) and $CEP[N(iPr)_2]_2$ (1.3 g, 4.3 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 3 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 22 monomer (2.1 g, 2.7 mmol, 77.1%) as a white solid. ESI-LCMS: m/z 764 $[M+H]^+$; ^{1}H-NMR (400 MHz, ACN-d3): 6 9.45-8.90 (m, 1H, exchanged with D_2O), 7.88-7.66 (m, 1H), 7.50-7.18 (m, 9H), 6.93-6.80 (m, 4H), 5.85 (d, J=8.2 Hz, 1H), 5.29-5.16 (m, 1H), 4.57-4.37 (m, 1H), 4.18-4.09 (m, 1H), 3.98-3.90 (m, 1H), 3.90-3.74 (m, 7H), 3.74-3.50 (m, 3H), 3.48-3.31 (m, 2H), 2.70-2.61 (m, 1H), 2.56-2.46 (m, 1H), 1.24-1.12 (m, 9H), 1.09-0.99 (m, 3H). ^{31}P-NMR (162 MHz, ACN-d_3): δ=149.87, 149.55.

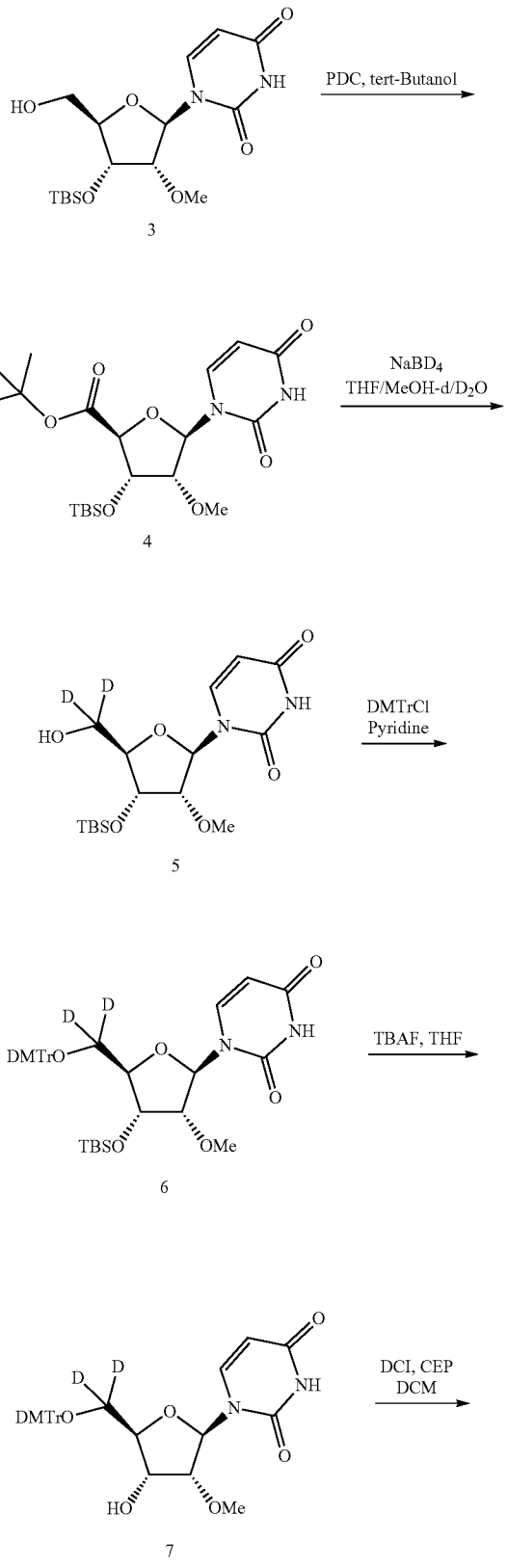
Example 23. Synthesis of Monomer

[0520]

Scheme-3



-continued



3

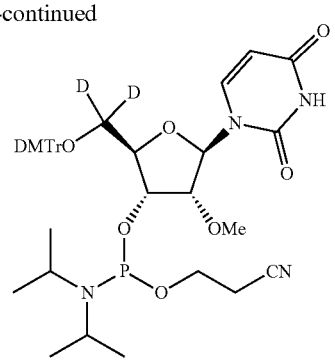
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7

-continued



Example 23 monomer

[0521] Preparation of (2): To the solution of 1 (39.2 g, 151.9 mmol) in DMF (390.0 mL) was added imidazole (33.0 g, 485.3 mmol) and TBSCl (57.2 g, 379.6 mmol) at 0° C. The reaction mixture was stirred at room temperature for 15 hrs under N_2 atmosphere. After addition of water, the resulting mixture was extracted with EA (500.0 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated to give the crude 2 (85.6 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 487.7 $[M+H]^+$.

[0522] Preparation of (3): A solution of crude 2 (85.6 g) in a mixture solvent of TFA/H_2O=1/1 (400.0 mL) and THE (400.0 mL) was stirred at 0° C. for 30 min. After completion of reaction, the resulting mixture was added con.NH_3*H_2O to pH=7, and then extracted with EA (500.0 mL). The organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 3 (36.6 g, 98.4 mmol, 64.7% over two step) as a white solid. ESI-LCMS: m/z 372.5 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.36 (d, J=1 Hz, 1H), 7.92 (d, J=8 Hz, 1H), 5.83 (d, J=5 Hz, 1H), 5.67-5.65 (m, 1H), 5.19 (s, 1H), 4.30 (t, J=5 Hz, 1H), 3.85-3.83 (m, 2H), 3.68-3.52 (m, 2H), 0.88 (s, 9H), 0.09 (s, 6H).

[0523] Preparation of (4): To the solution of 3 (36.6 g, 98.4 mmol) in dry DCM (200.0 mL) and DMF (50.0 mL) was added PDC (73.9 g, 196.7 mmol), tert-butyl alcohol (188.0 mL) and Ac20 (93.0 mL) at r.t under N_2 atmosphere, the reaction mixture was stirred at r.t for 2 hrs. The solvent was removed to give a residue which was purified by silica gel column chromatography (eluent, PE/EA=4:1 ~ 2:1) to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 4 (24.3 g, 54.9 mmol, 55.8%) as a white solid. ESI-LCMS: m/z 443.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.30 (d, J=1 Hz, 1H), 7.92 (d, J=8 Hz, 1H), 5.86 (d,

J=6 Hz, 1H), 5.67-5.65 (m, 1H), 4.33-4.31 (m, 1H), 4.13 (d, J=3 Hz, 1H), 3.73-3.70 (m, 1H), 1.34 (s, 9H), 0.77 (s, 9H), 0.08 (s, 6H).

[0524] Preparation of (5): To the solution of 4 (18.0 g, 40.7 mmol) in dry THF/MeOD/D_2O=10/2/1 (145.0 mL) was added $NaBD_4$ (5.1 g, 122.1 mmol) three times during an hour at 50° C., the reaction mixture was stirred at r.t. for 2 hrs. After completion of reaction, adjusted pH value to 7 with CH_3COOD, after addition of water, the resulting mixture was extracted with EA (300.0 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 5 (10.4 g, 27.8 mmol, 68.3%) as a white solid. ESI-LCMS: m/z 375.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.36 (d, J=1 Hz, 1H), 7.92 (d, J=8 Hz, 1H), 5.83 (d, J=5 Hz, 1H), 5.67-5.65 (m, 1H), 5.19 (s, 1H), 4.30 (t, J=5 Hz, 1H), 3.85-3.83 (m, 2H), 0.88 (s, 9H), 0.09 (s, 6H).

[0525] Preparation of (6): To a stirred solution of 5 (10.4 g, 27.8 mmol) in pyridine (100.0 mL) was added DMTrCl (12.2 g, 36.1 mmol) at r.t., The reaction mixture was stirred at r.t. for 2.5 hrs, the reaction was quenched with water and extracted with EA (200.0 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 6 (13.5 g, 19.9 mmol, 71.6%) as a white solid. ESI-LCMS: m/z 677.8 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.39 (d, J=1 Hz, 1H), 7.86 (d, J=4 Hz, 1H), 7.35-7.21 (m, 9H), 6.90-6.88 (m, 4H), 5.78 (d, J=2 Hz, 1H), 5.30-5.27 (m, 1H), 4.33-4.30 (m, 1H), 3.91 (d, J=7 Hz, 1H), 3.85-3.83 (m, 1H), 3.73 (s, 6H), 3.38 (s, 3H), 0.77 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

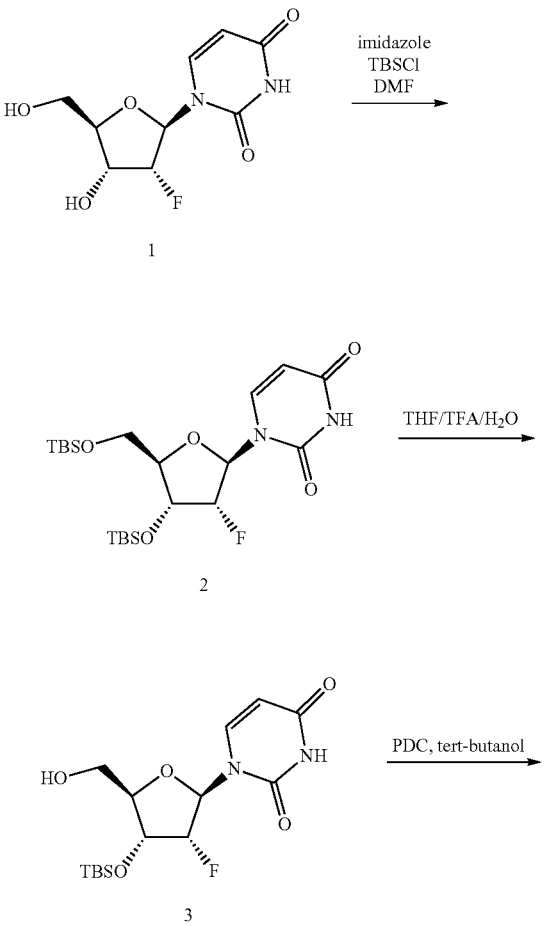
[0526] Preparation of (7): To a solution of 6 (13.5 g, 19.9 mmol) in THE (130.0 mL) was added 1 M TBAF solution (19.0 mL). The reaction mixture was stirred at r.t. for 1.5 hrs. LC-MS showed 6 was consumed completely. Water (500.0 mL) was added and extracted with EA (300.0 mL), the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 7 (10.9 g, 19.4 mmol, 97.5%) as a white solid. ESI-LCMS: m/z 563.6 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 7.23 (d, J=8 Hz, 1H), 7.73 (d, J=8 Hz, 1H), 7.36-7.23 (m, 9H), 6.90 (d, J=8 Hz, 4H), 5.81 (d, J=3 Hz, 1H), 5.30-5.28 (m, 1H), 5.22 (d, J=7 Hz, 1H), 4.20 (q, J=7 Hz, 1H), 3.93 (d, J=7 Hz, 1H), 3.81 (t, J=5 Hz, 1H), 3.74 (s, 6H), 3.41 (s, 3H).

[0527] Preparation of Example 23 monomer: To a suspension of 7 (10.9 g, 19.4 mmol) in DCM (100.0 mL) was added DCI (1.8 g, 15.7 mmol) and $CEP[N(iPr)_2]_2$ (6.1 g, 20.4 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 7 was consumed completely. The mixture was washed with water twice and brine, dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 23 monomer (12.5 g, 14.5 mmol, 74.7%) as a white solid. ESI-LCMS: m/z 863.6 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 7.81-7.55 (m, 1H), 7.40-7.22 (m, 9H), 6.92-6.87 (m, 4H), 5.83-5.80 (m, 1H), 5.32-5.25 (m, 1H), 4.46-4.34 (m, 1H), 4.10-3.98 (m, 2H), 3.84-3.73 (m, 7H), 3.60-3.50 (m, 3H), 3.42, 3.40 (s, 3H), 2.78 (t, J=6 Hz, 1H), 2.62-2.59 (m, 1H), 2.07 (s, 1H), 1.17-0.96 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.37, 149.06.

Example 24. Synthesis of Monomer

[0528]

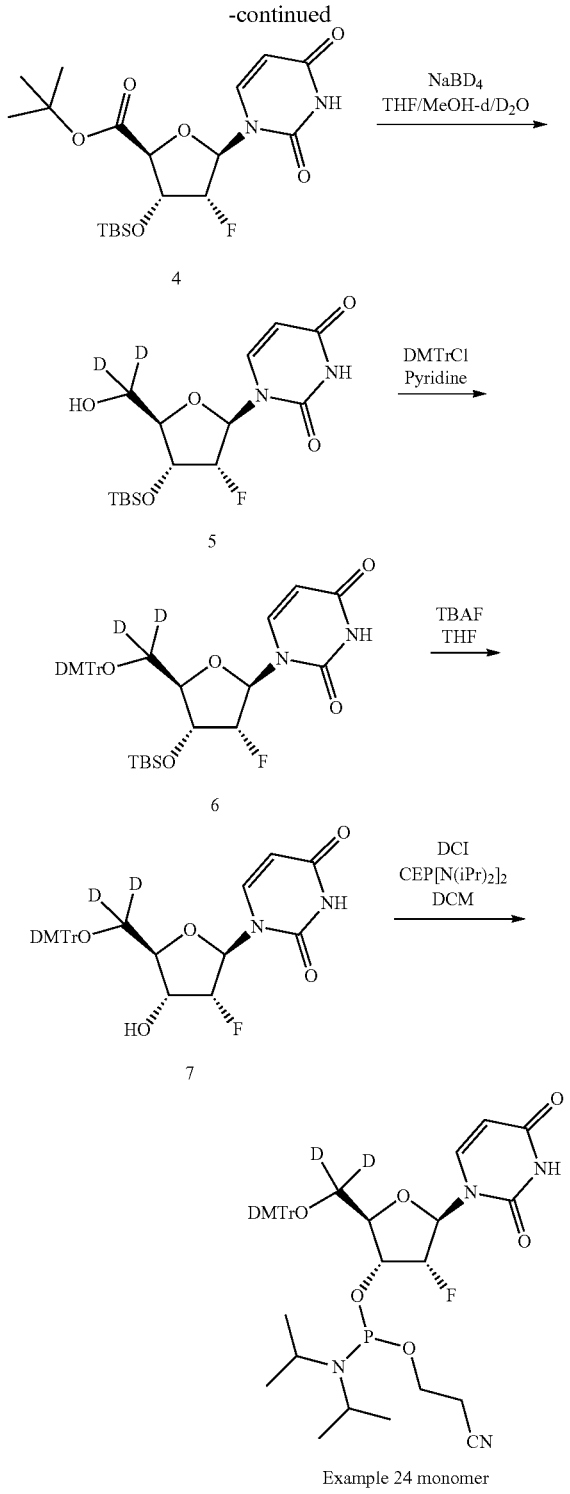
Scheme-4



1

2

3



[0529] Preparation of (2): To the solution of 1 (13.0 g, 52.8 mmol) in DMF (100 mL) was added imidazole (12.6 g, 184.8 mmol) and TBSCl (19.8 g, 132.0 mmol) at 0° C., and the reaction mixture was stirred at room temperature for 15 h under N_2 atmosphere. After addition of water, the resulting product was extracted with EA (500 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give the crude 2 (30.6 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 475 $[M+H]^+$. WO2017106710A1

[0530] Preparation of (3): A solution of crude 2 (30.6 g) in a mixture solvent of TFA/H_2O=1/1 (100 mL) and THE (100 mL) was stirred at 0° C. for 30 min. After completion of reaction, the resulting mixture was added con.NH_3*H_2O to pH=7.5, and then the mixture was extracted with EA (500 mL), the organic layer was washed with brine, dried over Na_2SO_4 and removed to give the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 3 (12.0 g, 33.3 mmol, 65.8% over two step) as a white solid. ESI-LCMS: m/z 361 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.39 (s, J=1 Hz, 1H, exchanged with D_2O), 7.88 (d, J=8 Hz, 1H), 5.91-5.86 (m, 1H), 5.66-5.62 (m, 1H), 5.21 (t, J=5.2 Hz, 1H, exchanged with D_2O), 5.18-5.03 (m, 1H), 4.37-4.29 (m, 1H), 3.87-3.83 (m, 1H), 3.78-3.73 (m, 1H), 3.56-3.51 (m, 1H), 0.87 (s, 9H), 0.09 (s, 6H). WO2017106710A1.

[0531] Preparation of (4): To the solution of 3 (11.0 g, 30.5 mmol) in dry DCM (60 mL) and DMF (15 mL) was added PDC (21. g, 61.0 mmol), tert-butyl alcohol (45 mL) and Ac20 (32 mL) at r.t under N_2 atmosphere. And the reaction mixture was stirred at r.t for 2 h. The solvent was removed to give a residue which was purified by silica gel column chromatography (eluent, PE:EA=4:1-2:1) to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 4 (9.5 g, 22.0 mmol, 72.3%) as a white solid. ESI-LCMS: m/z 431 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.45 (s, J=1 Hz, 1H, exchanged with D_2O), 7.93 (d, J=8.5 Hz, 1H), 6.02-5.97 (m, 1H), 5.76-5.74 (m, 1H), 5.29-5.14 (m, 1H), 4.59-4.52 (m, 1H), 4.29-4.27 (m, 1H), 1.46 (s, 9H), 0.89 (s, 9H), 0.12 (s, 6H).

[0532] Preparation of (5): To the solution of 4 (8.5 g, 19.7 mmol) in dry THF/MeOD/D_2O=10/2/1 (80 mL) was added $NaBD_4$ (2.5 g, 59.1 mmol) three times per an hour at 50° C. And the reaction mixture was stirred at r.t for 2 h. After completion of reaction, adjusted pH value to 7 with CH_3COOD, after addition of water, the resulting mixture was extracted with EA (300 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 5 (3.5 g, 9.7 mmol, 50.3%) as a white solid. ESI-LCMS: m/z 363 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.41 (s, J=1 Hz, 1H, exchanged with D_2O), 7.88 (d, J=8 Hz, 1H), 5.91-5.86 (m, 1H), 5.66-5.62 (m, 1H), 5.19 (t, J=5.2 Hz, 1H, exchanged with D_2O), 5.18-5.03 (m, 1H), 4.37-4.29 (m, 1H), 3.87-3.83 (m, 1H), 0.88 (s, 9H), 0.10 (s, 6H).

[0533] Preparation of (6): To a stirred solution of 5 (3.4 g, 9.7 mmol) in pyridine (35 mL) were added DMTrCl (3.4 g, 10.1 mmol) at r.t. And the reaction mixture was stirred at r.t for 2.5 h. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 6 (PCT Int. Appl., 2019173602), (5.5 g, 8.3 mmol, 85.3%) as a white solid. ESI-LCMS: m/z 665 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.50 (d, J=1 Hz, 1H, exchanged with D_2O), 7.92 (d, J=4 Hz, 1H), 7.44-7.27 (m, 9H), 6.96-6.93 (m, 4H), 5.94 (d, J=20.5 Hz, 1H), 5.39-5.37 (m, 1H), 5.32-5.17 (m, 1H), 4.60-4.51 (m, 1H), 4.01 (d, J=8.8 Hz, 1H), 3.80 (s, 6H), 0.80 (s, 9H), 0.09 (s, 3H), −0.05 (s, 3H).

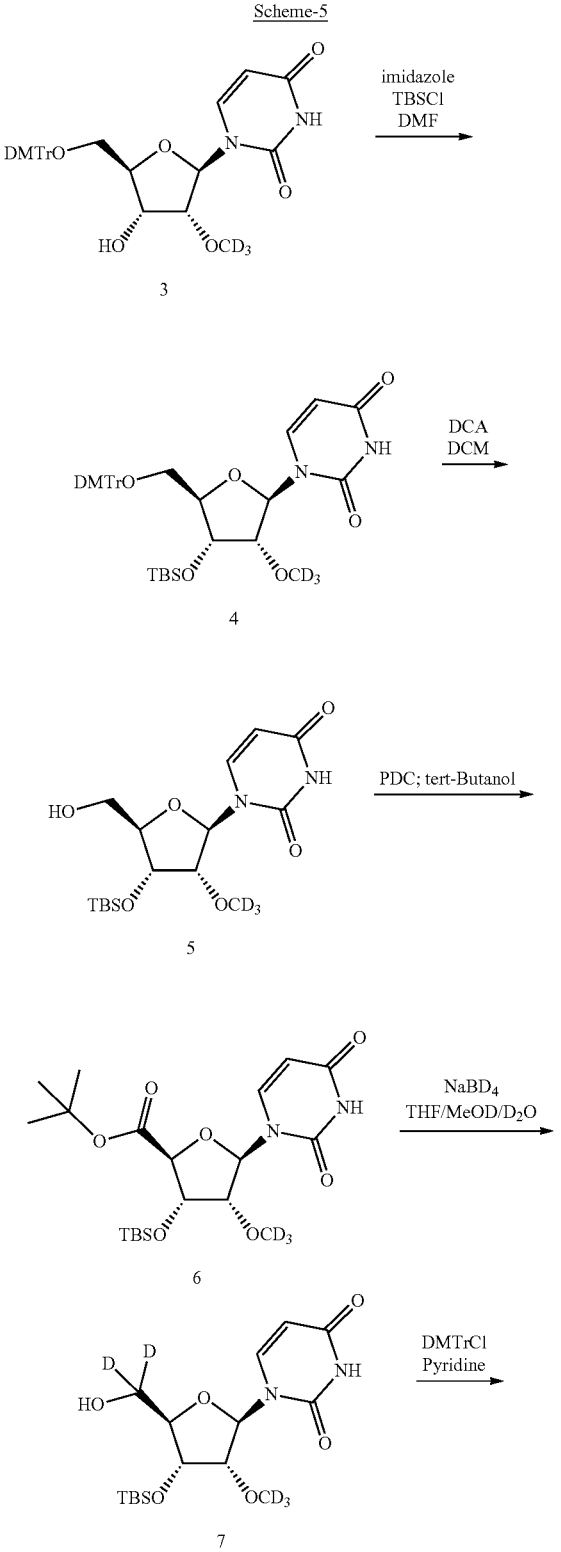
[0534] Preparation of (7): To a solution of 6 (5.5 g, 8.3 mmol) in THF (50 mL) was added 1 M TBAF solution (9 mL). The reaction mixture was stirred at r.t. for 1.5 h. LC-MS showed 6 was consumed completely. Water (500 mL) was added. The product was extracted with EA (300 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 7 (4.1 g, 7.5 mmol, 90.0%) as a white solid. ESI-LCMS: m/z 551 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H, exchanged with D_2O), 7.76 (d, J=8.2 Hz, 1H), 7.39-7.22 (m, 9H), 6.90-6.88 (m, 4H), 5.83 (d, J=20.5 Hz, 1H), 5.65 (d, J=7.0 Hz, 1H, exchanged with D_2O), 5.29 (d, J=7.2 Hz, 1H), 5.18-5.03 (m, 1H), 4.40-4.28 (m, 1H), 4.01 (d, J=8.8 Hz, 1H), 3.74 (s, 6H).

[0535] Preparation of Example 24 monomer: To a suspension of 7 (4.1 g, 7.5 mmol) in DCM (40 mL) was added DCI (0.7 g, 6.4 mmol) and $CEP[N(iPr)_2]_2$ (2.9 g, 9.7 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 7 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 24 monomer (5.0 g, 6.6 mmol, 90.0%) as a white solid. ESI-LCMS: m/z 751 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 7.85-7.82 (m, 1H), 7.40-7.23 (m, 9H), 6.90-6.85 (m, 4H), 5.94-5.86 (m, 1H), 5.40-5.24 (m, 2H), 4.74-4.49 (m, 1H), 4.12-4.09 (m, 2H), 3.79-3.47 (m, 10H), 2.78-2.59 (m, 2H), 1.14-0.93 (m, 12H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.67, 149.61, 149.32, 149.27.

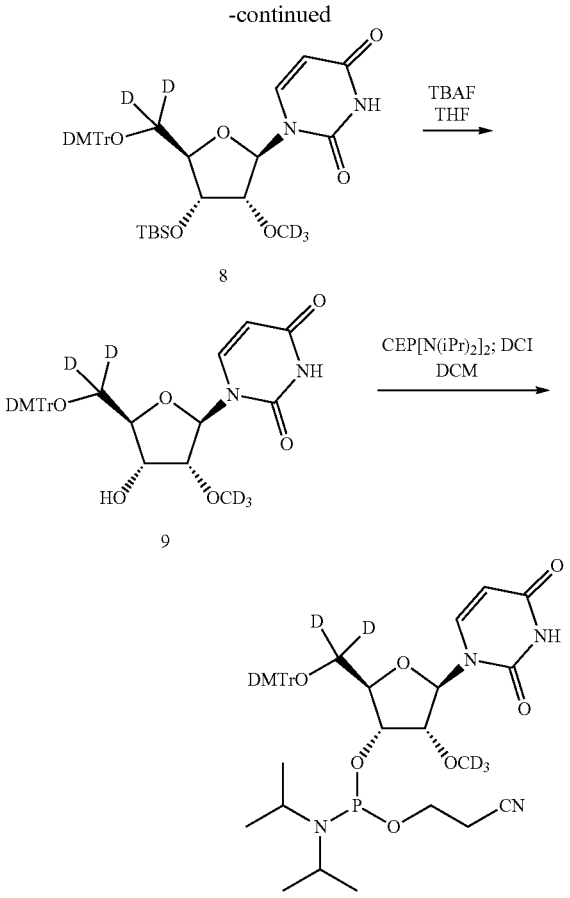
Example 25. Synthesis of Monomer

[0536]

Scheme-5



-continued



8

9

[0537] Preparation of (4): To the solution of 3 (14.3 g, 25.4 mmol, Scheme 2) in pyridine (150 mL) was added imidazole (4.5 g, 66.6 mmol) and TBSCl (6.0 g, 40.0 mmol) at 0° C., and the reaction mixture was stirred at room temperature for 15 h under N_2 atmosphere. After addition of water, the resulting mixture was extracted with EA (500 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give the crude 4 (18.0 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 676 $[M-H]^-$.

[0538] Preparation of (5): To the solution of crude 4 (18.0 g) in the solution of DCA (6%) in DCM (200 mL) was added TES (50 mL) at r.t, and the reaction mixture was stirred at room temperature for 5-10 min. After completion of reaction, the resulting mixture was added pyridine to pH=7, and then the solvent was removed and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 5 (6.5 g, 17.2 mmol, 67.7% for two step) as a white solid. ESI-LCMS: m/z 376 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J=8 Hz, 1H), 5.82 (d, J=5.2 Hz, 1H), 5.68-5.63 (m, 1H), 5.20-5.15 (m, 1H), 4.32-4.25 (m, 1H), 3.87-3.80 (m, 2H), 3.69-3.61 (m, 1H), 3.57-3.49 (m, 1H), 0.88 (s, 9H), 0.09 (s, 6H).

[0539] Preparation of (6): To the solution of 5 (6.5 g, 17.2 mmol) in dry DCM (35 mL) and DMF (9 mL) was added PDC (12.9 g, 34.3 mmol), tert-butyl alcohol (34 mL) and Ac20 (17 mL) at r.t under N_2 atmosphere. And the reaction mixture was stirred at r.t for 2 hrs. The solvent was removed to give a residue which was purified by silica gel column chromatography (eluent, PE:EA=4:1-2:1) to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 6 (5.5 g, 12.3 mmol, 70.1%) as a white solid. ESI-LCMS: m/z 446 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ=11.29 (s, 1H), 7.91 (d, J=8.4 Hz, 1H), 5.85 (d, J=6.4 Hz, 1H), 5.71-5.61 (m, 1H), 4.35-4.28 (m, 1H), 4.12 (d, J=3.2 Hz, 1H), 3.75-3.67 (m, 1H), 1.33 (s, 9H), 0.76 (s, 9H), 0.00 (d, J=1.6 Hz, 6H).

[0540] Preparation of (7): To the solution of 6 (5.4 g, 12.1 mmol) in THF/MeOD/D20=10/2/1 (44 mL) was added $NaBD_4$ (1.5 g, 36.3 mmol) at r.t. and the reaction mixture was stirred at 50° C. for 2 hrs. After completion of reaction, adjusted pH value to 7 with CH_3COOD. Water was added, the resulting mixture was extracted with EA (500 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HC03)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 7 (2.6 g, 6.8 mmol, 56.1%) as a white solid. ESI-LCMS: m/z 378 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.35 (s, 1H), 7.91 (d, J=8.0 Hz, 1H), 5.82 (d, J=5.2 Hz, 1H), 5.69-5.60 (m, 1H), 5.14 (s, 1H), 4.34-4.20 (m, 1H), 3.88-3.76 (m, 2H), 0.87 (s, 9H), 0.08 (s, 6H).

[0541] Preparation of (8): To a stirred solution of 7 (2.6 g, 6.8 mmol) in pyridine (30 mL) were added DMTrCl (3.5 g, 10.3 mmol) at r.t. And the reaction mixture was stirred at r.t. for 2.5 hrs. With ice-bath cooling, the reaction was quenched with water and the product was extracted into EA (200 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 8 (4.3 g, 6.3 mmol, 90.1%) as a white solid. ESI-LCMS: m/z 678 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.39 (s, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.42-7.17 (m, 9H), 6.96-6.83 (m, 4H), 5.82-5.69 (m, 2H), 5.29 (d, J=8.4 Hz, 1H), 4.36-4.25 (m, 1H), 3.90 (d, J=7.2 Hz, 1H), 3.86-3.80 (m, 1H), 3.73 (s, 6H), 0.75 (s, 9H), 0.02 (s, 3H), −0.04 (s, 3H).

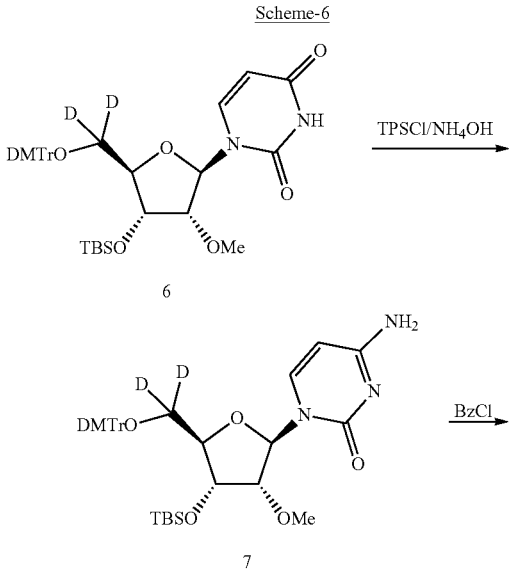
[0542] Preparation of (9): To a solution of 8 (4.3 g, 6.3 mmol) in THE (45 mL) was added 1 M TBAF solution (6 mL). The reaction mixture was stirred at r.t. for 1.5 hrs. LCMS showed 8 was consumed completely. Water (200 mL) was added. The product was extracted with EA (200 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to

give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 8 (3.5 g, 6.1 mmol, 90.1%) as a white solid. ESI-LCMS: m/z 678 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.38 (d, J=2.0 Hz, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.41-7.19 (m, 9H), 6.94-6.85 (m, 4H), 5.81 (d, J=4.0 Hz, 1H), 5.33-5.26 (m, 1H), 5.21 (d, J=7.2 Hz, 1H), 4.06-3.90 (m, 2H), 3.83-3.77 (m, 1H), 3.74 (s, 6H).

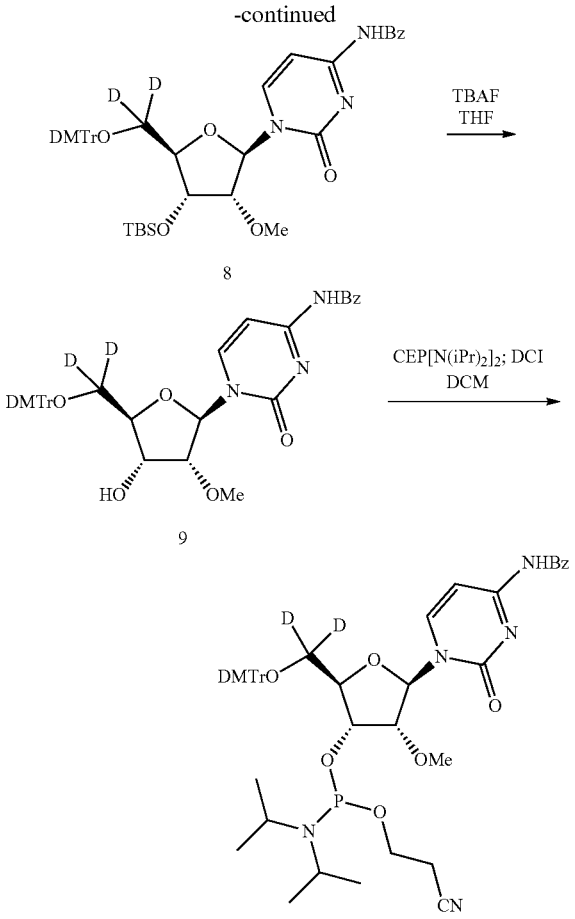
[0543] Preparation of Example 25 monomer: To a suspension of 9 (2.1 g, 3.7 mmol) in DCM (20 mL) was added DCI (373 mg, 3.1 mmol) and $CEP[N(iPr)_2]_2$ (1.3 g, 4.4 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 9 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 25 monomer (2.2 g, 3.5 mmol, 80%) as a white solid. ESI-LCMS: m/z 766 $[M+H]^+$; ^{1}H-NMR (400 MHz, ACN-d_3): 6 9.65-8.86 (m, 1H, exchanged with D_2O), 7.93-7.68 (m, 1H), 7.52-7.19 (m, 9H), 6.94-6.78 (m, 4H), 5.95-5.77 (m, 1H), 5.31-5.17 (m, 1H), 4.61-4.37 (m, 1H), 4.20-4.07 (m, 1H), 4.01-3.51 (m, 10H), 2.74-2.59 (m, 1H), 2.57-2.43 (m, 1H), 1.27-1.10 (m, 9H), 1.09-0.95 (m, 3H). ^{31}P-NMR (162 MHz, ACN-d_3): δ=149.88, 149.55.

Example 26. Synthesis of Monomer

[0544]



-continued



[0545] Preparation of (7): To a solution of 6 (17 g, 25.1 mmol, Scheme 3) in ACN (170 mL) was added DMAP (6.13 g, 50.3 mmol) and TEA (5.1 g, 50.3 mmol, 7.2 mL), Then added TPSCl (11.4 g, 37.7 mmol) at 0° C. under N_2 atmosphere and the mixture was stirred at r.t. for 3 h under N_2 atmosphere. Then con. $NH_3.H_2O$ (27.3 g, 233.7 mmol) was added at r.t. and the mixture was stirred at r.t. for 16 h. The reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was concentrated to give the crude 7 (17.0 g) as a white solid which was used directly for next step.

[0546] Preparation of (8): To a stirred solution of 7 (17.0 g, 25.1 mmol) in pyridine (170 mL) were added BzCl (4.3 g, 30.1 mmol) 0° C. under N_2 atmosphere. And the reaction mixture was stirred at r.t for 2.5 h. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 8 (19.0 g, 24.3 mmol, 95.6% over two step) as a white solid. ESI-LCMS: m/z 780 $[M+H]^+$.

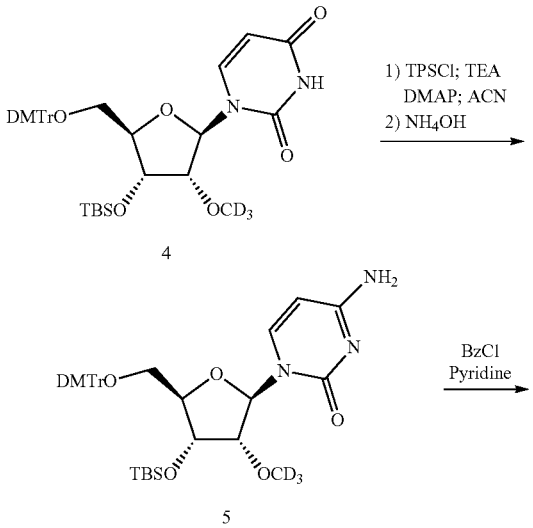
[0547] Preparation of (9): To a solution of 8 (19.0 g, 24.3 mmol) in THF (190 mL) was added 1 M TBAF solution (24 mL). The reaction mixture was stirred at r.t. for 1.0 h. LC-MS showed 8 was consumed completely. Water (500 mL) was added. The product was extracted with EA (300 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 9 (15.2 g, 23.1 mmol, 95.5%) as a white solid. ESI-LCMS: m/z 666 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 8.41 (m, 1H), 8.00-7.99 (m, 2H), 7.63-7.15 (m, 13H), 6.93-6.89 (m, 4H), 5.87 (s, 1H), 5.20 (d, J=7.4 Hz, 1H), 4.30 (m, 1H), 4.02 (m, 1H), 3.75 (s, 7H), 3.53 (s, 3H).

[0548] Preparation of Example 26 monomer: To a suspension of 9 (10.0 g, 15.0 mmol) in DCM (100 mL) was added DCI (1.5 g, 12.7 mmol) and $CEP[N(iPr)_2]_2$ (5.4 g, 18.0 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 9 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 26 monomer (11.5 g, 13.5 mmol, 90.7%) as a white solid. ESI-LCMS: m/z 866 $[M+H]^+$; iH-NMR (400 MHz, DMSO-d_6): δ=11.28 (s, 1H), 8.48-8.41 (m, 1H), 8.00-7.99 (m, 2H), 7.63-7.11 (m, 13H), 6.93-6.89 (m, 4H), 5.92 (m, 1H), 4.55-4.44 (m, 1H), 4.17 (m, 1H), 3.95 (m, 1H), 3.80-3.62 (m, 7H), 3.57-3.46 (m, 5H), 3.32 (s, 1H), 2.78 (m, 1H), 2.62-2.59 (m, 1H), 1.19-0.94 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ=149.52, 148.82.

Example 27. Synthesis of Monomer

[0549]

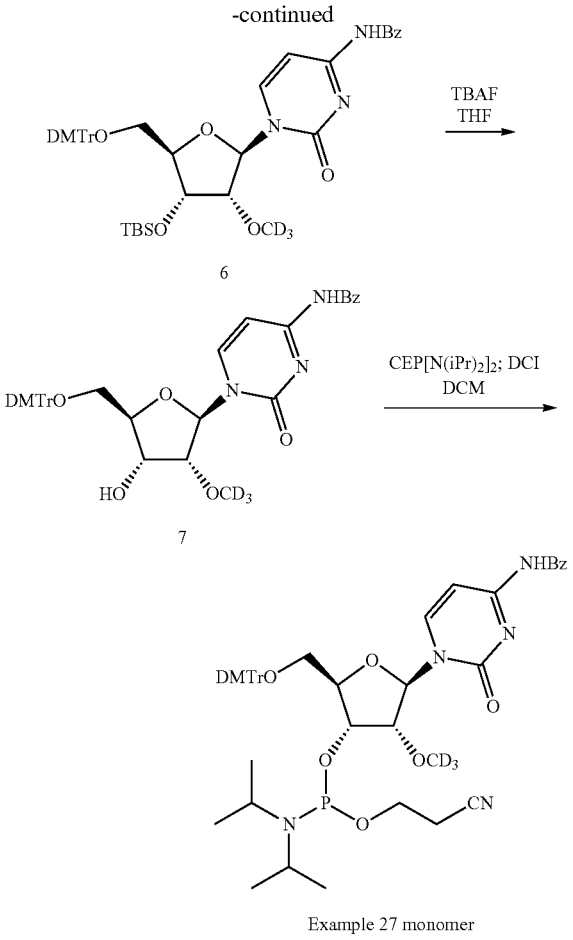
Scheme-7



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-continued



6

7

Example 27 monomer

[0550] Preparation of (5): To the solution of 4 (18.8 g, Scheme 5) in dry ACN (200 mL) was added TPSCl (16.8 g, 65.2 mmol) and TEA (5.6 g, 65.2 mmol) and DMAP (6.8 g, 65.2 mmol), and the reaction mixture was stirred at room temperature for 3.5 hrs under N_2 atmosphere. After addition of water, the resulting mixture was extracted with EA (300 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give the crude 5 (22.0 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 677 $[M-H]^+$.

[0551] Preparation of (6): To a solution of 5 (22.0 g) in pyridine (150 mL) was added BzCl (6.8 g, 48.9 mmol) under ice bath. The reaction mixture was stirred at r.t. for 2.5 hrs. LCMS showed 5 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give the crude 6 (20.8 g, 26.7 mmol, 82% yield over two steps) as a white solid. ESI-LCMS: m/z 781 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.30 (s, 1H), 8.55 (d, J=8.0 Hz, 1H), 8.00-7.98 (m, 2H), 7.74-7.66 (m, 1H), 7.60-7.50 (m, 2H), 7.47-7.31 (m, 4H), 7.30-7.2 (m, 5H), 7.20-7.1 (m, 1H), 6.91 (d, J=7.4 Hz, 4H), 5.91-5.86 (AB,

J=20.0 Hz, 1H), 4.30 (d, J=8.0 Hz, 1H), 3.87-3.78 (s, 1H), 3.78-3.70 (m, 6H), 3.62-3.51 (m, 1H), 3.28-3.2 (m, 1H), 2.15-2.05 (m, 3H), 0.73 (s, 9H), 0.00 (m, 6H).

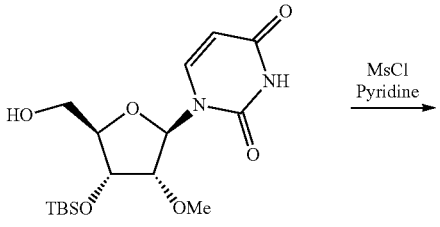
[0552] Preparation of (7): To a solution of 6 (20.8 g, 26.7 mmol) in THF (210 mL) was added 1 M TBAF solution (32 mL). The reaction mixture was stirred at r.t. for 1.5 hrs. LCMS showed 6 was consumed completely. Water (600 mL) was added. The product was extracted with EA (400 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 7 (12.4 g, 18.6 mmol, 70%) as a white solid. ESI-LCMS: m/z 667 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (m, 1H), 8.51-8.48 (m, 1H), 8.08-7.95 (m, 2H), 7.63-7.54 (m, 1H), 7.52-7.19 (m, 9H), 7.16-7.07 (m, 1H), 6.94-6.89 (m, 3H), 5.95-5.87 (m, 1H), 5.31-5.17 (m, 1H), 4.61-4.37 (m, 1H), 4.20-4.07 (m, 1H), 3.82-3.47 (m, 7H), 2.57-2.42 (m, 2H).

[0553] Preparation of Example 27 monomer: To a suspension of 7 (12.4 g, 18.6 mmol) in DCM (120 mL) was added DCI (1.7 g, 15.8 mmol) and CEP[N(iPr)$_2$]$_2$ (7.3 g, 24.2 mmol). The mixture was stirred at r.t. for 2 hrs. LC-MS showed 7 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 27 monomer (13.6 g, 15.7 mmol, 84.0%) as a white solid. ESI-LCMS: m/z 867 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (m, 1H), 8.51-8.48 (m, 1H), 8.08-7.95 (m, 2H), 7.63-7.54 (m, 1H), 7.52-7.19 (m, 9H), 7.16-7.07 (m, 1H), 6.94-6.89 (m, 3H), 5.95-5.87 (m, 1H), 5.31-5.17 (m, 1H), 4.61-4.37 (m, 1H), 4.20-4.07 (m, 1H), 3.82-3.47 (m, 10H), 2.74-2.59 (m, 1H), 2.57-2.43 (m, 1H), 1.27-1.10 (m, 9H), 1.09-0.95 (m, 3H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.59, 148.85.

Example 28. Synthesis of Monomer

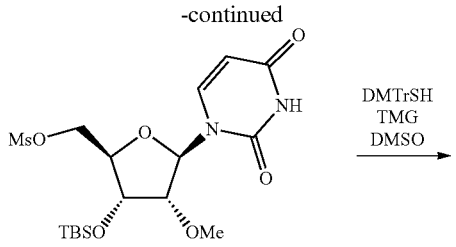
[0554]

Scheme-8

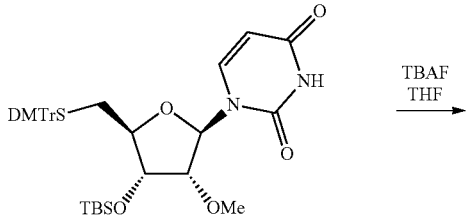


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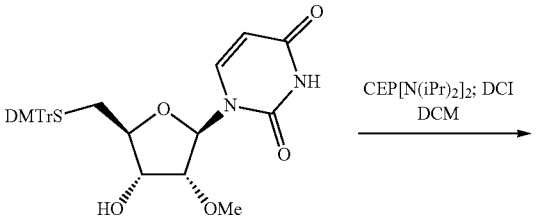
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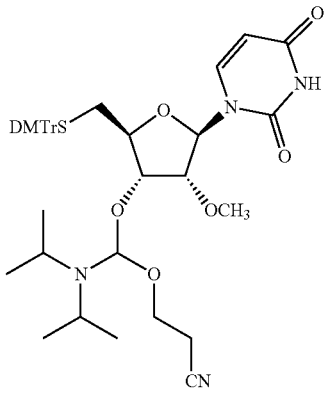
4



5



6



Example 28 monomer

[0555] Preparation of (4): To a solution of 3 (13.1 g, 35.2 mmol, Scheme 3) in pyridine (130 mL) was added MsCl (4.8 g, 42.2 mmol) under −10~0° C. The reaction mixture was stirred at r.t. for 2.5 h under N_2 atmosphere. TLC (DCM/MeOH=15:1) showed the reaction was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the

crude. This resulted in to give the product 4 (14.2 g) which was used directly for the next step. ESI-LCMS: m/z 451 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.43 (m, 1H), 7.67-7.65 (m, 1H), 5.90-5.80 (m, 1H), 5.75-5.64 (m, 1H), 4.52-4.21 (m, 3H), 4.12-3.90 (m, 2H), 3.48-3.21 (m, 6H), 0.95-0.78 (s, 9H), 0.13-0.03 (s, 6H).

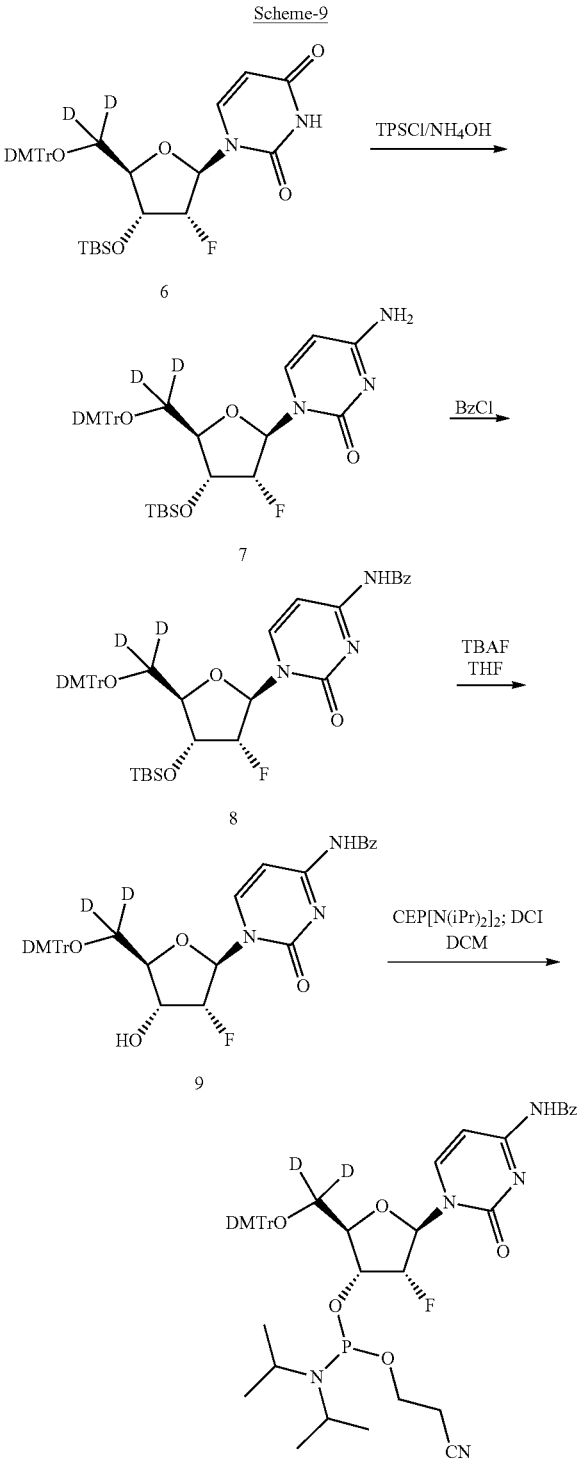
[0556] Preparation of (5): To a solution of 4 (14.2 g) in DMSO (200 mL) was added DMTrSH (19.6 g, 63.2 mmol) and tetramethylguanidine (5.1 g, 47.4 mmol) at r.t. The reaction mixture was stirred at r.t. for 3.5 h under N_2 atmosphere. LCMS showed 4 the reaction was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by silica gel column (SiO_2, PE/EA=10:1-1:1) to give 5 (14.2 g, 20.6 mmol, 58.5% yield over two steps) as a white solid. ESI-LCMS: m/z 689 $[M+H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.39 (m, 1H), 7.63-7.61 (d, J=8.0 Hz, 1H), 7.45-7.1 (m, 9H), 6.91-6.81 (m, 4H), 5.80-5.70 (m, 2H), 4.01-3.91 (m, 1H), 3.85-3.78 (m, 1H), 3.78-3.65 (m, 6H), 3.60-3.51 (m, 1H), 3.43-3.2 (m, 3H), 2.50-2.32 (m, 2H), 0.95-0.77 (s, 9H), −0.00-0.02 (s, 6H).

[0557] Preparation of (6): To a solution of 5 (14.2 g, 20.6 mmol) in THE (140 mL) was added 1 M TBAF solution (20 mL). The reaction mixture was stirred at r.t. under N_2 atmosphere for 2.5 h. LCMS showed 5 was consumed completely. Water was added. The product was extracted with EA and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3) =2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 6 (10.5 g, 18.2 mmol, 88.5%) as a white solid. ESI-LCMS: m/z 576 [M+H]*: iH-NMR (400 MHz, DMSO-d_6) δ 11.38 (m, 1H), 7.56-7.54 (d, J=8.0 Hz, 1H), 7.45-7.1 (m, 9H), 6.91-6.81 (m, 4H), 5.80-5.70 (m, 2H), 4.05-4.00 (m, 1H), 3.81-3.79 (m, 1H), 3.74 (m, 2H), 3.78-3.65 (m, 6H), 3.60-3.51 (m, 1H), 3.43-3.2 (m, 3H), 2.40-2.32 (m, 1H).

[0558] Preparation of Example 28 monomer: To a suspension of 9 (10.5 g, 18.2 mmol) in DCM (100 mL) was added DCI (1.7 g, 15.5 mmol) and $CEP[N(iPr)_2]_2$ (7.2 g, 23.7 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 9 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 28 monomer (12.5 g, 16.1 mmol, 88%) as a white solid. ESI-LCMS: m/z 776 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.41 (m, 1H), 7.64-7.59 (m, 1H), 7.40-7.25 (m, 4H), 7.25-7.10 (m, 5H), 6.89-6.86 (m, 4H), 5.72-5.67 (m, 2H), 4.02-4.00 (m, 2H), 3.76-3.74 (m, 8H), 3.74-3.73 (m, 3H), 3.51-3.49 (d, J=8 Hz, 1H), 3.33-3.29 (m, 1H), 2.77-2.73 (m, 1H), 2.63-2.60 (m, 1H), 2.50-2.47 (m, 1H), 1.12-0.99 (m, 12H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 148.92, 148.84.

Example 29. Synthesis of Monomer

[0559]



Example 29 monomer

[0560] Preparation of (7): To a solution of 6 (16 g, 24.1 mmol, Scheme 4) in ACN (160 mL) was added DMAP (5.9

g, 48.2 mmol) and TEA (4.8 g, 48.2 mmol), then added TPSCl (10.9 g, 36.1 mmol) at 0° C. under N_2 atmosphere and the mixture was stirred at r.t. for 5 hrs under N_2 atmosphere. Then con. $NH_3.H_2O$ (30 mL) was added at r.t. and the mixture was stirred at r.t. for 16 h. The reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was concentrated to give the crude 7 (16.0 g) as a white solid which was used directly for next step.

[0561] Preparation of (8): To a stirred solution of 7 (16.0 g, 24.1 mmol) in pyridine (160 mL) were added BzCl (4.1 g, 28.9 mmol) 0° C. under N_2 atmosphere. And the reaction mixture was stirred at r.t. for 2.5 h. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 8 (18.0 g, 23.4 mmol, 97.0%) as a white solid. ESI-LCMS: m/z 768 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.47 (d, J=7.2 Hz, 1H), 7.99 (d, J=7.6 Hz, 2H), 7.65-7.16 (m, 13H), 6.92 (d, J=8.8 Hz, 4H), 6.01 (d, J=18.4 Hz, 1H), 5.18-5.04 (dd, 1H), 4.58-4.52 (m, 1H), 4.07 (d, J=9.6 Hz, 1H), 3.75 (s, 6H), 0.73 (s, 9H), 0.05 (s, 3H), −0.06 (s, 3H).

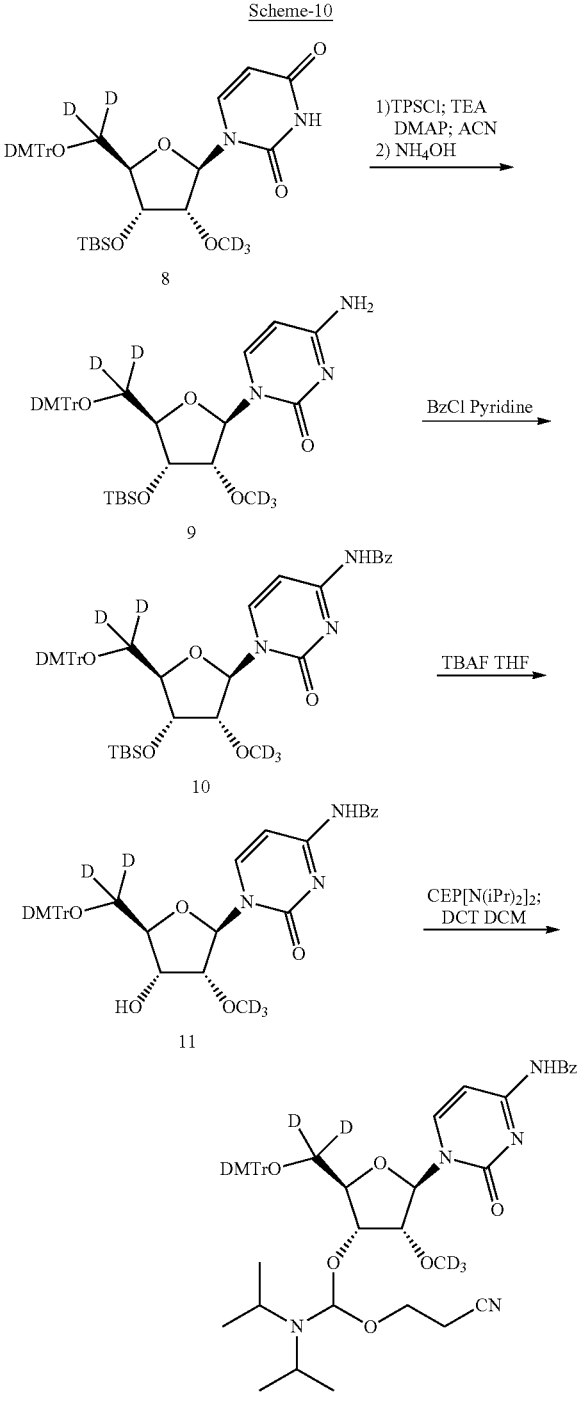
[0562] Preparation of (9): To a solution of 8 (18.0 g, 23.4 mmol) in THE (180 mL) was added 1 M TBAF solution (23 mL). The reaction mixture was stirred at r.t. for 1.5 h. LC-MS showed 8 was consumed completely. Water (500 mL) was added. The product was extracted with EA (300 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 7 (13.7 g, 21.1 mmol, 90.5%) as a white solid. ESI-LCMS: m/z 654.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.35 (d, J=7.4 Hz, 1H), 8.01 (m, 2H), 7.65-7.16 (m, 13H), 6.92 (d, J=8.8 Hz, 4H), 5.94 (d, J=18.0 Hz, 1H), 5.71 (d, J=7.0 Hz, 1H), 5.12-4.98 (dd, 1H), 4.51-4.36 (m, 1H), 4.09 (d, J=9.6 Hz, 1H), 3.75 (s, 6H).

[0563] Preparation of Example 29 monomer: To a suspension of 9 (10.6 g, 16.2 mmol) in DCM (100 mL) was added DCI (1.6 g, 13.7 mmol) and $CEP[N(iPr)_2]_2$ (5.8 g, 19.4 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 9 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 29 monomer (10.5 g, 14.5 mmol, 75.9%) as a white solid. ESI-LCMS: m/z 854.3 [M+H]-; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 1H), 8.41-8.37 (m, 1H), 8.01 (d, J=7.7 Hz, 2H), 7.65-7.16 (m, 13H), 6.92-6.88 (m, 4H), 6.06-5.98 (m, 1H), 5.33-5.15 (m, 1H), 4.78-4.58 (m, 1H), 4.23-4.19 (m, 1H), 3.81-3.73 (m, 6H), 3.60-3.50 (m, 3H), 3.32 (s, 1H), 2.76 (t, J=6.0 Hz, 1H), 2.60 (t, J=5.8 Hz, 1H), 1.15-0.94 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 150.23, 150.18, 149.43, 149.38.

Example 30. Synthesis of Monomer

[0564]

Scheme-10



8

9

10

11

Example 30 monomer

[0565] Preparation of (9): To a solution of 8 (18.8 g, 26.4 mmol, Scheme 5) in ACN (200 mL) was added TPSCl (16.8 g, 55.3 mmol) and DMAP (5.6 g, 55.3 mmol) and TEA (6.8 g, 55.3 mmol). The reaction mixture was stirred at r.t. for 3.5 hrs. LCMS showed the reaction was consumed. The mixture was diluted with con. NH_4OH (28 mL). The mixture was diluted with water and EA. The product was extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude 9 (18.5 g) which was used directly for the next step.

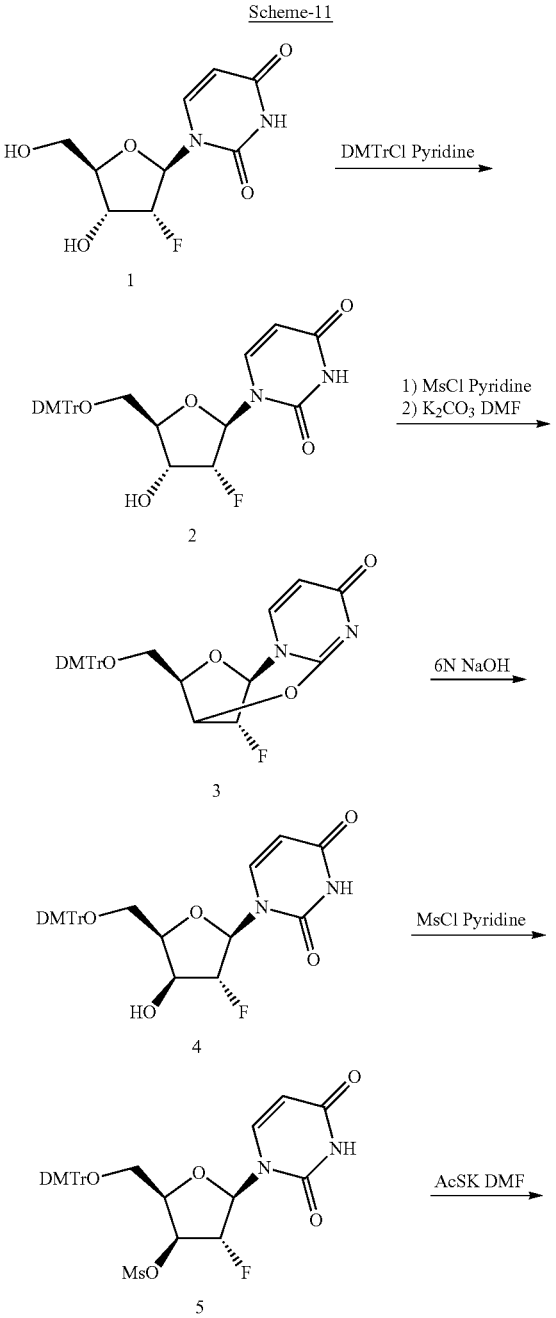
[0566] Preparation of (10): To a solution of 9 (18.8 g, 27.69 mmol) in pyridine (200 mL) was added BzCl (5.8 g, 41.5 mmol) under ice bath. The reaction mixture was stirred at r.t. for 2.5 hrs. LCMS showed 9 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=l/O; Detector, UV 254 nm. This resulted in to give 10 (19.8 g, 25.3 mmol, 91% yield) as a white solid. ESI-LCMS: m/z 783 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.29 (d, J=2.0 Hz, 1H), 8.42 (d, J=8.0 Hz, 1H), 8.02-8.00 (m, 2H), 7.64-7.62 (m, 1H), 7.60-7.41 (m, 2H), 7.47.41-7.19 (m, 9H), 6.94-6.85 (m, 4H), 5.81 (d, J=4.0 Hz, 1H), 5.33-5.26 (m, 1H), 5.21 (d, J=7.2 Hz, 1H), 4.06-3.90 (m, 2H), 3.83-3.77 (m, 1H), 3.74 (s, 6H).

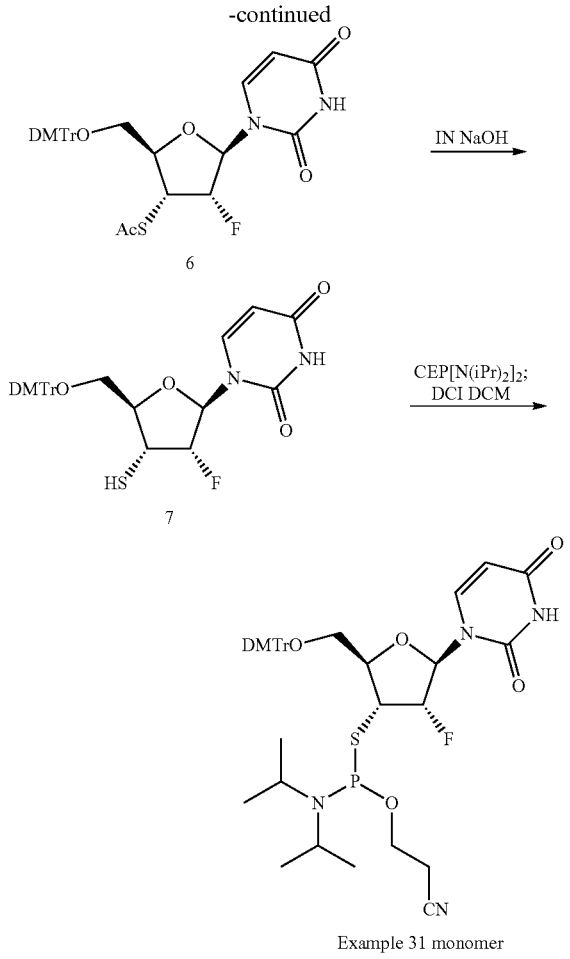
[0567] Preparation of (11): To a solution of 10 (18.8 g, 26.4 mmol) in THF (190 mL) was added 1 M TBAF solution (28 mL). The reaction mixture was stirred at r.t. for 1.5 hrs. LCMS showed 10 was consumed completely. Water (200 mL) was added. The product was extracted with EA (200 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 11 (17.1 g, 25.6 mmol, 96%) as a white solid. ESI-LCMS: m/z 669 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.29 (d, J=2.0 Hz, 1H), 8.42 (d, J=8.0 Hz, 1H), 8.02-8.00 (m, 2H), 7.64-7.62 (m, 1H), 7.60-7.41 (m, 2H), 7.47.41-7.19 (m, 9H), 6.94-6.85 (m, 4H), 5.81 (d, J=4.0 Hz, 1H), 5.33-5.26 (m, 1H), 5.21 (d, J=7.2 Hz, 1H), 4.06-3.90 (m, 2H), 3.83-3.77 (m, 1H), 3.74 (s, 6H).

[0568] Preparation of Example 30 monomer: To a suspension of 11 (10.8 g, 16.2 mmol) in DCM (100 mL) was added DCI (1.5 g, 13.7 mmol) and $CEP[N(iPr)_2]_2$ (5.8 g, 19.3 mmol). The mixture was stirred at r.t. for 2 hrs. LC-MS showed 11 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 30 monomer (11.3 g, 13 mmol, 80%) as a white solid. ESI-LCMS: m/z 868 [M+H]-; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.03 (m, 1H), 8.51-8.48 (m, 1H), 8.08-7.95 (m, 2H), 7.63-7.54 (m, 1H), 7.52-7.19 (m, 9H), 7.16-7.07 (m, 1H), 6.94-6.89 (m, 3H), 5.95-5.87 (m, 1H), 5.31-5.17 (m, 1H), 4.61-4.37 (m, 1H), 4.20-4.07 (m, 1H), 3.82-3.47 (m, 10H), 2.74-2.59 (m, 1H), 2.57-2.43 (m, 1H), 1.27-1.10 (m, 9H), 1.09-0.95 (m, 3H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.52, 148.81.

Example 31. Synthesis of Monomer

[0569]





Example 31 monomer

[0570] Preparation of (2): To a stirred solution of 1 (100.0 g, 406.5 mmol) in pyridine (1000 mL) were added DMTrCl (151.2 g, 447.1 mmol) at r.t. And the reaction mixture was stirred at r.t. for 2.5 hrs. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (3000 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by silica gel column chromatography (SiO_2, dichloromethane:methanol=100:1) to give 2 (210.0 g, 90%) as a white solid. ESI-LCMS: m/z 548.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.43 (d, J=1.8 Hz, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.40-7.21 (m, 9H), 6.92-6.88 (m, 4H), 5.89 (d, J=20.0 Hz, 1H), 5.31-5.29 (m, 1H), 5.19-5.04 (dd, 1H), 4.38-4.31 (m, 1H), 4.02-3.98 (m, 1H), 3.74 (s, 6H), 3.30 (d, J=3.2 Hz, 2H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ −199.51.

[0571] Preparation of (3): To a stirred solution of 2 (100.0 g, 182.8 mmol) in pyridine (1000 mL) were added MsCl (31.2 g, 274.2 mmol) at 0° C. under N_2 atmosphere. And the reaction mixture was stirred at r.t for 2.5 h. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was evaporated to dryness under reduced pressure to give the crude (114.0 g) as a white solid which was used directly for next step. To the solution of the crude (114.0 g, 187.8 mmol) in DMF (2000 mL) was added K_2CO_3 (71.5 g, 548.4 mmol), and the reaction mixture was stirred at 90° C. for 15 h under N_2 atmosphere. After addition of water, the resulting mixture was extracted with EA (500 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by silica gel column chromatography (SiO_2, dichloromethane:methanol=30:1) to give 3 (100.0 g, 90%) as a white solid. ESI-LCMS: m/z 531.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.79 (d, J=8.0 Hz, 1H), 7.40-7.21 (m, 9H), 6.89-6.83 (m, 4H), 6.14 (d, J=5.4 Hz, 1H), 6.02-5.90 (dd, 1H), 5.87 (d, J=20.0 Hz, 1H), 5.45 (m, 1H), 4.61 (m, 1H), 3.73 (d, J=1.9 Hz, 6H), 3.30-3.15 (m, 2H), 1.24-1.16 (m, 1H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−204.23.

[0572] Preparation of (4): A solution of 3 (100 g, 187.8 mmol) in THF (1000 mL) was added 6N NaOH (34 mL, 206.5 mmol). The mixture was stirred at r.t. for 6 h. After completion of reaction, the resulting mixture was added H_2O, and then the mixture was extracted with EA, the organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by silica gel column chromatography (SiO_2, dichloromethane:methanol=30:1) to give 4 (90.4 g, 90%) as a white solid. ESI-LCMS: m/z 548.2 $[M+H]^+$; ^{19}F-NMR (376 MHz, DMSO-d_6): δ−184.58.

[0573] Preparation of (5): To a stirred solution of 4 (90.4 g, 165.2 mmol) in pyridine (1000 mL) were added MsCl (61.5 g, 495.6 mmol) at 0° C. under N_2 atmosphere. And the reaction mixture was stirred at r.t for 16 hrs. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA. the organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by silica gel column chromatography (SiO_2, PE:EA=1:1) to give 5 (75.0 g, 90%) as a white solid. ESI-LCMS: m/z 626.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.51 (d, J=1.6 Hz, 1H), 7.43-7.23 (m, 10H), 6.92-6.88 (m, 4H), 6.08 (d, J=20.0 Hz, 1H), 5.55-5.39 (m, 2H), 4.59 (m, 1H), 3.74 (s, 6H), 3.48-3.28 (m, 2H), 3.17 (s, 3H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−187.72.

[0574] Preparation of (6): To the solution of 5 (75.0 g, 120.4 mmol) in DMF (1500 mL) was added KSAc (71.5 g, 548.4 mmol) at 110° C. under N_2 atmosphere, After the reaction mixture was stirred at 110° C. for 3 h were added KSAc (71.5 g, 548.4 mmol) under N_2 atmosphere. And the reaction mixture was stirred at r.t for 16 h. After addition of water, the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by silica gel column chromatography (SiO_2, PE:EA=1:1) to give 6 (29.0 g, 90%) as a white solid. ESI-LCMS: m/z 605.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.45 (d, J=1.9 Hz, 1H), 7.95 (d, J=8.0 Hz, 1H), 7.38-7.21 (m, 9H), 6.92-6.87 (m, 4H), 5.93 (m, 1H), 5.50-5.36 (dd, 1H), 5.25-5.23 (dd, 1H), 4.54-4.42 (m, 1H), 4.17-4.12 (m, 1H), 3.74 (m, 7H), 3.35-3.22 (m, 2H), 2.39 (s, 1H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−181.97.

[0575] Preparation of (7): A solution of 6 (22 g, 36.3 mmol) in a mixture solvent of THE/MeOH (1:1, 200 mL) was added iN NaOMe (70 mL, 72.6 mmol) was stirred at 20° C. for 4 h. After completion of reaction, the resulting mixture was added H_2O, and then the mixture was extracted with EA, the organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase,

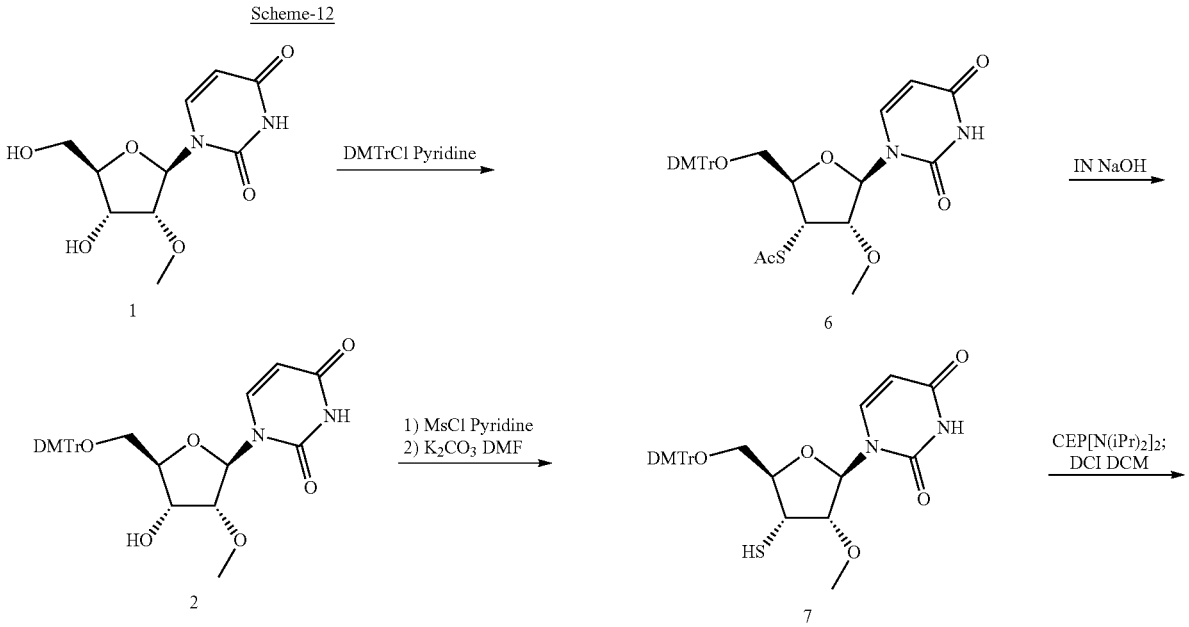
CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=4/3; Detector, UV 254 nm. This resulted in to give 7 (10.5 g, 14.5 mmol, 75.9%) as a white solid. ESI-LCMS: m/z 565.1 $[M+H]^+$; iH-NMR (400 MHz, DMSO-d_6): δ 11.45 (s, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.40-7.23 (m, 9H), 6.90 (d, J=8.8 Hz, 4H), 5.88 (m, 1H), 5.29-5.15 (m, 2H), 3.72 (m, 7H), 3.43 (m, 2H), 2.78 (d, J=10.6 Hz, 1H).

[0576] Preparation of Example 31 monomer: To a suspension of 7 (10.5 g, 18.6 mmol) in DCM (100 mL) was added DCI (1.8 g, 15.7 mmol) and $CEP[N(iPr)_2]_2$ (6.7 g, 22.3 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 8 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 31 monomer (10.5 g, 14.5 mmol, 75.9%) as a white solid. ESI-LCMS: m/z 765.3 [M+1H]; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.40 (d, J=12.2 Hz, 1H), 7.90-7.86 (m, 1H), 7.41-7.24 (m, 9H), 6.91-6.89 (m, 4H), 5.97 (m, 1H), 5.33-5.10 (m, 2H), 4.18-4.16 (m, 1H), 3.91-3.39 (m, 17H), 2.81 (t, J=5.6 Hz, 1H), 2.66 (t, J=6.0 Hz, 1H), 1.33-0.97 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 164.57, 160.13.

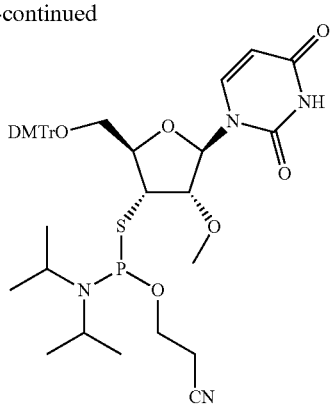
Example 32. Synthesis of Monomer

[0577]

Scheme-12



-continued



Example 32 monomer

[0578] Preparation of (2): To a stirred solution of 1 (100.0 g, 387.5 mmol) in pyridine (1000 mL) was added DMTrCl (151.2 g, 447.1 mmol) at r.t. And the reaction mixture was stirred at r.t. for 2.5 hrs. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (3000 mL). The organic phase was evaporated to dryness under reduced pressure to give a residue which was purified by silica gel column chromatography (SiO_2, dichloromethane:methanol=100:1) to give 2 (200.0 g, 90%) as a white solid. ESI-LCMS: m/z 561 $[M+H]^+$.

[0579] Preparation of (3): To a stirred solution of 2 (73.0 g, 130.3 mmol) in pyridine (730 mL) were added MsCl (19.5 g, 169.2 mmol) at 0° C. under N_2 atmosphere. And the reaction mixture was stirred at r.t for 2.5 h. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA (200 mL). The organic phase was evaporated to dryness under reduced pressure to give the crude (80.0 g) as a white solid which was used directly for next step. To the solution of the crude (80.0 g, 130.3 mmol) in DMF (1600 mL) was added K_2CO_3 (71.5 g, 390.9 mmol), and the reaction mixture was stirred at 90° C. for 15 h under N_2 atmosphere. After addition of water, the resulting mixture was extracted with EA (500 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by silica gel column chromatography (SiO_2, dichloromethane:methanol=30:1) to give 3 (55.0 g, 90%) as a white solid. ESI-LCMS: m/z 543. $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.68 (d, J=8.0 Hz, 1H), 7.40-7.21 (m, 9H), 6.89-6.83 (m, 4H), 5.96 (s, 1H), 5.83 (d, J=5.4 Hz, 1H), 5.26 (s, 1H), 4.59 (s, 1H), 4.46 (t, J=6.0 Hz, 1H), 3.72 (s, 6H), 3.44 (s, 3H), 3.18-3.12 (m, 2H).

[0580] Preparation of (4): A solution of 3 (55 g, 101.8 mmol) in THE (550 mL) was added 6N NaOH (34 mL, 206.5 mmol). The mixture was stirred at 20° C. for 6 hrs. After completion of reaction, the resulting mixture was added H_2O, and then the mixture was extracted with EA, the organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by silica gel column chromatography (SiO_2, dichloromethane:methanol=30:1) to give 4 (57.4 g, 87%) as a white solid. ESI-LCMS: m/z 561 $[M+H]^+$.

[0581] Preparation of (5): To a stirred solution of 4 (57.4 g, 101.8 mmol) in pyridine (550 mL) were added MsCl (61.5 g, 495.6 mmol) at 0° C. under N_2 atmosphere. And the reaction mixture was stirred at r.t for 16 h. With ice-bath cooling, the reaction was quenched with water and the product was extracted with EA. the organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by silica gel column chromatography (SiO_2, PE:EA=1:1) to give 5 (57.0 g, 90%) as a white solid. ESI-LCMS: m/z 639 $[M+H]^+$.

[0582] Preparation of (6): To the solution of 5 (57.0 g, 89.2 mmol) in DMF (600 mL) was added KSAc (71.5 g, 448.4 mmol) at 110° C. under N_2 atmosphere, After the reaction mixture was stirred at 110° C. for 3 h were added KSAc (71.5 g, 448.4 mmol) under N_2 atmosphere. And the reaction mixture was stirred at r.t for 16 h. After addition of water, the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give a residue which was purified by silica gel column chromatography (SiO_2, PE:EA=1:1) to give 6 (29.0 g, 47%) as a white solid. ESI-LCMS: m/z 619.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 8.06 (s, 1H), 7.40-7.23 (m, 9H), 6.90 (d, J=8.8 Hz, 4H), 5.82 (s, 1H), 5.10-5.08 (dd, 1H), 4.38-4.34 (m, 1H), 4.08-4.02 (m, 3H), 3.74 (s, 6H), 3.45 (s, 3H), 3.25 (m, 2H), 2.37 (s, 3H); ESI-LCMS: m/z 619 $[M-H]^+$.

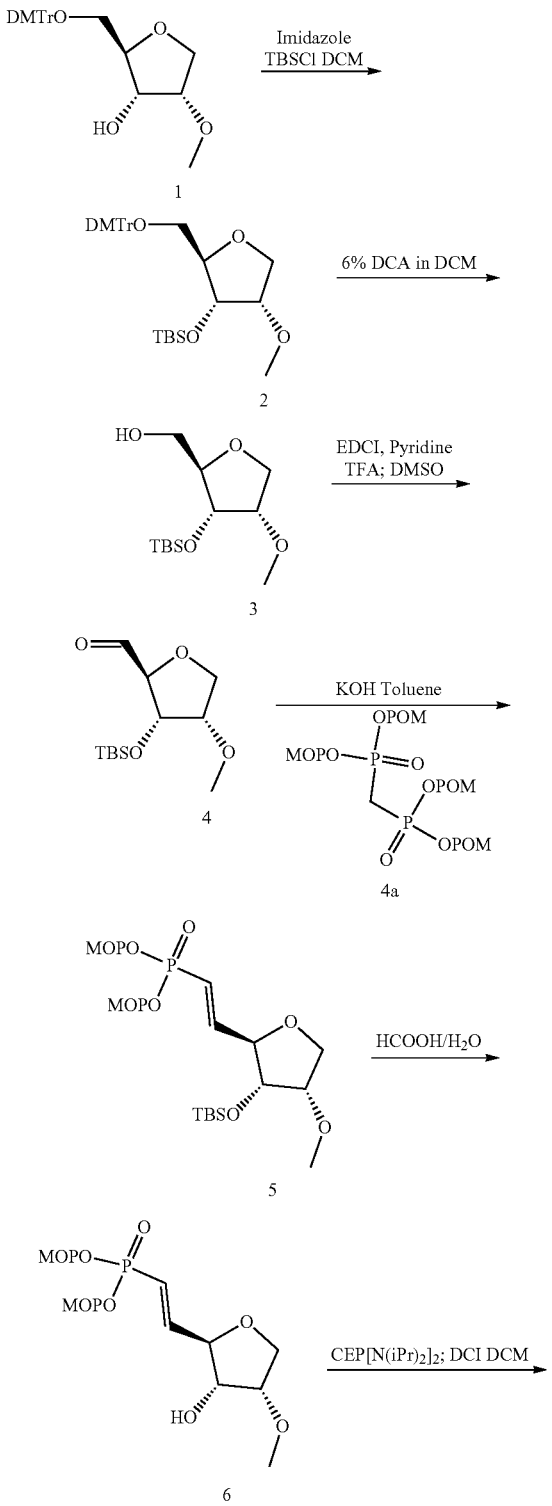
[0583] Preparation of (7): A solution of 6 (22 g, 35.3 mmol) in a mixture solvent of THE/MeOH (1:1, 200 mL) was added 1N NaOMe (70 mL, 72.6 mmol) was stirred at 20° C. for 4 h. After completion of reaction, the resulting mixture was added H_2O, and then the mixture was extracted with EA, the organic layer was washed with brine, dried over sodium sulfate and removed to give the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=4/3; Detector, UV 254 nm. This resulted in to give 7 (14.0 g, 70.9%) as a white solid. ESI-LCMS: m/z 576.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.38 (s, 1H), 7.90 (d, J=8.0 Hz, 1H), 7.40-7.23 (m, 9H), 6.90 (d, J=8.8 Hz, 4H), 5.80 (s, 1H), 5.15-5.13 (dd, 1H), 3.93 (m, 1H), 3.87 (d, J=5.0 Hz, 1H), 3.74 (s, 6H), 3.59 (m, 2H), 3.49 (s, 3H), 3.39 (d, J=2.2 Hz, 2H), 2.40 (d, J=10.2 Hz, 1H).

[0584] Preparation of Example 32 monomer: To a suspension of 7 (10.5 g, 18.6 mmol) in DCM (100 mL) was added DCI (1.8 g, 15.7 mmol) and $CEP[N(iPr)_2]_2$ (6.7 g, 22.3 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 7 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 32 monomer (10.5 g, 14.5 mmol, 75.9%) as a white solid. ESI-LCMS: m/z 776.3 $[M+H]^+$: ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.40 (d, J=12.2 Hz, 1H), 8.04-7.96 (dd, 1H), 7.43-7.24 (m, 9H), 6.92-6.87 (m, 4H), 5.84 (m, 1H), 4.93 (m, 1H), 4.13 (m, 1H), 3.91-3.39 (m, 17H), 2.82 (t, J=5.6 Hz, 1H), 2.68 (t, J=6.0 Hz, 1H), 1.22-0.97 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 165.06, 157.59.

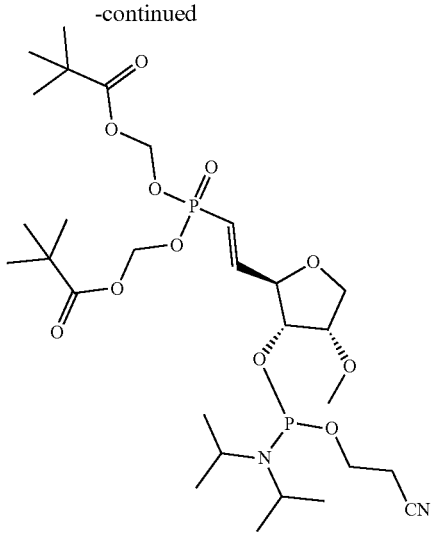
Example 33. Synthesis of 5' End Cap Monomer

[0585]

Scheme-13



-continued



Example 33 monomer

[0586] Preparation of (2): To a solution of 1 (11.2 g, 24.7 mmol) in DCM (120 mL), imidazole (4.2 g, 61.9 mmol) and TBSCl (5.6 g, 37.1 mmol) were added at r.t., mixture was stirred at r.t. for 15 hrs, LCMS showed 1 was consumed completely. Mixture was added water (500 mL) and extracted with DCM (50 mL*2). The organic phase was dried over Na_2SO_4 and concentrated to give 2 (16.0 g) as an oil for the next step.

[0587] Preparation of (3): To a solution of 2 (16.0 g, 28.4 mmol) was added 6% DCA in DCM (160 mL) and triethylsilane (40 mL) at r.t. The reaction mixture was stirred at r.t. for 2 hrs. TLC showed 2 was consumed completely. Water (300 mL) was added, mixture was extracted with DCM (50 mL*4), organic phase was dried by Na_2SO_4, concentrated by reduce pressure to give crude which was purified by column chromatography (SiO_2, PE/EA=10:1 to 1:1) to give 3 (4.9 g, 65.9% yield) as an oil. ESI-LCMS: m/z 263 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.84-4.50 (m, 1H), 4.3-4.09 (m, 1H), 3.90-3.80 (m, 1H), 3.75-3.67 (m, 1H), 3.65-3.57 (m, 2H), 3.50-3.44 (m, 1H), 3.37-3.28 (m, 4H), 0.95-0.78 (s, 9H), 0.13-0.03 (s, 6H).

[0588] Preparation of (4): To a solution of 3 (3.3 g, 12.6 mmol) in DMSO (33 mL) was added EDCI (7.2 g, 37.7 mmol).The mixture was added pyridine (1.1 g, 13.8 mmol) and TFA (788.6 mg, 6.9 mmol). The reaction mixture was stirred at r.t. for 3 hrs. TLC (PE/EA=4:1) showed 3 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. This resulted in to give 4 (3.23 g) as an oil for the next step.

[0589] Preparation of (5): To a solution of 4 (3.3 g, 12.6 mmol) in toluene (30 mL) was added POM ester 4a (reference for 4a *Journal of Medicinal Chemistry,* 2018, 61 (3), 734-744) (7.9 g, 12.6 mmol) and KOH (1.3 g, 22.6 mmol) at r.t. The reaction mixture was stirred at 40° C. for 8 hrs. LCMS showed 4 was consumed. The mixture was diluted with water and EA was added. The product was extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by Flash-Prep-HPLC with the following con-

ditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=91/9 Detector, UV 254 nm. This resulted in to give 5 (5.4 g, 9.5 mmol, 75.9% yield) as an oil. ESI-LCMS: m/z 567.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.89-6.77 (m, 1H), 6.07-5.96 (m, 1H), 5.86-5.55 (m, 4H), 4.85-4.73 (m, 1H), 4.36-4.27 (m, 1H), 4.05-3.96 (m, 1H), 3.95-3.85 (m, 1H), 3.73-3.65 (m, 1H), 3.44-3.35 (m, 3H), 1.30-1.25 (s, 18H), 0.94-0.84 (s, 9H), 0.14-0.05 (s, 6H). ^{31}P-NMR (162 MHz, $CDCl_3$) δ 18.30, 15.11.

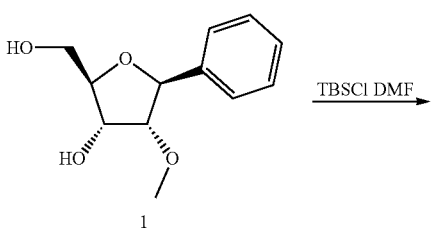
[0590] Preparation of (6): To a solution of 5 (5.4 g, 9.5 mmol) in HCOOH (30 mL)/H_2O (30 mL)=1:1 at r.t. The reaction mixture was stirred at r.t. for 15 hrs. LCMS showed the reaction was consumed. The mixture was diluted with con. NH_4OH till pH=7.5. The product was extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% HCOOH)=30/70 increasing to CH_3CN/H_2O (0.5% HCOOH)=70/30 within 45 min, the eluted product was collected at CH_3CN/H_2O (0.5% HCOOH)=59/41 Detector, UV 220 nm. This resulted in to give 6 (2.4 g, 5.7 mmol, 59.4% yield) as an oil. ESI-LCMS: m/z 453.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.84-6.68 (m, 1H), 6.07-5.90 (m, 1H), 5.64-5.55 (m, 4H), 5.32-5.24 (m, 1H), 4.23-4.15 (m, 1H), 4.00-3.90 (m, 1H), 3.89-3.80 (m, 1H), 3.78-3.69 (m, 2H), 3.37-3.30 (s, 3H), 1.30-1.10 (s, 18H). ^{31}P-NMR (162 MHz, DMSO-d_6) δ 18.14.

[0591] Preparation of Example 33 monomer: To a solution of 6 (2.1 g, 4.5 mmol) in DCM (21 mL) were added DCI (452.5 mg, 3.8 mmol) and $CEP[N(iPr)_2]_2$ (1.8 g, 5.9 mmol) at r.t. The reaction mixture was stirred at r.t. for 15 hrs under N_2 atmosphere. LCMS showed 6 was consumed. The mixture was diluted with water. The product was extracted with DCM (30 mL). The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 28 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=80/20 Detector, UV 254 nm. This resulted in to give Example 33 monomer (2.8 g, 4.3 mmol, 95.2% yield) as an oil. ESI-LCMS: m/z 653.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.89-6.77 (m, 1H), 6.11-5.96 (m, 1H), 5.65-5.50 (m, 4H), 4.39-4.34 (d, J=20 Hz, 1H), 4.18-3.95 (m, 2H), 3.94-3.48 (s, 6H), 3.40-3.28 (m, 4H), 2.84-2.75 (m, 2H), 1.26-1.98 (s, 30H). ^{31}P-NMR (162 MHz, DMSO-d_6) δ 149.018, 148.736, 17.775, 17.508.

Example 34. Synthesis of 5' End Cap Monomer

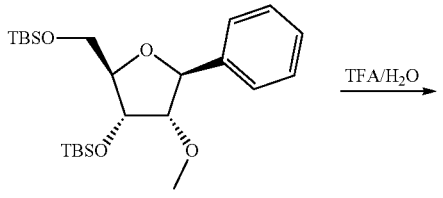
[0592]

Scheme-14

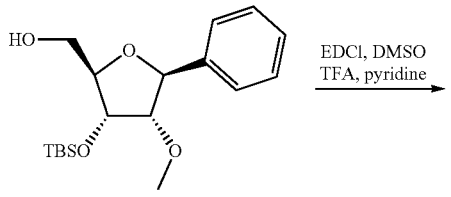


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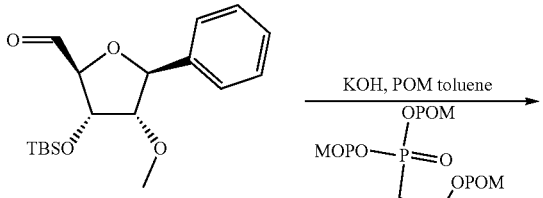
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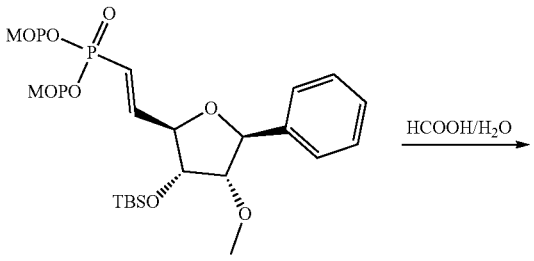


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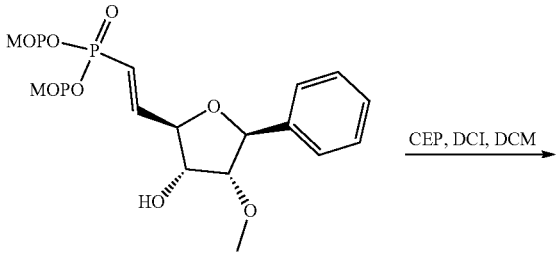


4

4a

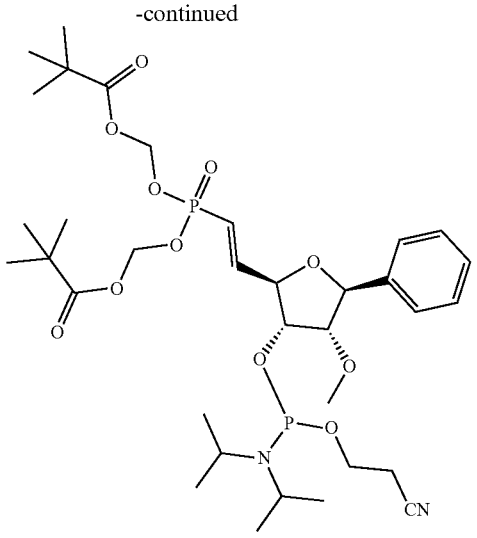


5



6

-continued



Example 34 monomer

[0593] Preparation of (2): To a solution of 1 (ref for 1 *Tetrahedron,* 2013, 69, 600-606) (10.60 g, 47.32 mmol) in DMF (106 mL), imidazole (11.26 g, 165.59 mmol) and TBSCl (19.88 g, 132.53 mmol) were added. The mixture was stirred at r.t. for 3.5 hrs, LCMS showed 1 was consumed completely. Water was added and extracted with EA, dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give 2 (20.80 g, 45.94 mmol, 97.19% yield) for the next step.

[0594] Preparation of (3): To a solution of 2 (20.80 g, 45.94 mmol) in THF (248 mL), was added TFA (124 mL) and H_2O (124 mL) at 0° C., reaction mixture was stirred for 30 min. LCMS showed 2 was consumed completely. Then was extracted with EA, washed with sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 3 (10.00 g, 29.59 mmol, 64.31% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.33-7.18 (m, 5H), 4.83-4.80 (m, 1H), 4.61-4.59 (m, 1H), 4.21-4.19 (m, 1H), 3.75-3.74 (m, 1H), 3.23 (m, 3H), 3.13 (m, 3H), 2.41-2.40 (m, 1H), 0.81 (m, 9H), 0.00 (m, 6H).

[0595] Preparation of (4): To a solution of 3(3.70 g, 10.95 mmol) in DMSO (37 mL) was added EDCI (6.30 g, 32.84 mmol). Then pyridine (0.95 g, 12.05 mmol) and TFA (0.69 g, 6.02 mmol) was added in N_2 atmosphere. The mixture was stirred for 3 hrs at r.t. LCMS showed 3 was consumed completely. Water was poured into and extracted with EA, washed with sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was directly used for next step.

[0596] Preparation of (5): To a solution of 4 in toluene (100.00 mL), was added 4a (6.93 g, 10.97 mmol) and KOH (1.11 g, 19.78 mmol). It was stirred for 3.5 hrs at 40° C. in N_2 atmosphere. TLC and LCMS showed 4 was consumed completely. Then was extracted with EA, washed with water and sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 5 (4.30 g, 6.70 mmol, 61.17% yield). iH-NMR (400 MHz, $CDCl_3$): δ 7.27-7.26 (m, 4H), 7.17 (m, 1H), 6.94-6.82 (m, 1H), 6.13-6.02 (m, 1H), 5.63-5.56 (m, 4H), 4.90-4.89 (m, 1H), 4.45-4.41 (m, 1H), 3.98-3.95 (m, 1H), 3.39-3.29 (m, 4H), 1.90 (m, 1H), 1.12-0.83 (m, 29H), 0.00 (m, 7H); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.021, 14.472.

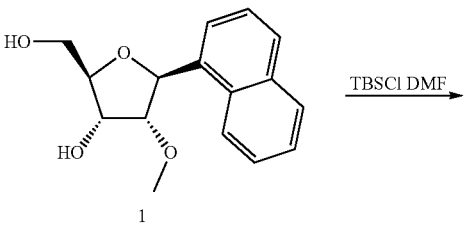
[0597] Preparation of (6): To a solution of 5 (4.30 g, 6.70 mmol) in THE (43.00 mL) was added HCOOH (100 mL) and H_2O (100 mL). It was stirred overnight at r.t. LCMS showed 5 was consumed completely. NH_4OH was poured into it and was extracted with EA, washed with sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 6 (2.10 g, 3.98 mmol, 59.32% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.28 (m, 5H), 7.11-7.00 (m, 1H), 6.19-6.14 (m, 1H), 5.71-5.68 (m, 4H), 4.95-4.94 (m, 1H), 4.48-4.47 (m, 1H), 4.05-4.03 (m, 1H), 3.62-3.61 (m, 1H), 3.46 (m, 3H), 3.00-2.99 (m, 1H), 1.22 (m, 18H); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.134.

[0598] Preparation of Example 34 monomer: To a solution of 6 (2.10 g, 3.98 mmol) in DCM (21 mL) was added DCI (410 mg, 3.47 mmol). CEP (1.40 g, 4.65 mmol) was added in a N_2 atmosphere. LCMS showed 6 was consumed completely. DCM and H_2O was poured, the organic phase was washed with water and sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure at 40° C. to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 34 monomer (2.10 g, 2.88 mmol). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.39-7.32 (m, 6H), 6.21-6.11 (m, 1H), 5.64-5.61 (m, 4H), 4.91-4.85 (m, 1H), 4.59 (m, 1H), 4.28-4.25 (m, 1H), 3.84-3.60 (m, 5H), 3.36-3.36 (m, 2H), 2.83-2.79 (m, 2H), 1.18-1.14 (m, 29H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.588, 148.920, 17.355, 17.010.

Example 35. Synthesis of 5' End Cap Monomer

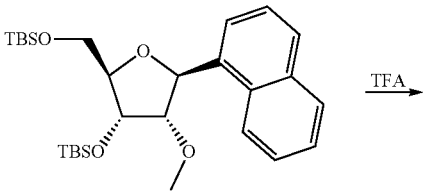
[0599]

Scheme-15

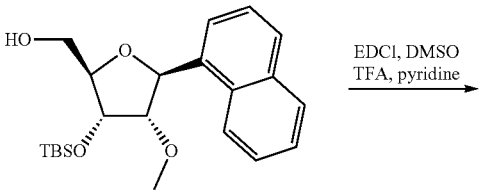


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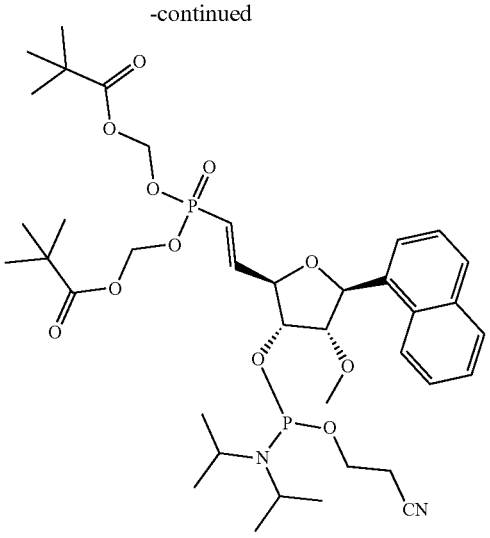


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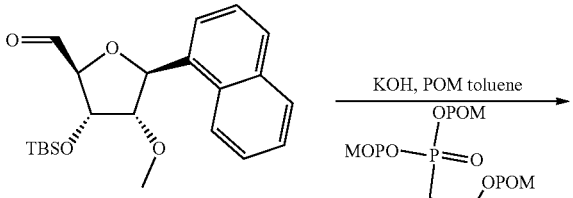


3

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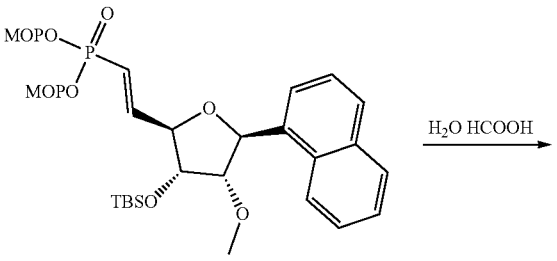


Example 35 monomer

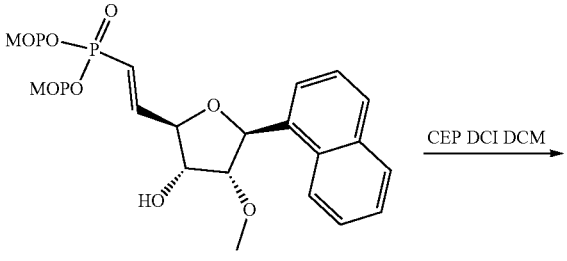


4

4a



5



6

[0600] Preparation of (2): To a solution of 1 (5.90 g, 21.50 mmol) in DMF (60.00 mL), imidazole (4.39 g, 64.51 mmol) and TBSCl (7.63 g, 49.56 mmol) were added. The mixture was stirred at r.t. for 3.5 hrs, LCMS showed 1 was consumed completely. Water was added and extracted with EA, dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give 2 (11.00 g, 21.91 mmol, 98.19% yield) for the next step. ESI-LCMS: m/z 225.1 $[M+H]^+$.

[0601] Preparation of (3): To a solution of 2 (11.00 g, 21.91 mmol) in THF (55.00 mL) was added TFA (110.00 mL) and H_2O (55.00 mL) at 0° C., reaction mixture was stirred for 30 min. LCMS showed 2 was consumed completely. Then was extracted with EA, washed with sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 3 (6.20 g, 16.32 mmol, 72.94% yield). ESI-LCMS: m/z 411.2 $[M+H]^+$.

[0602] Preparation of (4): To a solution of 3 (3.50 g, 9.02 mmol) in DMSO (35.00 mL) was added EDCI (5.19 g, 27.06 mmol). Then pyridine (0.78 g, 9.92 mmol) and TFA (0.57 g, 4.96 mmol) was added in N_2 atmosphere. The mixture was stirred for 3h at r.t. Water was poured into it and was extracted with EA, washed with sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was directly used for next step. ESI-LCMS: m/z 406.2 $[M+H]^+$.

[0603] Preparation of (5): To a solution of 4 in toluene (100.00 mL) was added 4a (5.73 g, 9.07 mmol) and KOH (916.3 g, 16.33 mmol). It was stirred for 3.5h at 40° C. in N_2 atmosphere. Then was extracted with EA, washed with water and sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min,

the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 5 (5.02 g, 7.25 mmol, 80.44% yield). ESI-LCMS: m/z 693.2 $[M+H]^+$; ^{31}P-NMR (162 MHz, DMSO-d_6): δ 17.811

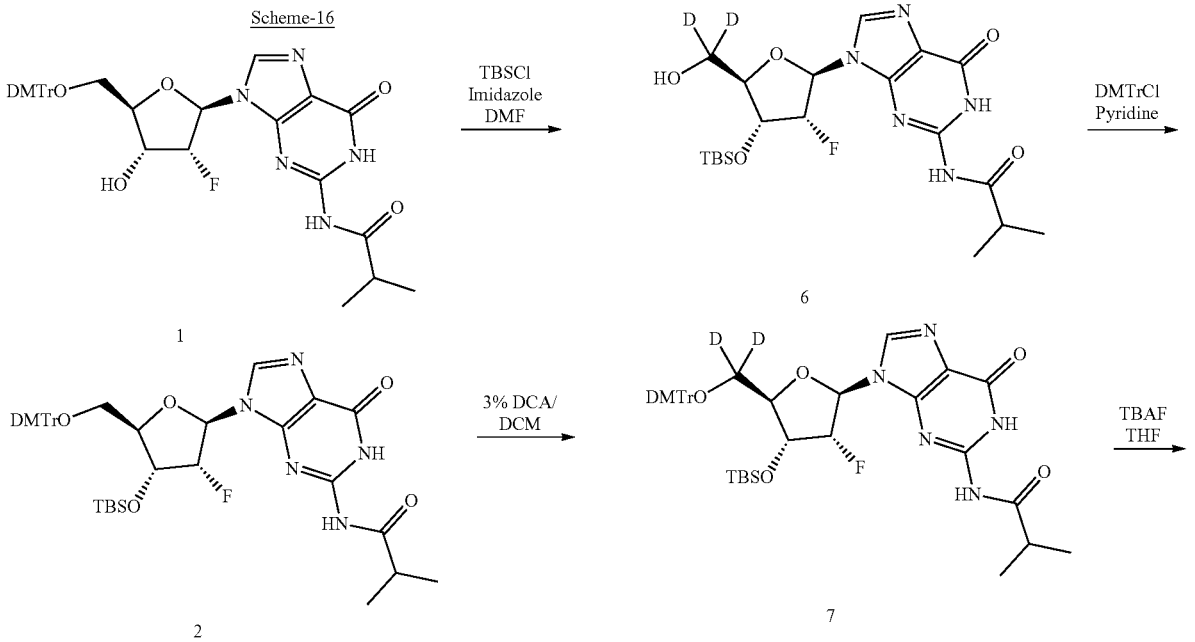
[0604] Preparation of (6): To a solution of 5 (4.59 g, 6.63 mmol) in THE (46.00 mL) was added HCOOH (92.00 mL) and H_2O (92.00 mL). It was stirred overnight at r.t. NH_4OH was poured into it and extracted with EA, washed with sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 6 (2.52 g, 4.36 mmol, 65.80% yield).

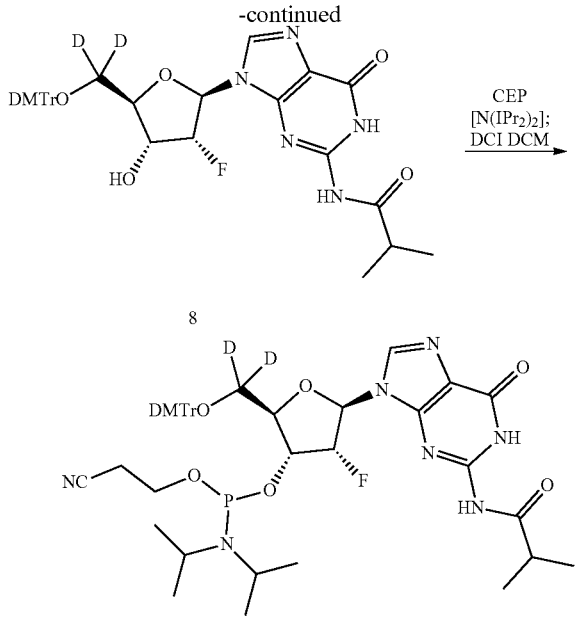
[0605] Preparation of Example 35 monomer: To a solution of 6 (2.00 g, 3.46 mmol) in DCM (21.00 mL) was added DCI (370.00 mg, 3.11 mmol) and CEP (1.12 g, 4.15 mmol) was added in N_2 atmosphere. DCM and H_2O was poured, the organic phase was washed with water and sat. NaCl (aq.), dried over by Na_2SO_4. The filtrate was evaporated under reduced pressure at 38° C. to give the crude product which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 35 monomer (2.10 g, 2.70 mmol, 78.07% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.39-7.32 (m, 6H), 6.21-6.11 (m, 1H), 5.64-5.61 (m, 4H), 4.91-4.85 (m, 1H), 4.59 (m, 1H), 4.28-4.25 (m, 1H), 3.84-3.60 (m, 5H), 3.36-3.36 (m, 2H), 2.83-2.79 (m, 2H), 1.18-1.14 (m, 29H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.588, 148.920, 17.355, 17.010.

Example 36. Synthesis of Monomer

[0606]

Scheme-16





Example 36 monomer

[0607] Preparation of (2): To a solution of 1 (35.0 g, 53.2 mmol) in DMF (350 mL) was added imidazole (9.0 g, 133.0 mmol) then added TBSCl (12.0 g, 79.8 mmol) at 0° C. The mixture was stirred at r.t. for 14 hrs. TLC showed 1 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure the crude 2 (41.6 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 772 $[M+H]^+$.

[0608] Preparation of (3): To a solution of 2 (41.0 g, 53.1 mmol) in 3% DCA (53.1 mmol, 350 mL) and Et_3SiH (53.1 mmol, 100 mL) at 0° C. The mixture was stirred at 0° C. for 0.5 h. TLC showed 2 was consumed completely. $NaHCO_3$ was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure. The residue silica gel column chromatography (eluent, DCM/MeOH=100:1-20:1). This resulted in to give 3 (20.0 g, 41.7 mmol, 78.6% over two step) as a white solid. ESI-LCMS: m/z 470 $[M+H]^+$; ^1H-NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H), 11.67 (s, 1H), 8.28 (s, 1H), 6.12-6.07 (dd, J=15 Hz, 1H), 5.75 (d, J=5 Hz, 1H), 5.48-5.24 (m, 2H), 4.55-4.49 (m, 1H), 3.97 (s, 1H), 3.75-3.55 (m, 2H), 2.79-2.76 (m, 1H), 1.12 (d, J=6 Hz, 6H), 0.88 (s, 9H), 0.11 (d, J=6 Hz, 6H).

[0609] Preparation of (4): To the solution of 3 (20 g, 42.6 mmol) in dry DCM (100 mL) and DMF (60 mL) was added PDC (20. g, 85.1 mmol), tert-butyl alcohol (63.1 g, 851.8 mmol) and Ac20 (43.4 g, 425.9 mmol) at r.t. under N_2 atmosphere. And the reaction mixture was stirred at r.t. for 2 h. The solvent was removed to give a residue which was purified by silica gel column chromatography (eluent, PE:EA=4:1-2:1) to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 4 (16.0 g, 29.0 mmol, 68.2% yield) as a white solid. ESI-LCMS: m/z 540 $[M+H]^+$; ^1H-NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H), 11.69 (s, 1H), 8.28 (s, 1H), 6.21-6.17 (dd, J=15 Hz, 1H), 5.63-5.55 (m, 1H), 4.75-4.72 (m, 1H), 4.41 (d, J=5 Hz, 1H), 2.79-2.76 (m, 1H), 1.46 (s, 9H), 1.13-1.11 (m, 6H), 0.90 (s, 9H), 0.14 (d, J=2 Hz, 6H).

[0610] Preparation of (5): To the solution of 4 (16.0 g, 29.6 mmol) in dry THF/MeOD/D_2O=10/2/1 (195 mL) was added $NaBD_4$ (3.4 g, 88.9 mmol) at r.t. and the reaction mixture was stirred at 50° C. for 2 h. After completion of reaction, adjusted pH value to 7 with CH_3COOD, after addition of water, the resulting mixture was extracted with EA (300 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, Then the solution was concentrated under reduced pressure the crude 5 (11.8 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 402 $[M+H]^+$.

[0611] Preparation of (6): To a solution of 5 (5.0 g, 12.4 mmol) in pyridine (50 mL) was added iBuCl (2.6 g, 24.9 mmol) at 0° C. under N_2 atmosphere. The mixture was stirred at r.t. for 14 h. TLC showed 5 was consumed completely. Then the solution diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure to give the crude. To a solution of the crude in pyridine (50 mL) was added 2N NaOH (MeOH/H_2O=4:1, 15 mL) at 0° C. The mixture was stirred at 0° C. for 10 min. Then the solution diluted with EA. The organic layer was washed with NH_4Cl and brine. Then the solution was concentrated under reduced pressure the residue was purified by Flash-Prep-HPLC with the following conditions(IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2; Detector, UV 254 nm. This resulted in to give 6 (6 g, 10.86 mmol, 87.17% yield) as a white solid. ESI-LCMS: m/z 472.2 $[M+H]^+$; ^1H-NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H), 11.67 (s, 1H), 8.28 (s, 1H), 6.12-6.07 (dd, J=15 Hz, 1H), 5.48-5.24 (m, 2H), 5.22 (s, 1H), 4.55-4.49 (m, 1H), 3.97 (d, J=5 Hz, 1H), 2.79-2.76 (m, 1H), 1.12 (d, J=6 Hz, 6H), 0.88 (s, 9H), 0.11 (d, J=6 Hz, 6H).

[0612] Preparation of (7): To a solution of 6 (3.8 g, 8.1 mmol) in pyridine (40 mL) was added DMTrCl (4.1 g, 12.1 mmol) at 20° C. The mixture was stirred at 20° C. for 1 h. TLC showed 7 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure to give the crude product of 7 (6 g, 7.6 mmol, 94.3% yield) as a yellow solid. ESI-LCMS: m/z 775 $[M+H]^+$.

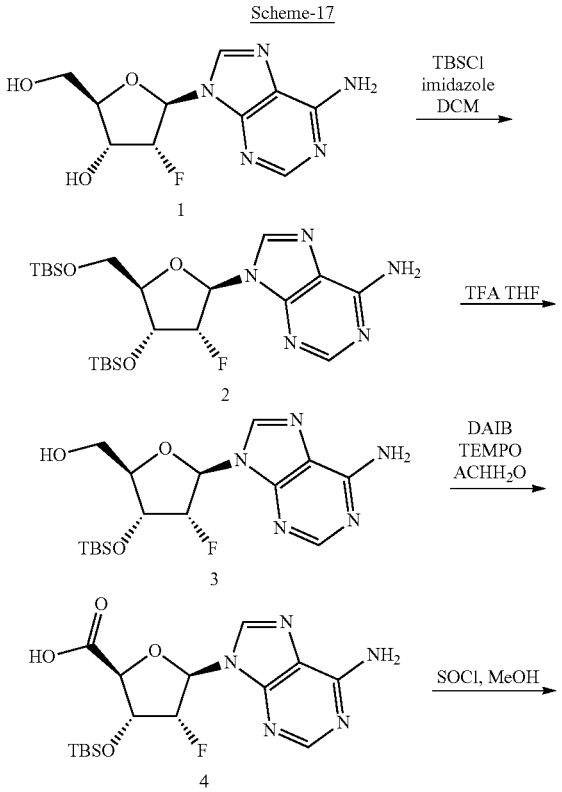
[0613] Preparation of (8): To a solution of 7 (6.0 g, 7.75 mmol) in THE (60 mL) was added TBAF (2.4 g, 9.3 mmol). The mixture was stirred at r.t. for 1 h. TLC showed 7 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure, the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1;

Detector, UV 254 nm. This resulted in to give 8 (4.0 g, 5.9 mmol, 76.6% yield) as a white solid. ESI-LCMS: m/z 660 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H), 11.67 (s, 1H), 8.12 (s, 1H), 7.34-7.17 (m, 9H), 6.83-6.78 (m, 4H), 6.23-6.18 (m, 1H), 5.66 (d, J=7 Hz, 1H), 5.48-5.35 (m, 1H), 4.65-4.54 (m, 1H), 3.72 (d, J=2 Hz, 6H), 2.79-2.73 (m, 1H), 1.19-1.06 (m, 6H).

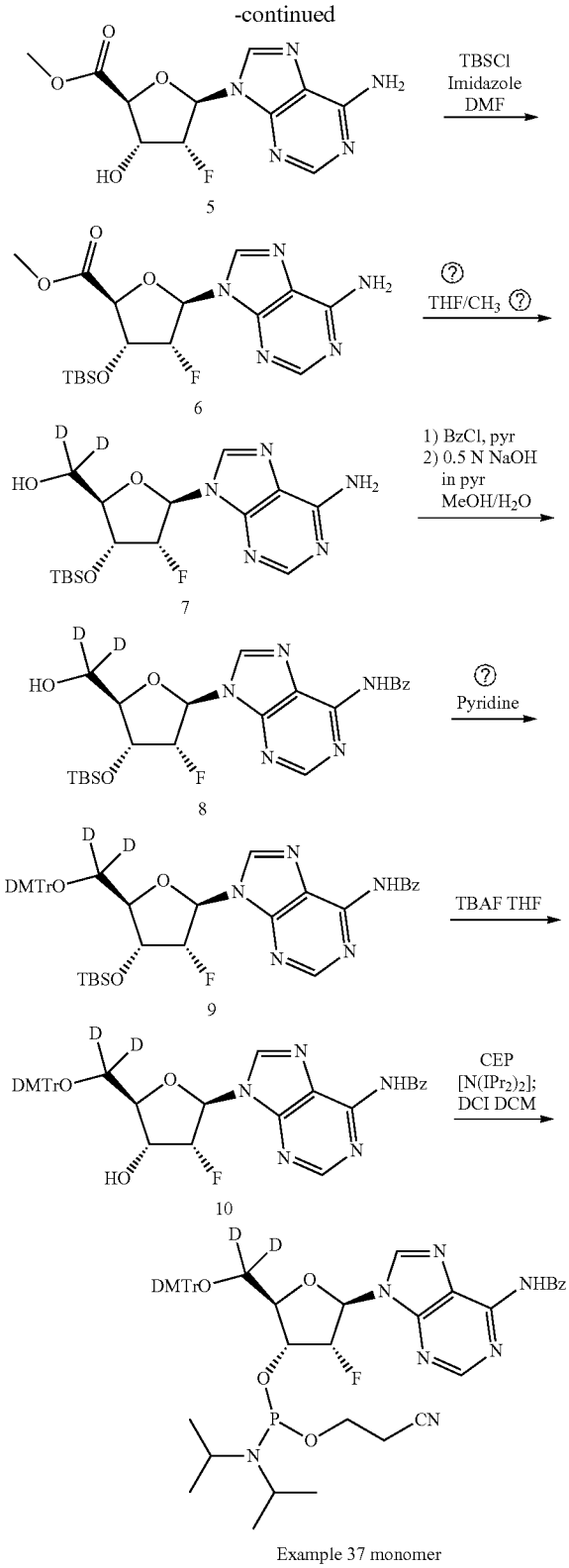
[0614] Preparation of Example 36 monomer: To a solution of 9 (4.0 g, 6.1 mmol) in DCM (40 mL) was added DCI (608 mg, 5.1 mmol) and CEP (2.2 g, 7.3 mmol) under N_2 pro. The mixture was stirred at 20° C. for 0.5 h. TLC showed 9 was consumed completely. The product was extracted with DCM, The organic layer was washed with H_2O and brine. Then the solution was concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 36 monomer (5.1 g, 5.81 mmol, 95.8% yield) as a white solid. ESI-LCMS: m/z 860 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H), 11.67 (s, 1H), 8.12 (s, 1H), 7.34-7.17 (m, 9H), 6.83-6.78 (m, 4H), 6.23-6.18 (m, 1H), 5.67-5.54 (m, 1H), 4.70-4.67 (m, 1H), 4.23-4.20 (m, 1H), 3.72 (m, 6H), 3.60-3.48 (m, 3H), 2.79-2.58 (m, 3H), 1.13-0.94 (m, 18H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 150.31, 150.26, 140.62, 149.57.

Example 37: Synthesis of Monomer

[0615]



-continued



Example 37 monomer

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[0616] Preparation of (2): To a solution of 1 (35 g, 130.2 mmol) in DMF (350 mL) was added imidazole (26.5 g,

390.0 mmol) then added TBSCl (48.7 g, 325.8 mmol) at 0° C. The mixture was stirred at r.t. for 14 h. TLC showed 1 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure the crude 2 (64.6 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 498 $[M+H]^+$.

[0617] Preparation of (3): To a solution of 2 (64.6 g, 130.2 mmol) in THF (300 mL) and added TFA/H_2O (1:1, 300 mL) at 0° C. The mixture was stirred at 0° C. for 2 h. TLC showed 2 was consumed completely. $NaHCO_3$ was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent, DCM: MEOH=100:1-20:1). This resulted in to give 3 (31.3 g, 81.7 mmol, 62.6% over two step) as a white solid. ESI-LCMS: m/z 384 $[M+H]^+$.

[0618] Preparation of (4): To a solution of 3 (31.3 g, 81.7 mmol) in ACN/H_2O (1:1, 350 mL) was added DAIB (78.0 g, 244.0 mmol) and Tempo (3.8 g, 24.4 mmol). The mixture was stirred at 40° C. for 2 h. TLC showed 3 was consumed completely. Then filtered to give 4 (22.5 g, 55.5 mmol, 70.9%) as a white solid. ESI-LCMS: m/z 398 $[M+H]^+$.

[0619] Preparation of (5): To a solution of 4 (22.5 g, 55.5 mmol) in MeOH (225 mL) held at −15° C. with an ice/MeOH bath was added $SOCl_2$ (7.6 mL, 94.5 mmol), dropwise at such a rate that the reaction temp did not exceed 7° C. After the addition was complete, cooling was removed, the reaction was allowed to stir at room temp. The mixture was stirred at r.t. for 14 h. TLC showed 4 was consumed completely. Then the solution was concentrated under reduced pressure to get crude 5 (23.0 g) as a white solid which was used directly for next step. ESI-LCMS: m/z 298 $[M+H]^+$.

[0620] Preparation of (6): To a solution of 5 (23 g, 55.5 mmol) in DMF (220 mL) was added imidazole (11.6 g, 165.0 mmol) then added TBSCl (12.3 g, 82.3 mmol) at 0° C. The mixture was stirred at 20° C. for 14 h. TLC showed 1 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent, DCM: MEOH=100:1~20:1). This resulted in to give 6 (21.3 g, 51.1 mmol, 90% over two step) as a white solid. ESI-LCMS: m/z 412 $[M+H]^+$.

[0621] Preparation of (7): To the solution of 6 (21.0 g, 51.0 mmol) in dry THF/MeOD/D_2O=10/2/1 (260.5 mL) was added $NaBD_4$ (6.4 g, 153.1 mmol) at r.t. and the reaction mixture was stirred at 50° C. for 2 h. After completion of reaction, the resulting mixture was added CH_3COOD to pH=7, after addition of water, the resulting mixture was extracted with EA (300 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4. Then the solution was concentrated under reduced pressure and the residue was used for next step without further purification. ESI-LCMS: m/z 386 $[M+H]^+$.

[0622] Preparation of (8): To a stirred solution of 7 (14.0 g, 35 mmol) in pyridine (50 mL) were added BzCl (17.2 g, 122.5 mmol) at 0° C. under N_2 atmosphere. The mixture was stirred at r.t. for 14 h. TLC showed 7 was consumed completely. Then the solution diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure and the residue was used for next step without further purification. To a solution of the crude in pyridine (300 mL) then added 2M NaOH (MeOH: H_2O=4:1, 60 mL) at 0° C. The mixture was stirred at 0° C. for 10 min. Then the solution diluted with EA. The organic layer was washed with NH_4Cl and brine. Then the solution was concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2; Detector, UV 254 nm. This resulted in to give 8 (14 g, 28.02 mmol, 69.21% yield) as a white solid. ESI-LCMS: m/z 490 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.24 (s, 1H), 8.76 (s, 1H), 8.71 (m, 1H), 8.04 (d, J=7 Hz, 2H), 7.66-7.10 (m, 5H), 6.40-6.35 (dd, 1H), 5.71-5.56 (m, 1H), 5.16 (s, 1H), 4.79-4.72 (m, 1H), 4.01 (m, 1H), 0.91 (s, 9H), 0.14 (m, 6H).

[0623] Preparation of (9): To a solution of 8 (5.1 g, 10.4 mmol) in pyridine (50 mL) was added DMTrCl (5.3 g, 15.6 mmol). The mixture was stirred at r.t. for 1 h. TLC showed 8 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure and the residue was used for next step without further purification. ESI-LCMS: m/z 792 $[M+H]^+$.

[0624] Preparation of (10): To a solution of 9 (7.9 g, 10.0 mmol) in THF (80 mL) was added 1M TBAF in THE (12 mL). The mixture was stirred at r.t. for 1 h. TLC showed 9 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1; Detector, UV 254 nm. This resulted in to give 10 as a white solid. ESI-LCMS: m/z 678 [M+H]-; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.25 (s, 1H), 8.74 (s, 1H), 8.62 (s, 1H), 8.04 (d, J=7 Hz, 2H), 7.66-7.53 (m, 3H), 7.33-7.15 (m, 9H), 6.82-6.78 (m, 4H), 6.43 (d, J=20 Hz, 1H), 5.76-5.60 (m, 1H), 4.88-4.80 (m, 1H), 4.13 (d, J=8 Hz, 1H), 3.71 (m, 6H).

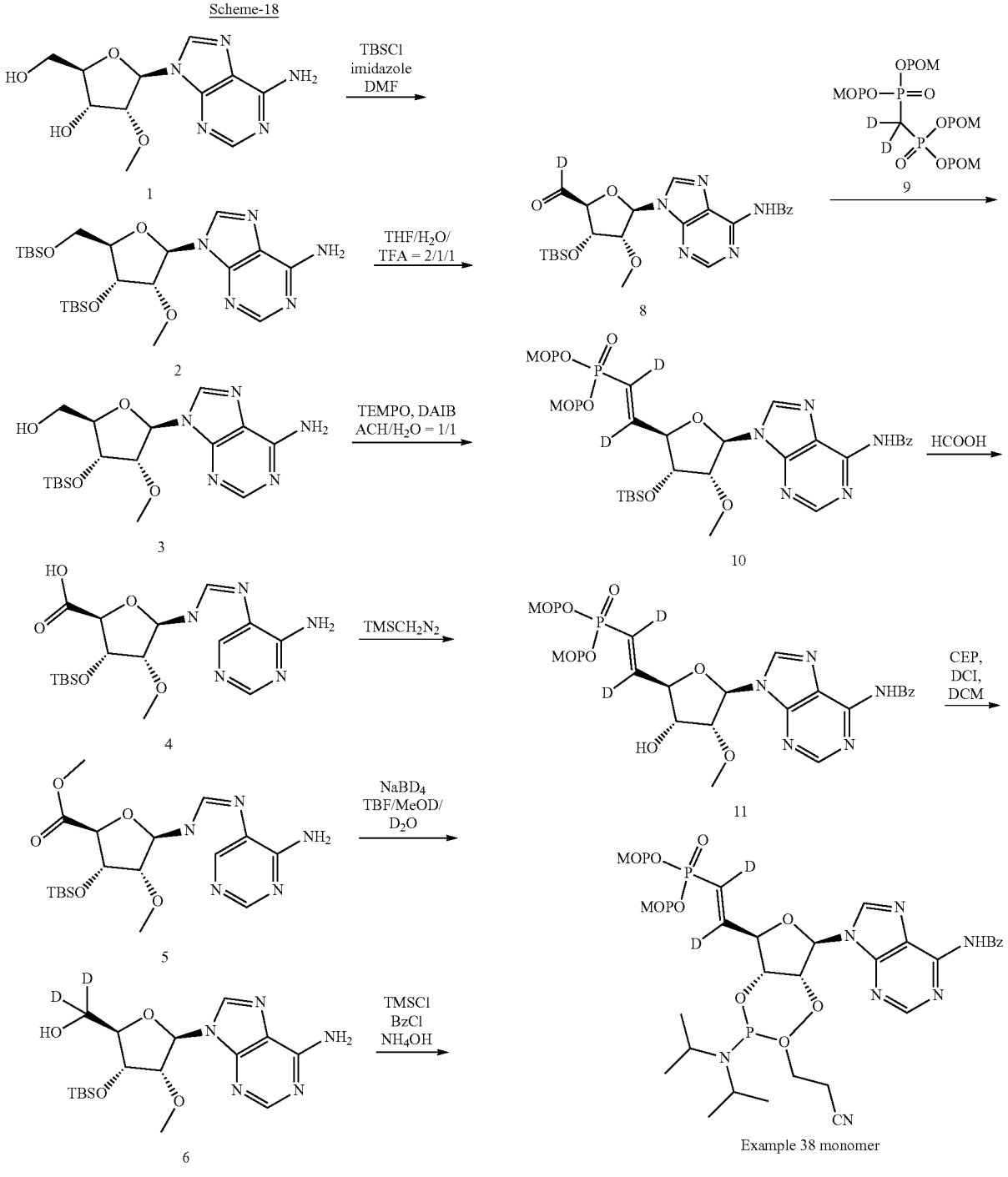
[0625] Preparation of Example 37 monomer: To a solution of 10 (6.2 g, 9.1 mmol) in DCM (60 mL) was added DCI (1.1 g, 9.4 mmol) and CEP (3.3 g, 10.9 mmol) under N_2 pro. The mixture was stirred at 20° C. for 0.5 h. TLC showed 10 was consumed completely. The product was extracted with DCM, The organic layer was washed with H_2O and brine. Then the solution was concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 37 monomer (7.5 g, 8.3 mmol, 90.7%) as a white solid. ESI-LCMS: m/z 878 [M+H]-; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.25 (s, 1H), 8.68-8.65 (dd, 2H), 8.04 (m, 2H), 7.66-7.53 (m, 3H), 7.33-7.15 (m, 9H), 6.82-6.78

(m, 4H), 6.53-6.43 (m, 1H), 5.96-5.81 (m, 1H), 5.36-5.15 (m, 1H), 4.21 (m, 1H), 3.86-3.52 (m, 10H), 2.79-2.61 (m, 2H), 1.21-0.99 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.60, 149.56, 149.48.

Example 38. Synthesis of End Cap Monomer

[0626]

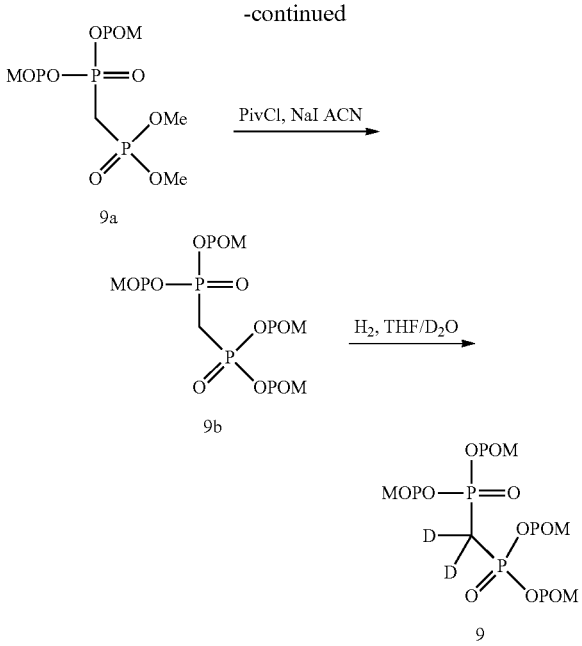
Scheme-18



-continued

Example 38 monomer

-continued



[0627] Preparation of (2): To a solution of 1 (20.0 g, 71.2 mmol) in dry pyridine (200.0 mL) was added TBSCl (26.8 g, 177.9 mmol) and imidazole (15.6 g, 227.8 mmol). The mixture was stirred at r.t. for 15 h. TLC showed 1 was consumed completely. The reaction mixture was concentrated to give residue. The residue was quenched with DCM (300.0 mL). The DCM layer was washed with H_2O (100.0 mL*2) and brine. The DCM layer concentrated to give crude 2 (45.8 g) as a yellow oil. The crude used to next step directly. ESI-LCMS m/z 510.5 $[M+H]^+$.

[0628] Preparation of (3): To a mixture solution of 2 (45.8 g) in THF (300.0 mL) was added mixture of H_2O (100.0 mL) and TFA (100.0 mL) at 0° C. over 30 min. Then the reaction mixture was stirred at 0° C. for 4 h. TLC showed the 2 was consumed completely. The reaction mixture pH was adjusted to 7-8 with $NH_3.H_2O$ (100 mL). Then the mixture was extracted with EA (500.0 mL*2). The combined EA layer was washed with brine and concentrated to give crude which was purified by c.c. (PE:EA=5:1 ~ 1:0) to give compound 3 (21.0 g, 53.2 mmol, 74.7% yield over 2 steps) as a white solid. ESI-LCMS m/z 396.2 $[M+H]^+$.

[0629] Preparation of (4): To a solution of 3 (21.0 g, 53.2 mmol) in ACN (100.0 mL) and water (100.0 mL) were added (diacetoxyiodo)benzene (51.0 g, 159.5 mmol) and TEMPO (2.5 g, 15.9 mmol), The reaction mixture was stirred at 40° C. for 1 h. TLC showed the 3 was consumed completely. The reaction mixture was cooled down to r.t. and filtered, the filtrate was concentrated to give crude which was purified by crystallization (ACN) to give 4 (14.5 g, 35.4 mmol, 66.2% yield). ESI-LCMS m/z 410.1$[M+H]^+$.

[0630] Preparation of (5): To a solution of 4 (14.5 g, 35.4 mmol) in toluene (90.0 mL) and MeOH (60.0 mL) was added trimethylsilyldiazomethane (62.5 mL, 2.0 M, 141.8 mmol) at 0° C., then stirred at r.t. for 2h. TLC showed the 4 was consumed completely. The solvent was removed under reduce pressure, the residue was purified by crystallization (ACN) to give 5 (10.0 g, 23.6 mmol, 66.6% yield). ESI-LCMS m/z 424.2 [M+H]+

[0631] Preparation of (6): To the solution of 5 (10.0 g, 23.6 mmol) in dry THF/MeOD/D_2O=10/2/1 (100.0 mL) was added $NaBD_4$ (2.98 g, 70.9 mmol) three times during an hour at 40° C., the reaction mixture was stirred at r.t. for 2.0 h. The resulting mixture was added CH_3COOD change pH=7.5, after addition of water, the resulting mixture was extracted with EA (50.0 mL*3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated to give a residue which was purified by c.c. (PE/EA=1:1 ~ 1:0). This resulted in to give 6 (6.1 g, 15.4 mmol, 65.3% yield) as a white solid. ESI-LCMS m/z 398.1 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.02 (s, 1H), 7.23 (s, 2H), 5.86 (d, J=6.4 Hz, 1H), 5.26 (s, 1H), 4.42-4.41 (m, 1H), 4.35-4.32 (m, 1H), 3.82 (d, J=2.6 Hz, 1H), 3.14 (s, 3H), 0.78 (s, 9H), 0.00 (d, J=0.9 Hz, 6H).

[0632] Preparation of (7): To a solution of 6 (6.1 g, 15.4 mmol) in pyridine (60.0 mL) was added the benzoyl chloride (6.5 g, 46.2 mmol) drop wise at 5° C. The reaction mixture was stirred at r.t. for 2 h. TLC showed the 6 was consumed completely. The reaction mixture was cooled down to 10° C. and quenched with H_2O (20.0 mL), extracted with EA (200.0 mL*2), combined the EA layer. The organic phase was washed with brine and dried over Na_2SO_4, concentrated to give the crude (12.0 g) which was dissolved in pyridine (60.0 mL), cooled to 0° C., 20.0 mL NaOH (2 M in methanol:H_2O=4:1) was added and stirred for 10 min. The reaction was quenched by saturated solution of ammonium chloride, the aqueous layer was extracted with EA (200.0 mL*2), combined the EA layer, washed with brine and dried over Na_2SO_4, concentrated. The residue was purified by c.c. (PE/EA=10:1 1:1) to give 7 (7.0 g, 13.9 mmol, 90.2% yield). ESI-LCMS m/z 502.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H, exchanged with D_2O) 8.77 (s, 2H), 8.04-8.06 (m, 2H), 7.64-7.66 (m, 2H), 7.54-7.58 (m, 2H), 6.14-6.16 (d, J=5.9 Hz, 1H), 5.20-5.23 (m, 1H), 4.58-4.60 (m, 1H), 4.52-4.55 (m, 1H), 3.99-4.01 (m, 1H), 3.34 (s, 4H), 0.93 (s, 9H), 0.14-0.15 (d, J=1.44 Hz, 6H).

[0633] Preparation of (8): To a stirred solution of 7 (5.5 g, 10.9 mmol) in DMSO (55.0 mL) was added EDCI (6.3 g, 32.9 mmol), pyridine (0.9 g, 10.9 mmol) and TFA (0.6 g, 5.5 mmol), the reaction mixture was stirred at r.t. for 15 h. The reaction was quenched with water and extracted with EA (100.0 mL). The organic phase was washed by brine, dried over Na_2SO_4, The organic phase was evaporated to dryness under reduced pressure to give a residue 8 (4.8 g) which was used directly to next step. ESI-LCMS: m/z 517.1 $[M+H_2O]^+$.

[0634] Preparation of (9b): A solution of 9a (35.0 g, 150.8 mmol) and NaI (90.5 g, 603.4 mmol) in dry ACN (180.0 mL) was added chloromethyl pivalate (113.6 g, 754.3 mmol) at r.t., the reaction was stirred at 80° C. for 4 h. The reaction was cooled to r.t. and quenched by water, then the mixture was extracted with EA (500.0 mL*3), combined the organic layer was washed with saturated solution of ammonium chloride, followed by with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by c.c., this resulted in to give 9b (38.0 g, 60.1 mmol, 39.8% yield) as a white solid. ESI-LCMS m/z 655.2 $[M+Na]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.74-5.67 (m, 8H), 2.67 (t, J=21.6 Hz, 2H), 1.23 (s, 36H).

[0635] Preparation of (9): 3.8 g 10% Pd/C was washed with dry THE (30.0 mL) three times. Then transferred into a round-bottom flask charged with 9b (38.0 g, 60.1 mmol) and solvent (dry THF:D_2O=5:1, 400.0 mL), the mixture was

stirred at 80° C. under 1 L H_2 balloon for 15 h. The reaction was cooled to r.t. and extracted with EA (500.0 mL*3), combined the organic layer was washed with brine and dried over Na_2SO_4. The residue 9 (3.0 g, 3.7 mmol, 38.8% yield) as a white solid was used directly to next step without further purification. ESI-LCMS m/z 657.2 $[M+Na]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.74-5.67 (m, 8H), 1.23 (s, 36H).

[0636] Preparation of (10): A solution of 8 (4.8 g, 9.6 mmol), 9 (7.3 g, 11.5 mmol) and K_2CO_3 (4.0 g, 38.8 mmol) in dry THE (60.0 mL) and D20 (20.0 mL) was stirred at r.t. 18h. LC-MS showed 8 was consumed completely. The product was extracted with EA (300.0 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by c.c. (PE/EA=5:1 ~ 1:1) and MPLC. This resulted in to give 10 (3.0 g, 3.7 mmol, 38.8% yield) as a white solid. ESI-LCMS m/z 806.4$[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.25 (s, 1H, exchanged with D_2O) 8.75 (s, 2H), 8.07-8.05 (d, J=8.0 Hz, 2H), 7.67-7.54 (m, 3H), 6.05 (d, J=5.1 Hz, 1H), 5.65-5.58 (m, 4H), 4.80-4.70 (m, 2H), 4.59-4.57 (m, 1H), 3.36 (s, 3H), 1.11 (s, 9H), 1.10 (s, 9H), 0.94 (s, 9H), 0.17-0.16 (m, 6H); ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.02.

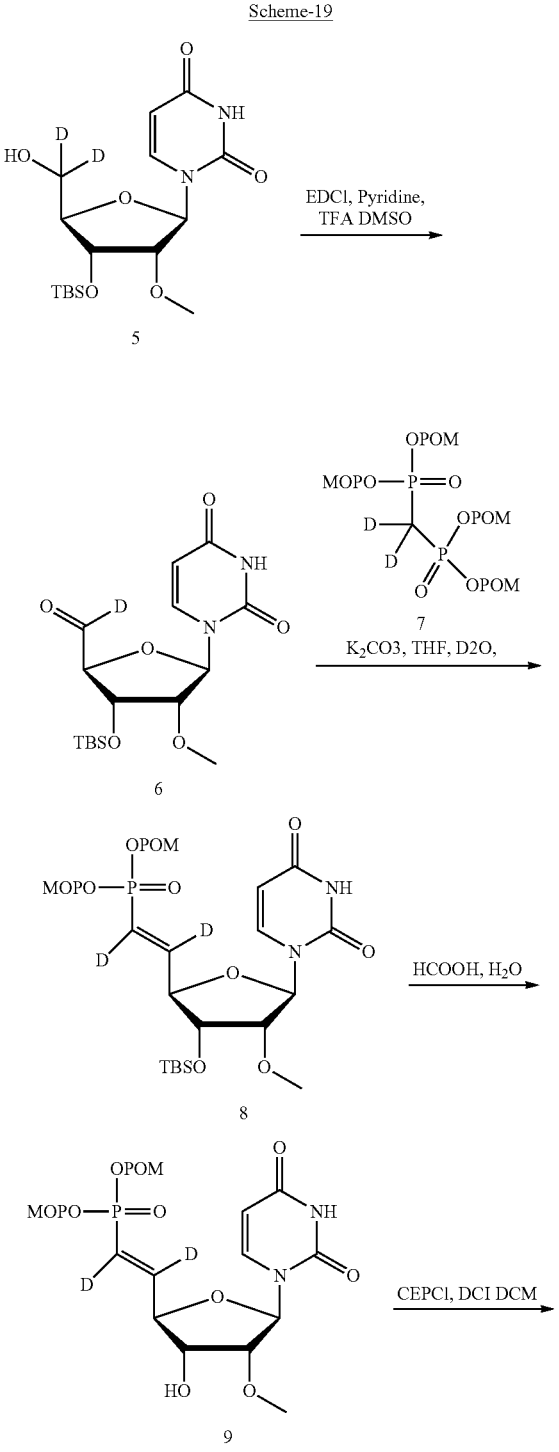
[0637] Preparation of (11): To a round-bottom flask was added 10 (3.0 g, 3.7 mmol) in a mixture of H_2O (30.0 mL), HCOOH (30.0 mL). The reaction mixture was stirred at 40° C. for 15 hrs. LC-MS showed the 10 was consumed completely. The reaction mixture was adjusted the pH=6-7 with con. $NH_3.H_2O$ (100.0 mL). Then the mixture was extracted with DCM (100.0 mL*3). The combined DCM layer was dried over Na_2SO_4. Filtered and filtrate was concentrated to give crude which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/2 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2; Detector, UV 254 nm. To give product 11 (1.8 g, 2.6 mmol, 70.3% yield). ESI-LCMS m/z=692.2$[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 1H, exchanged with D_2O) 8.71-8.75 (d, J=14.4, 2H), 8.04-8.06 (m, 2H), 7.64-7.65 (m, 1H), 7.54-7.58 (m, 2H), 6.20-6.22 (d, J=5.4, 2H), 5.74-5.75 (d, J=5.72, 2H), 5.56-5.64 (m, 4H), 4.64-4.67 (m, 1H), 4.58-4.59 (m, 1H), 4.49-4.52 (m, 1H), 3.37 (s, 3H), 1.09-1.10 (d, J=1.96, 18H); ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.46.

[0638] Preparation of Example 38 monomer: To a solution of 11 (1.8 g, 2.6 mmol) in DCM (18.0 mL) was added the DCI (276.0 mg, 2.3 mmol), then $CEP[N(ipr)_2]_2$ (939.5 mg, 3.1 mmol) was added. The mixture was stirred at r.t. for 1h. TLC showed 11 consumed completely. The reaction mixture was washed with H_2O (50.0 mL*2) and brine (50.0 mL*2), dried over Na_2SO_4 and concentrated to give crude which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=9/1; Detector, UV 254 nm. The product was concentrated to give Example 38 monomer (2.0 g, 2.2 mmol, 86.2% yield) as a white solid. ESI-LCMS m/z 892.3$[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H, exchanged with D_2O) 8.72-8.75 (m, 2H), 8.04-8.06 (m, 2H), 7.54-7.68 (m, 3H), 6.20-6.26 (m, 1H), 5.57-5.64 (m, 4H), 4.70-4.87 (m, 3H), 3.66-3.88 (m, 4H), 3.37-3.41 (m, 3H), 2.82-2.86 (m, 2H), 1.20-1.21 (m, 12H), 1.08-1.09 (m, 18H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 150.03, 149.19, 17.05, 16.81.

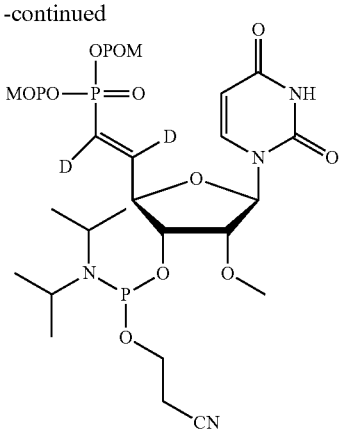
Example 39. Synthesis of 5' End Cap Monomer

[0639]

Scheme-19



-continued



Example 39 monomer

[0640] Preparation of (6): To a stirred solution of 5 (8.0 g, 21.3 mmol, Scheme 3) in DMSO (80.0 mL) were added EDCI (12.2 g, 63.9 mmol), pyridine (1.7 g, 21.3 mmol), TFA (1.2 g, 10.6 mmol) at r.t. And the reaction mixture was stirred at r.t. for 1.5 h. The reaction was quenched with water and extracted with EA (200.0 mL). The organic phase was washed by brine, dried over Na_2SO_4, The organic phase was evaporated to dryness under reduced pressure to give a residue 6 which was used directly to next step. ESI-LCMS: m/z 372.3 $[M+H]^+$.

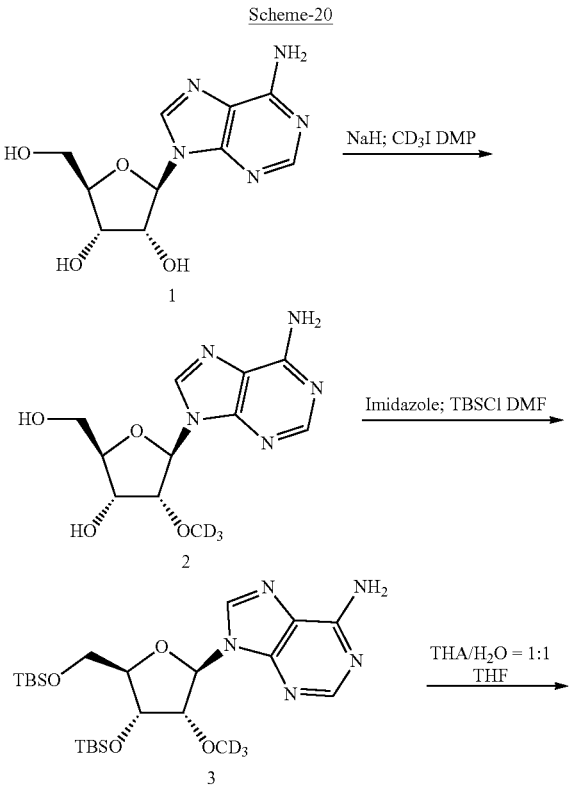
[0641] Preparation of (8): To a solution of K_2CO_3 (5.5 g, 8.3 mmol) in dry THF (60.0 mL) and D20 (20.0 mL) was added a solution of 6 (8.0 g, 21.5 mmol) in dry THF (10.0 mL). The reaction mixture was stirred at r.t. overnight. LC-MS showed 6 was consumed completely. The product was extracted with EA (300.0 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (Intel-Flash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 8 (5.0 g, 7.3 mmol, 40.0%) as a white solid. ESI-LCMS: m/z 679.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, Chloroform-d): δ 9.91 (s, 1H), 7.29 (d, J=8.1 Hz, 1H), 5.82 (d, J=2.7 Hz, 1H), 5.72 (d, J=8.1 Hz, 1H), 5.65-5.54 (m, 4H), 4.43 (dd, J=7.2, 3.2 Hz, 1H), 3.92 (dd, J=7.2, 5.0 Hz, 1H), 3.65 (dd, J=5.1, 2.7 Hz, 1H), 3.44 (s, 3H), 1.13 (s, 18H), 0.82 (s, 9H), 0.01 (d, J=4.8 Hz, 6H); ^{31}P NMR (162 MHz, Chloroform-d): δ 16.40.

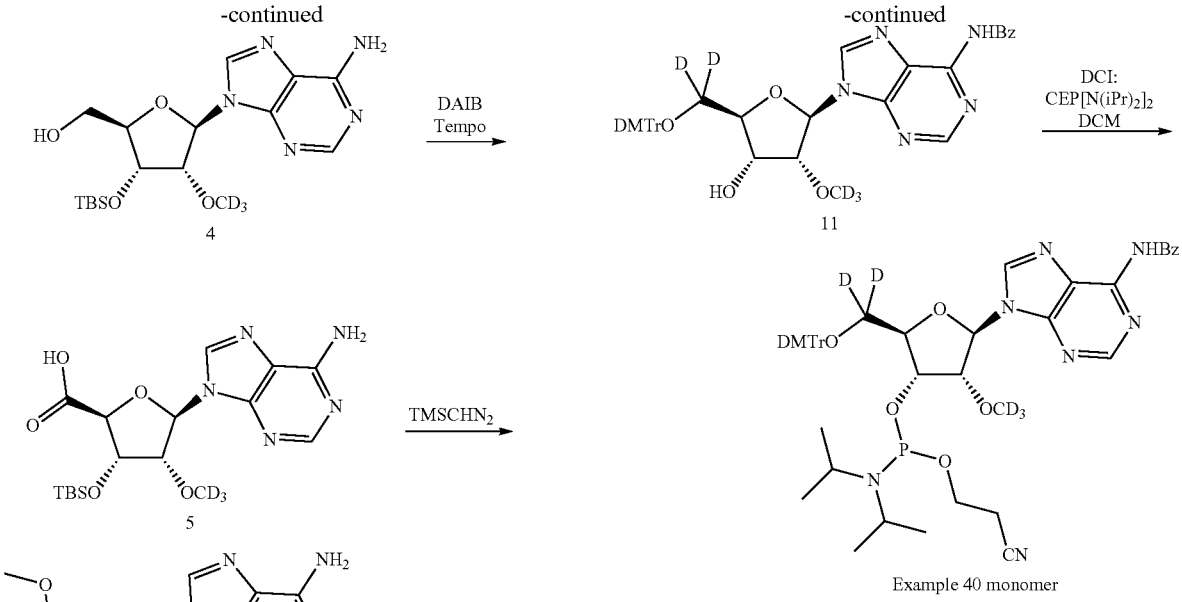
[0642] Preparation of (9): To a solution of HCOOH (50.0 mL) and H_2O (50.0 mL) was added 8 (5.0 g, 7.3 mmol). The reaction mixture was stirred at 40° C. overnight. LC-MS showed 8 was consumed completely. A solution of $NaHCO_3$ (500.0 mL) was added. The product was extracted with EA (300.0 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C_{18} silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3) =2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 9 (3.0 g, 5.4 mmol, 73.2%) as a white solid. ESI-LCMS: m/z 565.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 7.64 (d, J=8.1 Hz, 1H), 5.83 (d, J=4.3 Hz, 1H), 5.69-5.56 (m, 5H), 5.54 (d, J=6.7 Hz, 1H), 4.37 (dd, J=6.1, 2.9 Hz, 1H), 4.12 (q, J=6.1 Hz, 1H), 3.96 (dd, J=5.4, 4.3 Hz, 1H), 3.39 (s, 3H), 1.16 (s, 18H); ^{31}P NMR (162 MHz, DMSO-d_6): δ 17.16.

[0643] Preparation of Example 39 monomer: To a suspension of 9 (2.6 g, 4.6 mmol) in DCM (40.0 mL) was added DCI (0.5 g, 5.6 mmol) and $CEP[N(iPr)_2]_2$ (1.7 g, 5.6 mmol). The mixture was stirred at r.t. for 1.0 h. LC-MS showed 9 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 39 monomer (3.0 g, 3.9 mmol, 85.2%) as a white solid. ESI-LCMS: m/z 765.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.44 (s, 1H), 7.71 (dd, J=8.1, 3.8 Hz, 1H), 5.81 (dd, J=4.4, 2.5 Hz, 1H), 5.74-5.53 (m, 5H), 4.59-4.33 (m, 2H), 4.20-4.14 (m, 1H), 3.88-3.53 (m, 4H), 3.39 (d, J=16.2 Hz, 3H), 2.80 (td, J=5.9, 2.9 Hz, 2H), 1.16 (d, J=1.9 Hz, 30H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 147.68, 149.16, 16.84, 16.55.

Example 40. Synthesis of Monomer

[0644]





[0645] Preparation of (2): To a solution of 1 (26.7 g*2, 0.1 mol) in DMF (400 mL) was added sodium hydride (4.8 g, 0.1 mol) for 30 min, then was added CD_3I (16 g, 0.1 mol) at 0° C. for 2.5 hr (ref. for selective 2'-O-alkylation reaction conditions, *J. Org. Chem.* 1991, 56, 5846-5859). The mixture was stirring at r.t. for another 1h. LCMS showed the reaction was consumed. The mixture was filtered and the clear solution was evaporated to dryness and was evaporated with CH_3OH. The crude was purified by slice gel column (SiO_2, DCM/MeOH=50:1~15:1). This resulted in to give the product 2 (35.5 g, 124.6 mmol, 62% yield) as a solid. ESI-LCMS: m/z 285 $[M+H]^+$.

[0646] Preparation of (3): To a solution of 2 (35.5 g, 124.6 mmol) in pyridine (360 mL) was added imidazole (29.7 g, 436.1 mmol) and TBSCl (46.9 g, 311.5 mmol). The mixture was stirred at r.t. over night. LCMS showed 2 was consumed completely. The reaction was quenched with water (500 mL). The product was extracted into ethyl acetate (1 L). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude was purified by slice gel column (SiO_2, PE/EA=4:1-1:1). This resulted in to give the product 3 (20.3 g, 39.6 mmol, 31.8% yield) as a solid. ESI-LCMS: m/z 513 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.32 (m, 1H), 8.13 (m, 1H), 7.31 (m, 2H), 6.02-6.01 (d, J=4.0 Hz, 1H), 4.60-4.58 (m, 1H), 4.49-4.47 (m, 1H), 3.96-3.86 (m, 2H), 3.72-3.68 (m, 1H), 0.91-0.85 (m, 18H), 0.13-0.01 (m, 12H).

[0647] Preparation of (4): To a solution of 3 (20.3 g, 39.6 mmol) in THE (80 mL) was added TFA (20 mL) and water (20 mL) at 0° C. The reaction mixture was stirred at 0° C. for 5 h. LC-MS showed 3 was consumed completely. Con. NH_4OH was added to the mixture at 0° C. to quench the reaction until the pH=7.5. The product was extracted into ethyl acetate (200 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was then concentrated under reduced pressure and the residue was washed by PE/EA=5:1. This resulted in to give 4 (10.5 g, 26.4 mmol, 66.6% yield) as a white solid. ESI-LCMS: m/z 399 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.41 (m, 1H), 8.14 (m, 1H), 7.37 (m, 2H), 5.99-5.97 (d, J=8.0 Hz,

1H), 5.43 (m, 1H), 4.54-4.44 (m, 2H), 3.97-3.94 (m, 1H), 3.70-3.53 (m, 2H), 0.91 (m, 9H), 0.13-0.12 (m, 6H).

[0648] Preparation of (5): To a solution of 4 (10.5 g, 26.4 mmol) in ACN/H_2O=1:1 (100 mL) was added DAIB (25.4 g, 79.2 mmol) and TEMPO (1.7 g, 7.9 mmol). The reaction mixture was stirred at 40° C. for 2 h. LCMS showed 4 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was then concentrated under reduced pressure and the residue was washed by ACN. This resulted in to give 5 (6.3 g, 15.3 mmol, 57.9% yield) as a white solid. ESI-LCMS: m/z 413 [M+H]-; ^{1}H-NMR (400 MHz, DMSO-d_6): δ=8.48 (m, 1H), 8.16 (m, 1H), 7.41 (m, 2H), 6.12-6.10 (d, J=8.0 Hz, 1H), 4.75-4.73 (m, 1H), 4.42-4.36 (m, 2H), 3.17 (m, 6H), 2.07 (m, 2H), 0.93 (m, 9H), 0.17-0.15 (m, 6H).

[0649] Preparation of (6): To a solution of 5 (6.3 g, 15.3 mmol) in toluene (36 mL) and methanol (24 mL) was added (trimethylsilyl)diazomethane (7.0 g, 61.2 mmol) till the yellow color not disappear at r.t. for 2 min. LCMS showed the reaction was consumed. The solvent was removed to give the cured 6 (6.0 g) as a solid witch used for the next step. ESI-LCMS: m/z 427 [M+H]$^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.45 (m, 1H), 8.15 (m, 1H), 7.35 (m, 2H), 6.12-6.10 (d, J=8.0 Hz, 1H), 4.83-4.81 (m, 1H), 4.50-4.46 (m, 1H), 3.73 (m, 3H), 3.31 (m, 1H), 0.93 (m, 9H), 0.15-0.14 (m, 6H).

[0650] Preparation of (7): To the solution of 6 (6 g) in dry THF/MeOD/D_2O=10/2/1 (78 mL) was added $NaBD_4$ (2.3 g, 54.8 mmol) at r.t. And the reaction mixture was stirred at r.t for 2.5 hr. After completion of reaction, adjusted pH value to 7 with CH_3COOD, after addition of water, the resulting mixture was extracted with EA (100 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give 7 (5.7 g) which was used for the next step. ESI-LCMS: m/z 401 [M+H]$^+$.

[0651] Preparation of (8): To a solution of 7 (5.7 g) in pyridine (60 mL) was added BzCl (10.0 g, 71.3 mmol) under ice bath. The reaction mixture was stirred at r.t. for 2.5 hrs. LCMS showed 7 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=7/3; Detector, UV 254 nm. This resulted in to give the crude 8 (6.2 g, 8.7 mmol, 57% yield, over two steps) as a white solid. ESI-LCMS: m/z 713 [M+H]$^+$.

[0652] Preparation of (9): To a solution of 8 (6.2 g, 8.7 mmol) in pyridine (70 mL) and was added 1M NaOH (MeOH/H_2O=4/1) (24 mL). LCMS showed 8 was consumed. The mixture was added saturated NH_4Cl till pH=7.5. The mixture was diluted with water and EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=67/33 Detector, UV 254 nm. This resulted in to give the product 10 (4.3 g, 8.5 mmol, 98% yield) as a white solid. ESI-LCMS: m/z 505 [M+H]$^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.23 (m, 1H), 8.77 (m, 2H), 8.06-8.04 (m, 2H), 7.66-7.63 (m, 2H), 7.57-7.53 (m, 3H), 6.16-6.14 (d, J=8.0 Hz, 1H), 5.17 (m, 1H), 4.60-4.52 (m, 2H), 3.34 (m, 1H), 0.93 (m, 9H), 0.14 (m, 6H).

[0653] Preparation of (10): To a stirred solution of 9 (4.3 g, 8.5 mmol) in pyridine (45 mL) were added DMTrCl (3.3 g, 9.8 mmol) at r.t. And the reaction mixture was stirred at r.t for 2.5 hr. With ice-bath cooling, the reaction was quenched with water and the product was extracted into EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=97/3 Detector, UV 254 nm. This resulted in to give the product 10 (6.5 g, 8.1 mmol, 95% yield) as a white solid. ESI-LCMS: m/z 807 [M+H]-; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.23 (m, 1H), 8.70-8.68 (m, 2H), 8.04-8.02 (m, 2H), 7.66-7.62 (m, 1H), 7.56-7.52 (m, 2H), 7.35-7.26 (m, 2H), 7.25-7.17 (m, 7H), 6.85-6.82 (m, 4H), 6.18-6.16 (d, J=8.0 Hz, 1H), 4.73-4.70 (m, 1H), 4.61-4.58 (m, 1H), 3.71 (m, 6H), 3.32 (m, 1H), 0.83 (m, 9H), 0.09-0.03 (m, 6H).

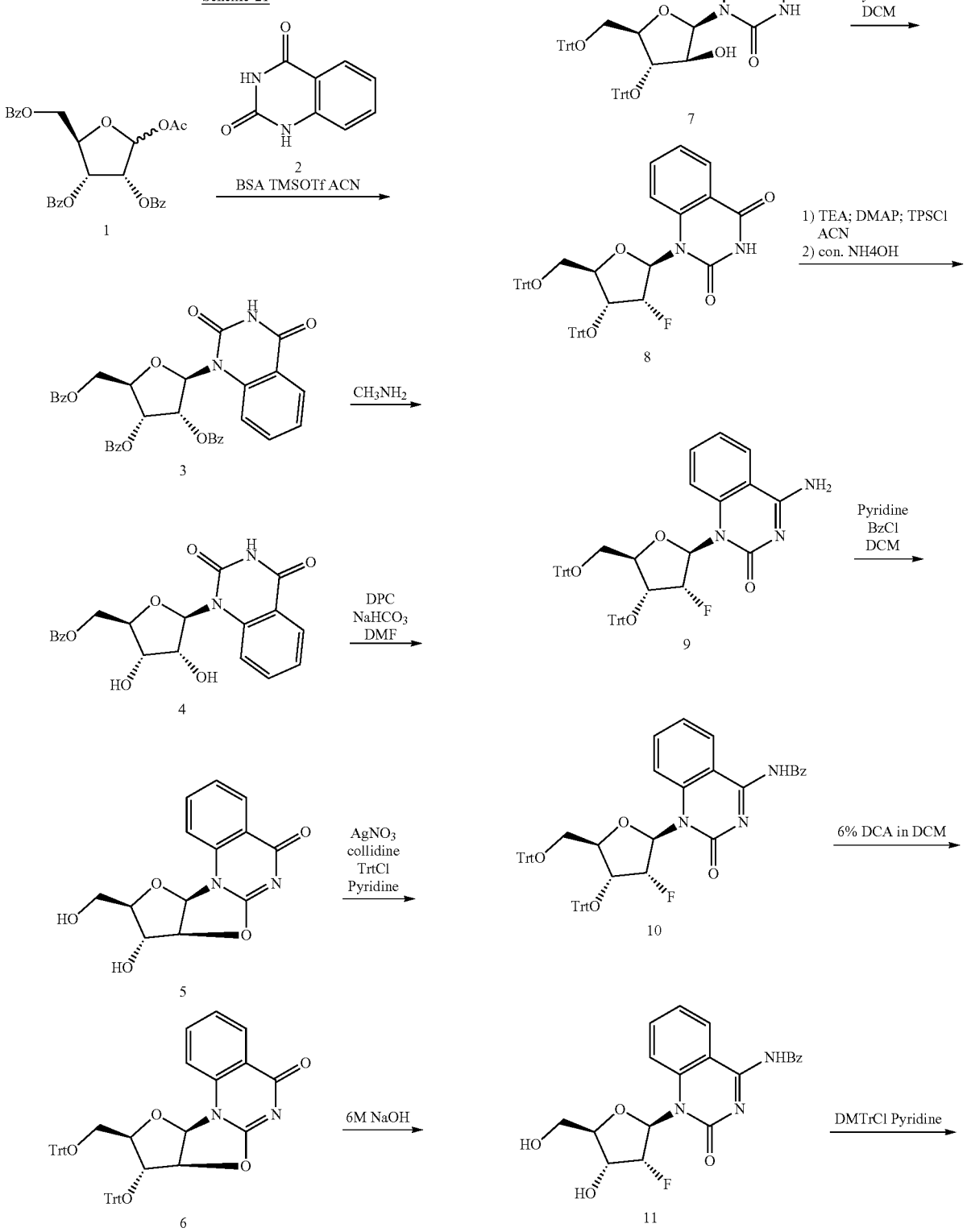
[0654] Preparation of (11): To a solution of 10 (3.5 g, 4.3 mmol) in THE (35 mL) was added 1 M TBAF solution (5 mL). The reaction mixture was stirred at r.t. for 1.5 h. LCMS showed 10 was consumed completely. Water (100 mL) was added. The product was extracted with EA (100 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=62/38; Detector, UV 254 nm. This resulted in to give 11 (2.7 g, 3.9 mmol, 90.7%) as a white solid. ESI-LCMS: m/z 693 [M+H]$^+$.

[0655] Preparation of Example 40 monomer: To a suspension of 11 (2.7 g, 3.9 mmol) in DCM (30 mL) was added DCI (0.39 g, 3.3 mmol) and $CEP[N(iPr)_2]_2$ (1.4 g, 4.7 mmol). The mixture was stirred at r.t. for 2 h. LC-MS showed 11 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=73/27; Detector, UV 254 nm. This resulted in to give Example 40 monomer (3.3 g, 3.7 mmol, 94.9%) as a white solid. ESI-LCMS: m/z 893 [M+H]$^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ=11.24 (m, 1H), 8.66-8.64 (m, 2H), 8.06-8.03 (m, 2H), 7.65-7.53 (m, 3H), 7.42-7.38 (m, 2H), 7.37-7.34 (m, 2H), 7.25-7.19 (m, 7H), 6.86-6.80 (m, 4H), 6.20-6.19 (d, J=4.0 Hz, 1H), 4.78 (m, 2H), 4.22-4.21 (m, 1H), 3.92-3.83 (m, 1H), 3.72 (m, 6H), 3.62-3.57 (m, 3H), 2.81-2.78 (m, 1H), 2.64-2.61 (m, 1H), 1.17-1.04 (m, 12H); ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.51, 149.30.

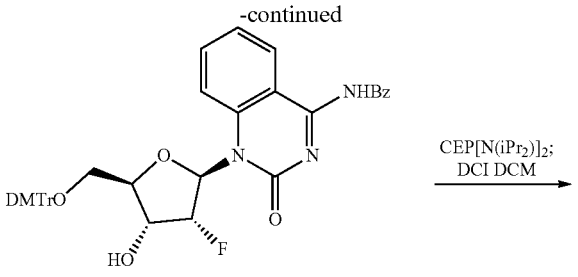
Example 41. Synthesis of Monomer

[0656]

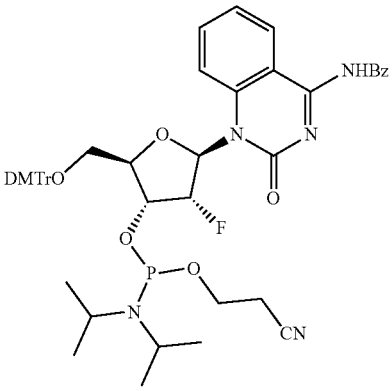
Scheme-21



-continued



11



Example 41 monomer

[0657] Preparation of (3): To the solution of 1 (70 g, 138.9 mmol) in dry acetonitrile (700 mL) was added 2 (27.0 g, 166.7 mmol), BSA (112.8 g, 555.5 mmol). The mixture was stirred at 50° C. for 1 h. Then the mixture was cooled to −5° C. and TMSOTf (46.2 g, 208.3 mmol) slowly added to the mixture. Then the reaction mixture was stirred at r.t for 48 h. Then the solution was cooled to 0° C. and saturated aq. $NaHCO_3$ was added and the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography (eluent, PE:EA=3:1-1:1) to give 3 (70 g, 115.3 mmol, 81.6%) as a white solid. ESI-LCMS: m/z 605 $[M-H]^+$.

[0658] Preparation of (4): To the solution of 3 (70.0 g, 115.3 mmol) in methylammonium solution (1 M, 700 mL), and the reaction mixture was stirred at 40° C. for 15 h. After completion of reaction, the resulting mixture was concentrated. The residue was crystallized from EA. Solid was isolated by filtration, washed with PE and dried overnight at 45° C. in vacuum to give 4 (31.0 g, 105.4 mmol, 91.1%) as a white solid. ESI-LCMS: m/z 295 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO): δ 11.63 (s, 1H), 8.07-7.99 (m, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.72-7.63 (m, 1H), 7.34-7.26 (m, 1H), 6.18 (d, J=6.4 Hz, 1H), 5.24 (s, 1H), 5.00 (s, 2H), 4.58-4.47 (m, 1H), 4.19-4.10 (m, 1H), 3.85-3.77 (m, 1H), 3.75-3.66 (m, 1H), 3.66-3.57 (m, 1H).

[0659] Preparation of (5): To the solution of 4 (20.0 g, 68.0 mmol) in dry DMF (200 mL) was added DPC (18.9 g, 88.0 mmol) and $NaHCO_3$(343 mg, 4 mmol) at r.t, and the reaction mixture was stirred at 150° C. for 35 min. After completion of reaction, the resulting mixture was poured into tert-Butyl methyl ether (4 L). Solid was isolated by filtration, washed with PE and dried in vacuum to give crude 5 (21.0 g) as a brown solid which was used directly for next step (ref for 5, *Journal of Organic Chemistry,* 1989, vol. 33, p. 1219-1225). ESI-LCMS: m/z 275 $[M-H]^-$.

[0660] Preparation of (6): To the solution of 5 (crude, 21.0 g) in Pyridine (200 mL) was added $AgNO_3$ (31.0 g, 180.0 mmol) and collidine (88.0 g, 720 mmol) and TrtCl (41.5 g, 181 mmol) at r.t, and the reaction mixture was stirred at r.t for 15 h. After addition of water, the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give the crude. The crude was by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 6 (10.0 g, 13.1 mmol, 20% yield over 3 steps) as a white solid. ESI-LCMS: m/z 761 $[M+H]^+$.

[0661] Preparation of (7): To the solution of 6 (10.0 g, 13.1 mmol) in THE (100 mL) was added 6 N NaOH (30 mL) at r.t, and the reaction mixture was stirred at r.t for 1 hr. After addition of NH_4Cl, the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3) =1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=9/1; Detector, UV 254 nm. This resulted in to give 7 (9.3 g, 11.9 mmol, 90%) as a white solid. ESI-LCMS: m/z 777 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.57 (s, 1H), 8.02 (d, J=8.7 Hz, 1H), 7.88-7.81 (m, 1H), 7.39-7.18 (m, 30H), 7.09-6.99 (m, 30H), 6.92-6.84 (m, 30H), 6.44 (d, J=4.0 Hz, 1H), 4.87 (d, J=4.0 Hz, 1H), 4.37-4.29 (m, 1H), 4.00-3.96 (m, 1H), 3.76-3.70 (m, 1H), 3.22-3.13 (m, 1H), 3.13-3.04 (m, 1H).

[0662] Preparation of (8): To the solution of 7 (8.3 g, 10.7 mmol) in dry DCM (80 mL) was added Pyridine (5.0 g, 64.2 mmol) and DAST (6.9 g, 42.8 mmol) at 0° C., and the reaction mixture was stirred at r.t for 15 hr. After addition of NH_4Cl, the resulting mixture was extracted with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 8 (6.8 g, 8.7 mmol, 81.2%) as a white solid. ESI-LCMS: m/z 779 $[M-H]^+$; ^{19}F-NMR (376 MHz, DMSO-d_6): δ−183.05.

[0663] Preparation of (9): To the solution of 8 (5.8 g, 7.5 mmol) in dry ACN (60 mL) was added TEA (1.5 g, 15.1 mmol), DMAP (1.84 g, 15.1 mmol) and TPSCl (4.1 g, 13.6 mmol) at r.t, and the reaction mixture was stirred at room temperature for 3 h under N_2 atmosphere. After completion of reaction, the mixture was added $NH_3.H_2O$ (12 mL). After addition of water, the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)

=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 9 (5.5 g, 7 mmol, 90.2%) as a white solid. ESI-LCMS: m/z 780 $[M+H]^+$.

[0664] Preparation of (10): To a solution of 9 (5.5 g, 7 mmol) in DCM (50 mL) with an inert atmosphere of nitrogen was added pyridine (5.6 g, 70.0 mmol) and BzCl (1.2 g, 8.5 mmol) in order at 0° C. The reaction solution was stirred for 30 minutes at room temperature. The solution was diluted with DCM (100 mL) and the combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography (eluent, PE:EA=5:1-2:1) to give 10 (5.4 g, 6.1 mmol, 90.6%) as a white solid. ESI-LCMS: m/z 884 $[M+H]^+$; ^{19}F-NMR (376 MHz, DMSO-d_6): δ−183.64.

[0665] Preparation of (11): To the solution of 10 (5.4 g, 6.1 mmol) in the solution of DCA (6%) in DCM (60 mL) was added TES (15 mL) at r.t, and the reaction mixture was stirred at room temperature for 5-10 min. After completion of reaction, the resulting mixture was added $NaHCO_3$, the resulting mixture was extracted with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure and the residue was crystallized from EA. Solid was isolated by filtration, washed with PE and dried overnight at 450 in vacuum to give 11 (2.0 g, 5.0 mmol, 83.2%) as a white solid. ESI-LCMS: m/z 400 $[M+H]^+$.

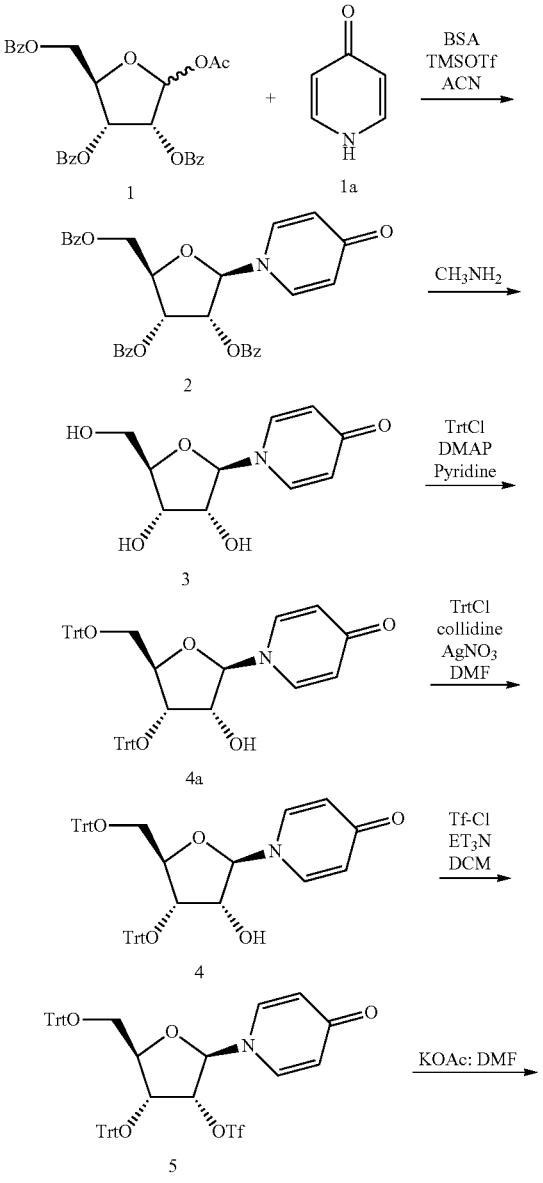
[0666] Preparation of (12): To a solution of 11 (2.0 g, 5.0 mmol) in dry Pyridine (20 mL) was added DMTrCl (2.0 g, 6.0 mmol). The reaction mixture was stirred at r.t. for 2.5 h. LCMS showed 11 was consumed and water (200 mL) was added. The product was extracted with EA (200 mL) and the organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by c.c. (PE:EA=4:1-1:1) to give crude 12. The crude was further purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give 12 (2.1 g, 3 mmol, 60%) as a white solid. ESI-LCMS: m/z 702 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.63 (s, 1H), 8.54 (d, J=7.8 Hz, 1H), 8.25 (d, J=7.2 Hz, 2H), 7.82 (d, J=3.6 Hz, 2H), 7.67-7.58 (m, 1H), 7.57-7.49 (m, 2H), 7.49-7.39 (m, 1H), 7.39-7.31 (m, 2H), 7.27-7.09 (m, 7H), 6.82-6.69 (m, 4H), 6.23 (d, J=26.1 Hz, 1H), 5.59-5.49 (m, 1H), 4.83-4.61 (m, 1H), 4.15-4.01 (m, 1H), 3.74-3.59 (m, 6H), 3.33-3.28 (m, 1H), 3.16-3.05 (m, 1H). ^{19}F-NMR (376 MHz, DMSO-d_6): δ−191.66.

[0667] Preparation of Example 41 monomer: To a suspension of 12 (2.1 g, 3.0 mmol) in DCM (20 mL) was added DCI (310 mg, 2.6 mmol) and $CEP[N(iPr)_2]_2$ (1.1 g, 3.7 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 12 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give the crude. The crude was by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 41 monomer (2.1 g, 2.3 mmol, 80.0%) as a white solid. ESI-LCMS: m/z 902 $[M+H]^+$; iH-NMR (400 MHz, DMSO-d_6): δ 12.64 (s, 1H), 8.54 (d, J=7.6 Hz, 1H), 8.24 (d, J=7.7 Hz, 2H), 7.93-7.88 (m, 2H), 7.67-7.58 (m, 1H), 7.56-7.42 (m, 3H), 7.41-7.29 (m, 2H), 7.27-7.08 (m, 7H), 6.82-6.64 (m, 4H), 6.37-6.18 (m, 1H), 6.03-5.72 (m, 1H), 5.26-4.83 (m, 1H), 4.28-4.12 (m, 1H), 3.88-3.72 (m, 1H), 3.71-3.37 (m, 9H), 3.15-3.00 (m, 1H), 2.83-2.75 (m, 1H), 2.66-2.57 (m, 1H), 1.21-0.88 (m, 12H). ^{19}F-NMR (376 MHz, DMSO-d_6): δ−189.71. ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.48, 149.50, 148.95, 148.88.

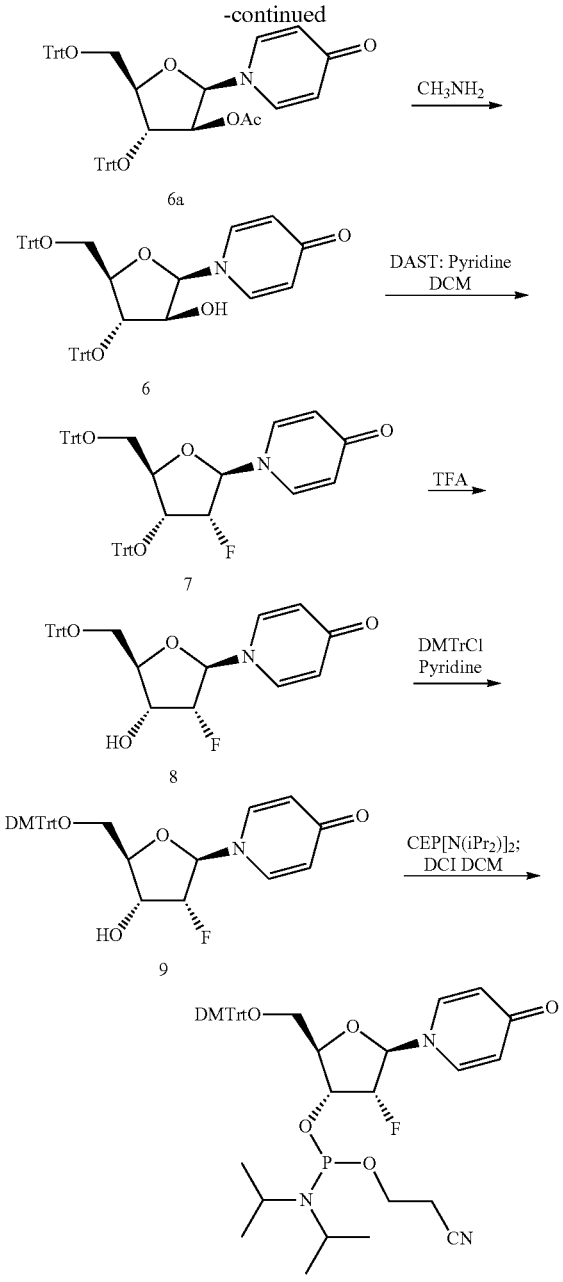
Example 42. Synthesis of Monomer

[0668]

Scheme-22



-continued



Example 42 monomer

[0669] Preparation of (2): To a solution of 1 (40.0 g, 79.3 mmol), la (7.6 g, 80.1 mmol) in ACN (100 mL). Then added BSA (35.2 g, 174.4 mmol) under N_2 atmosphere. The mixture was stirred at 50° C. for 1 h until the solution was clear. Then cool down to 0° C. and dropped TMSOTf (18.5 g, 83.2 mmol).The mixture was stirred at 75° C. for 1 h, TLC showed 1 was consumed completely. Then the solution was diluted with EA, washed with H_2O twice. The solvent was concentrated under reduced pressure and the residue was used for next step. ESI-LCMS: m/z 540 $[M+H]^+$.

[0670] Preparation of (3): To a solution of 2 (37.1 g, 68.7 mmol) in 30% CH_2NH_2/MeOH solution (200 mL). The mixture was stirred at 25° C. for 2 h. TLC showed 2 was consumed completely. The solvent was concentrated under reduced pressure and the residue was washed with EA twice to give 3 (12.5 g, 55.2 mmol) (ref for intermediate 3 *Bioorganic & Medicinal Chemistry Letters,* 1996, Vol. 6, No. 4, pp. 373-378) which was used directly for the next step. ESI-LCMS: m/z 228 $[M+H]^+$.

[0671] Preparation of (4): To a solution of 3 (12.5 g, 55.2 mmol) in pyridine (125 mL) and added DMAP (1.3 g, 11.0 mmol), TrtCl (30.7 g, 110.5 mmol). The mixture was stirred at r.t. for 24 h. TLC showed 3 was consumed completely. H_2O was added to the mixture. Then filtered and the solution diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. The solvent was concentrated under reduced pressure and then added ACN, filtered to give 4a (17.0 g, 35.4 mmol, 64% yield) as a white solid.

[0672] To a solution of 4a (17.0 g, 35.4 mmol) in DMF (200 mL), collidine (5.2 g, 43.5 mmol), TrCl (13.1 g, 47.1 mmol) were added after 2h and then again after 3h TrCl (13.1 g, 47.1 mmol), $AgNO_3$ (8.0 g, 47.1 mmol). The mixture was stirred at 25° C. for 24 h. TLC showed 4a was consumed completely. Then filtered and the solution diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. The solvent was concentrated under reduced pressure and then added ACN, filtered to get 4 (14.2 g, 19.5 mmol, 54% yield) as a white solid. ESI-LCMS: m/z 712 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.83 (d, J=8 Hz, 2H), 7.42-7.20 (m, 30H), 6.18 (d, J=7 Hz, 1H), 6.09 (d, J=8 Hz, 2H), 5.60 (d, J=7 Hz, 1H), 4.22 (m, 1H), 3.90 (d, J=5 Hz, 1H), 2.85 (d, J=10 Hz, 1H), 2.76 (s, 1H), 2.55-2.50 (dd, 1H).

[0673] Preparation of (5): To a solution of 4 (14.2 g, 19.9 mmol) in DCM (150 mL), DMAP (2.4 g, 19.9 mmol), TEA (4.0 g, 39.9 mmol, 5.6 mL) were added. Then cool down to 0° C., TfCl (6.7 g, 39.9 mmol) dissolved in DCM (150 mL) were dropped. The mixture was stirred at 25° C. for 1 h. TLC showed 4 was consumed completely. Then filtered and the solution diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. The solvent was concentrated under reduced pressure to get 5 (16.8 g, 19.9 mmol) as a brown solid. ESI-LCMS: m/z 844 $[M+H]^+$.

[0674] Preparation of (6): To a solution of 5 (16.8 g, 19.9 mmol) in DMF (200 mL), KOAc (9.7 g, 99.6 mmol) were added, The mixture was stirred at 25° C. for 14 h and 50° C. for 3 h, TLC showed 5 was consumed completely. Then filtered and the solution diluted with EA. The organic layer was washed with H_2O and brine. The solvent was concentrated under reduced pressure to get 6a (15.0 g, 18.9 mmol, 90% yield) as a brown solid. To a solution of 6a (15.0 g, 19.9 mmol) in 30% CH_3NH_2/MeOH solution (100 mL) were added. The mixture was stirred at 25° C. for 2 h, TLC showed 6a was consumed completely. Then the solvent was concentrated under reduced pressure and the residue was purified by cc (0-5% MeOH in DCM) to give 6 (11.6 g, 16.3 mmol, 82% yield) as a yellow solid. ESI-LCMS: m/z 712 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.59 (d, J=8 Hz, 2H), 7.37-7.22 (m, 30H), 6.01 (d, J=8 Hz, 2H), 5.84 (d, J=3 Hz, 1H), 5.42 (d, J=4 Hz, 1H), 3.78-3.70 (m, 3H), 3.10 (t, J=9 Hz, 1H), 2.53 (d, J=4 Hz, 6H), 1.77 (s, 6H).

[0675] Preparation of (7): To a solution of 6 (11.6 g, 16.32 mmol) in DCM (200 mL), DAST (7.9 g, 48.9 mmol) were added at 0° C., The mixture was stirred at 25° C. for 16 h, TLC showed 6 was consumed completely. Then the solution was diluted with EA, washed with $NaHCO_3$ twice, The solvent was concentrated under reduced pressure the residue purified by Flash-Prep-HPLC with the following conditions

(IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1; Detector, UV 254 nm. This resulted in to give 7 (11.6 g, 13.8 mmol, 84% yield) as a white solid. ESI-LCMS: m/z 714 $[M+H]^-$.

[0676] Preparation of (8): To a solution of 7 (11.6 g, 16.2 mmol) in DCM (100 mL) was added TFA (10 mL). The mixture was stirred at 20° C. for 1 h. TLC showed 7 was consumed completely. Then the solution was concentrated under reduced pressure the residue was purified by silica gel column (0~20% MeOH in DCM) and Flash-Prep-HPLC with the following conditions(IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3) =0/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=0/1; Detector, UV 254 nm. This resulted in to give 9 (1.7 g, 7.2 mmol, 45% yield) as a white solid. ESI-LCMS: m/z 229.9 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J=8 Hz, 2H), 6.14 (d, J=8 Hz, 2H), 5.81-5.76 (m, 2H), 5.28 (t, J=5 Hz, 1H), 5.13-4.97 (t, J=4 Hz, 1H), 4.23 (m, 1H), 3.97 (m, 1H), 3.74-3.58 (m, 2H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−206.09.

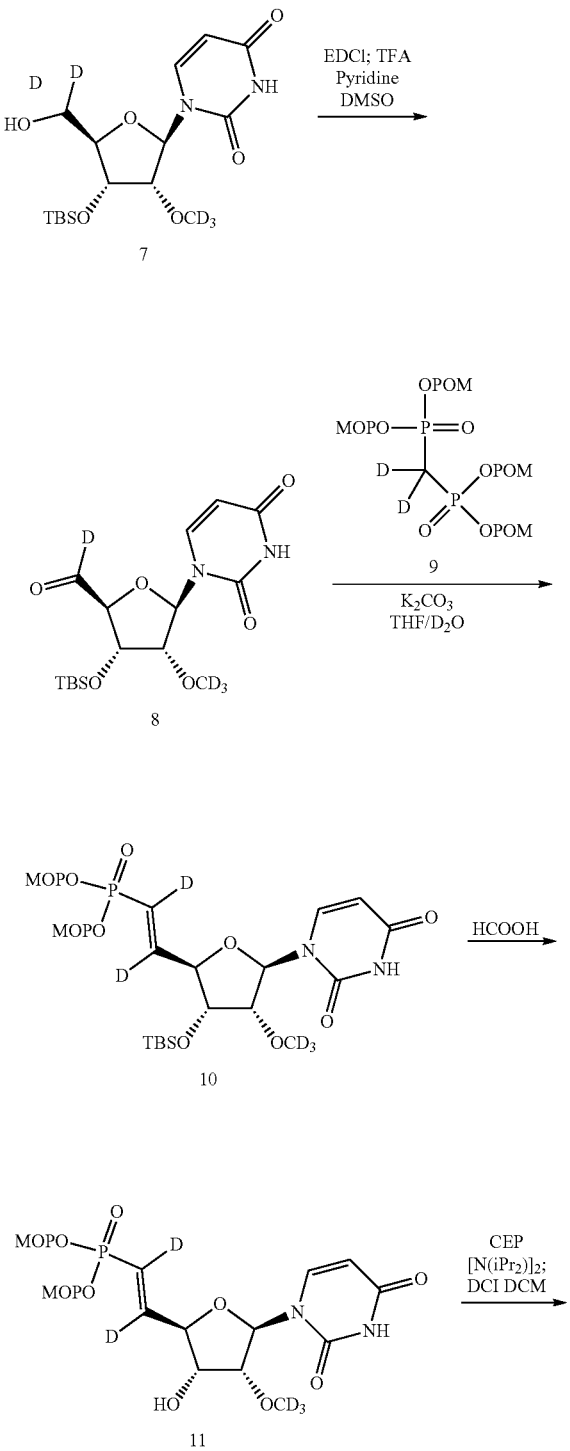
[0677] Preparation of (9): To a solution of 8 (1.4 g, 6.1 mmol) in pyridine (14 mL) was added DMTrCl (2.5 g, 7.3 mmol) at 20° C. The mixture was stirred at 20° C. for 1 h. TLC showed 8 was consumed completely. Water was added to the reaction. The product was extracted with EA, The organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to give 9 (2.5 g, 4.6 mmol, 76 yield) as a white solid. ESI-LCMS: m/z 532.2 $[M+H]^+$; iH-NMR (400 MHz, DMSO-d_6): δ 7.87-7.84 (m, 2H), 7.40-7.22 (m, 9H), 6.91-6.87 (m, 4H), 5.98-5.95 (m, 2H), 5.88-5.77 (m, 2H), 5.16-5.02 (m, 1H), 4.42 (m, 1H), 4.05 (m, 1H), 3.74 (s, 6H), 3.35 (m, 2H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−202.32.

[0678] Preparation of Example 42 monomer: To a solution of 9 (2.2 g, 4.1 mmol) in DCM (20 mL) was added DCI (415 mg, 3.5 mmol) and CEP (1.5 g, 4.9 mmol) under N_2 pro. The mixture was stirred at 20° C. for 0.5 h. TLC showed 9 was consumed completely. The product was extracted with DCM, The organic layer was washed with H_2O and brine. Then the solution was concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 42 monomer (2.6 g, 3.5 mmol, 85% yield) as a white solid. ESI-LCMS: m/z 732.2 $[M-+H]$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.87-7.84 (m, 2H), 7.40-7.22 (m, 9H), 6.91-6.87 (m, 4H), 5.98-5.95 (m, 2H), 5.90-5.88 (m, 1H), 5.30-5.17 (m, 1H), 4.62 (m, 1H), 4.19 (m, 1H), 3.78-3.73 (m, 7H), 3.62-3.35 (m, 5H), 2.78 (t, J=5 Hz, 1H), 2.63 (t, J=6 Hz, 1H), 1.14-0.96 (m, 12H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−200.77, 200.80, 201.62, 201.64. ^{31}P-NMR (162 MHz, DMSO-d_6): δ 150.31, 150.24, 149.66, 149.60.

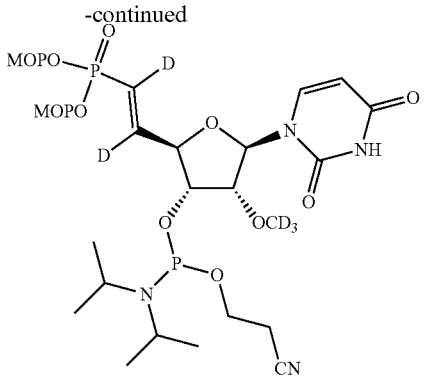
Example 43. Synthesis of End Cap Monomer

[0679]

Scheme-23



-continued



Example 43 monomer

[0680] Preparation of (8): To a stirred solution of 7 (13.4 g, 35.5 mmol, Scheme 5) in DMSO (135 mL) were added EDCI (6.3 g, 32.9 mmol) and pyridine (0.9 g, 10.9 mmol), TFA (0.6 g, 5.5 mmol) at r.t. And the reaction mixture was stirred at r.t for 2 h. LCMS showed 7 consumed completely. The reaction was quenched with water and the product was extracted with EA (1800 mL). The organic phase was washed by brine, dried over Na_2SO_4, The organic phase was evaporated to dryness under reduced pressure to give a residue 8 (13.2 g, 35.3 mmol, 99.3% yield). Which was used directly to next step. ESI-LCMS: m/z=375 $[M+H_2O]^+$

[0681] Preparation of (10): A solution of 8 (13.2 g, 35.3 mmol), 9 (26.8 g, 42.3 mmol, Scheme 18) and K_2CO_3 (19.5 g, 141.0 mmol) in dry THE (160 mL) and D20 (53 mL) was stirred at r.t. 17 h. LCMS showed most of 8 was consumed. The product was extracted with EA (2500 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by c.c. (PE:EA=10:1 ~ 1:2) to give product 10 (8.1 g, 11.8 mmol, 33.4% yield) as a white solid. ESI-LCMS m/z=682 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 7.69-7.71 (d, J=8.1 Hz, 1H), 5.78-5.79 (d, J=3.7 Hz, 1H), 5.65-5.67 (m, 1H), 5.59-5.63 (m, 4H), 4.29-4.35 (m, 2H), 3.97-3.99 (m, 1H), 1.15 (s, 18H), 0.87 (s, 9H), 0.07-0.08 (d, J=5.1 Hz, 6H). ^{31}P-NMR (162 MHz, DMS O-d_6) δ 16.62.

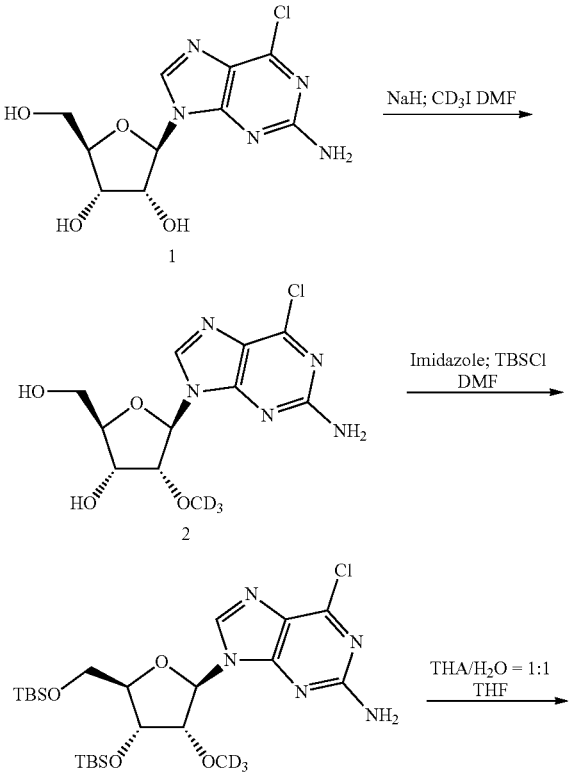
[0682] Preparation of (11): To a round-bottom flask was added 10 (7.7 g, 11.1 mmol) in a mixture of HCOOH (80 mL) and H_2O (80 mL). The reaction mixture was stirred at 40° C. for 3 h. LCMS showed the 10 was consumed completely. The reaction mixture was adjusted the pH=7.0 with con.$NH_3.H_2O$ (100 mL). Then the mixture was extracted with DCM (100 mL*3). The combined DCM layer was dried over Na_2SO_4. Filtered and filtrate was concentrated to give crude which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3) =1/2 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. To give product 11 (5.5 g, 9.6 mmol, 86.1% yield) as a white solid. ESI-LCMS m/z=568 [M+H]-; iH-NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H, exchanged with D_2O), 7.62-7.64 (d, J=8.1, 1H), 5.81-5.82 (d, J=4.3, 1H), 5.58-5.66 (m, 5H), 5.52-5.53 (d, J=6.6, 1H), 4.34-4.37 (m, 1H), 4.09-4.13 (m, 1H), 3.94-3.96 (t, J=9.7, 1H), 1.15 (s, 18H), 0 (s, 1H). ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.16.

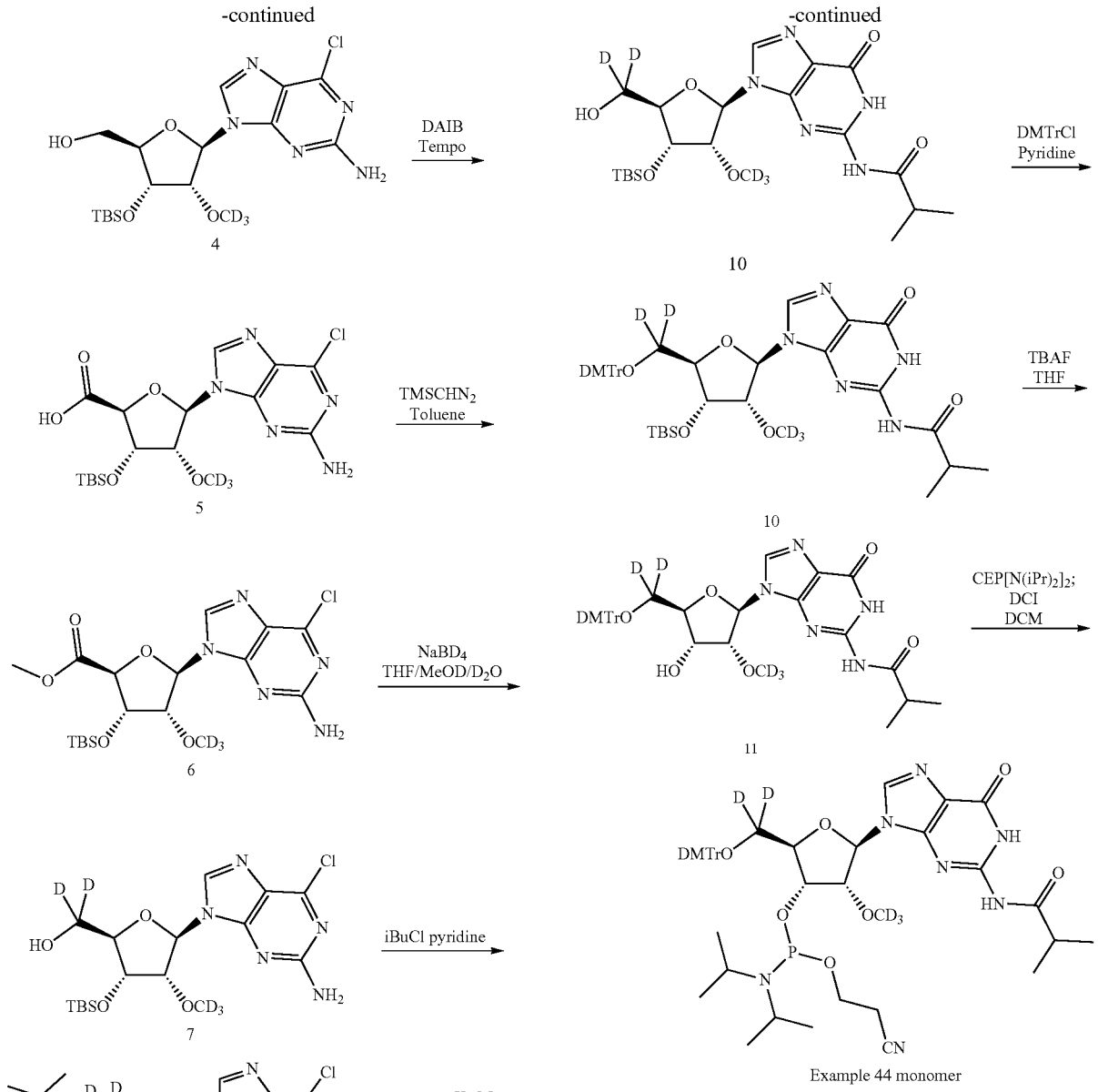
[0683] Preparation of Example 43 monomer: To a solution of 11 (5.3 g, 9.3 mmol) in DCM (40 mL) was added the DCI (1.1 g, 7.9 mmol), then $CEP[N(ipr)_2]_2$ (3.4 g, 11.2 mmol) was added. The mixture was stirred at r.t. for 1 h. LCMS showed 11 consumed completely. The reaction mixture was washed with H_2O (50 mL*2) and brine (50 mL*1). Dried over Na_2SO_4 and concentrated to give crude which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. The product was concentrated to give Example 43 monomer (6.2 g, 8.0 mmol, 85.6% yield) as a white solid. ESI-LCMS m/z=768 $[M+H]^+$; iH-NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 7.68-7.71 (m, 1H), 5.79-5.81 (m, 1H), 5.58-5.67 (m, 5H), 4.34-4.56 (m, 2H), 4.14-4.17 (m, 1H), 3.54-3.85 (m, 4H), 2.78-2.81 (m, 2H), 1.13-1.17 (m, 30H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.66, 149.16, 16.84, 16.56.

Example 44. Synthesis of Monomer

[0684]

Scheme-24





[0685] Preparation of (2): To a solution of 1 (20.0 g, 66.4 mmol) in dry DMF (400 mL) was added sodium hydride (1.9 g, 79.7 mmol) for 30 min, then was added CD_3I (9.1 g, 79.7 mmol) in dry DCM (40 mL) at −20° C. for 5.5 hr. LCMS showed the reaction was consumed. The mixture was filtered and the clear solution was evaporated to dryness and was evaporated with $CH_{30}H$. The crude was purified by silica gel column (SiO_2, DCM/MeOH=50:1~10:1). This resulted in to give the product 2 (7.5 g, 23.5 mmol, 35.5% yield) as a solid. ESI-LCMS: m/z 319 [M+H]f; TH-NMR (400 MHz, DMSO-d_3): δ=8.38 (m, 1H), 6.97 (m, 2H), 5.93-5.81 (m, 1H), 5.27-5.26 (d, J=4 Hz, 1H), 5.13-5.11 (m, 1H), 4.39-4.31 (m, 1H), 4.31-4.25 (m, 1H), 3.96-3.94 (m, 1H), 3.66-3.63 (m, 1H), 3.63-3.56 (m, 1H).

[0686] Preparation of (3): To a solution of 2 (7.5 g, 23.5 mmol) in dry DMF (75 mL) was added Imidazole (5.6 g, 82.3 mmol) and TBSCl (8.9 g, 58.8 mmol). The mixture was stirred at r.t. over night. LCMS showed 2 was consumed

completely. The reaction was quenched with water (300 mL). The product was extracted into ethyl acetate (100 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed to give the cured 3 (9.8 g) as a solid witch used for the next step. ESI-LCCMS: m/z 547 $[M+H]^+$.

[0687] Preparation of (4): To a solution of 3 (9.8 g) in THE (40 mL) was added TFA (10 mL) and water (10 mL) at 0° C. The reaction mixture was stirred at 0° C. for 5 h. LC-MS showed 3 was consumed completely. Con. NH_4OH was added to the mixture at 0° C. to quench the reaction until the pH=7.5. The product was extracted into ethyl acetate (200 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed to give the cured 4 (8.4 g) as a solid witch used for the next step. ESI-LCMS: m/z 433 $[M-H]^-$.

[0688] Preparation of (5): To a solution of 4 (8.4 g) in DCM/H_2O=2:1 (84 mL) was added DAIB (18.8 g, 58.4 mmol) and TEMPO (0.87 g, 5.8 mmol). The reaction mixture was stirred at 40° C. for 2 h. LCMS showed 4 was consumed. The mixture was diluted with DCM and water was added. The product was extracted with DCM. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was then concentrated under reduced pressure. This resulted in to give 5 (14.4 g) as a white solid. ESI-LCMS: m/z 447 $[M+H]^+$.

[0689] Preparation of (6): To a solution of 5 (14.4 g) in toluene (90 mL) and methanol (60 mL) was added 2M $TMSCHN_2$ (8.9 g, 78.1 mmol) till the yellow color not disappear at r.t. for 10 min. LCMS showed 5 was consumed. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=65/35 Detector, UV 254 nm. This resulted in to give the product 6 (3.5 g, 7.6 mmol, 32.3% yield over three steps, 70% purity) as a white solid. ESI-LCMS: m/z 461 $[M+H]^+$.

[0690] Preparation of (7): To the solution of 6 (3.5 g, 7.6 mmol) in dry THF/MeOD/D_2O=10/2/1 (45 mL) was added $NaBD_4$ (0.96 g, 22.8 mmol). And the reaction mixture was stirred at r.t for 2.5 hr. After completion of reaction, the resulting mixture was added CH_3COOD to pH=7, after addition of water, the resulting mixture was extracted with EA (100 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give 7 (3.3 g) which was used for the next step. ESI-LCMS: m/z 435 $[M+H]^-$.

[0691] Preparation of (8): To a solution of 7 (3.3 g) in dry DCM (30 mL) was added pyridine (5.9 g, 74.5 mmol) and iBuCl (2.4 g, 22.4 mmol) in DCM (6 mL) under ice bath. The reaction mixture was stirred at 0° C. for 2.5 hr. LCMS showed 7 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=87/13; Detector, UV 254 nm. This resulted in to give the crude 8 (1.6 g, 2.8 mmol, 36.8% yield over two steps) as a white solid. ESI-LCMS: m/z 575 $[M+H]^-$.

[0692] Preparation of (9): To a solution of 8 (1.6 g, 2.8 mmol) in H_2O/dioxane=1:1 (30 ml) was added K_2CO_3 (772.8 mg, 5.6 mmol) and DABCO (739.2 mg, 2.9 mmol). The reaction mixture was stirred at 50° C. for 3 hr. LCMS showed 8 was consumed. The mixture was diluted with EA and water was added. The product was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give 9 (1.8 g) which was used for the next step. ESI-LCMS: m/z 557 $[M+H]^+$.

[0693] Preparation of (10): To a solution of 9 (1.8 g) in pyridine (20 mL) and was added 2M NaOH (MeOH/H_2O=4/1) (5 mL) at 0° C. for 1 h. LCMS showed 9 was consumed. The mixture was added saturated NH_4Cl till pH=7.5. The mixture was diluted with water and EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. This resulted in to give the product 10 (1.5 g) as a white solid which was used for the next step. ESI-LCMS: m/z 487 $[M-H]^+$.

[0694] Preparation of (11): To a stirred solution of 10 (1.5 g) in pyridine (20 mL) were added DMTrCl (1.1 g, 3 mmol) at r.t. And the reaction mixture was stirred at r.t for 2.5 hr. With ice-bath cooling, the reaction was quenched with water and the product was extracted into EA. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=7/3 Detector, UV 254 nm. This resulted in to give the product 11 (1.9 g, 2.4 mmol, 85.7% yield over two steps) as a white solid. ESI-LCMS: m/z 789.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.10 (m, 1H), 11.63 (m, 1H), 8.20 (m, 1H), 7.35-7.33 (m, 2H), 7.29-7.19 (m, 7H), 6.86-6.83 (m, 4H), 5.89-5.88 (d, J=4 Hz, 1H), 4.40-4.28 (m, 2H), 3.72 (m, 6H), 2.81-2.76 (m, 1H), 1.13-1.11 (m, 6H), 0.80 (m, 9H), 0.05-0.01 (m, 7H).

[0695] Preparation of (12): To a solution of 11 (1.9 g, 2.4 mmol) in THE (20 mL) was added 1 M TBAF solution (3 mL). The reaction mixture was stirred at r.t. for 1.5 h. LCMS showed 11 was consumed completely. Water (100 mL) was added. The product was extracted with EA (50 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Then the organic layer was concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=58/42; Detector, UV 254 nm. This resulted in to give 12 (1.5 g, 2.2 mmol, 91.6% yield) as a white solid. ESI-LCMS: m/z 675.3 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.09 (m, 1H), 11.60 (m, 1H), 8.14 (m, 1H), 7.35-7.27 (m, 2H), 7.25-7.20 (m, 7H), 6.85-6.80 (m, 4H), 5.96-5.94 (d, J=8 Hz, 1H), 5.26-5.24 (m, 1H), 4.35-4.28 (m, 2H), 3.72 (m, 6H), 3.32 (m, 1H), 2.79-2.72 (m, 1H), 1.13-1.11 (m, 6H).

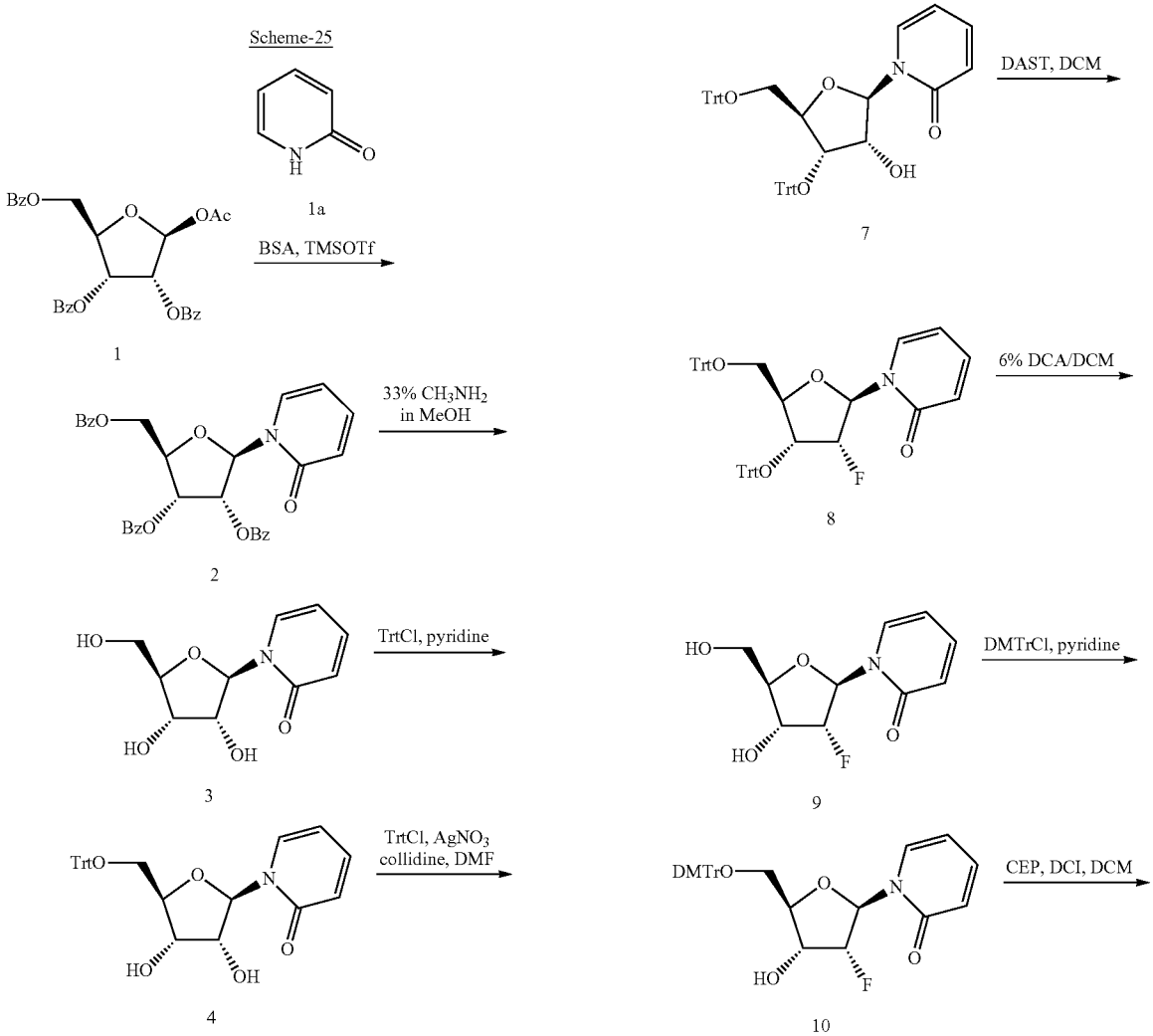
[0696] Preparation of Example 44 monomer: To a suspension of 11 (1.5 g, 2.2 mmol) in DCM (15 mL) was added DCI (220.8 mg, 1.9 mmol) and $CEP[N(iPr)_2]_2$ (795.7 mg, 2.6 mmol) under N_2 pro. The mixture was stirred at r.t. for 2 h. LCMS showed 11 was consumed completely. The

solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1; Detector, UV 254 nm. This resulted in to give Example 44 monomer (1.6 g, 1.8 mmol, 83% yield) as a white solid. ESI-LCMS: m/z 875 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.12 (m, 1H), 11.60 (m, 1H), 8.15 (m, 1H), 7.37-7.29 (m, 2H), 7.27-7.20 (m, 7H), 6.86-6.81 (m, 4H), 5.94-5.88 (m, 1H), 4.54-4.51 (m, 2H), 4.21-4.20 (m, 1H), 3.73-3.54 (m, 10H), 2.80-2.75 (m, 1H), 2.61-2.58 (m, 1H), 1.19-1.11 (m, 19H). ^{31}P-NMR (162 MHz, DMSO-d_6): δ=149.77, 149.71.

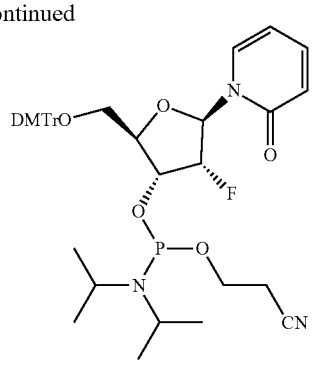
Example 45. Synthesis of Monomer

[0697]

Scheme-25



-continued



Example 45 monomer

[0698] Preparation of (2): To a solution of 1 (50.0 g, 99.2 mmol) and 1a (11.3 g, 119.0 mmol) in ACN (500.0 mL). Then added BSA (53.2 g, 218.0 mmol) under N_2 Pro. The mixture was stirred at 50° C. for 1 h until the solution was clear. Then cool down to 0° C. and dropped TMSOTf (26.4 g, 119.0 mmol).The mixture was stirred at 75° C. for 1 h, TLC showed 1 was consumed completely. The reaction was quenched by sodium bicarbonate solution at 0° C., then the solution was diluted with EA, washed with H_2O twice. The solvent was concentrated under reduced pressure and the crude 2 (60.1 g) was used for next step. ESI-LCMS: m/z 540.2 $[M+H]^+$.

[0699] Preparation of (3): To a solution of 2 (60.1 g) in CH_3NH_2/ethanol (500.0 mL). The mixture was stirred at 25° C. for 2 h. TLC showed 2 was consumed completely. The solvent was concentrated under reduced pressure and the residue was purified by c.c. (MeOH:DCM=50:1 ~ 10:1) to give 3 (22.0 g, 96.9 mmol, 97.3% yield over two steps). ESI-LCMS: m/z 228.0 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.01-7.98 (m, 1H), 7.43-7.38 (m, 1H), 6.37-6.35 (m, 1H), 6.27-6.23 (m, 1H), 6.03 (d, J=3.5 Hz, 1H), 5.39 (d, J=4.2 Hz, 1H), 5.11 (t, J=5.1 Hz, 1H), 5.03 (d, J=5.1 Hz, 1H), 3.98-3.95 (m, 2H), 3.91-3.88 (m, 1H), 3.74-3.57 (m, 2H).

[0700] Preparation of (4): To a solution of 3 (22.0 g, 96.9 mmol) in pyridine (250.0 mL), TrtCl (30.7 g, 110.5 mmol) was added. The mixture was stirred at 25° C. for 24 h. TLC showed 3 was consumed completely, H_2O was added to the mixture. Then filtered and the filtrate diluted with EA, the organic layer was washed with $NaHCO_3$ and brine. The solvent was concentrated under reduced pressure and then purified by c.c. (PE/EA=5:1 ~ 0:1) to give 4 (38.8 g, 82.5 mmol, 85.1% yield) as a white solid. ESI-LCMS: m/z 470.1 $[M+H]^+$.

[0701] Preparation of (5): To a solution of 4 (38.8 g, 82.5 mmol) in DMF (500.0 mL), collidine (10.0 g, 107.3 mmol), TrtCl (27.6 g, 99.1 mmol) were added followed by $AgNO_3$ (18.0 g, 105.1 mmol). The mixture was stirred at 25° C. for 4 h. TLC showed 4 was consumed completely. Then filtered and the filtrate diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. The solvent was concentrated under reduced pressure and then purified by c.c. (PE/EA=5:1 ~ 1:1) to give a mixture of 5 (52.3 g, 73.5 mmol, 86.3% yield) as white solid. ESI-LCMS: m/z 711.1 $[M+H]^+$.

[0702] Preparation of (6): To a solution of 5 (52.3 g, 73.5 mmol) in DCM (500.0 mL), DMAP (8.9 g, 73.5 mmol), TEA (14.9 g, 147.3 mmol, 20.6 mL) were added, cool down to 0° C., TfCl (16.1 g, 95.6 mmol) dissolved in DCM (100.0 mL) were dropped. The mixture was stirred at 25° C. for 1 h. TLC showed 5 was consumed completely. Then filtered and the solution diluted with EA. The organic layer was washed with $NaHCO_3$ and brine. The solvent was concentrated under reduced pressure to get crude 6 (60.2 g) as a brown solid. ESI-LCMS: m/z 844.2 $[M+H]^+$.

[0703] Preparation of (7): To a solution of 6 (60.2 g) in DMF (500.0 mL), KOAc (36.1 g, 367.8 mmol) were added, The mixture was stirred at 25° C. for 14 h and 50° C. for 3 h, TLC showed 6 was consumed completely. Then filtered and the solution diluted with EA. The organic layer was washed with H_2O and brine. The solvent was concentrated under reduced pressure, residue was purified by c.c. (PE/EA=5:1 ~ 1:1) to give 7 (28.0 g, 39.3 mmol, 53.5% yield) as yellow solid. ESI-LCMS: m/z 710.2 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.37-7.25 (m, 33H), 6.34-6.31 (m, 2H), 6.13-6.10 (m, 1H), 5.08 (d, J=4.2 Hz, 1H), 3.99 (d, J=7.6 Hz, 1H), 3.74 (s, 1H), 3.12 (t, J=9.2 Hz, 1H), 2.72-2.69 (m, 1H).

[0704] Preparation of (8): To a solution of 7 (28.0 g, 39.3 mmol) in DCM (300.0 mL), DAST (31.6 g, 196.6 mmol) was added at 0° C., the mixture was stirred at 25° C. for 16 h, TLC showed 7 was consumed completely. Then the solution was diluted with EA, washed with $NaHCO_3$ twice, the solvent was removed under reduced pressure, residue was purified by c.c. (PE/EA=5:1 ~ 3:1) to give 8 (5.0 g, 7.0 mmol, 17.8% yield) as a white solid. ESI-LCMS: m/z 748.2 $[M+2NH_4]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.57-7.18 (m, 35H), 6.30 (d, J=8.8 Hz, 1H), 6.00 (d, J=19.5 Hz, 1H), 5.92-5.88 (m, 1H), 4.22-4.17 (m, 2H), 3.94 (s, 0.5H), 3.80 (s, 0.5H), 3.35-3.31 (m, 1H), 3.14-3.10 (m, 1H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−193.54.

[0705] Preparation of (9): To a solution of 8 (5.0 g, 7.0 mmol) in DCM (60.0 mL) was added DCA (3.6 mL) and TES (15.0 mL). The mixture was stirred at 20° C. for 1 h, TLC showed 8 was consumed completely. Then the solution was concentrated under reduced pressure, the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=0/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=0/1; Detector, UV 254 nm. This resulted in to give 9 (1.6 g, 6.9 mmol, 98.5% yield) as a white solid. ESI-LCMS: m/z 229.9 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.06-8.04 (m, 1H), 7.48-7.43 (m, 1H), 6.39 (d, J=9.0 Hz, 1H), 6.31-6.27 (m, 1H), 6.16-6.11 (m, 1H), 5.63 (s, 1H), 5.26 (s, 1H), 4.95-4.81 (m, 1H), 4.20-411 (m, 1H), 3.95 (d, J=8.2 Hz, 1H), 3.84 (d, J=12.4 Hz, 1H), 3.64 (d, J=12.1 Hz, 1H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−201.00.

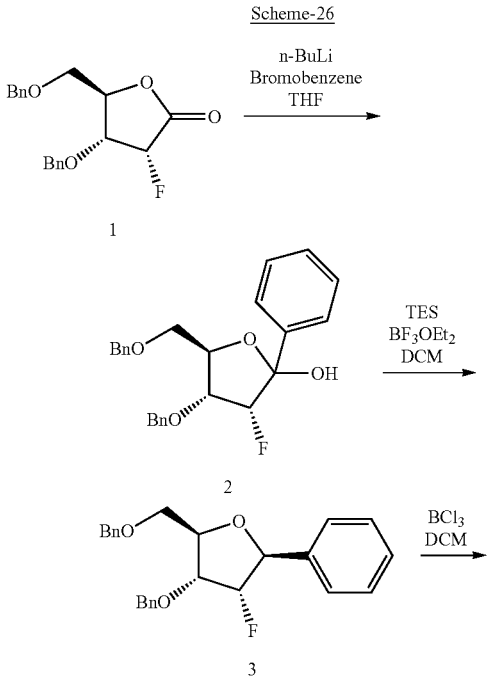
[0706] Preparation of (10): To a solution of 9 (1.6 g, 6.9 mmol) in pyridine (20.0 mL) was added DMTrCl (3.5 g, 10.5 mmol) at 20° C. and stirred for 1 h. TLC showed 9 was consumed completely. Water was added and extracted with EA, the organic layer was washed with $NaHCO_3$ and brine. Then the solution was concentrated under reduced pressure and the residue was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1; Detector, UV 254 nm. This resulted in to

give 10 (2.2 g, 4.2 mmol, 60.8% yield) as a white solid. ESI-LCMS: m/z 530.1 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.93-7.91 (m, 1H), 7.47-7.23 (m, 10H), 6.91-6.89 (m, 4H), 6.41 (d, J=8.8 Hz, 1H), 6.13 (d, J=18.8 Hz, 1H), 6.00-5.96 (m, 1H), 5.68 (d, J=6.6 Hz, 1H), 5.01 (d, J=4.2 Hz, 0.5H), 4.88 (d, J=4.2 Hz, 0.5H), 4.42-4.31 (m, 1H), 4.10-4.08 (m, 1H), 3.74 (s, 6H), 3.40-3.34 (m, 2H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−199.49.

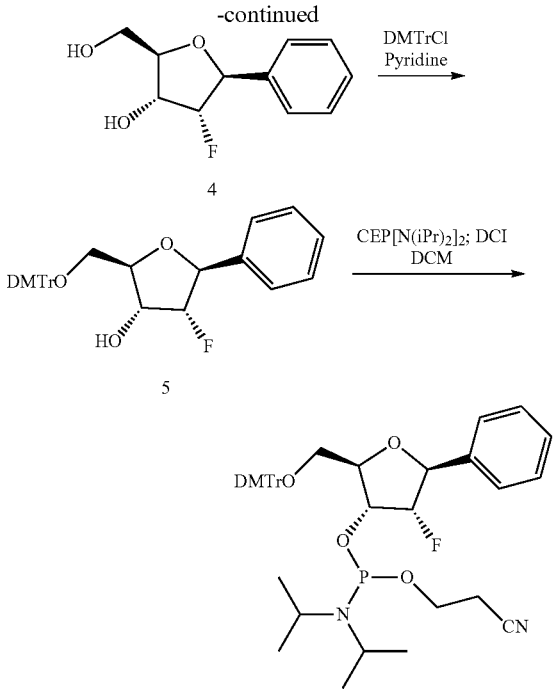
[0707] Preparation of Example 45 monomer: To a solution of 10 (2.2 g, 4.2 mmol) in DCM (20.0 mL) was added DCI (415 mg, 3.5 mmol) and CEP (1.5 g, 4.9 mmol) under N_2 pro. The mixture was stirred at 20° C. for 0.5 h. TLC showed 10 was consumed completely. The product was extracted with DCM, the organic layer was washed with H_2O and brine. Then the solution was concentrated under reduced pressure and the residue was purified by cc (PE/EA=5:1 ~ 1:1) and Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 45 monomer (2.1 g, 3.0 mmol, 73.1% yield) as a white solid. ESI-ESI-LCMS: m/z 732.2 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.98-7.92 (m, 1H), 7.42-7.24 (m, 10H), 6.91-6.85 (m, 4H), 6.43-6.39 (m, 1H), 6.18-6.11 (m, 1H), 6.01-5.97 (m, 1H), 5.22-5.19 (m, 0.5H), 5.09-5.06 (m, 0.5H), 4.73-4.52 (m, 1H), 4.21-4.19 (m, 1H), 3.79-3.62 (m, 7H), 3.57-3.47 (m, 4H), 3.32-3.28 (m, 1H), 2.75-2.58 (m, 1H), 1.13-0.92 (m, 12H); ^{19}F-NMR (376 MHz, DMSO-d_6): δ−196.82, −196.84, −197.86, −197.88; ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.88, 149.83, 149.39, 149.35.

Example 46. Synthesis of Monomer

[0708]



-continued



Example 46 monomer

[0709] Preparation of (2): To the solution of Bromobenzene (2.1 g, 13.6 mmol) in dry THE (15 mL) was added 1.6 M n-BuLi (7 mL, 11.8 mmol) drop wise at −78° C. The mixture was stirred at −78° C. for 0.5 h. Then the 1 (3.0 g, 9.1 mmol, Wang, Guangyi et al, Journal of Medicinal Chemistry, 2016,59(10), 4611-4624) was dissolved in THE (15 mL) and added to the mixture drop wise with keeping at −78° C. Then the reaction mixture was stirred at −78° C. for 1 hr. LC-MS showed 1 was consumed completely. Then the solution was added to saturated aq. NH_4Cl and the resulting mixture was extracted with EA. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=3/2; Detector, UV 254 nm. This resulted in to give 2 (3.0 g, 7.3 mmol, 80.0%) as a white solid. ESI-LCMS: m/z 391 $[M-OH]^-$.

[0710] Preparation of (3): To the solution of 2 (4.0 g, 9.8 mmol) in DCM (40 mL) was added TES (1.9 g, 11.7 mmol) at −78° C., and the mixture was added $BF_3.OEt_2$ (2.1 g, 14.7 mmol) drop wise at −78° C. The mixture was stirred at −40° C. for 1 hr. LC-MS showed 2 was consumed completely. Then the solution was added to saturated aq. $NaHCO_3$ and the resulting mixture was extracted with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=2/3 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=4/1 within 25 min, the eluted product was collected at CH_3CN/H_2O (0.5%

NH_4HCO_3)=7/3; Detector, UV 254 nm. This resulted in to give 3 (3.1 g, 5.3 mmol, 54.0%) as a water clear oil. ESI-LCMS: m/z 410 $[M+H_2O]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$: δ 7.48-7.25 (m, 15H), 5.24-5.13 (m, 1H), 4.93-4.74 (m, 1H), 4.74-4.46 (m, 4H), 4.37-4.25 (m, 1H), 4.19-4.05 (m, 1H), 4.00-3.80 (m, 1H), 3.77-3.63 (m, 1H). ^{19}F-NMR (376 MHz, $CDCl_3$): δ−196.84.

[0711] Preparation of (4): To the solution of 3 (2.1 g, 5.3 mmol) in dry DCM (20 mL) was added 1 M BCl_3 (25 mL, 25.5 mmol) drop wise at −78° C., and the reaction mixture was stirred at −78° C. for 0.5 hr. LC-MS showed 3 was consumed completely. After completion of reaction, the resulting mixture was poured into water (50 mL). The solution was extracted with DCM and the combined organic layer was concentrated under reduced pressure to give a crude. The crude in MeOH (4 mL) was added 1 M NaOH (15 mL), and the mixture was stirred at r.t for 5-10 min. The mixture was extracted with EA. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography (eluent, DCM: MeOH=40:1-15:1) to give 4 (1.0 g, 4.7 mmol, 88.6%) as a water clear oil. ESI-LCMS: m/z 211 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.58-7.19 (m, 5H), 5.41 (d, J=6.1 Hz, 1H), 5.09-5.95 (m, 1H), 5.95-4.84 (m, 1H), 4.82-4.59 (m, 1H), 4.14-3.94 (m, 1H), 3.89-3.80 (m, 1H), 3.78-3.67 (m, 1H), 3.65-3.53 (m, 1H). ^{19}F-NMR (376 MHz, DMSO-d_6): δ−196.46.

[0712] Preparation of (5): To a solution of 4 (1.0 g, 4.7 mmol) in Pyridine (10 mL) was added DMTrCl (2.0 g, 5.7 mmol). The reaction mixture was stirred at r.t. for 2 hr. LCMS showed 4 was consumed and water (100 mL) was added. The product was extracted with EA (100 mL) and the organic layer was washed with brine and dried over Na_2SO_4 and concentrated to give the crude. The crude was further purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=9/1; Detector, UV 254 nm. This resulted in to give 5 (2.1 g, 4.1 mmol, 87.0%) as a red oil. ESI-LCMS: M/z 513 $[M-H]^-$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.56-7.16 (m, 14H), 6.94-9.80 (m, 4H), 5.45 (d, J=6.3 Hz, 1H), 5.21-5.09 (m, 1H), 4.89-4.68 (m, 1H), 4.18-4.03 (m, 2H), 3.74 (s, 6H), 3.33-3.29 (m, 1H), 3.26-3.17 (m, 1H). ^{19}F-NMR (376 MHz, DMSO-d_6): δ−194.08.

[0713] Preparation of Example 46 monomer: To a suspension of 5 (2.1 g, 4.1 mmol) in DCM (20 mL) was added DCI (410 mg, 3.4 mmol) and $CEP[N(iPr)_2]_2$ (1.5 g, 4.9 mmol). The mixture was stirred at r.t. for 1 h. LC-MS showed 5 was consumed completely. The solution was washed with water twice and washed with brine and dried over Na_2SO_4. Then concentrated to give the crude. The crude was purification by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, CH_3CN/H_2O (0.5% NH_4HCO_3)=1/1 increasing to CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0 within 20 min, the eluted product was collected at CH_3CN/H_2O (0.5% NH_4HCO_3)=1/0; Detector, UV 254 nm. This resulted in to give Example 46 monomer (2.1 g, 2.9 mmol, 70.0%) as a white solid. ESI-LCMS: m/z 715 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.59-7.16 (m, 14H), 6.94-9.80 (m, 4H), 5.26-5.12 (m, 1H), 5.06-4.77 (m, 1H), 4.50-4.20 (m, 1H), 4.20-4.10 (m, 1H), 3.83-3.63 (m, 7H), 3.59-3.37 (m, 4H), 3.25-3.13 (m, 1H), 2.80-2.66 (m, 1H), 2.63-2.53 (m, 1H), 1.18-0.78 (m, 12H). ^{19}F-NMR (376 MHz, DMSO-d_6): δ−194.40, −194.42, −194.50,-194.53. ^{31}P-NMR (162 MHz, DMSO-d_6): δ 149.38, 149.30, 149.02, 148.98.

Example 47. Deuterated Vinyl Phosphonate Improves Potency of siNA

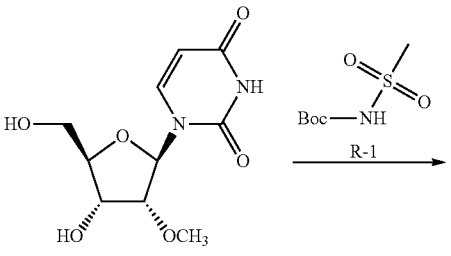
[0714] This example investigates whether a deuterated vinyl phosphonate improves potency of siNA in an AAV-HBV mouse. AAV-HBV mice were subcutaneously injected with vehicle, ds-siNA-0165 (e.g., siNA without a deuterated vinyl phosphonate), or ds-siNA-0144 (e.g., siNA with a deuterated vinyl phosphonate). For siNA-treated AAV-HBV mice, AAV-HBV mice were subcutaneously injected with a single dose of 5 mg/kg of siNA. As shown in FIG. **11**, siNA molecules having 2'-fluoro nucleotides at positions 3, 7-9, 12, and 17 from the 5' end of the sense strand and 2'-fluoro nucleotides at positions 2 and 14 from the 5' end of the antisense strand resulted in at least a 0.5-log reduction in HBsAg, with the greatest reduction in HBsAg found in mice treated with the deuterated vinylphopshonate siNA (ds-siNA-0165). Thus, FIG. **11** demonstrates that the presence of a deuterated vinyl phosphonate improves potency of the siNA.

Example 48. Deuterated Vinyl Phosphonate Results in a Greater Reduction in Serum HBsAg

[0715] AAV-HBV mice were subcutaneously injected with vehicle, ds-siNA-0163 (e.g., siNA without a vinyl phosphonate), ds-siNA-0122 (e.g., siNA with a vinyl phosphonate), or ds-siNA-0123 (e.g., siNA with a deuterated vinyl phosphonate). For siNA-treated AAV-HBV mice, AAV-HBV mice were subcutaneously injected with a single dose of 5 mg/kg of siNA. As shown in FIG. **12**, siNA molecules having 2'-fluoro nucleotides at positions 7, 9-11 from the 5' end of the sense strand and 2'-fluoro nucleotides at positions 2 and 14 from the 5' end of the antisense strand resulted in at least a 0.5-log reduction in HBsAg, with the greatest reduction in HBsAg found in mice treated with the deuterated vinylphopshonate siNA (ds-siNA-0165). Thus, FIG. **12** demonstrates that the presence of a deuterated vinyl phosphonate improves potency of the siNA, as compared to the siNA without a vinyl phosphonate and the siNA with the vinyl phosphonate.

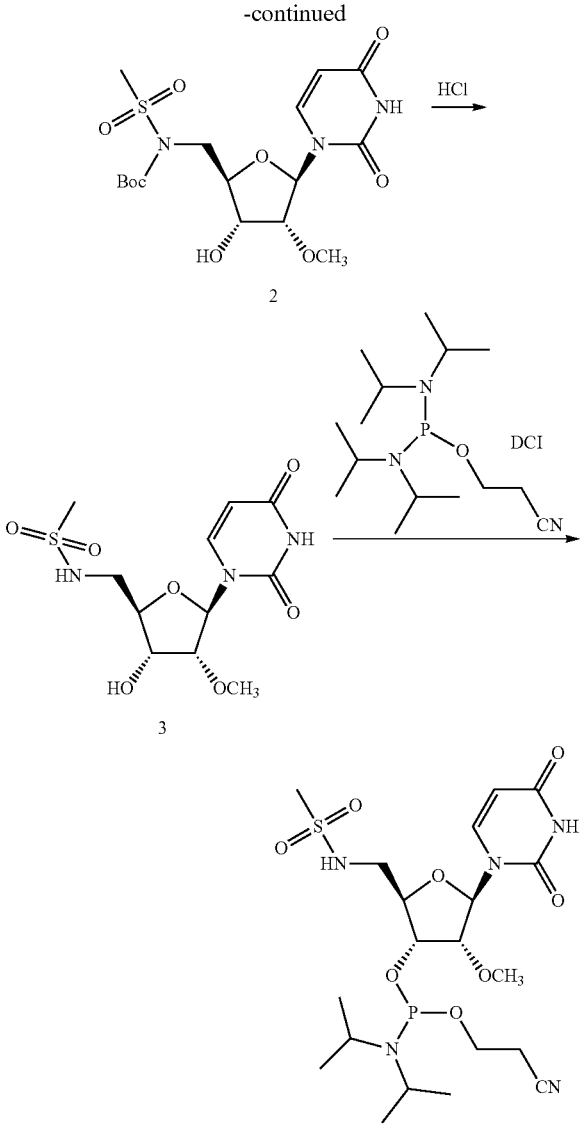
Example 49: Synthesis of 5' End Cap Monomer

[0716]



1

-continued



Example 49 Monomer

Example 49 Monomer Synthesis Scheme

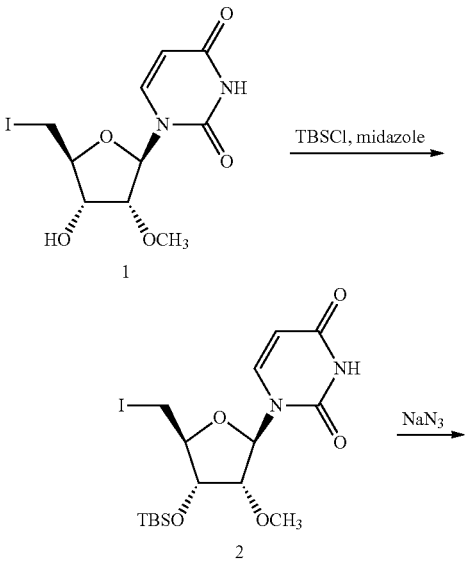
[0717] Preparation of (2): 1 (15 g, 58.09 mmol) and tert-butyl N-methylsulfonylcarbamate (17.01 g, 87.13 mmol) were dissolved in THE (250 mL), and PPh_3 (30.47 g, 116.18 mmol) was added followed by dropwise addition of DIAD (23.49 g, 116.18 mmol, 22.59 mL) at 0° C. The reaction mixture was stirred at 15° C. for 12 h. Upon completion as monitored by TLC (DCM/MeOH=10/1), the reaction mixture was evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% MeOH/DCM gradient @ 60 mL/min) to give 2 (6.9 g, 24.28% yield) as a white solid. ESI-LCMS: m/z 457.9 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=8.64 (br s, 1H), 7.64 (d, J=8.2 Hz, 1H), 5.88 (d, J=1.9 Hz, 1H), 5.80 (dd, J=2.2, 8.2 Hz, 1H), 4.19-4.01 (m, 3H), 3.90 (dt, J=5.5, 8.2 Hz, 1H), 3.82-3.78 (m, 1H), 3.64 (s, 3H), 3.32 (s, 3H), 2.75 (d, J=8.9 Hz, 1H), 1.56 (s, 9H).

[0718] Preparation of (3): 2 (6.9 g, 15.85 mmol) was dissolved in MeOH (40 mL), and a solution of HCl/MeOH (4 M, 7.92 mL) was added dropwise. The reaction mixture was stirred at 15° C. for 12 h, and then evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0-10% MeOH/DCM gradient @ 40 mL/min) to give 3 (2.7 g, 50.30% yield) as a white solid. ESI-LCMS: m/z 336.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ=9.20 (br s, 1H), 7.52 (d, J=8.1 Hz, 1H), 5.75 (d, J=3.8 Hz, 1H), 5.64 (dd, J=2.0, 8.1 Hz, 1H), 5.60-5.52 (m, 1H), 4.15-3.99 (m, 1H), 3.96-3.81 (m, 2H), 3.46 (s, 3H), 3.44-3.35 (m, 1H), 3.34-3.26 (m, 1H), 2.92 (s, 3H).

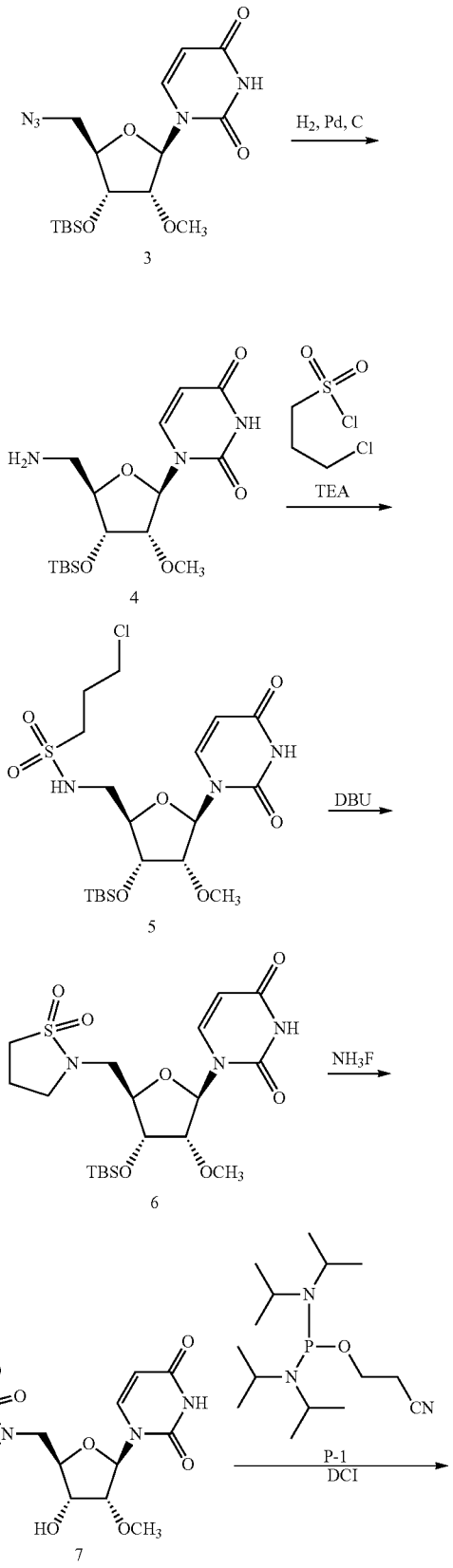
[0719] Preparation of (Example 49 monomer): To a solution of 3 (2.14 g, 6.38 mmol) in DCM (20 mL) was added dropwise 3-bis(diisopropylamino)phosphanyloxypropanenitrile (2.50 g, 8.30 mmol, 2.63 mL) at 0° C., followed by 1H-imidazole-4, 5-dicarbonitrile (829 mg, 7.02 mmol), and the mixture was purged under Ar for 3 times. The reaction mixture was stirred at 15° C. for 2 h. Upon completion, the mixture was quenched with 5% $NaHCO_3$ (20 mL), extracted with DCM (20 mL*2), washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% (Phase B: i-PrOH/DCM=1/2)/Phase A: DCM with 5% TEA gradient @ 40 mL/min) to give Example 49 monomer (1.73 g, 48.59% yield) as a white solid. ESI-LCMS: m/z 536.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ=7.58-7.48 (m, 1H), 5.83-5.78 (m, 1H), 5.71-5.64 (m, 1H), 4.40-4.29 (m, 1H), 4.19-4.07 (m, 1H), 3.98 (td, J=5.3, 13.3 Hz, 1H), 3.90-3.78 (m, 2H), 3.73-3.59 (m, 3H), 3.41 (d, J=14.8 Hz, 4H), 2.92 (br d, J=7.0 Hz, 3H), 2.73-2.63 (m, 2H), 1.23-1.11 (m, 12H); ^{31}P NMR (162 MHz, CD_3CN) δ=149.81, 150.37.

Example 50: Synthesis of 5' End Cap Monomer

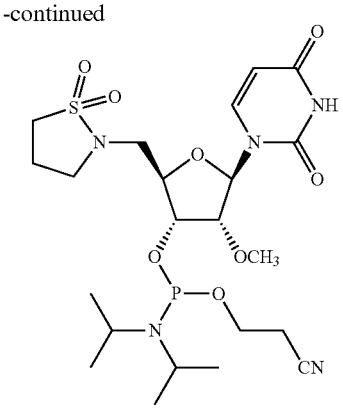
[0720]



-continued



-continued



Example 50 Monomer

Example 50 Monomer Synthesis Scheme

[0721] Preparation of (2): To a solution of 1 (10 g, 27.16 mmol) in DMF (23 mL) were added imidazole (3.70 g, 54.33 mmol) and TBSCl (8.19 g, 54.33 mmol) at 25° C. The mixture was stirred at 25° C. for 2 hr. Upon completion, the reaction mixture was diluted with H_2O (20 mL) and extracted with EA (30 mL*2). The combined organic layers were washed with brine (20 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2 (13 g, 99.2% yield) as a white solid. ESI-LCMS: m/z 482.9 $[M+H]^+$.

[0722] Preparation of (3): To a solution of 2 (35.00 g, 72.56 mmol) in DMF (200 mL) was added NaN_3 (14.15 g, 217.67 mmol). The mixture was stirred at 60° C. for 17 h. Upon completion, the reaction mixture was diluted with H_2O (200 mL) and extracted with EA (200 mL*2). The combined organic layers were washed with brine (100 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3 (31.8 g, crude) as a yellow solid. ESI-LCMS: m/z 398.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.21 (d, J=1.3 Hz, 1H), 7.50 (d, J=8.1 Hz, 1H), 5.57 (d, J=4.5 Hz, 1H), 5.46 (dd, J=2.1, 8.0 Hz, 1H), 4.06 (t, J=5.2 Hz, 1H), 3.81-3.64 (m, 2H), 3.44-3.30 (m, 2H), 2.31-2.25 (m, 3H), 0.65 (s, 9H), −0.13 (s, 6H).

[0723] Preparation of (4): To a solution of 3 (7 g, 17.61 mmol) in THE (60 mL) was added Pd/C (2 g) at 25° C. The reaction mixture was stirred at 25° C. for 3 h under H_2 atmosphere (15 PSI). The reaction mixture was filtered, and the filtrate was concentrated to give 4 (5.4 g, 75.11% yield) as a gray solid. ESI-LCMS: m/z 372.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=7.93 (d, J=8.0 Hz, 1H), 5.81 (d, J=5.5 Hz, 1H), 5.65 (d, J=8.3 Hz, 1H), 4.28 (t, J=4.6 Hz, 1H), 3.88 (t, J=5.3 Hz, 1H), 3.74 (q, J=4.6 Hz, 1H), 3.31 (s, 3H), 2.83-2.66 (m, 2H), 0.88 (s, 9H), 0.09 (s, 6H).

[0724] Preparation of (5): To a solution of 4 (3 g, 8.08 mmol) in DCM (30 mL) was added TEA (2.45 g, 24.23 mmol, 3.37 mL) followed by dropwise addition of 3-chloropropane-1-sulfonyl chloride (1.50 g, 8.48 mmol, 1.03 mL) at 25° C. The reaction mixture was stirred at 25° C. for 18 h under N_2 atmosphere. Upon completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (50 mL*2). The combined organic layers were washed with brine (50 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was puri-

fied by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~30% MeOH/DCM @ 50 mL/min) to give 5 (3.6 g, 84.44% yield) as a white solid. ESI-LCMS: m/z 512.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.42 (s, 1H), 7.75 (d, J=8.1 Hz, 1H), 7.49 (t, J=6.2 Hz, 1H), 5.83 (d, J=5.8 Hz, 1H), 5.70-5.61 (m, 1H), 4.33-4.23 (m, 1H), 3.95 (t, J=5.5 Hz, 1H), 3.90-3.78 (m, 1H), 3.73 (t, J=6.5 Hz, 2H), 3.30 (s, 3H), 3.26-3.12 (m, 4H), 2.14-2.02 (m, 2H), 0.88 (s, 9H), 0.11 (d, J=3.3 Hz, 6H).

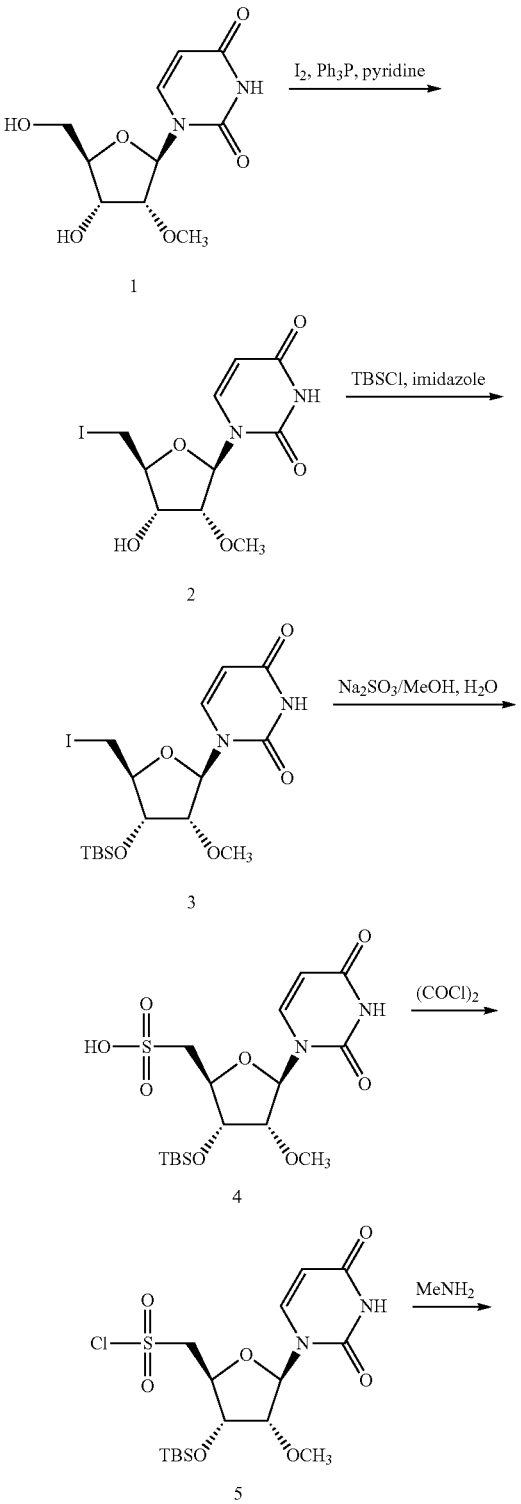
[0725] Preparation of (6): To a solution of 5 (5 g, 9.76 mmol) in DMF (45 mL) was added DBU (7.43 g, 48.82 mmol, 7.36 mL). The mixture was stirred at 25° C. for 16 h. The reaction mixture was concentrated to give a residue, diluted with H_2O (50 mL) and extracted with EA (50 mL*2). The combined organic layers were washed with brine (50 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~80% EA/PE @ 40 mL/min) to give 6 (4.4 g, 89.06% yield) as a white solid. ESI-LCMS: m/z 476.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.43 (d, J=1.7 Hz, 1H), 7.72 (d, J=8.1 Hz, 1H), 5.82 (d, J=4.8 Hz, 1H), 5.67 (dd, J=2.1, 8.1 Hz, 1H), 4.22 (t, J=5.1 Hz, 1H), 3.99-3.87 (m, 2H), 3.33-3.27 (m, 6H), 3.09 (dd, J=6.6, 14.7 Hz, 1H), 2.26-2.16 (m, 2H), 0.88 (s, 9H), 0.10 (d, J=3.8 Hz, 6H).

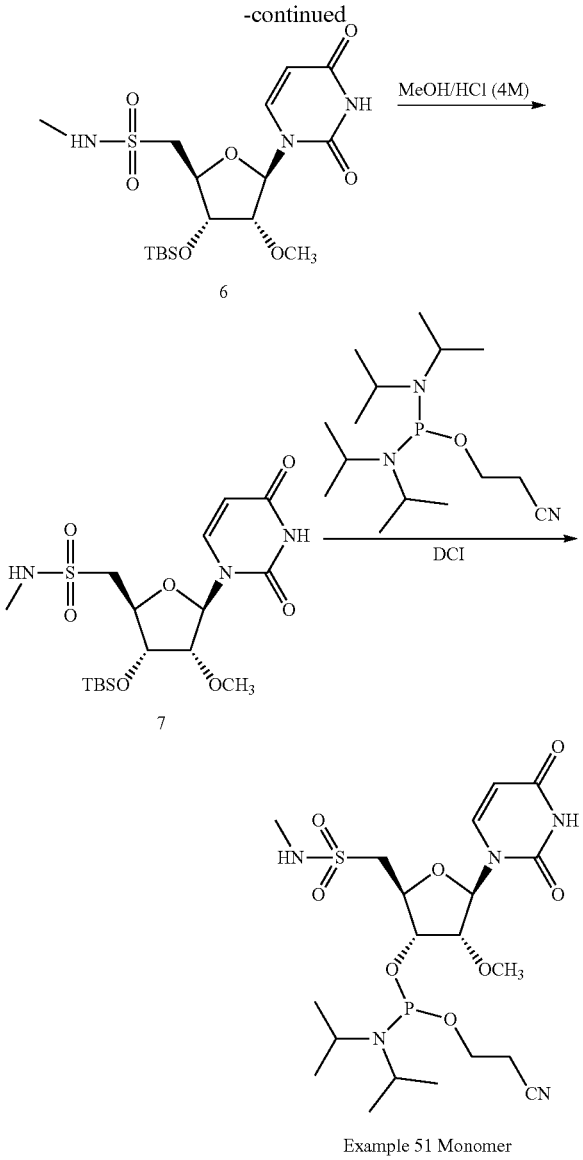
[0726] Preparation of (7): To a solution of 6 (200 mg, 420.49 umol) in MeOH (2 mL) was added NH_4F (311.48 mg, 8.41 mmol, 20 eq), and the mixture was stirred at 80° C. for 2 h. The mixture was filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% MeOH/DCM @ 20 mL/min) to give 7 (120 mg, 76.60% yield) as a white solid. ESI-LCMS: m/z 362.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.37 (br s, 1H), 7.68 (d, J=8.1 Hz, 1H), 5.81 (d, J=4.6 Hz, 1H), 5.65 (d, J=8.0 Hz, 1H), 4.02 (q, J=5.6 Hz, 1H), 3.95-3.83 (m, 2H), 3.34 (s, 9H), 3.09 (dd, J=6.9, 14.6 Hz, 1H), 2.26-2.14 (m, 2H).

[0727] Preparation of (Example 50 monomer): To a solution of 7 (1.5 g, 4.15 mmol) in CH_3CN (12 mL) were added 3-bis(diisopropylamino)phosphanyloxypropanenitrile (1.63 g, 5.40 mmol, 1.71 mL) and 1H-imidazole-4,5-dicarbonitrile (539.22 mg, 4.57 mmol) in one portion at 0° C. The reaction mixture was gradually warmed to 25° C. The reaction mixture was stirred at 25° C. for 2 h under N_2 atmosphere. Upon completion, the reaction mixture was diluted with $NaHCO_3$(20 mL) and extracted with DCM (20 mL*2). The combined organic layers were washed with brine (20 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~85% EA/PE with 0.5% TEA @ 30 mL/min to give Example 50 monomer (800 mg, 33.6% yield) as a white solid. ESI-LCMS: m/z 562.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ=9.28 (br s, 1H), 7.55 (br dd, J=8.3, 12.8 Hz, 1H), 5.86 (br d, J=3.9 Hz, 1H), 5.65 (br d, J=8.0 Hz, 1H), 4.33-4.06 (m, 2H), 4.00-3.89 (m, 1H), 4.08-3.86 (m, 1H), 3.89-3.72 (m, 4H), 3.43 (br d, J=15.1 Hz, 6H), 3.23-3.05 (m, 3H), 2.69 (br s, 2H), 2.36-2.24 (m, 2H), 1.26-1.10 (m, 12H)^{31}P NMR (162 MHz, CD_3CN) δ=149.94, 149.88.

Example 51: Synthesis of 5' End Cap Monomer

[0728]





Example 51 Monomer Synthesis Scheme

[0729] Preparation of (2): To a solution of 1 (30 g, 101.07 mmol, 87% purity) in CH_3CN (1.2 L) and Py (60 mL) were added 12 (33.35 g, 131.40 mmol, 26.47 mL) and PPh_3 (37.11 g, 141.50 mmol) in one portion at 10° C. The reaction was stirred at 25° C. for another 48 h. The mixture was diluted with aq.$Na_2S_2O_3$ (300 mL) and aq.$NaHCO_3$(300 mL), concentrated to remove CH_3CN, and then extracted with EtOAc (300 mL*3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~60% Methanol/Dichloromethane gradient @ 100 mL/min) to give 2 (28.2 g, 72.00% yield, 95% purity) as a brown solid. ESI-LCMS: m/z 369.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.43 (s, 1H), 7.68 (d, J=8.1 Hz, 1H), 5.86 (d, J=5.5 Hz, 1H), 5.69 (d, J=8.1 Hz, 1H), 5.46 (d, J=6.0 Hz, 1H), 4.08-3.96 (m, 2H), 3.90-3.81 (m, 1H), 3.60-3.51 (m, 1H), 3.40 (dd, J=6.9, 10.6 Hz, 1H), 3.34 (s, 3H).

[0730] Preparation of (3): To a solution of 2 in DMF (90 mL) were added imidazole (4.25 g, 62.48 mmol) and TBSCl (6.96 g, 46.18 mmol) in one portion at 15° C. The mixture was stirred at 15° C. for 6 h. The reaction mixture was quenched by addition of H_2O (300 mL) and extracted with EtOAc (300 mL*2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3 (13.10 g, crude) as a white solid. ESI-LCMS: m/z 483.0 $[M+H]^+$.

[0731] Preparation of (4): To a solution of 3 (10 g, 20.73 mmol) in MeOH (20 mL), H_2O (80 mL), and dioxane (20 mL) was added Na_2SO_3 (15.68 g, 124.38 mmol), and the mixture was stirred at 80° C. for 24 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The aqueous layer was extracted with EtOAc (80 mL*2) and concentrated under reduced pressure to give a residue. The residue was triturated with MeOH (100*3 mL) to give 4 (9.5 g, 94.48% yield, 90% purity) as a white solid. ESI-LCMS: m/z 437.0 $[M+H]^+$.

[0732] Preparation of (5): To a solution of 4 (11 g, 21.42 mmol, 85% purity) in DCM (120 mL) was added DMF (469.65 mg, 6.43 mmol, 494.37 uL) at 0° C., followed by dropwise addition of oxalyl dichloride (13.59 g, 107.10 mmol, 9.37 mL). The mixture was stirred at 20° C. for 2 h. The reaction mixture was quenched by addition of water (60 mL) and the organic layer 5 (0.1125 M, 240 mL DCM) was used directly for next step. (This reaction was set up for two batches and combined) ESI-LCMS: m/z 455.0 $[M+H]^+$.

[0733] Preparation of (6): 5 (186.4 mL, 0.1125 M in DCM) was diluted with DCM (60 mL) and treated with methylamine (3.26 g, 41.93 mmol, 40% purity). The mixture was stirred at 20° C. for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10%, MeOH/DCM gradient @ 40 mL/min) to give AGS-9-3-008 (1.82 g, 18.53% yield, 96% purity) as a yellow solid. ESI-LCMS: m/z 472.0 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=9.08 (s, 1H), 7.31 (d, J=8.1 Hz, 1H), 5.78 (d, J=8.1 Hz, 1H), 5.57 (d, J=3.8 Hz, 1H), 4.61-4.48 (m, 1H), 4.41-4.27 (m, 2H), 4.13-4.03 (m, 1H), 3.46 (s, 3H), 3.43-3.33 (m, 2H), 2.78 (d, J=5.2 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 6H).

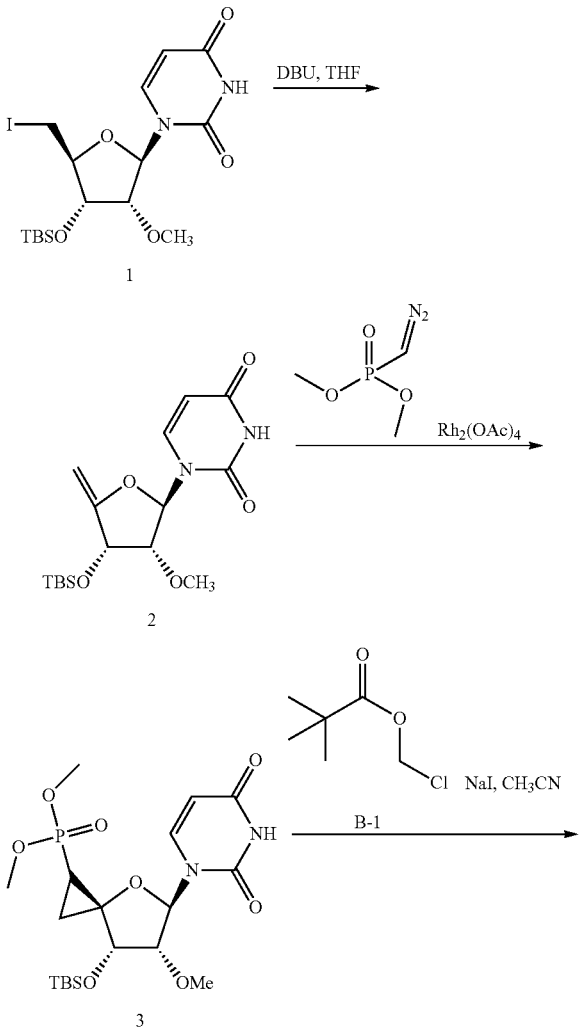
[0734] Preparation of (7): To a solution of 6 (2.3 g, 5.12 mmol) in MeOH (12 mL) was added HCl/MeOH (4 M, 6.39 mL). The mixture was stirred at 20° C. for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~15%, MeOH/DCM gradient @ 30 mL/min) to give 7 (1.4 g, 79.98% yield) as a pink solid. ESI-LCMS: m/z 336.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=9.12 (s, 1H), 7.39 (d, J=8.0 Hz, 1H), 5.79 (d, J=3.3 Hz, 1H), 5.66 (dd, J=2.1, 8.2 Hz, 1H), 5.13 (s, 1H), 4.13 (t, J=4.0, 7.4 Hz, 1H), 4.07-4.02 (m, 1H), 3.87 (dd, J=3.3, 5.5 Hz, 1H), 3.47 (s, 3H), 3.43-3.37 (m, 2H), 2.65 (d, J=4.5 Hz, 3H).

[0735] Preparation of (Example 51 monomer): To a mixture of 7 (1.7 g, 5.07 mmol) and 4A MS (1.4 g) in MeCN (18 mL) was added 3-bis(diisopropylamino)phosphanyloxypropanenitrile (1.99 g, 6.59 mmol, 2.09 mL) at 0° C., followed by addition of 1H-imidazole-4,5-dicarbonitrile (658.57 mg,

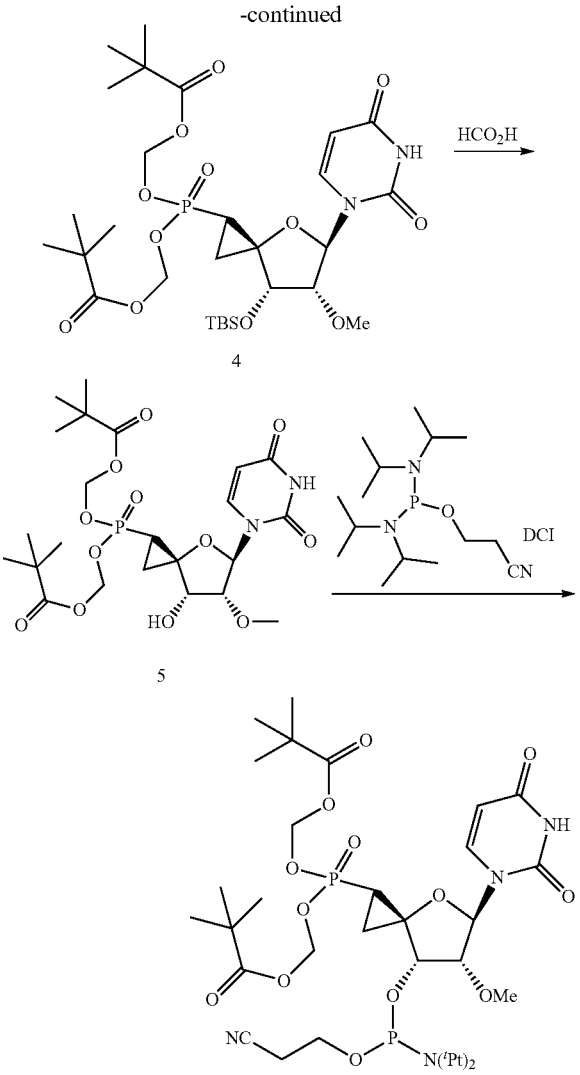
5.58 mmol) in one portion at 0° C. The mixture was stirred at 20° C. for 2 h. Upon completion, the reaction mixture was quenched by addition of sat. $NaHCO_3$ solution (20 mL) and diluted with DCM (40 mL). The organic layer was washed with sat. $NaHCO_3$(20 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by a flash silica gel column (0% to 5% i-PrOH in DCM with 5% TEA) to give Example 51 monomer (1.30 g, 46.68% yield) as a white solid. ESI-LCMS: m/z 536.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3CN) δ=9.00 (s, 1H), 7.40 (d, J=8.0 Hz, 1H), 5.85-5.76 (m, 1H), 5.64 (d, J=8.0 Hz, 1H), 5.08 (d, J=5.0 Hz, 1H), 4.42-4.21 (m, 2H), 4.00 (td, J=4.6, 9.3 Hz, 1H), 3.89-3.61 (m, 4H), 3.47-3.40 (m, 4H), 3.37-3.22 (m, 1H), 2.71-2.60 (m, 5H), 1.21-1.16 (m, 11H), 1.21-1.16 (m, 1H); ^{31}P NMR (162 MHz, CD_3CN) δ=150.07, 149.97

Example 52: Synthesis of 5' End Cap Monomer

[0736]



-continued



Example 52 Monomer Synthesis Scheme

[0737] Preparation of (2): To a solution of 1 (13.10 g, 27.16 mmol) in THF (100 mL) was added DBU (20.67 g, 135.78 mmol, 20.47 mL). The mixture was stirred at 60° C. for 6 h. Upon completion, the reaction mixture was quenched by addition of sat.NH_4C_1 solution (600 mL) and extracted with EA (600 mL*2). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~50% (Phase B: ethyl acetate:dichloromethane=1:1)/Phase A: petroleum ethergradient@ 45 mL/min) to give 2 (5.9 g, 60.1% yield) as a white solid. ESI-LCMS: m/z 355.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.61-11.30 (m, 1H), 7.76-7.51 (m, 1H), 6.04 (d, J=5.4 Hz, 1H), 5.75 (s, 1H), 5.73-5.67 (m, 1H), 4.78 (d, J=4.9 Hz, 1H), 4.41 (d, J=1.1 Hz, 1H), 4.30 (t, J=4.8 Hz, 1H), 4.22 (d, J=1.4 Hz, 1H), 4.13 (t, J=5.1 Hz, 1H), 4.06-3.97 (m, 1H), 3.94-3.89 (m, 1H), 3.82-3.75 (m, 1H), 3.33 (s, 3H), 3.30 (s, 2H), 1.17 (t, J=7.2 Hz, 1H), 0.89 (s, 9H), 0.16-0.09 (m, 6H).

[0738] Preparation of (3): To a solution of 2 (4 g, 11.28 mmol) in DCM (40 mL) was added Ru(II)-Pheox (214.12 mg, 338.53 umol) in one portion followed by addition of diazo(dimethoxyphosphoryl)methane (2.54 g, 16.93 mmol) dropwise at 0° C. under N_2. The reaction was stirred at 20° C. for 16 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~4% MeOH/DCM@ 60 mL/min) to give 3 (5 g, 86.47% yield) as a red liquid. ESI-LCMS: m/z 477.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ=11.46 (s, 1H), 7.49 (d, J=8.0 Hz, 1H), 6.01-5.87 (m, 1H), 5.75 (dd, J=2.0, 8.0 Hz, 1H), 4.58 (d, J=3.8 Hz, 1H), 4.23 (dd, J=3.8, 7.8 Hz, 1H), 3.80-3.68 (m, 6H), 3.30 (s, 3H), 1.65-1.46 (m, 2H), 1.28-1.16 (m, 1H), 0.91 (s, 9H), 0.10 (d, J=4.3 Hz, 6H); ^{31}P NMR (162 MHz, DMSO-d_6) δ=27.5

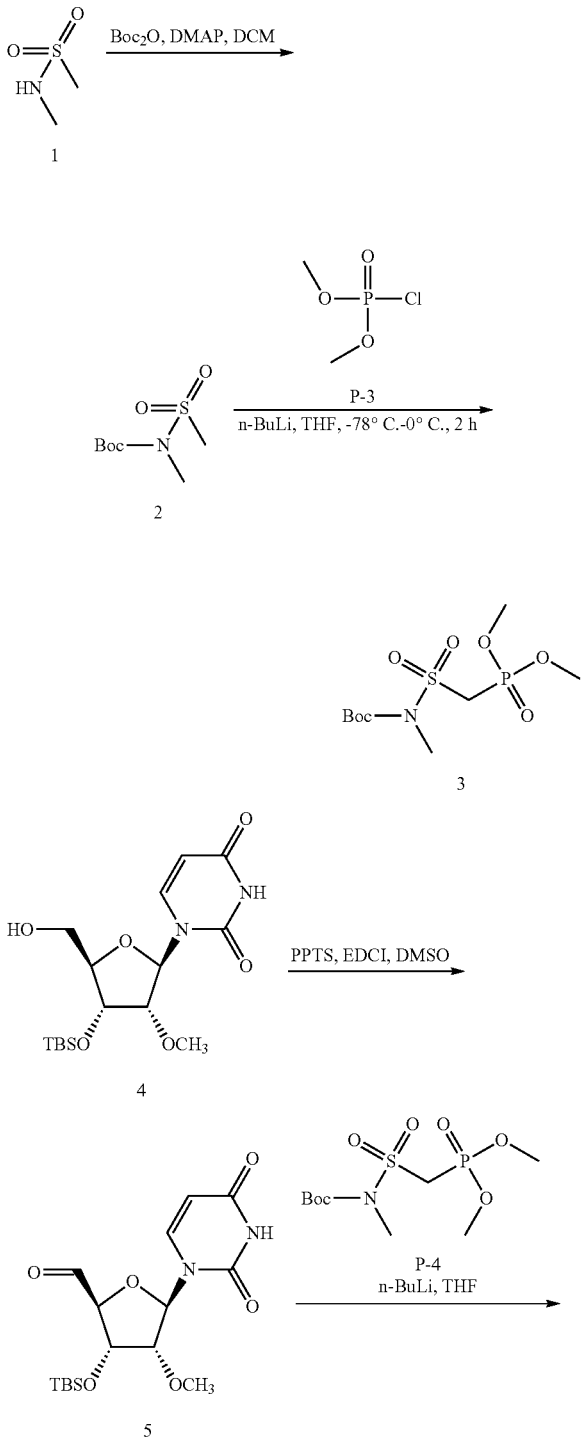
[0739] Preparation of (4): To a mixture of 3 (2.8 g, 5.88 mmol) and NaI (1.76 g, 11.75 mmol) in CH_3CN (30 mL) was added chloromethyl 2,2-dimethylpropanoate (2.21 g, 14.69 mmol, 2.13 mL) at 25° C. The mixture was stirred at 80° C. for 40 h under Ar. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ether gradient @ 40 mL/min) to give 4 (2.1 g, 51.23% yield, 97% purity) as a yellow solid. ESI-LCMS: 677.3 $[M+H]^+$.

[0740] Preparation of (5): A mixture of 4 (2.09 g, 3.09 mmol) in H_2O (1.5 mL) and HCOOH (741.81 mg, 15.44 mmol, 6 mL) was stirred at 15° C. for 40 h. Upon completion, the reaction mixture was quenched by saturated aq.$NaHCO_3$(300 mL) and extracted with EA (300 mL*2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~5% Methanol/Dichloromethane@ 45 mL/min) to give 5 (1.51 g, 85.19% yield) as a yellow solid. ESI-LCMS: 585.1 $[M+Na]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ=11.45 (d, J=1.8 Hz, 1H), 7.44 (d, J=8.2 Hz, 1H), 6.04 (d, J=7.5 Hz, 1H), 5.78-5.51 (m, 6H), 4.39 (t, J=4.4 Hz, 1H), 4.15 (dd, J=4.3, 7.4 Hz, 1H), 4.03 (q, J=7.1 Hz, 1H),1.99 (s, 1H), 1.66 (dd, J=8.6, 10.8 Hz, 1H), 1.55-1.29 (m, 2H), 1.18 (d, J=2.0 Hz, 18H).

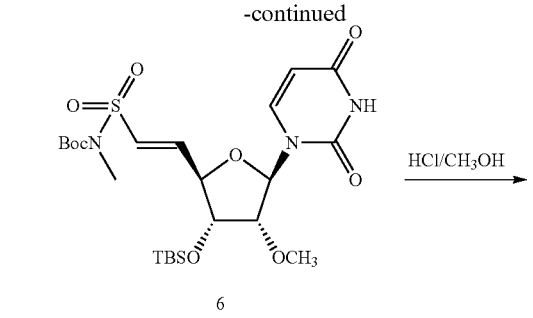
[0741] Preparation of (Example 52 monomer): To a solution of 5 (2.5 g, 4.44 mmol) in MeCN (30 mL) was added 3-bis(diisopropylamino)phosphanyloxypropanenitrile (1.74 g, 5.78 mmol, 1.84 mL) at 0° C., followed by 1H-imidazole-4,5-dicarbonitrile (577.36 mg, 4.89 mmol) in one portion under Ar. The mixture was gradually warmed to 20° C. and stirred at 20° C. for 1 h. The reaction mixture was quenched by addition of sat.$NaHCO_3$ solution (50 mL) and diluted with DCM (250 mL). The organic layer was washed with sat.$NaHCO_3$ solution (50 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by a flash silica gel column (0% to 50% EA/PE with 0.5% TEA) to give Example 52 monomer (1.85 g, 54.1% yield) as a white solid. ESI-LCMS: 785.2 $[M+Na]^+$; ^{1}H NMR (400 MHz, CD_3CN) δ=9.18 (s, 1H), 7.31 (d, J=8.3 Hz, 1H), 6.06 (d, J=7.8 Hz, 1H), 5.72-5.60 (m, 5H), 4.85-4.76 (m, 1H), 4.27 (m, 1H), 3.93-3.64 (m, 4H), 3.41 (d, J=16.6 Hz, 3H), 2.80-2.62 (m, 2H), 1.76-1.49 (m, 3H), 1.23-1.19 (m, 30H); ^{31}P NMR (162 MHz, CD_3CN) δ=150.66 (s), 150.30, 24.77, 24.66.

Example 53: Synthesis of 5' End Cap Monomer

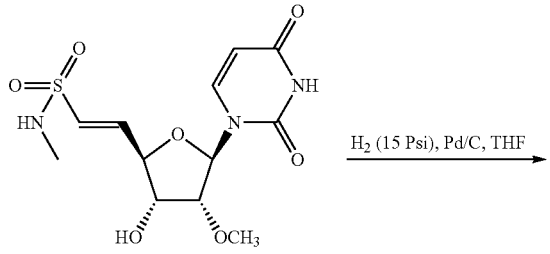
[0742]



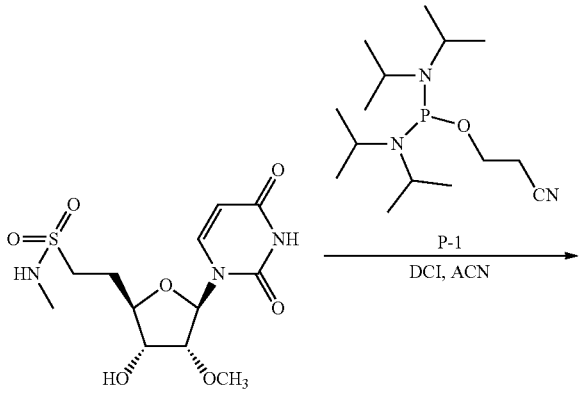
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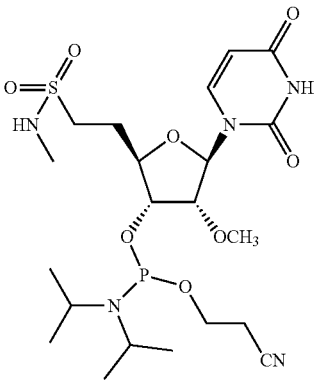
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7



8



Example 53 Monomer

Example 53 Monomer Synthesis Scheme

[0743] Preparation of (2): To a solution of 1 (15 g, 137.43 mmol) in DCM (75 mL) were added Boc_2O (31.49 g, 144.30 mmol, 33.15 mL) and DMAP (839.47 mg, 6.87 mmol, 0.05 eq) at 0° C. The mixture was stirred at 20° C. for 16 hr, and concentrated under reduced pressure to give 2 (29.9 g, crude) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ=3.23 (s, 3H), 3.16 (s, 3H), 1.51 (s, 9H).

[0744] Preparation of (3): To a solution of 2 (24.9 g, 118.99 mmol) in THE (250 mL) was added n-BuLi (2.5 M, 47.60 mL) dropwise at −78° C. under Ar and stirred at −78° C. for 1 hr. P-3 (17.19 g, 118.99 mmol, 12.83 mL) was added at 0° C. and stirred for 1 hr. The reaction mixture was quenched by saturated aq. NH_4Cl (100 mL), and then extracted with EA (100 mL*2). The combined organic layers were washed with brine (100 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0-50% Ethylacetate/Petroleum ethergradient @ 65 mL/min) to give 3 (7.1 g, 18.62% yield) as a yellow oil. ESI-LCMS: 339.9 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=4.12 (s, 1H), 4.08 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.22 (s, 3H), 1.51 (s, 9H).

[0745] Preparation of (5): To a mixture of 4 (15 g, 40.27 mmol) and PPTS (10.12 g, 40.27 mmol) in DMSO (75 mL) was added EDCI (23.16 g, 120.81 mmol) at 20° C. The mixture was stirred at 20° C. for 4 hr. The reaction mixture was diluted with water (150 mL) and extracted with EA (150 mL*2). The combined organic layers were washed with brine (150 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 5 (12 g, crude) as a white solid. ESI-LCMS: 371.2$[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=9.77 (s, 1H), 7.62 (d, J=8.1 Hz, 1H), 5.83-5.76 (m, 2H), 4.53 (d, J=4.3 Hz, 1H), 4.43 (br t, J=4.4 Hz, 1H), 3.95 (br t, J=4.7 Hz, 1H), 3.47-3.35 (m, 5H), 0.92 (s, 9H), 0.13 (d, J=5.8 Hz, 6H).

[0746] Preparation of (6): To a solution of P4 (8.02 g, 25.27 mmol) in THE (40 mL) was added n-BuLi (2.5 M, 8.42 mL) dropwise under Ar at −78° C., and the mixture was stirred at −78° C. for 0.5 hr. A solution of 4 (7.8 g, 21.05 mmol) in THE (40 mL) was added dropwise. The mixture was allowed to warm to 0° C. and stirred for another 2 hr. The reaction mixture was quenched by saturated aq. NH_4Cl solution (80 mL) and extracted with EA (80 mL). The combined organic layers were washed with brine (80 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0-38% ethylacetate/petroleum ether gradient @ 60 mL/min) to give 7 (7.7 g, 13.43 mmol, 63.8% yield) as a white solid. ESI-LCMS: 506.2 $[M-tBu]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ=8.97 (s, 1H), 7.25 (d, J=8.3 Hz, 1H), 6.95-6.88 (m, 1H), 6.87-6.81 (m, 1H), 5.83-5.77 (m, 2H), 4.58 (dd, J=4.4, 6.7 Hz, 1H), 4.05 (dd, J=5.0, 7.5 Hz, 1H), 3.82-3.77 (m, 1H), 3.53 (s, 3H), 3.20 (s, 3H), 1.50 (s, 9H), 0.91 (s, 9H), 0.11 (d, J=2.5 Hz, 6H).

[0747] Preparation of (7): To a solution of 6 (7.7 g, 13.71 mmol) in MeOH (10 mL) was added HCl/MeOH (4 M, 51.40 mL) at 20° C. The mixture was stirred at 20° C. for 16 hr. Upon completion, the reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~4% MeOH/

DCM @ 60 mL/min) to give 7 (4.1 g, 86.11% yield) as a white solid. ESI-LCMS: 369.9 $[M+Na]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.44 (s, 1H), 7.66 (d, J=8.3 Hz, 1H), 7.11 (q, J=4.9 Hz, 1H), 6.69 (dd, J=6.0, 15.1 Hz, 1H), 6.56-6.47 (m, 1H), 5.82 (d, J=4.0 Hz, 1H), 5.67 (dd, J=2.0, 8.0 Hz, 1H), 5.56 (br s, 1H), 4.42 (t, J=6.1 Hz, 1H), 4.13 (t, J=5.8 Hz, 1H), 3.97 (t, J=4.8 Hz, 1H), 3.39 (s, 3H), 2.48 (d, J=5.3 Hz, 3H)

[0748] Preparation of (8): To a solution of 7 (2.5 g, 7.20 mmol) in THE (25 mL) was added Pd/C (2.5 g, 10% purity) under H_2 atmosphere, and the suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 20° C. for 1 hr. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethylacetate/Petroleum ethergradient @ 50 mL/min) to give 8 (2.2 g, 87.49% yield) as a white solid. ESI-LCMS: 372.1 $[M+Na]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ=11.40 (s, 1H), 7.62 (d, J=8.0 Hz, 1H), 6.93 (q, J=4.9 Hz, 1H), 5.76 (d, J=4.5 Hz, 1H), 5.66 (d, J=8.0 Hz, 1H), 5.26 (d, J=6.3 Hz, 1H), 3.97 (q, J=5.9 Hz, 1H), 3.91-3.79 (m, 2H), 3.36 (s, 3H), 3.14-3.00 (m, 2H), 2.56 (d, J=5.0 Hz, 3H), 2.07-1.87 (m, 2H).

[0749] Preparation of (Example 53 monomer): To a solution of 8 (2.2 g, 6.30 mmol, 1 eq) in CH_3CN (25 mL) was added P-1 (2.47 g, 8.19 mmol, 2.60 mL, 1.3 eq) at 0° C., and then 1H-imidazole-4,5-dicarbonitrile (818.07 mg, 6.93 mmol, 1.1 eq) was added in one portion at 0° C. under Ar. The mixture was stirred at 20° C. for 2 hr. Upon completion, the reaction mixture was quenched by saturated aq. $NaHCO_3$(25 mL), and extracted with DCM (25 mL*2). The combined organic layers were washed with brine (25 mL*2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 40-85% ethylacetate/petroleum ether gradient @ 40 mL/min) to give Example 53 monomer (2.15 g, 61.32% yield) as a white solid. ESI-LCMS: 572.2 $[M+Na]^+$; ^1H NMR (400 MHz, CD_3CN) δ=9.32 (br s, 1H), 7.39 (d, J=8.1 Hz, 1H), 5.82-5.75 (m, 1H), 5.66 (dd, J=0.7, 8.1 Hz, 1H), 5.14 (qd, J=4.9, 9.4 Hz, 1H), 4.24-4.02 (m, 2H), 3.99-3.93 (m, 1H), 3.90-3.60 (m, 4H), 3.43 (d, J=17.5 Hz, 3H), 3.18-3.08 (m, 2H), 2.74-2.61 (m, 5H), 2.19-2.11 (m, 1H), 2.09-1.98 (m, 1H), 1.19 (ddd, J=2.4, 4.0, 6.6 Hz, 12H). ^{31}P NMR (162 MHz, CD_3CN) δ=149.77 (s), 149.63 (br s).

Example 54. Long-Term Efficacy of siNA in an AAV-HBV Mouse Model

[0750] AAV/HBV is a recombinant AAV carrying replicable HBV genome. Taking advantage of the highly hepatotropic feature of genotype 8 AAV, the HBV genome can be efficiently delivered to the mouse liver cells. Infection of immune competent mouse with AAV/HBV can result in long term HBV viremia, which mimics chronic HBV infection in patients. The AAV/HBV model can be used to evaluate the in vivo activity of various types of anti-HBV agents. Mice were infected with AAV-HBV on day −28 of the study. AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0147 on day 0. Serial blood collections were usually taken every 5 days on day 0, 5, 10, and 15, etc. until the termination of the study. Serum HBV S antigen (HBsAg) was assayed through ELISA. FIG. **13** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 15) or ds-siNA-0147 (G 19). As shown in FIG. **13**, ds-siNA-0147 was effective in reducing serum HBsAg levels and the reduction in serum HBsAg levels was observed for the duration of the study (i.e., 100 days). Thus, FIG. **13** demonstrates that ds-siNA-0147 is effective and durable after a single dose of 5 mg/kg.

ds-siNA ID	Strand	Sequence	SEQ ID NO:
ds-siNA-0147	Sense	5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmU mCmAmAmU-p-ps2-GalNAc4-3'	438
	Antisense	3'-mApsmGpsmCmAmCfCmAfCmCmUmGmAmAmG mAfGmAmGmUpsfUpsmA-5'	501

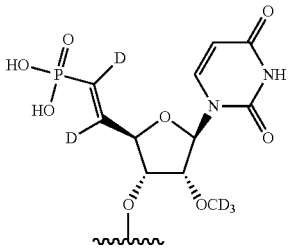
Example 55. Deuterated Vinyl Phosphonate Improves Potency of siNA

[0751] This example investigates whether a deuterated vinyl phosphonate improves potency of siNA in an AAV-HBV mouse. AAV-HBV mice were subcutaneously injected with vehicle, ds-siNA-0109 (e.g., siNA without a deuterated vinyl phosphonate), or ds-siNA-0172 (e.g., siNA with a deuterated vinyl phosphonate). AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0149 or ds-siNA-0172 at day 0. Serial blood collections were usually taken every 5 days on day 0, 5, 10, and 15, etc. until the termination of the study. Serum HBV S antigen (HBsAg) was assayed through ELISA.

[0752] As shown in FIG. **14**, siNA molecules having 2'-fluoro nucleotides at positions 5 and 7-9 from the 5' end of the sense strand and 2'-fluoro nucleotides at positions 2, 5, 8, 14, and 17 from the 5' end of the antisense strand resulted in greater than a 0.5-log reduction in HBsAg, with the greatest reduction in HBsAg found in mice treated with the deuterated vinylphopshonate siNA (ds-siNA-0172). In addition, the duration of the reduction in serum HBsAg levels was significantly longer for the deuterated vinylphosphonate siNA (ds-siNA-0172). Thus, FIG. **14** demonstrates that the presence of a deuterated vinyl phosphonate improves potency and durability of the siNA.

ds-siNA ID	Strand	Sequence	SEQ ID NO:
ds-siNA-0109	Sense	5'-mCpsmCpsmGmUfGmUfGfCfAmCmUmUmCmGmC mUmUmCmAp-ps2-GalNAc4	424
	Antisense	3'-mCpsmUpsmGmGfCmAmCfAmCmGmUmGmAfAmG mCfGmAmApsfGpsmU-5'	485
ds-siNA-0172	Sense	5'-mCpsmCpsmGmUfGmUfGfCfAmCmUmUmCmGmC mUmUmCmA-p-ps2-GalNAc4-3'	424
	Antisense	3'-mCpsmUpsmGmGfCmAmCfAmCmGmUmGmAfAmG mCfGmAmApsfGpsd2vd3U-5'	536

d2vd3U =



Example 56. Comparison of siNAs

[0753] AAV/HBV is a recombinant AAV carrying replicable HBV genome. Taking advantage of the highly hepatotropic feature of genotype 8 AAV, the HBV genome can be efficiently delivered to the mouse liver cells. Infection of immune competent mouse with AAV/HBV can result in long term HBV viremia, which mimics chronic HBV infection in patients. The AAV/HBV model can be used to evaluate the in vivo activity of various types of anti-HBV agents. Mice were infected with AAV-HBV on day −28 of the study. AAV-HBV mice were subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0109, ds-siNA-0119, or ds-siNA-0153 on day 0. Serial blood collections were usually taken every 5 days on day 0, 5, 10, and 15, etc. until the termination of the study. Serum HBV S antigen (HBsAg) was assayed through ELISA. FIG. **15** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 01, circle), ds-siNA-0109 (G 07, square), ds-siNA-0119 (G11, triangle), or ds-siNA-0153 (G13, diamond). As shown in FIG. **14**, all three ds-siNAs were effective in reducing serum HBsAg levels and the reduction in serum HBsAg levels was observed for the duration of the study (i.e., 100 days), with the best potency and durability observed for ds-siNA-0153. Thus, FIG. **15** demonstrates that ds-siNA-0109, ds-siNA-0119, and ds-siNA-0153 were effective and durable after a single dose of 5 mg/kg.

ds-siNA ID	Strand	Sequence	SEQ ID NO:
ds-siNA-0109	Sense	5'-mCpsmCpsmGmUfGmUfGfCfAmCmUmUmCmGmC mUmUmCmAp-ps2-GalNAc4	424
	Antisense	3'-mCpsmUpsmGmGfCmAmCfAmCmGmUmGmAfAmG mCfGmAmApsfGpsmU-5'	485
ds-siNA-0119	Sense	5'-mGpsmCpsmUmGfCmUmAmUfGfCfCmUmCfAmU mCmUmUfCmUmU-p-ps2-GalNAc4	430
	Antisense	3'-mGpsmApsmCmGmAmCmGmAmUfAmCmGmGmA mGmUmAmGmAmAmGpsfApsmA-5'	595
ds-siNA-0153	Sense	5'-mUpsmGpsfUmGmCmAfCfUfUmCmGfCmUmUmC mAfCmCmU-p-ps2-GalNAc4-3'	441
	Antisense	3'-mGpsmCpsmAfCmAmCmGfUmGmAmAfGmCmGmA fAmGmUmGpsfGpsmA-5	526

Example 57. Efficacy of a Combination Therapy in AAV-HBV Mouse Model

[0754] This example investigates the efficacy of a combination therapy comprising an antisense oligonucleotide (ASO 1, 5' GalNAc4-ps-GalNAc4-ps-GalNAc4-po-mA-po-lnGpslnApslnTpslnApslnApsApsAps(50H)CpsGps(5m) Cps(5m)CpsGps(5m)CpslnApslnG pslnApscp(5m)C-3' (SEQ ID NO: 534)) and a ds-siNA-0147 for treating HBV in an AAV-HBV mouse model.

[0755] AAV-HBV mice were subcutaneously injected with (a) 5 mL/kg of vehicle, three times a week, on days 0, 7, and 14 (G 01); (b) 5 mg/kg of ASO 1 on a weekly basis, on days 0, 7, and 14 (G 20); (c) a single dose of 5 mg/kg of ds-siNA-0147 on day 0 (G 24); or (d) a combination of ASO 1 and ds-siNA-0147, wherein ASO 1 was administered at a dose of 5 mg/kg on a weekly basis, on days 0, 7, and 14; and ds-siNA-0160 was administered as a single dose of 5 mg/kg at day 0 (G25). Serial blood collections were usually taken every 5 days on day 0, 5, 10, and 15, etc. until the

termination of the study. Serum HBV S antigen (HBsAg) was assayed through ELISA. FIG. **16** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 01, circle), ASO 1 (G 20, square), ds-siNA-0147 (G 24, diamond), or a combination of ds-siNA-0147 and ASO 1 (G 25, triangle). As shown in FIG. **16**, treatment with ASO 1, ds-siNA-0147, or a combination of ASO 1 and ds-siNA-0147 resulted in a reduction in serum, with the greatest reduction observed in mice treated with the combination of ASO 1 and ds-siNA-0147.

ds-siNA ID	Strand	Sequence	SEQ ID NO:
ds-siNA-0147	Sense	5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmU mCmAmAmU-p-ps2-GalNAc4-3'	438
	Antisense	3'-mApsmGpsmCmAmCfCmAfCmCmUmGmAmAmG mAfGmAmGmUpsfUpsmA-5'	501

Example 58. Efficacy of a Combination Therapy in AAV-HBV Mouse Model

[0756] This example investigates the efficacy of a combination therapy comprising an antisense oligonucleotide (ASO 1, 5' GalNAc4-ps-GalNAc4-ps-GalNAc4-po-mA-po-lnGpslnApslnTpslnApslnApsApsAps(5OH)CpsGps(5m) Cps(5m)CpsGps(5m)CpslnApslnG pslnApscp(5m)C-3' (SEQ ID NO: 534)) and a ds-siNA-0109 for treating HBV in an AAV-HBV mouse model.

[0757] AAV-HBV mice were subcutaneously injected with (a) 5 mL/kg of vehicle, three times a week, on days 0, 7, and 14 (G 01); (b) 5 mg/kg of ASO 1 on a weekly basis, on days 0, 7, and 14 (G 20); (c) a single dose of 5 mg/kg of ds-siNA-0109 on day 0 (G 26); or (d) a combination of ASO 1 and ds-siNA-0109, wherein ASO 1 was administered at a dose of 5 mg/kg on a weekly basis, on days 0, 7, and 14; and ds-siNA-0160 was administered as a single dose of 5 mg/kg at day 0 (G27). Serial blood collections were usually taken every 5 days on day 0, 5, 10, and 15, etc. until the termination of the study. Serum HBV S antigen (HBsAg) was assayed through ELISA. FIG. **17** shows a graph of the change in serum HBsAg from AAV-HBV mice treated with vehicle (G 01, circle), ASO 1 (G 20, square), ds-siNA-0109 (G 26, diamond), or a combination of ds-siNA-0109 and ASO 1 (G 27, triangle). As shown in FIG. **17**, treatment with ASO 1, ds-siNA-0109, or a combination of ASO 1 and ds-siNA-0109 resulted in a reduction in serum, with the greatest reduction observed in mice treated with the combination of ASO 1 and ds-siNA-0109.

ds-siNA ID	Strand	Sequence	SEQ ID NO:
ds-siNA-0109	Sense	5'-mCpsmCpsmGmUfGmUf GfCfAmCmUmUmCmGmC mUmUmCmAp-ps2-GalNAc4	424
	Antisense	3'-mCpsmUpsmGmGfCmAm CfAmCmGmUmGmAfAmG mCfGmAmApsfGpsmU-5'	485

Example 59. Role of 2'-Fluoro Mimics on siNA Activity

[0758] This example investigates the role of 2'-fluoro mimics, f4P and f2P monomers, on siNA activity. The f4P monomer was produced as described in Example 42. The f2P monomer was produced as described in Example 45.

[0759] The activity of ds-siNA-0173, ds-siNA-0174, and ds-siNA-0175 was assayed using an in vitro HBsAg secretion assay with HepG2.2.15 cells. Generally, HepG2.2.15 cells were maintained in DMEM medium with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin, 1% Glutamine, 1% non-essential amino acids, 1% Sodium Pyruvate and 250 ug/ml G418. Cells were maintained at 37° C. in a 5% CO^2 atmosphere. For HBsAg release assay, an assay medium was made that DMEM with 5% FBS, 1% penicillin/streptomycin, 1% Glutamine and 1% DMSO. The day before the assay, HepG2.2.15 cells were trypsinized and washed with Assay Medium once, then spun at 250 g×5 min, resuspended with Assay Medium. The resuspenced cells were seeded at 50,000/well in assay medium in collagen coated 96 well plates. On the next day, siRNA was diluted with Opti-MEM, 9-pt, 3-fold dilution and dilute Lipofectamine RNAiMAX (Invitrogen) according manufacturer's manual. siRNA dilution and RNAiMAX dilution were mixed and incubated at room temperature for 5 minutes. 15 μl of the siRNA/RNAiMax mixture was added each well of the collagen coated 96 well plate. The plates were placed in a 37° C., 5% CO^2 incubator for 4 days. After incubation, the supernatant was harvested and measured for HBsAg with ELISA kit (Diasino). The cell viability was measured with CellTiter-Glo (Promega). The EC50, the concentration of the drug required for reducing HBsAg secretion by 50% in relation to the untreated cell control, was calculated using the Prism Graphpad. The CC50, the concentration of the drug required for reducing cell viability by 50% in relation to the untreated cell control, was calculated with the same software. The EC50 and CC50 values are shown in Table 11.

TABLE 11

siNA Activity

ds-siNA ID	Strand	Sequence	SEQ ID NO:	EC50 (nM)*	CC50 (nM)
ds-siNA-0173	Sense	5'-mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmAmU	438	C	>1
	Anti-sense	3'-mApsmGpsmCmAmCfCmA fCmCmUmGmAmAmGmAf GmAmGmUpsf4PpsmA-5'	537		
ds-siNA-0174	Sense	5'-mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmAmU	438	A	>1
	Anti-sense	3'-mApsmGpsmCmAmCfCmAf2P mCmUmGmAmAmGmAfGm AmGmUpsfUpsmA-5'	538		
ds-siNA-0175	Sense	5'-mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmAmU	438	B	>1
	Anti-	5'-mApsfUpsmUmGmAfGmAmG	501		

TABLE 11-continued

siNA Activity					
ds-siNA ID	Strand	Sequence	SEQ ID NO:	EC50 (nM)*	CC50 (nM)
(control)	sense	mAmAmGmUmCfCmAfCmCmAmCpsmGpsmA-3'			

*A = EC50 < 0.2 nM; B = 0.2 nM < EC50 < 0.1 nm; C = EC50 > 0.1 nm

f4P =

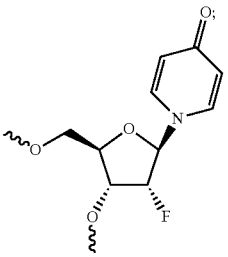
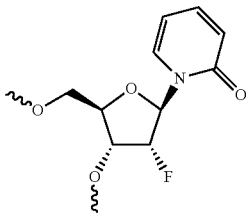


TABLE 11-continued

siNA Activity					
ds-siNA ID	Strand	Sequence	SEQ ID NO:	EC50 (nM)*	CC50 (nM)

f2P =

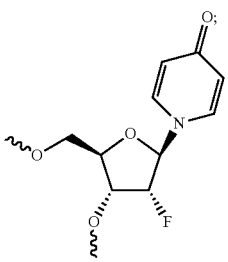


Example 60. Role of 2'-Fluoro Mimics on siNA Activity

[0760] This example investigates the role of 2'-fluoro mimics, f4P, f2P, and fx monomers, on siNA activity of GalNAc4 conjugated siNAs. The f4P monomer was produced as described in Example 42. The f2P monomer was produced as described in Example 45. The fx monomer was produced as described in Example 41.

ds-siNA ID	Strand	Sequence	SEQ ID NO:
ds-siNA-0176	Sense	5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-(PS)2-GalNAc4	438
	Antisense	3'-mApsmGpsmCmAmCfCmAfCmCmUmGmAmAmGmAfGmAmGmUpsf4PpsmA-5'	537
ds-siNA-0177	Sense	5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-(PS)2-GalNAc4	438
	Antisense	3'-mApsmGpsmCmAmCfCmAf2PmCmUmGmAmAmGmAfGmAmGmUpsfUpsmA-5'	538
ds-siNA-0178	Sense	5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-(PS)2-GalNAc4	438
	Antisense	3'-mApsmGpsmCmAmCfCmAfXmCmUmGmAmAmGmAfGmAmGmUpsfUpsmA-5'	539
ds-siNA-0147	Sense	5'-mGpsmUpsmGmGfUmGfGfAfCmUmUmCmUmCmUmCmAmAmU-p-ps2-GalNAc4	438
	Antisense	3'-mApsmGpsmCmAmCfCmAfCmCmUmGmAmAmGmAfGmAmGmUpsfUpsmA-5'	501

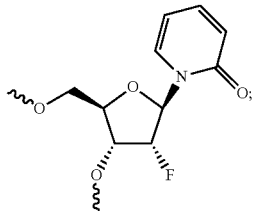
f4P =



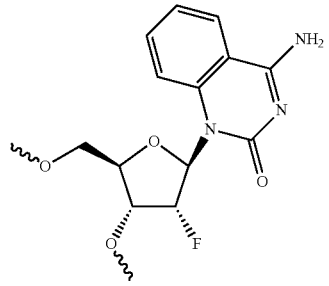
-continued

ds-siNA ID	Strand	Sequence	SEQ ID NO:

f2P =



fX =



[0761] The activity of ds-siNA-017, ds-siNA-017, ds-siNA-017, and ds-siNA-0147 can be assayed using in vitro or in vivo methods. An exemplary in vitro assay can be performed as follows:

[0762] *Homo sapiens* HepG2.2.15 cells are cultured in Dulbecco's Modified Eagle's Medium (DMEM) (ATCC 30-2002) supplemented to also contain 10% fetal calf serum (FCS). Cells were incubated at 37° C. in an atmosphere with 5% CO_2 in a humidified incubator. For transfection of HepG2.2.15 cells with HBV targeting siRNAs, cells are seeded at a density of 15000 cells/well in 96-well regular tissue culture plates. Transfection of cells is carried out using RNAiMAX (Invitrogen/Life Technologies) according to the manufacturer's instructions. Dose-response experiments are done with oligo concentrations of 40, 20, 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625 and 0.07813 nM. For each HBV targeting siRNA treatment (e.g., ds-siNA-0176, ds-siNA-0177, ds-siNA-0178, or ds-siNA-0147), four wells are transfected in parallel, and individual data points were collected from each well. After 24h of incubation with siRNA, media is removed, and cells are lysed and analyzed with a QuantiGene2.0 branched DNA (bDNA) probe set specific for HBV genotype D (also called Hepatitis B virus subtype ayw, complete genome of 3182 base-pairs) as present in cell line HepG2.2.15.

[0763] For each well, the HBV on-target mRNA levels is normalized to the GAPDH mRNA level. The activity of the HBV targeting ds-siNAs can be expressed as EC50, 50% reduction of normalized HBV RNA level from no drug control. The cytotoxicity of the HBV targeting ds-siRNAs can be expressed by CC50 of 50% reduction of GAPDH mRNA from no drug control.

[0764] The AAV/HBV model can be used to evaluate the in vivo activity of the siRNA treatment (e.g., ds-siNA-0173, ds-siNA-0174, ds-siNA-0175, and ds-siNA-0147). Mice are infected with AAV-HBV on day −28 of the study. AAV-HBV mice are subcutaneously injected with a single dose of 5 mL/kg of vehicle or 5 mg/kg of ds-siNA-0173, ds-siNA-0174, ds-siNA-0175, or ds-siNA-0147 on day 0. Serial blood collections can be taken every 5 days on day 0, 5, 10, and 15, etc. until the termination of the study. Serum HBV S antigen (HBsAg) can be assayed through ELISA.

Exemplary Embodiments

[0765] Exemplary embodiments are provided below:

1. A short interfering nucleic acid (siNA) molecule comprising:

[0766] (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence:

[0767] (i) is 15 to 30 nucleotides in length; and

[0768] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide; and

[0769] (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence:

[0770] (i) is 15 to 30 nucleotides in length; and

[0771] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide.

2. A short interfering nucleic acid (siNA) molecule comprising:

[0772] (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence:

[0773] (i) is 15 to 30 nucleotides in length; and

[0774] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and

[0775] (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence:

[0776] (i) is 15 to 30 nucleotides in length; and

[0777] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

3. The siNA of embodiment 1 or 2, wherein the first nucleotide sequence comprises 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

4. The siNA of embodiment 1 or 2, wherein 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the first nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

5. The siNA of any one of embodiments 1-4, wherein at least 2, 3, 4, 5, or 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides.

6. The siNA of any one of embodiments 1-5, wherein no more than 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides.

7. The siNA of any one of embodiments 1-6, wherein at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides.

8. The siNA of any one of embodiments 1-7, wherein no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides.

9. The siRNA of any one of embodiments 1-8, wherein the second nucleotide sequence comprises 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

10. The siNA of any one of embodiments 1-9, wherein 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the second nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

11. The siNA of any one of embodiments 1-10, wherein at least 2, 3, 4, 5, or 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides.

12. The siNA of any one of embodiments 1-11, wherein less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides.

13. The siNA of any one of embodiments 1-12, wherein at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides.

14. The siNA of any one of embodiments 1-12, wherein less than or equal to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides.

15. A short interfering nucleic acid (siNA) molecule comprising:

[0778] (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence:

[0779] (i) is 15 to 30 nucleotides in length;

[0780] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and

[0781] (iii) comprises 1 or more phosphorothioate internucleoside linkage; and

[0782] (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence:

[0783] (i) is 15 to 30 nucleotides in length;

[0784] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and

[0785] (iii) comprises 1 or more phosphorothioate internucleoside linkage.

16. A short interfering nucleic acid (siNA) molecule comprising:

[0786] (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence:

[0787] (i) is 15 to 30 nucleotides in length; and

[0788] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and

[0789] (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence:

[0790] (i) is 15 to 30 nucleotides in length; and

[0791] (ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide, wherein the siNA further comprises a phosphorylation blocker, a galactosamine, or 5'-stabilized end cap.

17. The siNA according to any preceding embodiment, wherein at least 1, 2, 3, 4, 5, 6, or 7 nucleotides at position 3, 5, 7, 8, 9, 10, 11, 12, and/or 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

18. The siNA according to any preceding embodiment, wherein the nucleotide at position 3 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

19. The siNA according to any preceding embodiment, wherein the nucleotide at position 5 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

20. The siNA according to any preceding embodiment, wherein the nucleotide at position 7 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

21. The siNA according to any preceding embodiment, wherein the nucleotide at position 8 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

22. The siNA according to any preceding embodiment, wherein the nucleotide at position 9 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

23. The siNA according to any preceding embodiment, wherein the nucleotide at position 12 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

24. The siNA according to any preceding embodiment, wherein the nucleotide at position 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

25. The siNA according to any preceding embodiment, wherein the nucleotide at position 10 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

26. The siNA according to any preceding embodiment, wherein the nucleotide at position 11 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

27. The siNA according to any preceding embodiment, wherein at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 nucleotides at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

28. The siNA according to any preceding embodiment, wherein the nucleotide at position 2 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

29. The siNA according to any preceding embodiment, wherein the nucleotide at position 5 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

30. The siNA according to any preceding embodiment, wherein the nucleotide at position 6 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

31. The siNA according to any preceding embodiment, wherein the nucleotide at position 8 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

32. The siNA according to any preceding embodiment, wherein the nucleotide at position 10 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

33. The siNA according to any preceding embodiment, wherein the nucleotide at position 14 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

34. The siNA according to any preceding embodiment, wherein the nucleotides at position 16 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

35. The siNA according to any preceding embodiment, wherein the nucleotide at position 17 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

36. The siNA according to any preceding embodiment, wherein the nucleotide at position 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

37. The siNA according to any preceding embodiment, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides.

38. The siNA of embodiment 37, wherein the alternating 1:3 modification pattern occurs 2-5 times.

39. The siNA according to embodiment 37 or 38, wherein at least two of the alternating 1:3 modification pattern occur consecutively.

40. The siNA according to any of embodiments 37-39, wherein at least two of the alternating 1:3 modification pattern occurs nonconsecutively.

41. The siNA according to any of clams 37-40, wherein at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand.

42. The siNA according to any of clams 37-41, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand.

43. The siNA according to any of clams 37-42, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand.

44. The siNA according to any of clams 37-43, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand.

45. The siNA according to any of clams 37-44, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand.

46. The siNA according to any of clams 37-45, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand.

47. The siNA according to any one of embodiments 1-37, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides.

48. The siNA of embodiment 47, wherein the alternating 1:2 modification pattern occurs 2-5 times.

49. The siNA according to embodiment 47 or 48, wherein at least two of the alternating 1:2 modification pattern occurs consecutively.

50. The siNA according to any of embodiments 47-49, wherein at least two of the alternating 1:2 modification pattern occurs nonconsecutively.

51. The siNA according to any of clams 47-50, wherein at least 1, 2, 3, 4, or 5 alternating 1:2 modification pattern begins at nucleotide position 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand.

52. The siNA according to any of clams 47-51, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand.

53. The siNA according to any of clams 47-52, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 5 from the 5' end of the antisense strand.

54. The siNA according to any of clams 47-53, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 8 from the 5' end of the antisense strand.

55. The siNA according to any of clams 47-54, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand.

56. The siNA according to any of clams 47-55, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 17 from the 5' end of the antisense strand.

57. A short interfering nucleic acid (siNA) molecule represented by Formula (VIII):

$$5'\text{-}A_n{}^1B_n{}^2A_n{}^3B_n{}^4A_n{}^5B_n{}^6A_n{}^7B_n{}^8A_n{}^9\text{-}3'$$

$$3'\text{-}C_q{}^1A_q{}^2B_q{}^3A_q{}^4B_q{}^5A_q{}^6B_q{}^7A_q{}^8B_q{}^9A_q{}^{10}B_q{}^{11}A_q{}^{12}\text{-}5'$$

wherein:

[0792] the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

[0793] the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

[0794] each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5'-stabilized end cap or a phosphorylation blocker;

B is a 2'-fluoro nucleotide;

C represents overhanging nucleotides and is a 2'-O-methyl nucleotide; n^1=1-4 nucleotides in length;

[0795] each n^2, n^6, n^8, q^3, q^5, q^7, q^9, q^{11}, and q^{12} is independently 0-1 nucleotides in length; each n^3 and n^4 is independently 1-3 nucleotides in length;

[0796] n^5 is 1-10 nucleotides in length;

[0797] n^7 is 0-4 nucleotides in length;

[0798] each n^9, q, and q^2 is independently 0-2 nucleotides in length;

[0799] q^4 is 0-3 nucleotides in length;

[0800] q^6 is 0-5 nucleotides in length;

[0801] q^8 is 2-7 nucleotides in length; and

[0802] q^{10} is 2-11 nucleotides in length.

58. A short interfering nucleic acid (siNA) molecule represented by Formula (IX):

$$5'\text{-}A_{2\text{-}4}B_1A_{1\text{-}3}B_{2\text{-}3}A_{2\text{-}10}B_{0\text{-}1}A_{0\text{-}4}B_{0\text{-}1}A_{0\text{-}2}\text{-}3'$$

$$3'\text{-}C_2A_{0\text{-}2}B_{0\text{-}1}A_{0\text{-}3}B_{0\text{-}1}A_{0\text{-}5}B_{0\text{-}1}A_{2\text{-}7}B_1A_{2\text{-}11}B_1A_1\text{-}5'$$

wherein:

[0803] the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

[0804] the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

[0805] each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5'-stabilized end cap or a phosphorylation blocker;

[0806] B is a 2'-fluoro nucleotide;

[0807] C represents overhanging nucleotides and is a 2'-O-methyl nucleotide.

59. A short interfering nucleic acid (siNA) molecule comprising

[0808] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12, and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, and 13-16 from the 5' end of the first nucleotide sequence; and

[0809] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end of the second nucleotide sequence.

60. The siNA molecule of embodiment 59, wherein the first nucleotide sequence consists of 19 nucleotides.

61. The siNA molecule of embodiment 60, wherein 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence.

62. The siNA molecule according to any one of embodiments 59-61, wherein the second nucleotide sequence consists of 21 nucleotides.

63. The siNA molecule of embodiment 62, wherein 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

64. A short interfering nucleic acid (siNA) molecule comprising

[0810] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7, 8, and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, and 9-16 from the 5' end of the first nucleotide sequence; and

[0811] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the first nucleotide sequence; and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end of the first nucleotide sequence.

65. The siNA molecule of embodiment 64, wherein the first nucleotide sequence consists of 19 nucleotides.

66. The siNA molecule of embodiment 65, wherein 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence.

67. The siNA molecule according to any one of embodiments 64-66, wherein the second nucleotide sequence consists of 21 nucleotides.

68. The siNA molecule of embodiment 67, wherein 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

69. A short interfering nucleic acid (siNA) molecule comprising

[0812] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12 and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, and 13-16 from the 5' end of the first nucleotide sequence; and

[0813] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides.

70. The siNA molecule of embodiment 69, wherein the first nucleotide sequence consists of 19 nucleotides.

71. The siNA molecule of embodiment 70, wherein 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence.

72. The siNA molecule according to any one of embodiments 69-71, wherein the second nucleotide sequence consists of 21 nucleotides.

73. The siNA molecule of embodiment 72, wherein 2'-O-methyl nucleotides are at positions 19-21 from the 5' end of the second nucleotide sequence.

74. The siRNA molecule according to any one of embodiments 69-73, wherein the alternating 1:3 modification pattern occurs 2-5 times.

75. The siRNA molecule according to any one of embodiments 69-74, wherein at least two of the alternating 1:3 modification pattern occur consecutively.

76. The siRNA molecule according to any one of embodiments 69-75, wherein at least two of the alternating 1:3 modification pattern occurs nonconsecutively.

77. The siNA according to any one of embodiments 69-76, wherein at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand.

78. The siNA according to any one of embodiments 69-77, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand.

79. The siNA according to any one of embodiments 69-78, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand.

80. The siNA according to any one of embodiments 69-79, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand.

81. The siNA according to any one of embodiments 69-80, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand.

82. The siNA according to any one of embodiments 69-81, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand.

83. A short interfering nucleic acid (siNA) molecule comprising

[0814] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence; and

[0815] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides.

84. The siNA molecule of embodiment 83, wherein the first nucleotide sequence consists of 19 nucleotides.

85. The siNA molecule of embodiment 84, wherein 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence.

86. The siNA molecule according to any one of embodiments 83-85, wherein the second nucleotide sequence consists of 21 nucleotides.

87. The siNA molecule of embodiment 86, wherein 2'-O-methyl nucleotides are at positions 19-21 from the 5' end of the second nucleotide sequence.

88. The siRNA molecule according to any one of embodiments 83-87, wherein the alternating 1:3 modification pattern occurs 2-5 times.

89. The siRNA molecule according to any one of embodiments 83-88, wherein at least two of the alternating 1:3 modification pattern occur consecutively.

90. The siRNA molecule according to any one of embodiments 83-89, wherein at least two of the alternating 1:3 modification pattern occurs nonconsecutively.

91. The siNA according to any one of embodiments 83-90, wherein at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand.

92. The siNA according to any one of embodiments 83-91, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand.

93. The siNA according to any one of embodiments 83-92, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 6 from the 5' end of the antisense strand.

94. The siNA according to any one of embodiments 83-93, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 10 from the 5' end of the antisense strand.

95. The siNA according to any one of embodiments 83-94, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand.

96. The siNA according to any one of embodiments 83-95, wherein at least one alternating 1:3 modification pattern begins at nucleotide position 18 from the 5' end of the antisense strand.

97. A short interfering nucleic acid (siNA) molecule comprising

[0816] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein

2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence; and

[0817] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides.

98. The siNA molecule of embodiment 97, wherein the first nucleotide sequence consists of 19 nucleotides.

99. The siNA molecule of embodiment 98, wherein 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence.

100. The siNA molecule according to any one of embodiments 97-99, wherein the second nucleotide sequence consists of 21 nucleotides.

101. The siNA molecule of embodiment 100, wherein 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

102. The siRNA molecule according to any one of embodiments 97-101, wherein the alternating 1:2 modification pattern occurs 2-5 times.

103. The siRNA molecule according to any one of embodiments 97-102, wherein at least two of the alternating 1:2 modification pattern occur consecutively.

104. The siRNA molecule according to any one of embodiments 97-103, wherein at least two of the alternating 1:2 modification pattern occurs nonconsecutively.

105. The siNA according to any one of embodiments 97-104, wherein at least 1, 2, 3, 4, or 5 alternating 1:2 modification pattern begins at nucleotide position 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand.

106. The siNA according to any one of embodiments 97-105, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 2 from the 5' end of the antisense strand.

107. The siNA according to any one of embodiments 97-106, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 5 from the 5' end of the antisense strand.

108. The siNA according to any one of embodiments 97-107, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 8 from the 5' end of the antisense strand.

109. The siNA according to any one of embodiments 74-85, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 14 from the 5' end of the antisense strand.

110. The siNA according to any one of embodiments 97-109, wherein at least one alternating 1:2 modification pattern begins at nucleotide position 17 from the 5' end of the antisense strand.

111. A short interfering nucleic acid (siNA) molecule comprising

[0818] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence; and

[0819] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2, 6, 14, and 16 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-5, 7-13, 15, and 17 from the 5' end the second nucleotide sequence.

112. The siNA molecule of embodiment 111, wherein the first nucleotide sequence consists of 19 nucleotides.

113. The siNA molecule of embodiment 112, wherein 2'-O-methyl nucleotides are at positions 18 and 19 from the 5' end of the first nucleotide sequence.

114. The siNA molecule according to any one of embodiments 111-113, wherein the second nucleotide sequence consists of 21 nucleotides.

115. The siNA molecule of embodiment 114, wherein 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the second nucleotide sequence.

116. A short interfering nucleic acid (siNA) molecule comprising:

[0820] (a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5, 9-11, and 14 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6-8, and 12-17 from the 5' end of the first nucleotide sequence; and

[0821] (b) an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end the second nucleotide sequence.

117. The siNA molecule of embodiment 116, wherein the first nucleotide sequence consists of 21 nucleotides.

118. The siNA molecule of embodiment 117, wherein 2'-O-methyl nucleotides are at positions 18-21 from the 5' end of the first nucleotide sequence.

119. The siNA molecule according to any one of embodiments 116-118, wherein the second nucleotide sequence consists of 23 nucleotides.

120. The siNA molecule of embodiment 119, wherein 2'-O-methyl nucleotides are at positions 18-23 from the 5' end of the second nucleotide sequence.

121. The siNA according to any preceding embodiment, wherein the sense strand further comprises TT sequence adjacent to the first nucleotide sequence.

122. The siNA according to any preceding embodiment, wherein the sense strand further comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate internucleoside linkages.

123. The siNA of embodiment 122, wherein at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the first nucleotide sequence.

124. The siNA of embodiment 122 or 123, wherein at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the first nucleotide sequence.

125. The siNA according to any preceding embodiment, wherein the antisense strand further comprises TT sequence adjacent to the second nucleotide sequence.

126. The siNA according to any preceding embodiment, wherein the antisense strand further comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate internucleoside linkages.

127. The siNA of embodiment 126, wherein at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the second nucleotide sequence.

128. The siNA of embodiment 126 or 127, wherein at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the second nucleotide sequence.

129. The siNA of any one of embodiments 126-128, wherein at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 3' end of the second nucleotide sequence.

130. The siNA of any one of embodiments 126-129, wherein at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 3' end of the second nucleotide sequence.

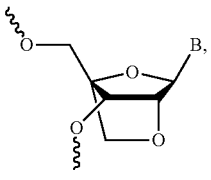
131. The siNA according to any preceding embodiment, wherein the first nucleotide from the 5' end of the first nucleotide sequence comprises a 5' stabilizing end cap.

132. The siNA according to any preceding embodiment, wherein the first nucleotide from the 5' end of the second nucleotide sequence comprises a 5' stabilizing end cap.

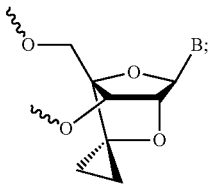
133. The siNA according to any preceding embodiment, wherein the first nucleotide from the 5' end of the first nucleotide sequence comprises a phosphorylation blocker.

134. The siNA according to any preceding embodiment, wherein the first nucleotide from the 5' end of the second nucleotide sequence comprises a phosphorylation blocker.

135. The siNA according to any preceding embodiment, wherein the first nucleotide sequence or second nucleotide sequence comprises at least one modified nucleotide selected

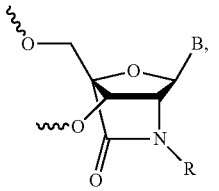


(LNA)



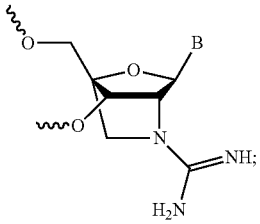
(ScpBNA or "cp")

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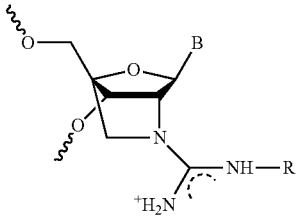


(AmNA)

where R is H or alkyl (or AmNA(N-Me)) when R is alkyl);



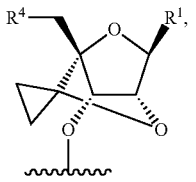
(GuNA)



and GuNA(N—R), R=Me, Et, iPr, tBu, wherein B is a nucleobase.

136. A short-interfering nucleic acid (siNA) molecule comprising:

[0822] (a) a phosphorylation blocker of Formula (IV):



[0823] wherein

[0824] R^1 is a nucleobase,

[0825] R^4 is —O—R^{30} or —$NR^{31}R^{32}$

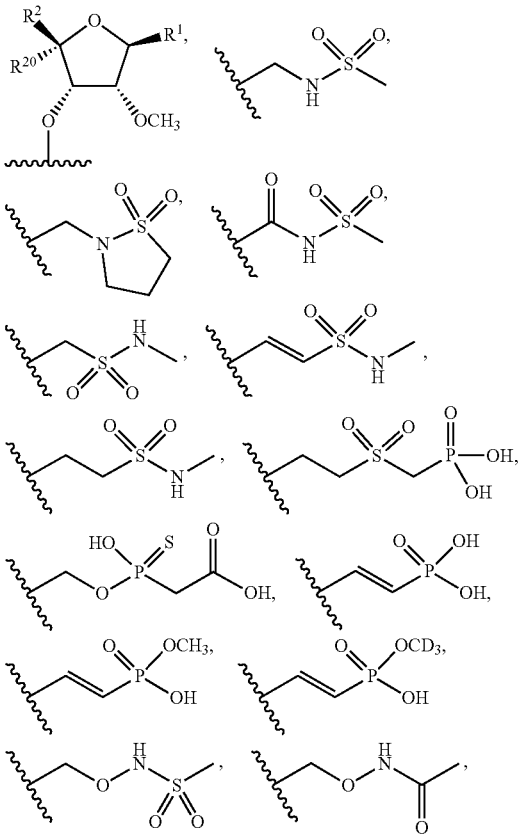
[0826] R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and

[0827] R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; and

[0828] (b) a short interfering nucleic acid (siNA).

137. A short-interfering nucleic acid (siNA) molecule comprising:

[0829] (a) a 5'-stabilized end cap of Formula (Ia):



[0830] wherein

[0831] R^1 is a nucleobase, aryl, heteroaryl, or H,

[0832] R^2 is —CH═CD-Z, —CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

[0833] R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

[0834] n is 1, 2, 3, or 4;

[0835] Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$,

[0836] R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl; R^{21} and R^{22} together form an oxo group;

[0837] R^{23} is hydrogen or C_1-C_6 alkyl;

[0838] R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

[0839] R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

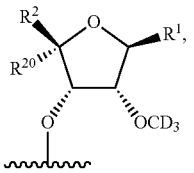
[0840] R^{25} is C_1-C_6 alkyl; and

[0841] m is 1, 2, 3, or 4; and

[0842] (b) a short interfering nucleic acid (siNA).

138. A short-interfering nucleic acid (siNA) molecule comprising:

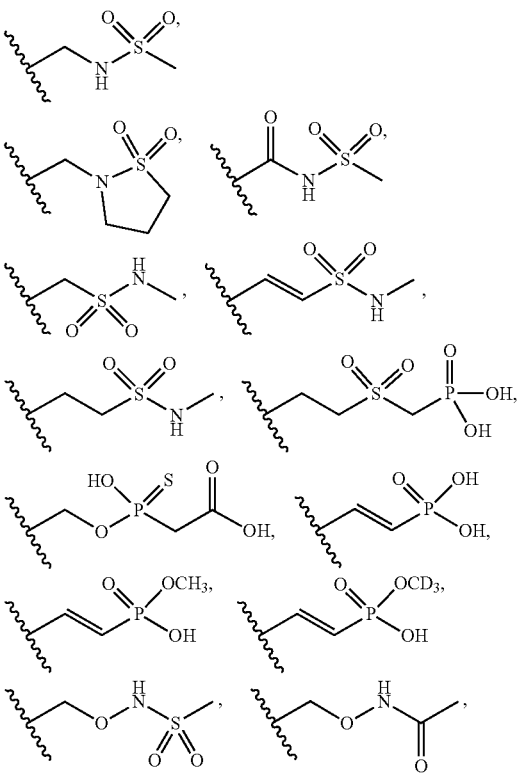
[0843] (a) a 5'-stabilized end cap of Formula (Ib):



[0844] wherein

[0845] R^1 is a nucleobase, aryl, heteroaryl, or H,

[0846] R^2 is



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

[0847] R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

[0848] n is 1, 2, 3, or 4;

[0849] Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$,

[0850] R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl; R^{21} and R^{22} together form an oxo group;

[0851] R^{23} is hydrogen or C_1-C_6 alkyl;

[0852] R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

[0853] R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

[0854] R^{25} is C_1-C_6 alkyl; and

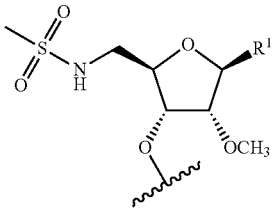
[0855] m is 1, 2, 3, or 4; and

[0856] (b) a short interfering nucleic acid (siNA).

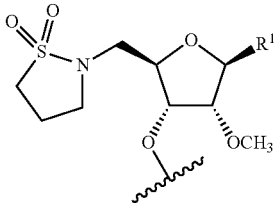
139. A short-interfering nucleic acid (siNA) molecule comprising:

[0857] (a) a 5'-stabilized end cap selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

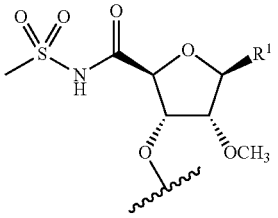
Formula (1)



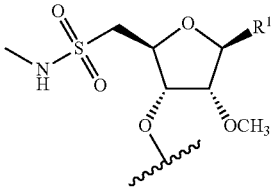
Formula (2)



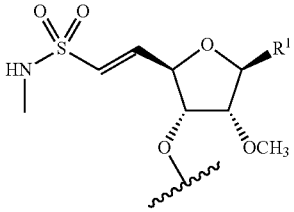
Formula (3)



Formula (4)

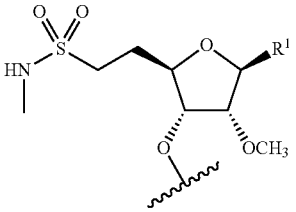


Formula (5)

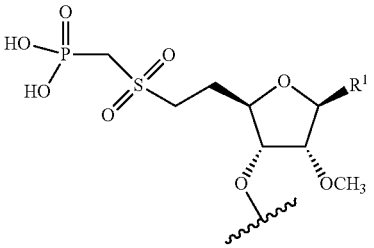


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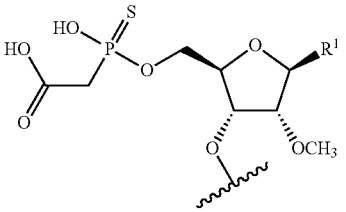
Formula (6)



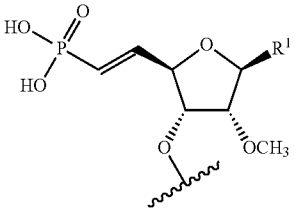
Formula (7)



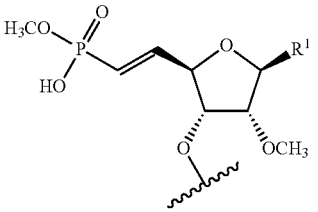
Formula (8)



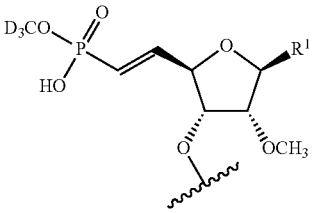
Formula (9)



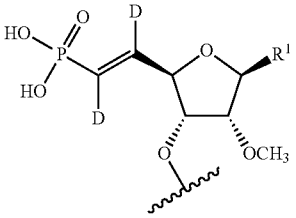
Formula (9X)



Formula (9Y)

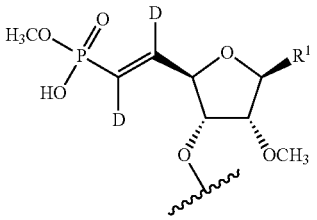


Formula (10)

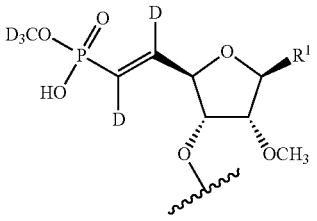


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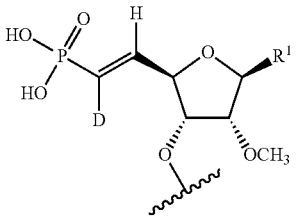
Formula (10X)



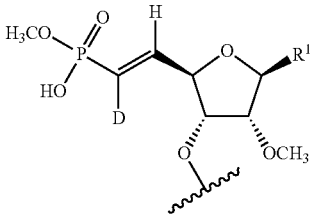
Formula (10Y)



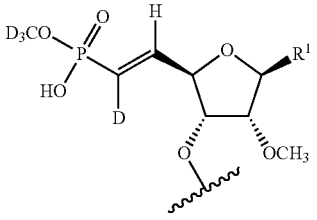
Formula (11)



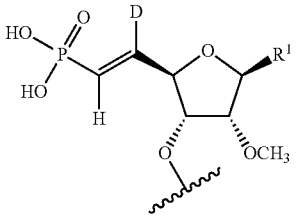
Formula (11X)



Formula (11Y)

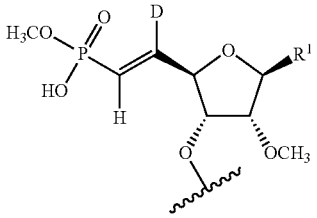


Formula (12)

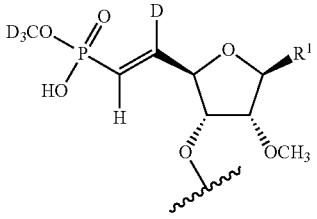


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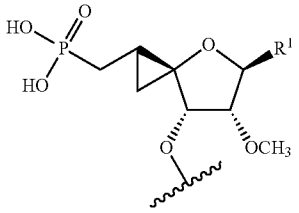
Formula (12X)



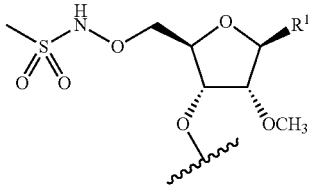
Formula (12Y)



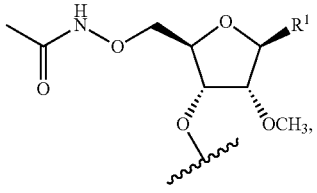
Formula (13)



Formula (14)



Formula (15)



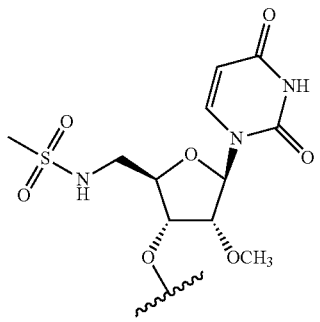
wherein R^1 is a nucleobase, aryl, heteroaryl, or H; and

[0858] (b) a short interfering nucleic acid (siNA).

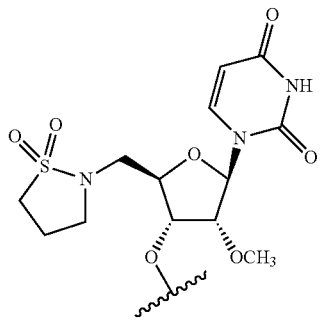
140. A short-interfering nucleic acid (siNA) molecule comprising:

[0859] (a) a 5'-stabilized end cap selected from the group consisting of Formulas (1A)-(15A), Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

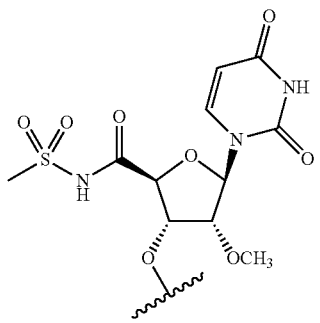
Formula (1A)



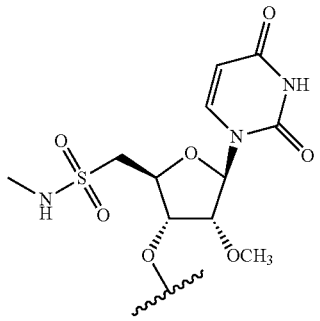
Formula (2A)



Formula (3A)

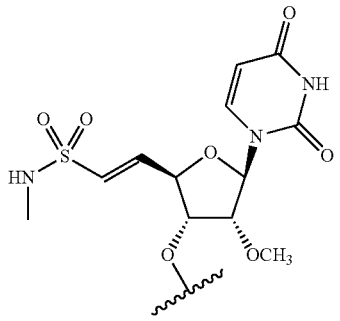


Formula (4A)

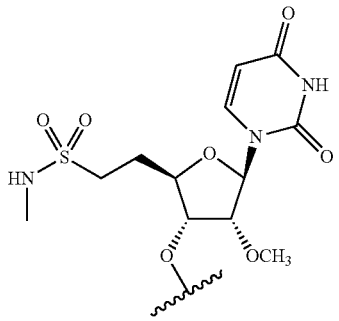


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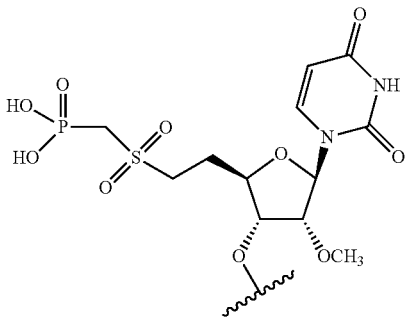
Formula (5A)



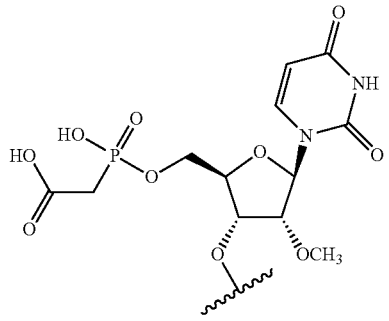
Formula (6A)



Formula (7A)

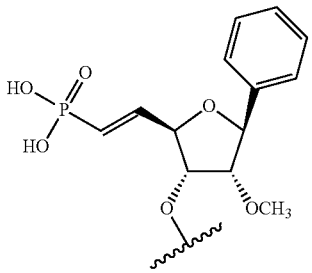


Formula (8A)

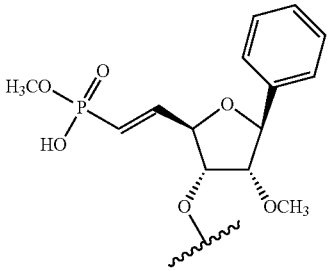


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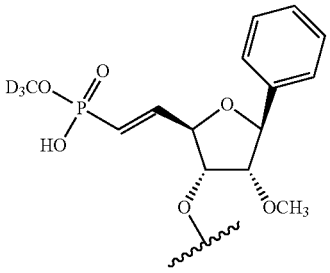
Formula (9A)



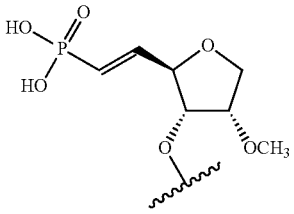
Formula (9AX)



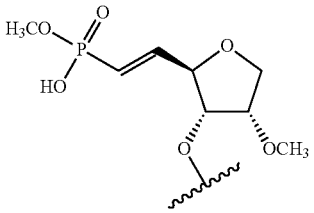
Formula (9AY)



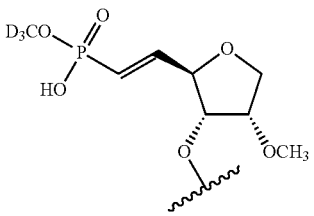
Formula (9B)



Formula (9BX)

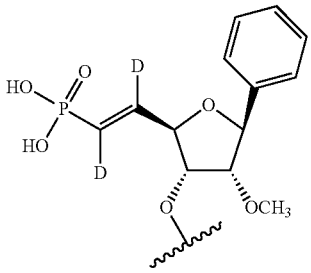


Formula (9BY)

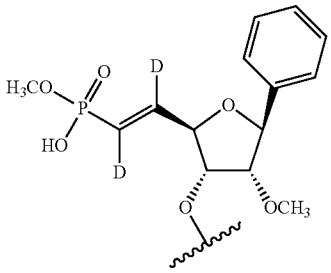


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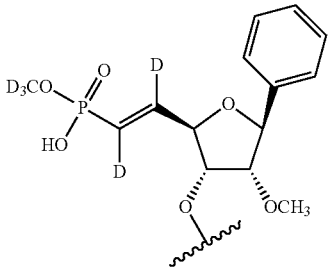
Formula (10A)



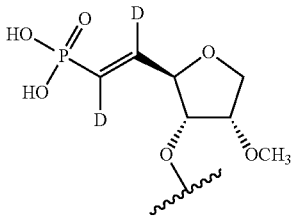
Formula (10AX)



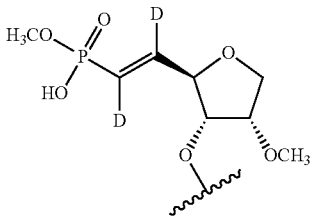
Formula (10AY)



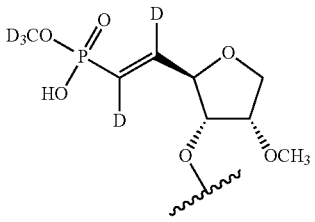
Formula (10B)



Formula (10BX)

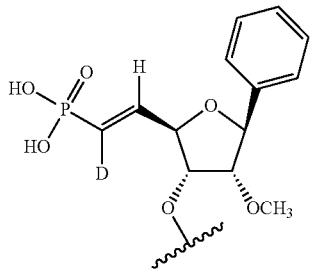


Formula (10BY)

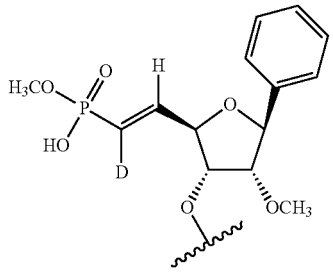


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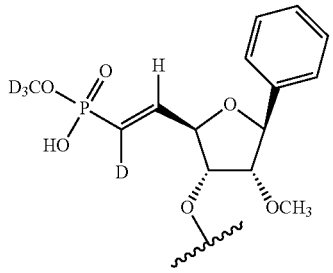
Formula (11A)



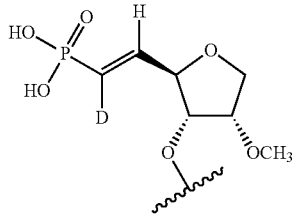
Formula (11AX)



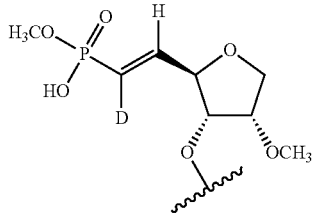
(Formula (11AY)



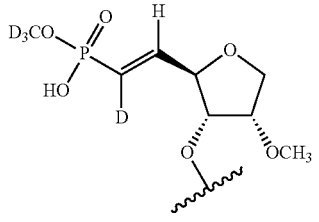
Formula (11B)



Formula (11BX)

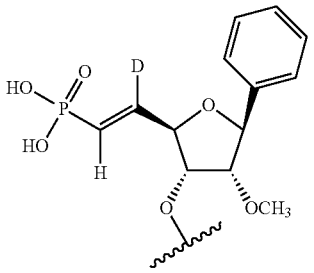


Formula (11BY)

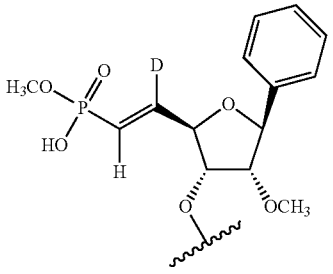


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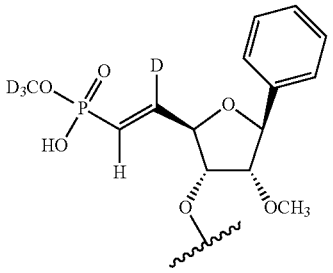
Formula (12A)



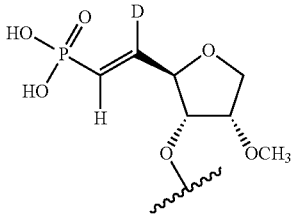
Formula (12AX)



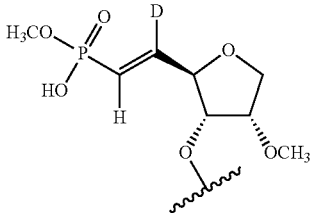
Formula (12AY)



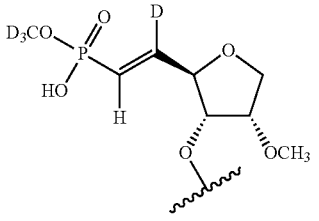
Formula (12B)



Formula (12BX)

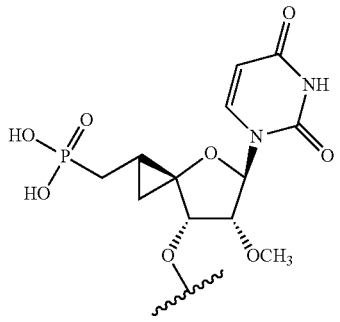


Formula (12BY)

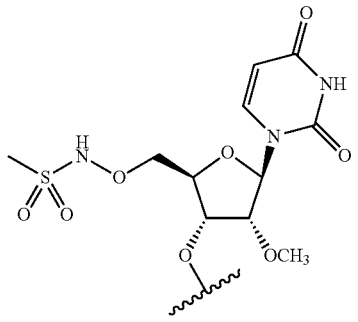


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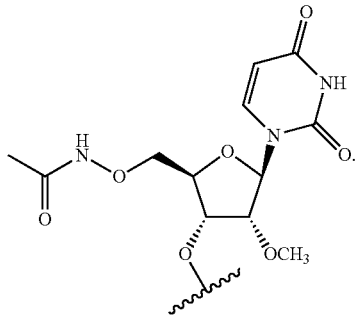
Formula (13A)



Formula (14A)



Formula (15A)



and

[0860] (b) a short interfering nucleic acid (siNA).

141. The siNA molecule according to any one of embodiments 136-140, wherein the siNA comprises the sense strand of any one of embodiments 1-135.

142. The siNA molecule according to any one of embodiments 136-141, wherein the siNA comprises the antisense strand of any one of embodiments 1-135.

143. A short interfering nucleic acid (siNA) molecule comprising:

[0861] (a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260; and

[0862] (b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306.

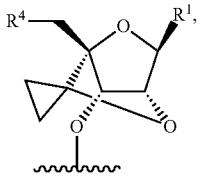
144. A interfering nucleic acid (siNA) molecule comprising:

[0863] (a) a sense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444; and

[0864] (b) an antisense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

145. The siNA according to any one of embodiments 1-132, 135, and 137-144, wherein the siNA further comprises a phosphorylation blocker.

146. The siNA according to any one of embodiments 16, 133, 134, and 145, wherein the phosphorylation blocker has the structure of Formula (IV):



wherein

R^1 is a nucleobase,

R^4 is —O—R^{30} or —N$R^{31}R^{32}$, R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and

R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring.

147. The siNA of embodiment 136 or 146, wherein R^4 is —OCH_3 or —$N(CH_2CH_2)_2O$.

148. The siNA according to any one of embodiments 16, 133, 134, 136, and 145-147, wherein the phosphorylation blocker is attached to the 5' end of the sense strand.

149. The siNA of embodiment 148, wherein the phosphorylation blocker is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

150. The siNA according to any one of embodiments 16, 133, 134, 136, and 145-147, wherein the phosphorylation blocker is attached to the 3' end of the sense strand.

151. The siNA of embodiment 150, wherein the phosphorylation blocker is attached to the 3' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

152. The siNA according to any one of embodiments 16, 133, 134, 136, and 145-147, wherein the phosphorylation blocker is attached to the 5' end of the antisense strand.

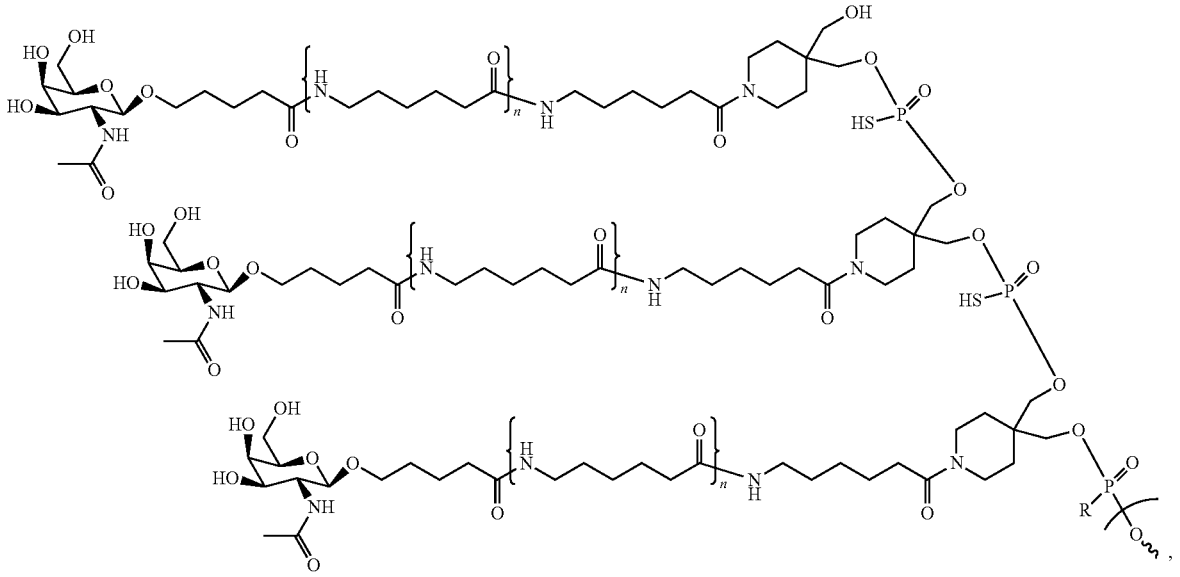
153. The siNA of embodiment 152, wherein the phosphorylation blocker is attached to the 5' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

154. The siNA according to any one of embodiments 16, 133, 134, 136, and 144-147, wherein the phosphorylation blocker is attached to the 3' end of the antisense strand.

155. The siNA of embodiment 154, wherein the phosphorylation blocker is attached to the 3' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

156. The siNA according to any preceding embodiment, wherein the siNA further comprises a galactosamine.

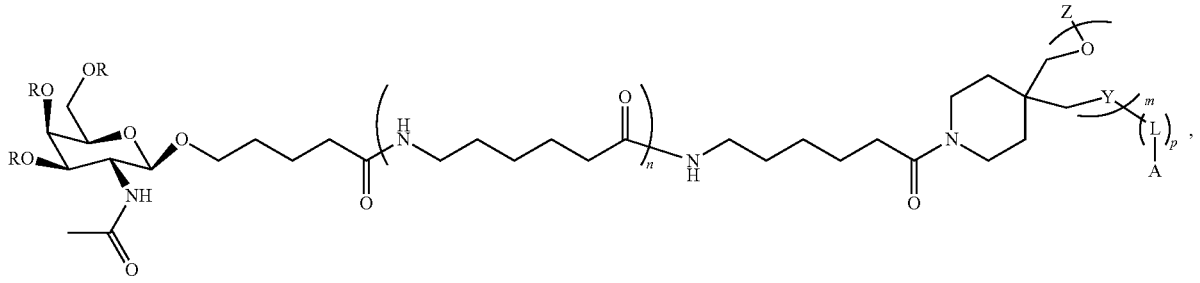
157. The siNA of embodiment 16 or 156, wherein the galactosamine is N-acetylgalactosamine (GalNAc) of Formula (VII):



R = OH or SH

wherein each n is independently 1 or 2.

158. The siNA of embodiment 16 or 156, wherein the galactosamine is N-acetylgalactosamine (GalNAc) of Formula (VI):



wherein

m is 1, 2, 3, 4, or 5;

each n is independently 1 or 2;

p is 0 or 1;

each R is independently H;

each Y is independently selected from —O—P(═O)(SH)—, —O—P(═O)(O)—, —O—P(═O)(OH)—, and —O—P(S)S—;

Z is H or a second protecting group;

either L is a linker or L and Y in combination are a linker; and

A is H, OH, a third protecting group, an activated group, or an oligonucleotide.

159. The siNA of embodiment 158, wherein A is an oligonucleotide.

160. The siNA of embodiment 158, wherein A is 1-2 oligonucleotides.

161. The siNA of any one of embodiments 158-160, wherein the oligonucleotide is dTdT.

162. The siNA according to any one of embodiments 16 and 156-161, wherein the galactosamine is attached to the 3' end of the sense strand.

163. The siNA of embodiment 162, wherein the galactosamine is attached to the 3' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

164. The siNA according to any one of embodiments 16 and 156-161, wherein the galactosamine is attached to the 5' end of the sense strand.

165. The siNA of embodiment 164, wherein the galactosamine is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

166. The siNA according to any one of embodiments 16 and 156-161, wherein the galactosamine is attached to the 3' end of the antisense strand.

167. The siNA of embodiment 166, wherein the galactosamine is attached to the 3' end of the atnisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

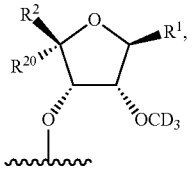
168. The siNA according to any one of embodiments 16 and 156-161, wherein the galactosamine is attached to the 5' end of the antisense strand.

169. The siNA of embodiment 168, wherein the galactosamine is attached to the 5' end of the atnisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

170. The siNA according to any one of embodiments 1-130, 133-136, and 139-169, wherein the siNA further comprises a 5'-stabilized end cap.

171. The siNA according to any one of embodiments 16, 131, 132, and 170, wherein the 5'-stabilized end cap is a 5' vinyl phosphonate or deuterated 5' vinyl phosphonate.

172. The siNA according to any one of embodiments 16, 131, 132, and 170, wherein the 5'-stabilized end cap has the structure of Formula (Ia):

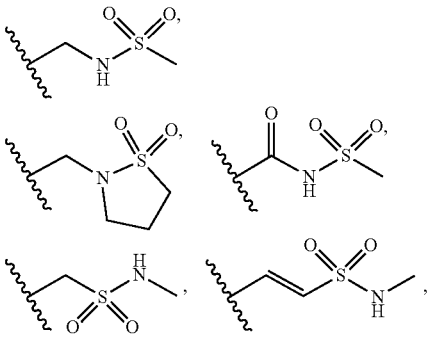


wherein

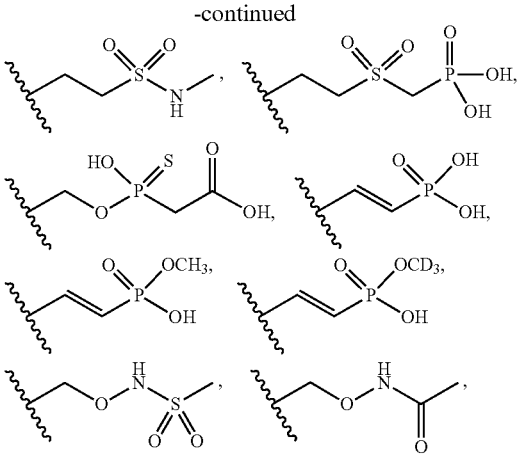
R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0865]



-continued



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$,

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

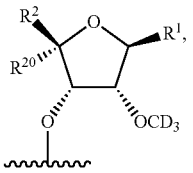
R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4.

173. The siNA according to any one of embodiments 131, 132, and 170, wherein the 5'-stabilized end cap has the structure of Formula (Ib):

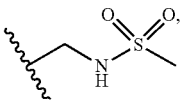


wherein

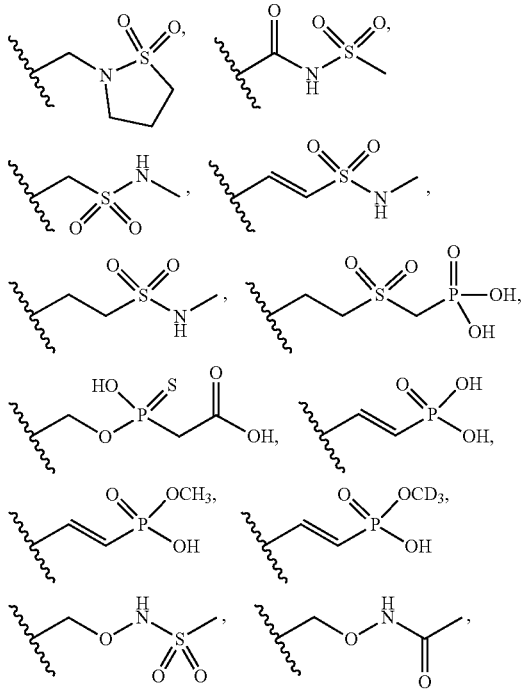
R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0866]



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—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —OP(S)$OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$,

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

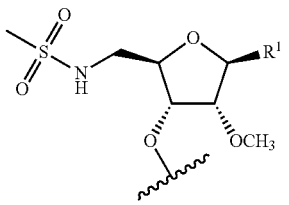
m is 1, 2, 3, or 4.

174. The siNA of embodiment 172 or 173, wherein R^1 is an aryl.

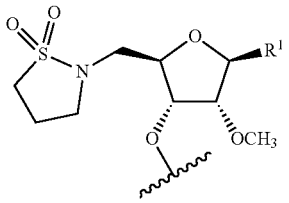
175. The siNA of embodiment 174, wherein the aryl is a phenyl.

176. The siNA according to any one of embodiments 16, 131, 132, and 170, wherein the 5'-stabilized end cap is selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

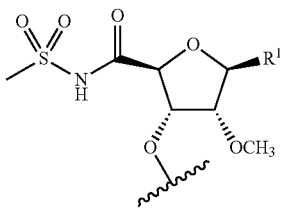
Formula (1)



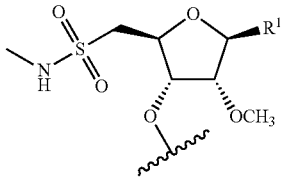
Formula (2)



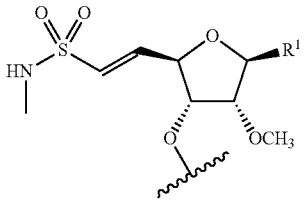
Formula (3)



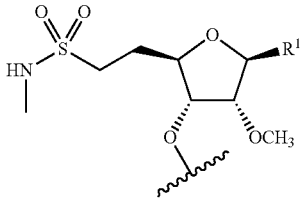
Formula (4)



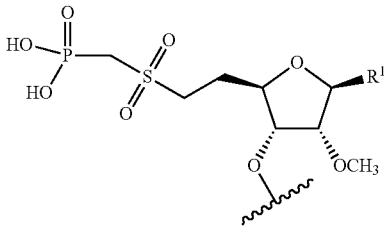
Formula (5)



Formula (6)

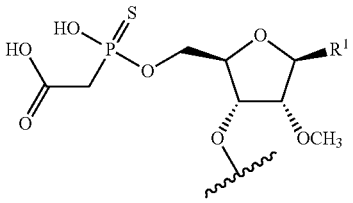


Formula (7)

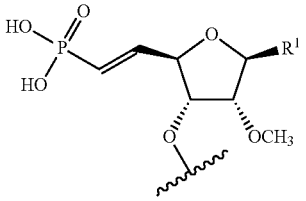


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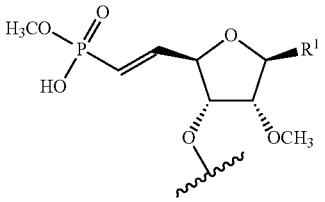
Formula (8)



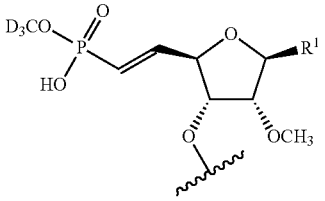
Formula (9)



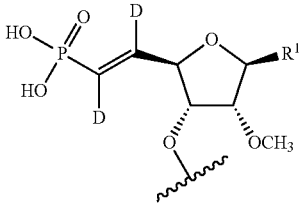
Formula (9X)



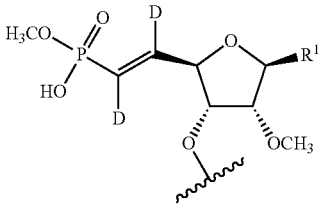
Formula (9Y)



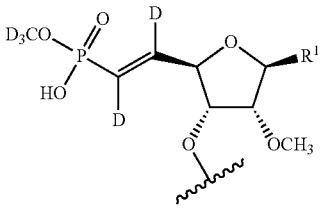
Formula (10)



Formula (10X)

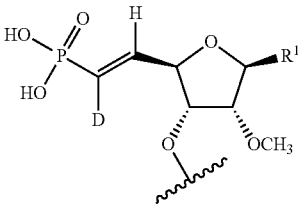


Formula (10Y)

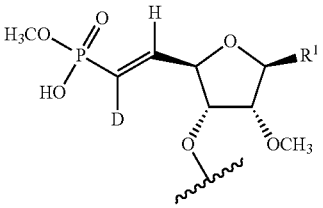


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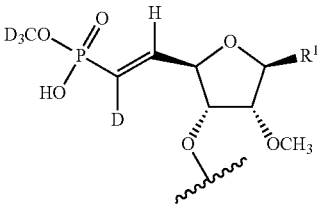
Formula (11)



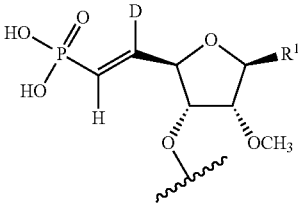
Formula (11X)



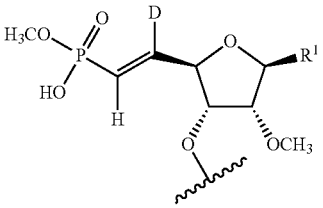
Formula (11Y)



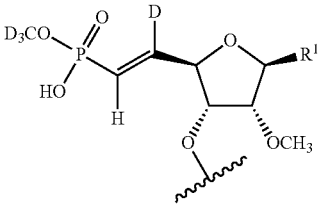
Formula (12)



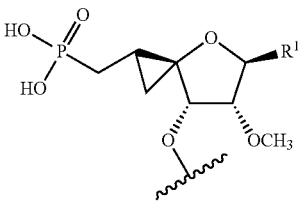
Formula (12X)



Formula (12Y)

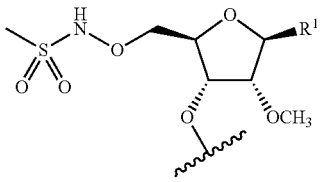


Formula (13)

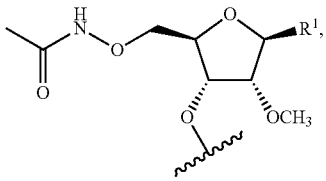


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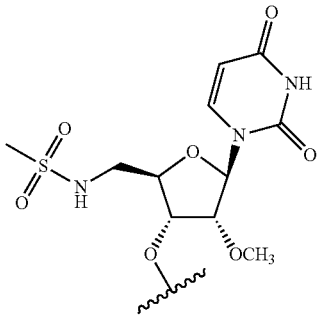
Formula (14)



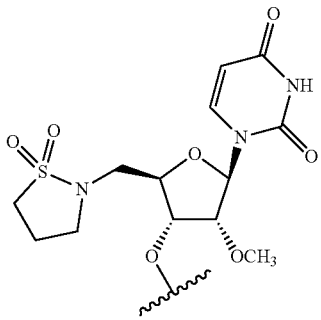
Formula (15)



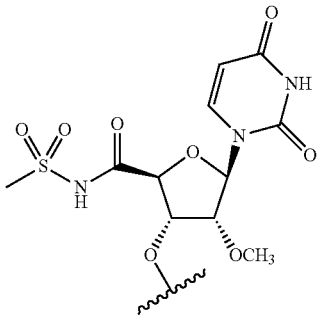
Formula (1A)



Formula (2A)

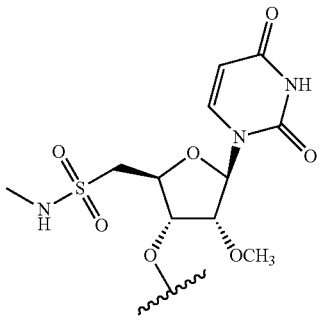


Formula (3A)

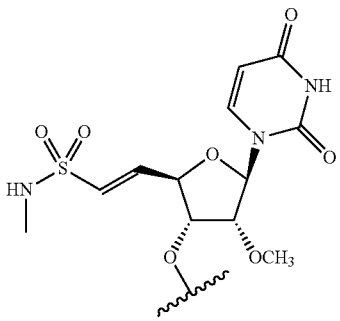


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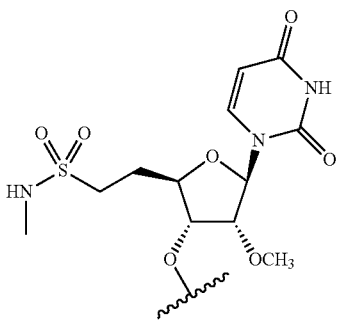
Formula (4A)



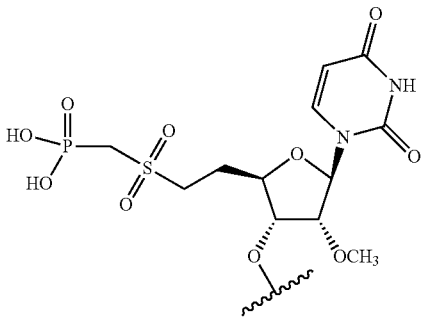
Formula (5A)



Formula (6A)

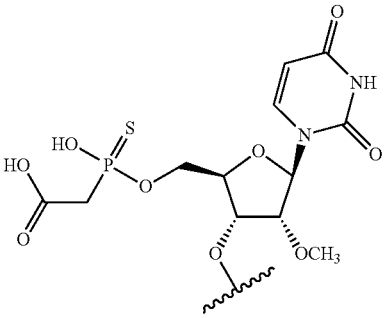


Formula (7A)

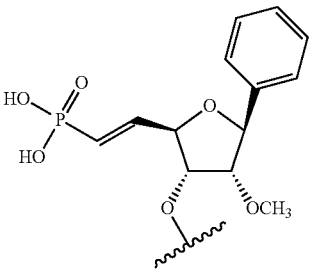


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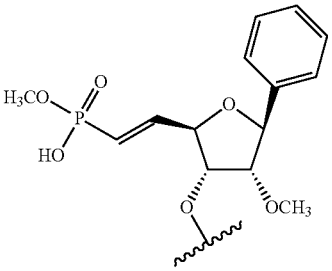
Formula (8A)



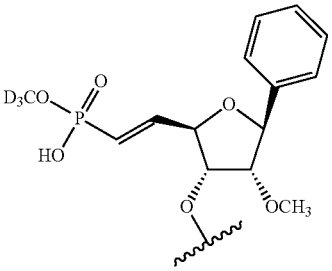
Formula (9A)



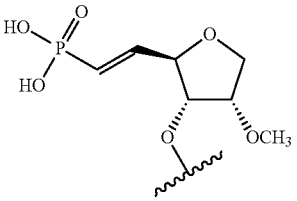
Formula (9AX)



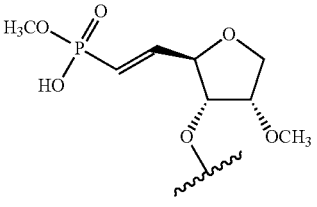
Formula (9AY)



Formula (9B)

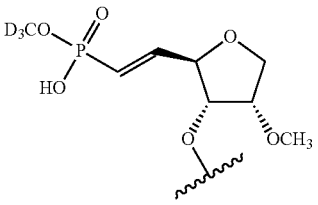


Formula (9BX)

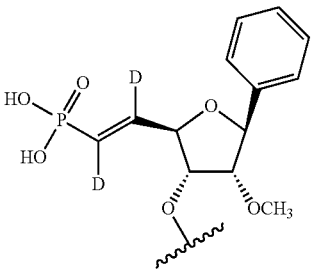


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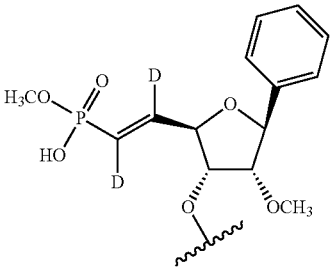
Formula (9BY)



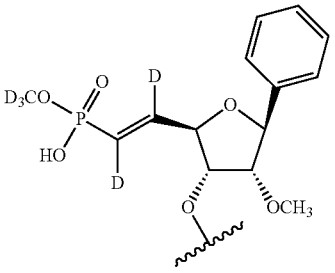
Formula (10A)



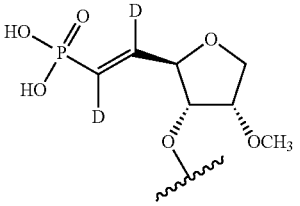
Formula (10AX)



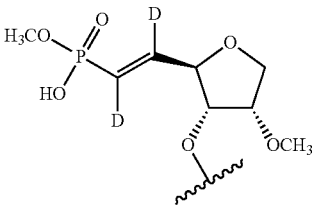
Formula (10AY)



Formula (10B)

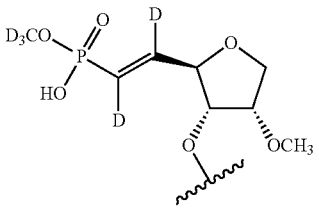


Formula (10BX)

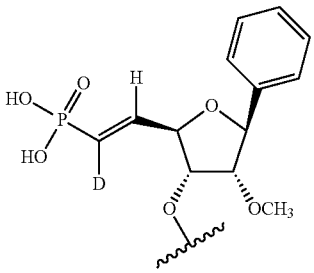


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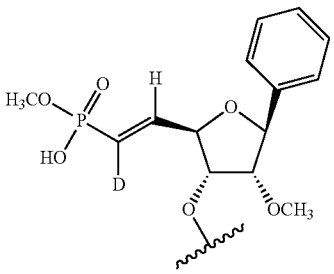
Formula (10BY)



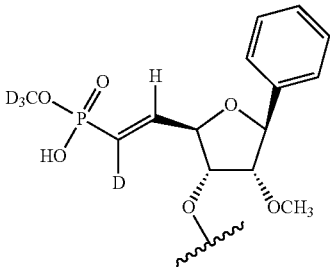
Formula (11A)



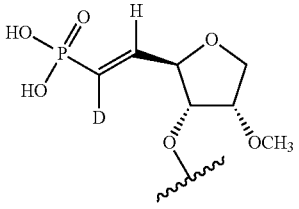
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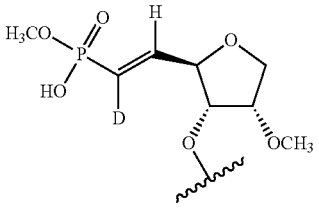
Formula (11AY)



Formula (11B)

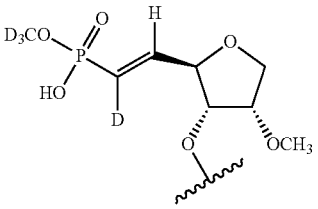


Formula (11BX)

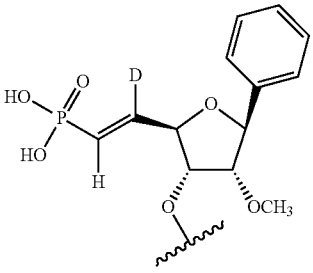


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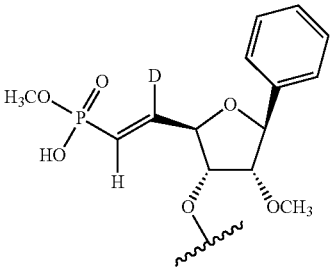
Formula (11BY)



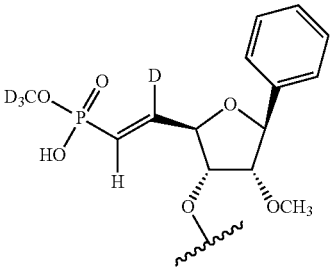
Formula (12A)



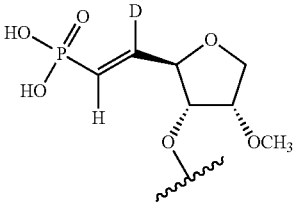
Formula (12AX)



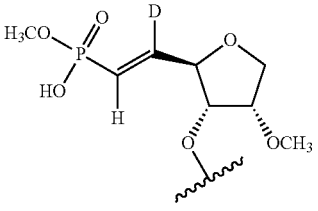
Formula (12AY)



Formula (12B)

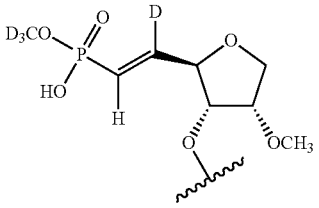


Formula (12BX)

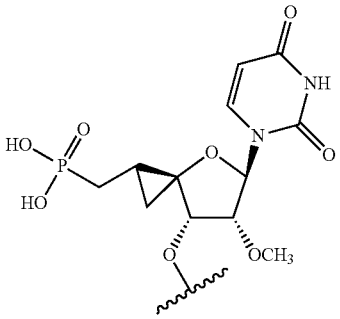


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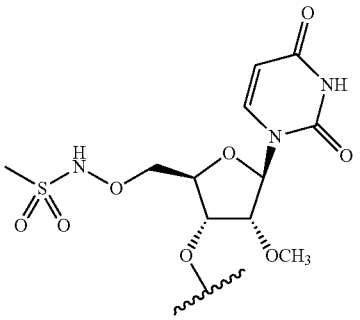
Formula (12BY)



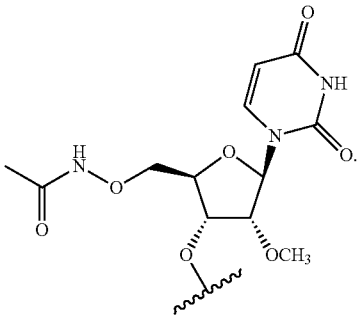
Formula (13A)



Formula (14A)



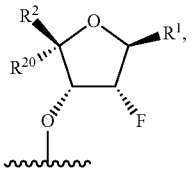
Formula (15A)



wherein R^1 is a nucleobase, aryl, heteroaryl, or H.

177. The siNA according to any one of embodiments 16, 131, 132, and 170, wherein the 5'-stabilized end cap is selected from the group consisting of Formulas (1A)-(15A), Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

178. The siNA according to any one of embodiments 131, 132, and 170, wherein the 5'-stabilized end cap has the structure of Formula (Ic):

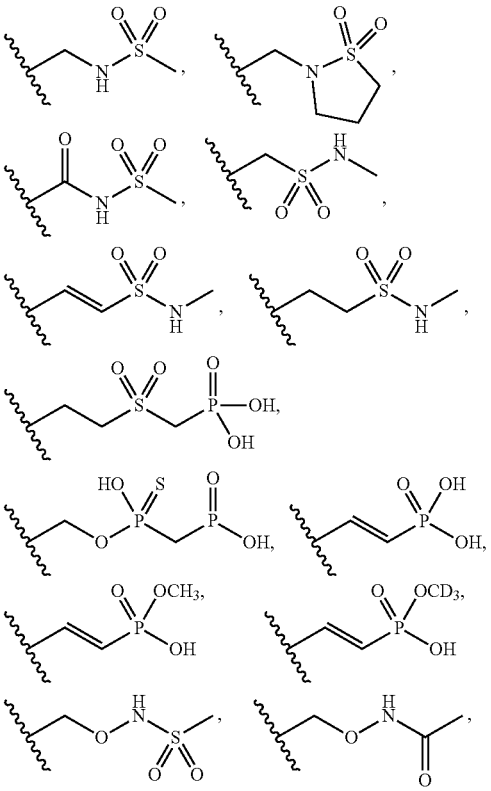


wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is

[0867]



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$,

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

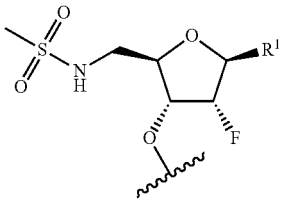
m is 1, 2, 3, or 4.

179. The siNA of embodiment 178, wherein R^1 is an aryl.

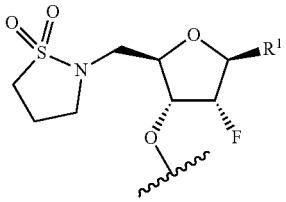
180. The siNA of embodiment 179, wherein the aryl is a phenyl.

181. The siNA according to any one of embodiments 16, 131, 132, and 170, wherein the 5'-stabilized end cap is selected from the group consisting of Formula (21) to Formula (35):

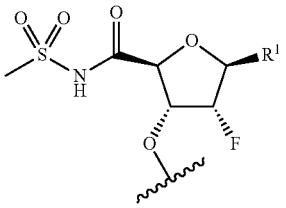
Formula (21)



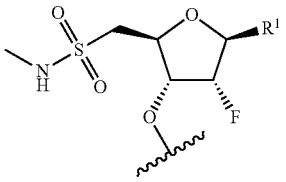
Formula (22)



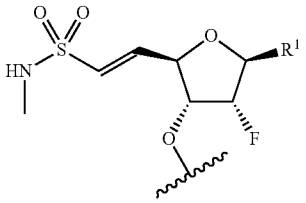
Formula (23)



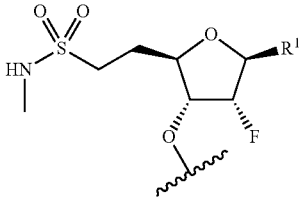
Formula (24)



Formula (25)

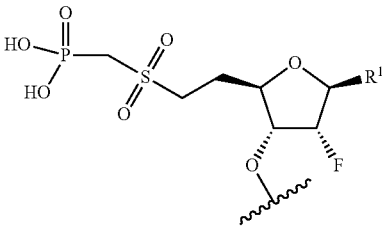


Formula (26)

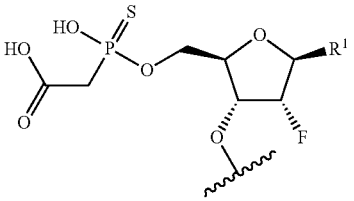


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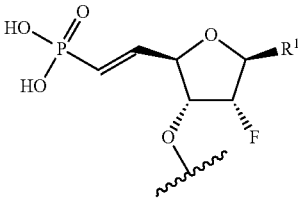
Formula (27)



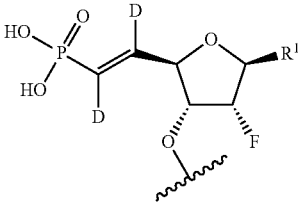
Formula (28)



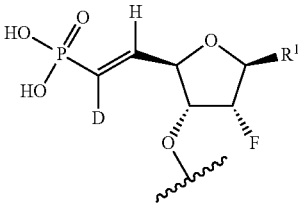
Formula (29)



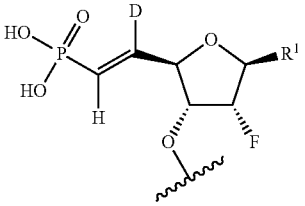
Formula (30)



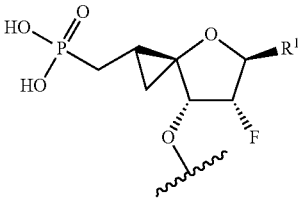
Formula (31)



Formula (32)

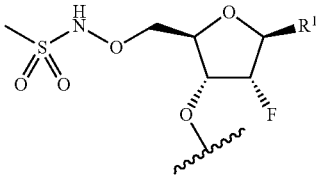


Formula (33)

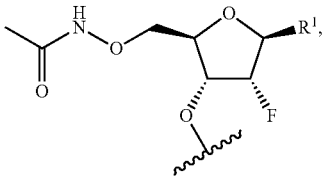


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Formula (34)



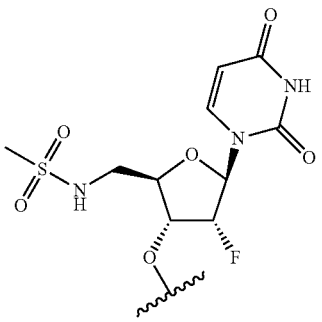
Formula (35)



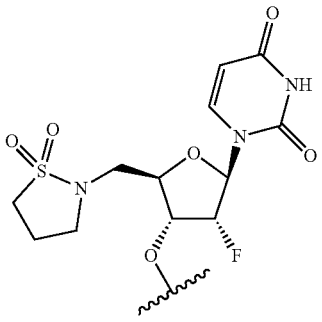
wherein R^1 is a nucleobase, aryl, heteroaryl, or H.

182. The siNA according to any one of embodiments 16, 131, 132, and 170, wherein the 5'-stabilized end cap is selected from the group consisting of Formulas (21A)-(35A), Formulas (29B)-(32B), Formulas (29AX)-(32AX), Formulas (29AY)-(32AY), Formulas (29BX)-(32BX), and Formulas (29BY)-(32BY):

Formula (21A)

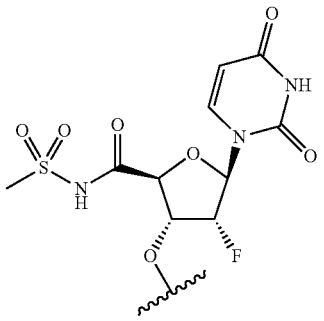


Formula (22A)

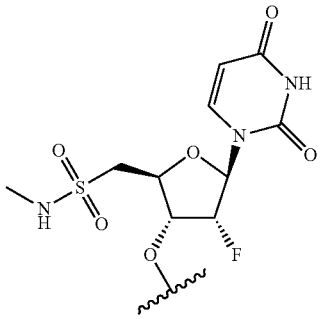


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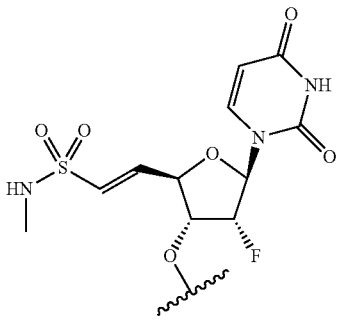
Formula (23A)



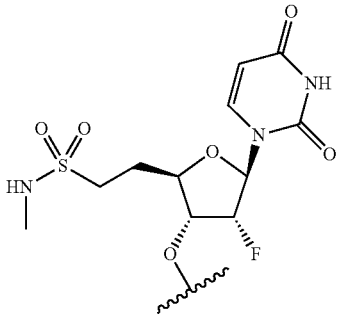
Formula (24A)



Formula (25A)

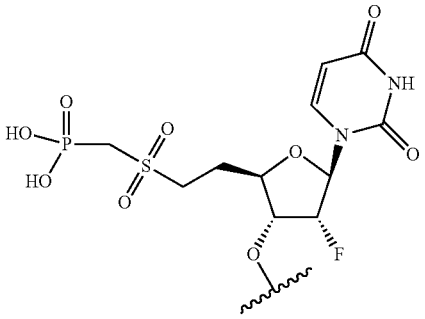


Formula (26A)

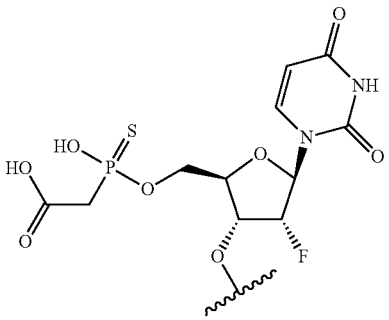


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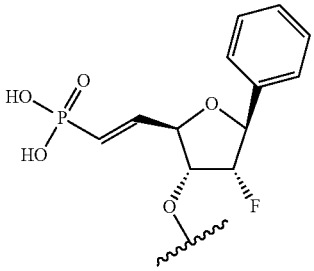
Formula (27A)



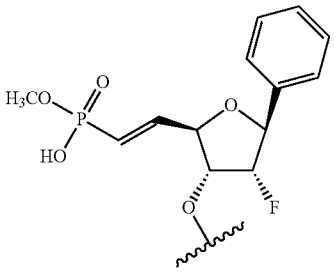
Formula (28A)



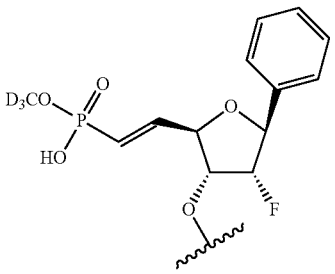
Formula (29A)



Formula (29AX)

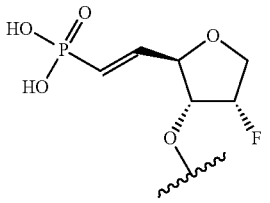


Formula (29AY)

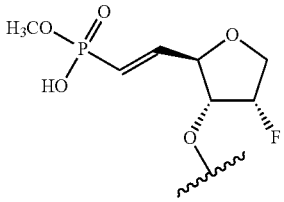


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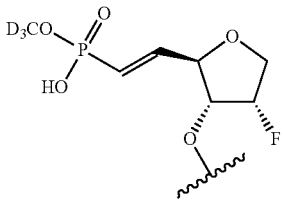
Formula (29BX)



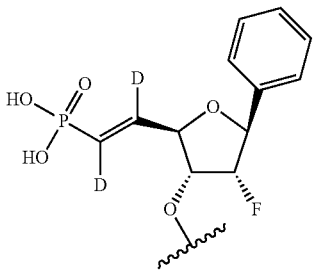
Formula (29BX)



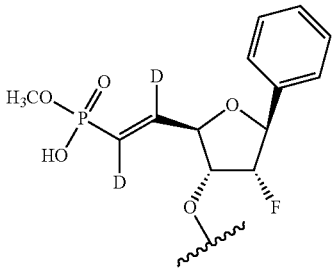
Formula (29BY)



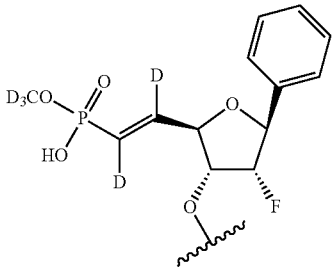
Formula (30A)



Formula (30AX)

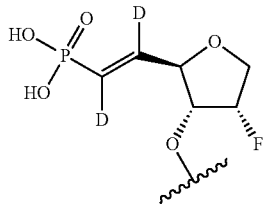


Formula (30AY)

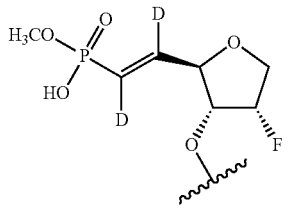


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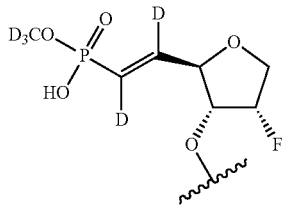
Formula (30B)



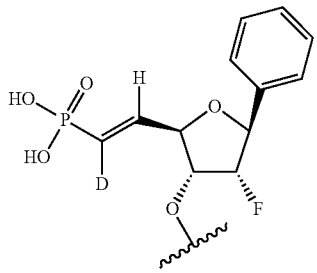
Formula (30BX)



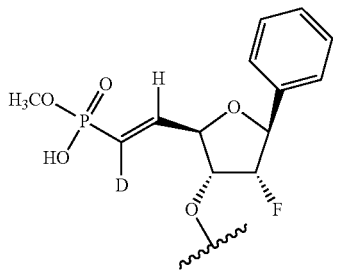
Formula (30BY)



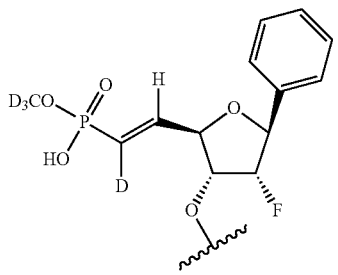
Formula (31A)



Formula (31AX)

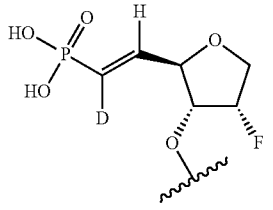


Formula (31AY)

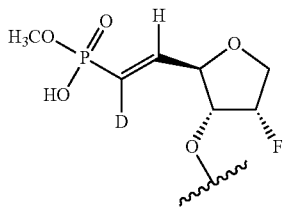


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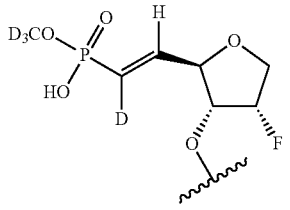
Formula (31B)



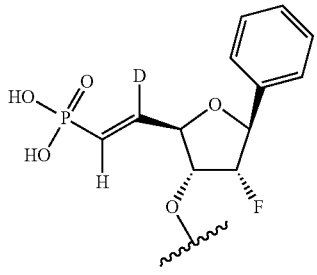
Formula (31BX)



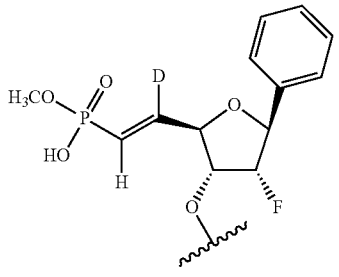
Formula (31BY)



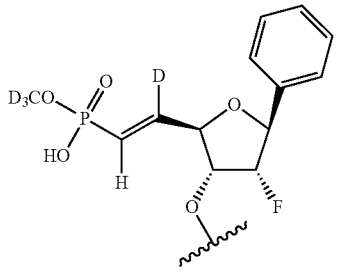
Formula (32A)



Formula (32AX)

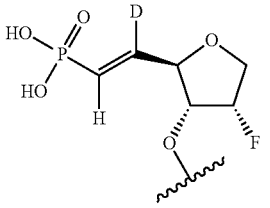


Formula (32AY)

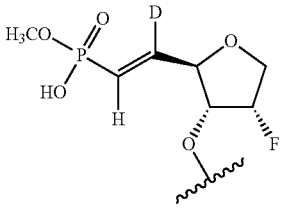


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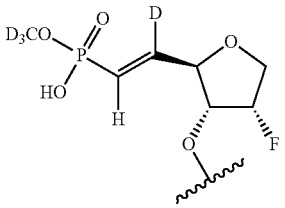
Formula (32B)



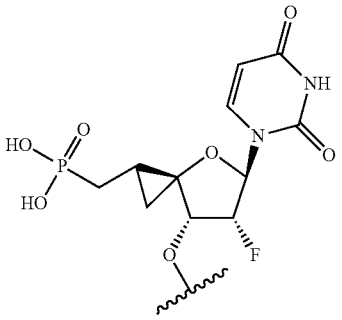
Formula (32BX)



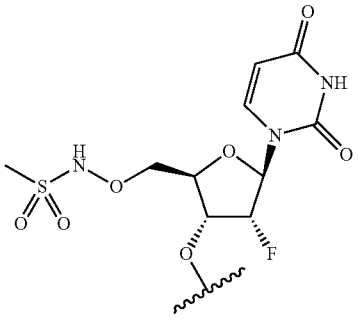
Formula (32BY)



Formula (33A)

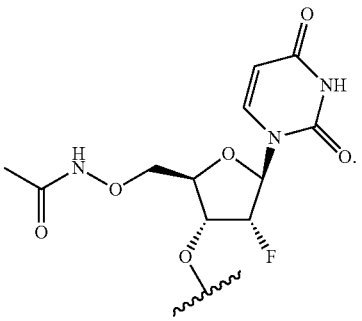


Formula (34A)

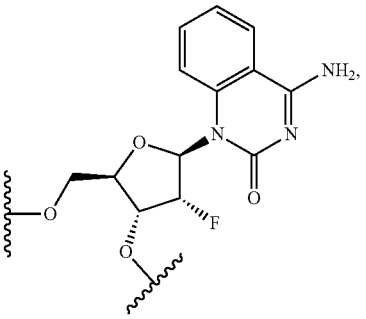


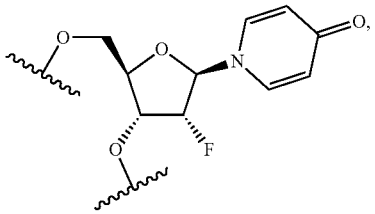
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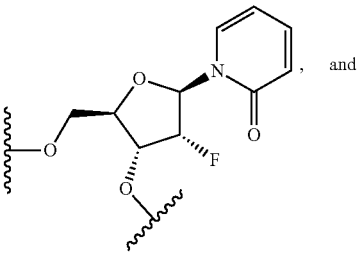
Formula (35A)



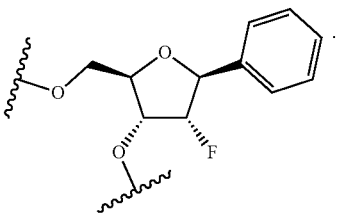
183. The siNA according to any one of embodiments 1-182, wherein the antisense strand comprises at least one thermally destabilizing nucleotide selected from:



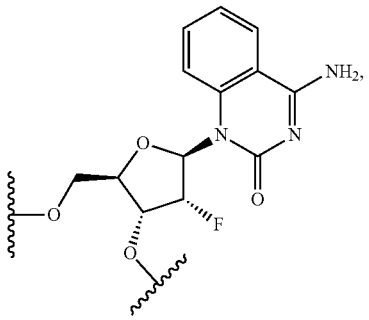


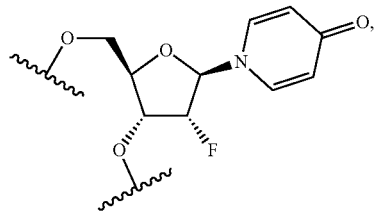


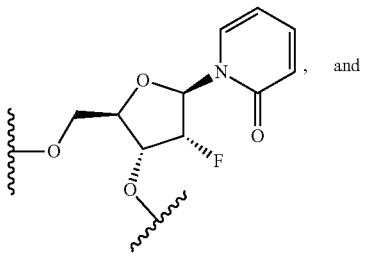
and



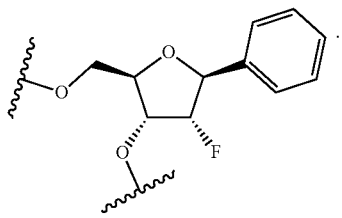
184. The siNA according to any one of embodiments 1-182, wherein the sense strand comprises at least one thermally destabilizing nucleotide selected from:



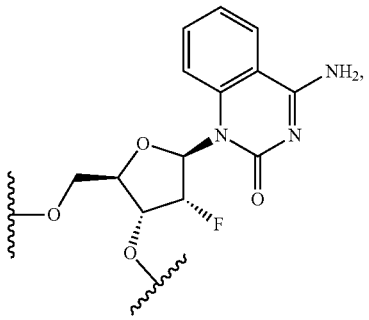




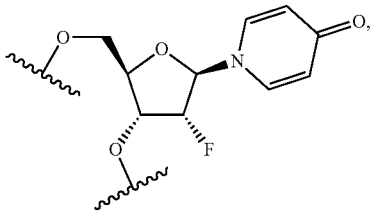
and

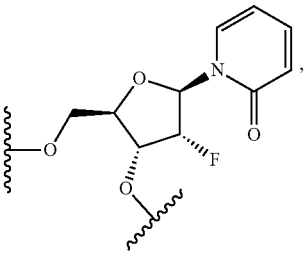


185. The siNA according to any one of embodiments 1-182, wherein the first nucleotide sequence comprises at least one thermally destabilizing nucleotide selected from:

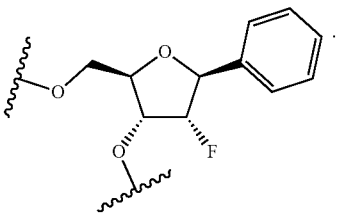


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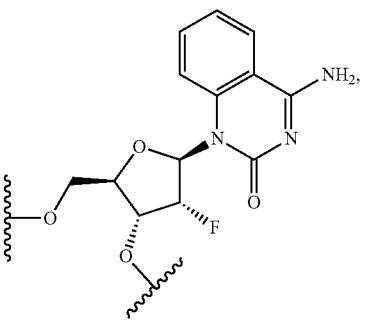


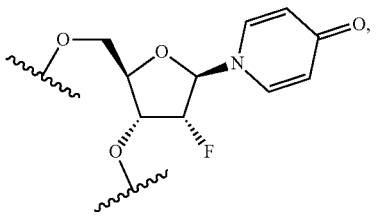


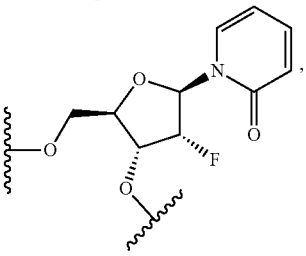
and



186. The siNA according to any one of embodiments 1-182, wherein the second nucleotide sequence comprises at least one thermally destabilizing nucleotide selected from:

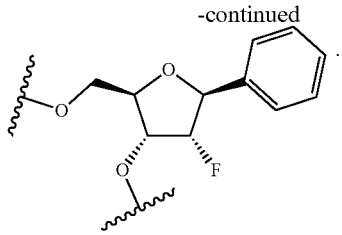






and

-continued



187. The siNA according to any one of embodiments 16, 131, 132, and 170-186, wherein the 5'-stabilized end cap is attached to the 5' end of the antisense strand.

188. The siNA of embodiment 187, wherein the 5'-stabilized end cap is attached to the 5' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

189. The siNA according to any one of embodiments 16, 131, 132, and 170-186, wherein the 5'-stabilized end cap is attached to the 5' end of the sense strand.

190. The siNA of embodiment 189, wherein the 5'-stabilized end cap is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

191. The siNA according to any preceding embodiment, wherein the target gene is a viral gene.

192. The siNA of embodiment 191, wherein the viral gene is from a DNA virus.

193. The siNA of embodiment 192, wherein the DNA virus is a double-stranded DNA (dsDNA) virus.

194. The siNA of embodiment 193, wherein the dsDNA virus is a hepadnavirus.

195. The siNA of embodiment 194, wherein the hepadnavirus is a hepatitis B virus (HBV).

196. The siNA of embodiment 195, wherein the HBV is selected from HBV genotypes A-J.

197. The siNA of embodiment 195 or 196, wherein the target gene is selected from the S gene or X gene of the HBV.

198. The siNA according to any one of embodiments 1-197, wherein the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410.

199. The siNA according to any one of embodiments 1-197, wherein the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410.

200. The siNA according to any one of embodiments 1-197, wherein the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410.

201. The siNA according to any one of embodiments 1-197, wherein the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

202. The siNA according to any one of embodiments 1-201, wherein the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410.

203. The siNA according to any one of embodiments 1-201, wherein the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410.

204. The siNA according to any one of embodiments 1-201, wherein the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410.

205. The siNA according to any one of embodiments 1-201, wherein the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

206. The siNA according to any preceding embodiment, wherein the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260.

207. The siNA according to any preceding embodiment, wherein the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306.

208. The siNA according to any preceding embodiment, wherein the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444.

209. The siNA according to any preceding embodiment, wherein the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

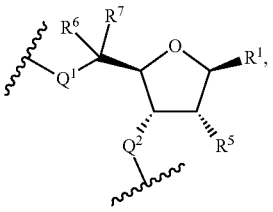
210. The siNA according to any preceding embodiment, wherein at least one end of the siNA is a blunt end.

211. The siNA according to any preceding embodiment, wherein at least one end of the siNA comprises an overhang, wherein the overhang comprises at least one nucleotide.

212. The siNA according to any one of embodiments 1-209, wherein both ends of the siNA comprise an overhang, wherein the overhang comprises at least one nucleotide.

213. The siNA according to any preceding embodiment, wherein the siNA is selected from ds-siNA-001 to ds-siNA-0178.

214. The siNA according to any preceding embodiment, wherein at least one 2'-fluoro nucleotide or 2'-O-methyl nucleotide is a 2'-fluoro or 2-O-methyl nucleotide mimic of Formula (V):



wherein

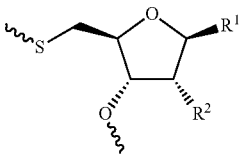
[0868] R^1 is independently a nucleobase, aryl, heteroaryl, or H, Q^1 and Q^2 are independently S or O,

[0869] R^5 is independently-OCD_3, —F, or —OCH_3, and

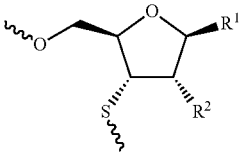
[0870] R^6 and R^7 are independently H, D, or CD_3.

215. The siNA of embodiment 214, wherein the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (16)-Formula (20):

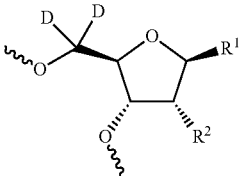
Formula (16)



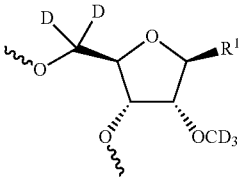
Formula (17)



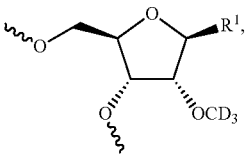
Formula (18)



Formula (19)



Formula (20)



wherein R^1 is a nucleobase and R^2 is independently F or —OCH_3.

216. The siNA according to any preceding embodiment, wherein at least one 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

217. The siNA according to embodiment 216, wherein at least one 2'-fluoro nucleotide on the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

218. The siNA according to embodiment 216 or 217, wherein the nucleotide at position 2 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

219. The siNA according to any one of embodiments 216-218, wherein the nucleotide at position 5 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

220. The siNA according to any one of embodiments 216-219, wherein the nucleotide at position 6 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

221. The siNA according any one of embodiments 216-220, wherein the nucleotide at position 8 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

222. The siNA according to any one of embodiments 216-221, wherein the nucleotide at position 10 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

223. The siNA according to any one of embodiments 216-222, wherein the nucleotide at position 14 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

224. The siNA according to any one of embodiments 216-223, wherein the nucleotide at position 16 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

225. The siNA according to any one of embodiments 216-224, wherein the nucleotide at position 17 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic.

226. The siNA according to any one of embodiments 216-225, wherein at least one 2'-fluoro nucleotide on the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

227. The siNA according to any one of embodiments 216-226, wherein the nucleotide at position 3 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

228. The siNA according to any one of embodiments 216-227, wherein the nucleotide at position 5 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

229. The siNA according to any one of embodiments 216-228, wherein the nucleotide at position 7 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

230. The siNA according to any one of embodiments 216-229, wherein the nucleotide at position 8 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

231. The siNA according to any one of embodiments 216-230, wherein the nucleotide at position 9 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

232. The siNA according to any one of embodiments 216-231, wherein the nucleotide at position 10 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

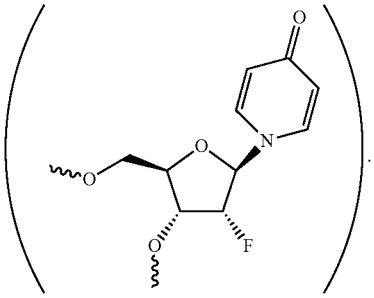
233. The siNA according to any one of embodiments 216-232, wherein the nucleotide at position 11 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

234. The siNA according to any one of embodiments 216-233, wherein the nucleotide at position 12 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

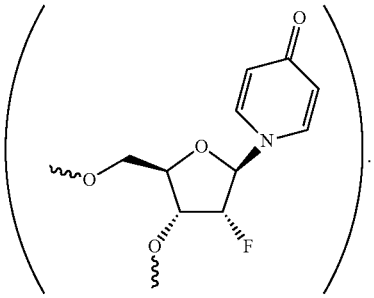
235. The siNA according to any one of embodiments 216-234, wherein the nucleotide at position 14 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

236. The siNA according to any one of embodiments 216-235, wherein the nucleotide at position 17 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

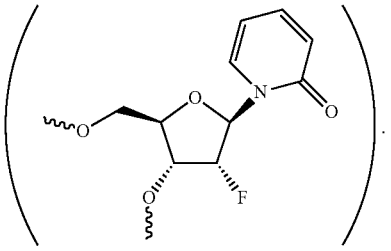
237. The siNA according to any one of embodiments 216-236, wherein at least 1, 2, 3, 4, 5, 6, or more 2'-fluoro nucleotide mimics is a f4P nucleotide



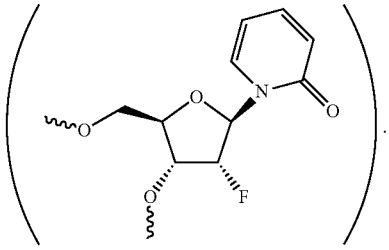
238. The siNA according to any one of embodiments 216-237, wherein less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 2'-fluoro nucleotide mimics is a f4P nucleotide



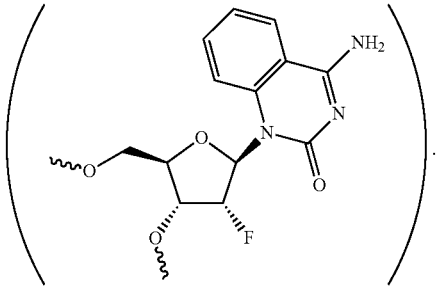
239. The siNA according to any one of embodiments 216-238, wherein 1, 2, 3, 4, 5, 6, or more 2'-fluoro nucleotide mimics is a f2P nucleotide



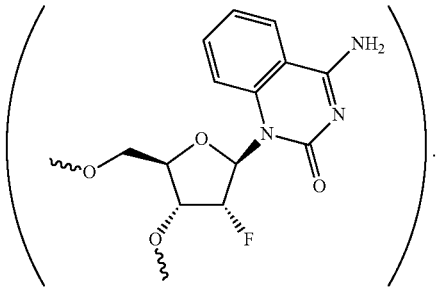
240. The siNA according to any one of embodiments 216-239, wherein less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 2'-fluoro nucleotide mimics is a f2P nucleotide



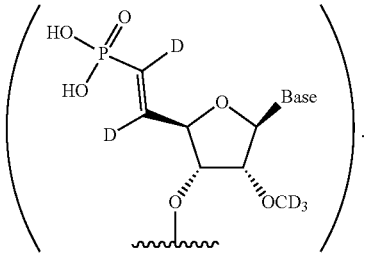
241. The siNA according to any one of embodiments 216-240, wherein 1, 2, 3, 4, 5, 6, or more 2'-fluoro nucleotide mimics is a fX nucleotide



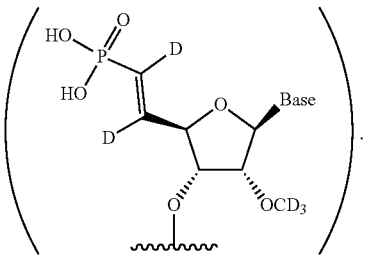
242. The siNA according to any one of embodiments 216-241, wherein less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 2'-fluoro nucleotide mimics is a fX nucleotide



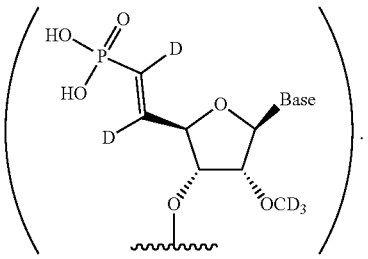
243. The siNA according to any preceding embodiment, wherein the first nucleotide from the 5' end of the sense strand or first nucleotide sequence is a d2vd3 nucleotide



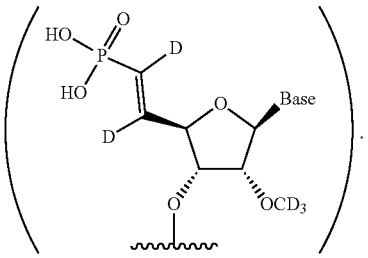
244. The siNA according to any preceding embodiment, wherein the first nucleotide from the 3' end of the sense strand or first nucleotide sequence is a d2vd3 nucleotide



245. The siNA according to any preceding embodiment, wherein the first nucleotide from the 5' end of the antisense strand or second nucleotide sequence is a d2vd3 nucleotide



246. The siNA according to any preceding embodiment, wherein the first nucleotide from the 3' end of the antisense strand or second nucleotide sequence is a d2vd3 nucleotide



247. A composition comprising the siNA according to any one of embodiments 1-246.

248. A composition comprising 2, 3, 4, 5, 6, 7, 8, 9, 10 or more siNAs according to any one of embodiments 1-246.

249. The composition of embodiment 248, wherein at least 1, 2, 3, 4, 5, or more siNAs target an S gene of HBV.

250. The composition of embodiment 248 or 249, wherein at least 1, 2, 3, 4, 5, or more siNAs target an X gene of HBV.

251. The composition according to any one of embodiments 247-250, further comprising an additional HBV treatment agent.

252. The composition of embodiment 251, wherein the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy.

253. The composition of embodiment 252, wherein the oligonucleotide therapy is an additional siNA.

254. The composition of embodiment 253, wherein the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178.

255. The composition of embodiment 252, wherein the oligonucleotide therapy is an antisense oligonucleotide (ASO), NAPs, or STOPS™

256. The composition of embodiment 255, wherein the ASO is ASO 1 or ASO 2.

257. The composition of embodiment 251 or 252, wherein the additional HBV treatment agent is selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H2158.

258. A method of treating a disease in a subject in need thereof, comprising administering to the subject the siNA according to any one of embodiments 1-246.

259. A method of treating a disease in a subject in need thereof, comprising administering to the subject the composition according to any one of embodiments 247-257.

260. The method of embodiment 258 or 259, wherein the disease is a viral disease.

261. The method of embodiment 260, wherein the viral disease is caused by a DNA virus.

262. The method of embodiment 261, wherein the DNA virus is a double stranded DNA (dsDNA) virus.

263. The method of embodiment 262, wherein the dsDNA virus is a hepadnavirus.

264. The method of embodiment 263, wherein the hepadnavirus is a hepatitis B virus (HBV).

265. The method of embodiment 264, wherein the HBV is selected from HBV genotypes A-J.

266. The method of any of embodiments 258-265, further comprising administering an additional HBV treatment agent.

267. The method of embodiment 266, wherein the siNA or the composition and the additional HBV treatment agent are administered concurrently.

268. The method of embodiment 266, wherein the siNA or the composition and the additional HBV treatment agent are administered sequentially.

269. The method of embodiment 266, wherein the siNA or the composition is administered prior to administering the additional HBV treatment agent.

270. The method of embodiment 266, wherein the siNA or the composition is administered after administering the additional HBV treatment agent.

271. The method of any one of embodiments 266-270, wherein the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy.

272. The method of embodiment 271, wherein the oligonucleotide therapy is an additional siNA.

273. The method of embodiment 272, wherein the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178.

274. The method of embodiment 271, wherein the oligonucleotide therapy is an antisense oligonucleotide (ASO), NAPs, or STOPs.
275. The method of embodiment 274, wherein the ASO is ASO 1 or ASO 2.
276. The method of embodiment 270 or 271, wherein the additional HBV treatment agent is selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H2158.
277. The method of embodiment 258 or 259, wherein the disease is a liver disease.
278. The method of embodiment 277, wherein the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC).
279. The method of embodiment 278, wherein the NAFLD is nonalcoholic steatohepatitis (NASH).
280. The method of any of embodiments 277-279 further comprising administering to the subject a liver disease treatment agent.
281. The method of embodiment 280, wherein the liver disease treatment agent is selected from a peroxisome proliferator-activator receptor (PPAR) agonist, farnesoid X receptor (FXR) agonist, lipid-altering agent, and incretin-based therapy.
282. The method of embodiment 281, wherein the PPAR agonist is selected from a PPARα agonist, dual PPARα/δ agonist, PPARγ agonist, and dual PPARα/γ agonist.
283. The method of embodiment 282, wherein the dual PPARα agonist is a fibrate.
284. The method of embodiment 282, wherein the PPARα/δ agonist is elafibranor.
285. The method of embodiment 282, wherein the PPARγ agonist is a thiazolidinedione (TZD).
286. The method of embodiment 282, wherein TZD is pioglitazone.
287. The method of embodiment 282, wherein the dual PPARα/γ agonist is saroglitazar.
288. The method of embodiment 281, wherein the FXR agonist is obeticholic acis (OCA).
289. The method of embodiment 281, wherein the lipid-altering agent is aramchol.
290. The method of embodiment 281, wherein the incretin-based therapy is a glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor.
291. The method of embodiment 290, wherein the GLP-1 receptor agonist is exenatide or liraglutide.
292. The method of embodiment 290, wherein the DPP-4 inhibitor is sitagliptin or vildapliptin.
293. The method of any one of embodiments 280-292, wherein the siNA or composition and the liver disease treatment agent are administered concurrently.
294. The method of any one of embodiments 280-292, wherein the siNA or composition and the liver disease treatment agent are administered sequentially.
295. The method of any one of embodiments 280-292, wherein the siNA or composition is administered prior to administering the liver disease treatment agent.
296. The method of any one of embodiments 280-292, wherein the siNA or composition is administered after administering the liver disease treatment agent.
297. The method of any of one embodiments 258-296, wherein the siNA or the composition is administered at a dose of at least 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg 14 mg/kg, or 15 mg/kg.
298. The method of any of one embodiments 258-296, wherein the siNA or the composition is administered at a dose of between 0.5 mg/kg to 50 mg/kg, 0.5 mg/kg to 40 mg/kg 0.5 mg/kg to 30 mg/kg, 1 mg/kg to 50 mg/kg, 1 mg/kg to 40 mg/kg, 1 mg/kg to 30 mg/kg, 1 mg/kg to 20 mg/kg, 3 mg/kg to 50 mg/kg, 3 mg/kg to 40 mg/kg, 3 mg/kg to 30 mg/kg, 3 mg/kg to 20 mg/kg, 3 mg/kg to 15 mg/kg, 3 mg/kg to 10 mg/kg, 4 mg/kg to 50 mg/kg, 4 mg/kg to 40 mg/kg, 4 mg/kg to 30 mg/kg, 4 mg/kg to 20 mg/kg, 4 mg/kg to 15 mg/kg, 4 mg/kg to 10 mg/kg, 5 mg/kg to 50 mg/kg, 5 mg/kg to 40 mg/kg, 5 mg/kg to 30 mg/kg, 5 mg/kg to 20 mg/kg, 5 mg/kg to 15 mg/kg, or 5 mg/kg to 10 mg/kg.
299. The method of any of one embodiments 258-298, wherein the siNA or the composition is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times.
300. The method of any of one embodiments 258-298, wherein the siNA or the composition is administered at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a day, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a week, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a month.
301. The method of any of one embodiments 258-300, wherein the siNA or the composition are administered at least once every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days.
302. The method of any of one embodiments 258-301, wherein the siNA or the composition is administered for a period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days, 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, 35, 40, 45, 50, 51, 52, 53, 54, or 55 weeks.
303. The method of any of one embodiments 258-302, wherein the siNA or the composition is administered at a single dose of 5 mg/kg.
304. The method of any of one embodiments 258-302, wherein the siNA or the composition is administered at a single dose of 10 mg/kg.
305. The method of any of one embodiments 258-302, wherein the siNA or the composition is administered at three doses of 10 mg/kg once a week.
306. The method of any of one embodiments 258-302, wherein the siNA or the composition is administered at three doses of 10 mg/kg once every three days.
307. The method of any of one embodiments 258-302, wherein the siNA or the composition is administered at five doses of 10 mg/kg once every three days.
308. The method of any of one embodiments 258-302, wherein the siNA or the composition is administered at six doses of ranging from 1 mg/kg to 15 mg/kg, 1 mg/kg to 10 mg/kg, 2 mg/kg to 15 mg/kg, 2 mg/kg to 10 mg/kg, 3 mg/kg to 15 mg/kg, or 3 mg/kg to 10 mg/kg.
309. The method of embodiment 308, wherein the first dose and second dose are administered at least 3 days apart.
310. The method of embodiment 308 or 309, wherein the second dose and third dose are administered at least 4 days apart.

311. The method of any one of embodiments 308-310, wherein the third dose and fourth dose, fourth dose and fifth dose, or fifth dose and sixth dose are administered at least 7 days apart.
312. The method of any one of embodiments 258-311, wherein the siNA or the composition are administered in a particle or viral vector.
313. The method of embodiment 312, wherein the viral vector is a vector of adenovirus, adeno-associated virus (AAV), alphavirus, flavivirus, herpes simplex virus, lentivirus, measles virus, picornavirus, poxvirus, retrovirus, or rhabdovirus.
314. The method of embodiment 312, wherein the viral vector is a recombinant viral vector.
315. The method according to any one of embodiments 312-314, wherein the viral vector is selected from AAVrh.74, AAVrh.10, AAVrh.20, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11, AAV-12 and AAV-13.
316. The method according to any one of embodiments 258-315, wherein the siNA or the composition is administered systemically.
317. The method according to any one of embodiments 258-315, wherein the siNA or the composition is administered locally.
318. The method according to any one of embodiments 258-317, wherein the siNA or the composition is administered intravenously, subcutaneously, or intramuscularly.
319. Use of the siNA according to any one of embodiments 1-246 or the composition according to any one of embodiments 247-257 in the manufacture of a medicament for treating a disease.
320. The use of embodiment 319, wherein the disease is a viral disease.
321. The use of embodiment 320, wherein the viral disease is caused by a DNA virus.
322. The use of embodiment 321, wherein the DNA virus is a double stranded DNA (dsDNA virus).
323. The use of embodiment 321, wherein the dsDNA virus is a hepadnavirus.
324. The use of embodiment 323, wherein the hepadnavirus is a hepatitis B virus (HBV).
325. The use of embodiment 324, wherein the HBV is selected from HBV genotypes A-J.
326. The use of any of one of embodiments 319-325, further comprising an additional HBV treatment agent in the manufacture of the medicament.
327. The use of embodiment 326, wherein the additional HBV treatment agent is selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy.
328. The use of embodiment 327, wherein the oligonucleotide therapy is an additional siNA.
329. The use of embodiment 328, wherein the additional siNA is selected from any of ds-siNA-001 to ds-siNA-0178.
330. The use of embodiment 327, wherein the oligonucleotide therapy is an antisense oligonucleotide (ASO), NAPs, or STOPs.
331. The use of embodiment 330, wherein the ASO is ASO 1 or ASO2.
332. The use of embodiment 326 or 327, wherein the additional HBV treatment agent is selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H2158.
333. The use of embodiment 319, wherein the disease is a liver disease.
334. The use of embodiment 333, wherein the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC).
335. The use of embodiment 334, wherein the NAFLD is nonalcoholic steatohepatitis (NASH).
336. The use of any of embodiments 333-335, further comprising a liver disease treatment agent in the manufacture of the medicament.
337. The use of embodiment 336, wherein the liver disease treatment agent is selected from a peroxisome proliferator-activator receptor (PPAR) agonist, farnesoid X receptor (FXR) agonist, lipid-altering agent, and incretin-based therapy.
338. The use of embodiment 337, wherein the PPAR agonist is selected from a PPARα agonist, dual PPARα/6 agonist, PPARγ agonist, and dual PPARα/γ agonist.
339. The use of embodiment 338, wherein the dual PPARα agonist is a fibrate.
340. The use of embodiment 338, wherein the PPARα/6 agonist is elafibranor.
341. The use of embodiment 338, wherein the PPARγ agonist is a thiazolidinedione (TZD).
342. The use of embodiment 341, wherein TZD is pioglitazone.
343. The use of embodiment 338, wherein the dual PPARα/γ agonist is saroglitazar.
344. The use of embodiment 337, wherein the FXR agonist is obeticholic acis (OCA).
345. The use of embodiment 337, wherein the lipid-altering agent is aramchol.
346. The use of embodiment 337, wherein the incretin-based therapy is a glucagon-like peptide 1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor.
347. The use of embodiment 346, wherein the GLP-1 receptor agonist is exenatide or liraglutide.
348. The use of embodiment 346, wherein the DPP-4 inhibitor is sitagliptin or vildapliptin.
349. The siNA according to any one of embodiments 1-246 for use as a medicament.
350. The composition according to any one of embodiments 247-257 for use as a medicament.
351. The siNA according to any one of embodiments 1-246 for use in the treatment of a disease.
352. The siNA of embodiment 351, wherein the disease is a viral disease.
353. The siNA of embodiment 352, wherein the viral disease is caused by a DNA virus.
354. The siNA of embodiment 353, wherein the DNA virus is a double stranded DNA (dsDNA virus).
355. The siNA of embodiment 354, wherein the dsDNA virus is a hepadnavirus.
356. The siNA of embodiment 355, wherein the hepadnavirus is a hepatitis B virus (HBV).

357. The siNA of embodiment 356, wherein the HBV is selected from HBV genotypes A-J.

358. The siNA of embodiment 351, wherein the disease is a liver disease.

359. The siNA of embodiment 358, wherein the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC).

360. The siNA of embodiment 359, wherein the NAFLD is nonalcoholic steatohepatitis (NASH).

361. The composition according to any one of embodiments 247-257, for use in the treatment of a disease.

362. The composition of embodiment 361, wherein the disease is a viral disease.

363. The composition of embodiment 362, wherein the viral disease is caused by a DNA virus.

364. The composition of embodiment 363, wherein the DNA virus is a double stranded DNA (dsDNA virus).

365. The composition of embodiment 364, wherein the dsDNA virus is a hepadnavirus.

366. The composition of embodiment 365, wherein the hepadnavirus is a hepatitis B virus (HIBV).

367. The composition of embodiment 366, wherein the disease is a liver disease.

368. The composition of embodiment 367, wherein the liver disease is a nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC).

369. The composition of embodiment 368, wherein the NAFLD is nonalcoholic steatohepatitis (NASH).

Tables

[0871]

TABLE 1

Non-modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
1	ACCGUGUGCACUUCGCUUC	57	GAAGCGAAGUGCACACGGUCC
2	ACCGUGUGCACUUCGCUUC	58	GAAGCGAAGUGCACACGGU
3	ACUUCGCUUCACCUCUGCA	59	UGCAGAGGUGAAGCGAAGUGC
4	AGUGUUUGCUGACGCAACC	60	GGUUGCGUCAGCAAACACUUG
5	CAGGCGGGGUUUUUCUUGU	61	ACAAGAAAAACCCCGCCUGUA
6	CAGGCGGGGUUUUUCUUGU	62	ACAAGAAAAAACCCCGCCUG
7	CAGUUUACUAGUGCCAUUU	63	AAAUGGCACUAGUAAACUGAG
8	CAGUUUACUAGUGCCAUUU	64	AAAUGGCACUAGUAAACUG
9	CAUCCUGCUGCUAUGCCUC	65	GAGGCAUAGCAGCAGGAUGAA
10	CAUCCUGCUGCUAUGCCUCAU	66	AUGAGGCAUAGCAGCAGGAUGAA
11	CAUCCUGCUGCUAUGCCUC	67	GAGGCAUAGCAGCAGGAUG
12	CCGUGUGCACUUCGCUUCA	68	UGAAGCGAAGUGCACACGGUC
13	CCGUGUGCACUUCGCUUCA	69	UGAAGCGAAGUGCACACGG
14	CCUGCUGCUAUGCCUCAUCUU	70	AAGAUGAGGCAUAGCAGCAGGAU
15	CUCAGUUUACUAGUGCCAU	71	AUGGCACUAGUAAACUGAGCC

TABLE 1-continued

Non-modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
16	CUCAGUUUACUAGUGCCAU	71	AUGGCACUAGUAAACUGAGCC
17	CUCAGUUUACUAGUGCCAU	71	AUGGCACUAGUAAACUGAGCC
18	CUCAGUUUACUAGUGCCAU	72	AUGGCACUAGUAAACUGAG
19	CUCAGUUUACUAGUGCCAU	72	AUGGCACUAGUAAACUGAG
20	CUGCUAUGCCUCAUCUUCU	73	AGAAGAUGAGGCAUAGCAGCA
21	CUGCUAUGCCUCAUCUUCU	73	AGAAGAUGAGGCAUAGCAGCA
22	CUGCUAUGCCUCAUCUUCU	74	AGAAGAUGAGGCAUAGCAG
23	CUGCUAUGCCUCAUCUUCU	74	AGAAGAUGAGGCAUAGCAG
24	CUGCUGCUAUGCCUCAUCU	75	AGAUGAGGCAUAGCAGCAGGA
25	CUGCUGCUAUGCCUCAUCU	76	AGAUGAGGCAUAGCAGCAG
26	CUGCUGCUAUGCCUCAUCU	76	AGAUGAGGCAUAGCAGCAG
27	CUUCGCUUCACCUCUGCACGU	77	ACGUGCAGAGGUGAAGCGAAGUG
28	GCACUUCGCUUCACCUCUGCA	78	UGCAGAGGUGAAGCGAAGUGCAC
29	GCCGAUCCAUACUGCGGAA	79	UUCCGCAGUAUGGAUCGGCAG
30	GCCGGGUUUUUCUUGUUGA	80	UUCCGCAGUAUGGAUCGGC
31	GCGGGGUUUUUCUUGUUGA	81	UCAACAAGAAAAACCCCGCCU
32	GCGGGGUUUUUCUUGUUGA	81	UCAACAAGAAAAACCCCGCCU
33	GCGGGGUUUUUCUUGUUGA	82	UCAACAAGAAAAACCCCGC
34	GCGGGGUUUUUCUUGUUGA	82	UCAACAAGAAAAACCCCGC
35	GCUGCUAUGCCUCAUCUUCUU	83	AAGAAGAUGAGGCAUAGCAGCAG
36	GGAUGUGUCUGCGGCGUUUUA	84	UAAAACGCCGCAGACACAUCCAG
37	GGCCAAAAUUCGCAGUCCC	85	GGGACUGCGAAUUUUGGCCAA
38	GGCGCACCUCUCUUUACGC	86	GCGUAAAGAGAGGUGCGCCCC
39	GUAUGUUGCCCGUUUGUCC	87	GGACAAACGGGCAACAUACCU
40	GUGGUGGACUUCUCUCAAU	88	AUUGAGAGAAGUCCACCACGA
41	GUGUGCACUUCGCUUCACC	89	GGUGAAGCGAAGUGCACACGG
42	GUUGCCCGUUUGUCCUCUA	90	UAGAGGACAAACGGGCAACAU
43	GUUGCCCGUUUGUCCUCUA	91	UAGAGGACAAACGGGCAAC
44	UCCAUACUGCGGAACUCCU	92	AGGAGUUCCGCAGUAUGGAUC
45	UCCAUACUGCGGAACUCCU	93	AGGAGUUCCGCAGUAUGGA
46	UCGUGGUGGACUUCUCUCAAU	94	AUUGAGAGAAGUCCACCACGAGU
47	UGCACUUCGCUUCACCUCU	95	AGAGGUGAAGCGAAGUGCACA
48	UGCCGAUCCAUACUGCGGA	96	UCCGCAGUAUGGAUCGGCAGA
49	UGCCGAUCCAUACUGCGGA	97	UCCGCAGUAUGGAUCGGCA
50	UGCUAUGCCUCAUCUUCUU	98	AAGAAGAUGAGGCAUAGCAGC
51	UGUGCACUUCGCUUCACCU	99	AGGUGAAGCGAAGUGCACACG

TABLE 1-continued

Non-modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
52	UGUGCACUUCGCUUCACCU	99	AGGUGAAGCGAAGUGCACACG
53	UGUGCACUUCGCUUCACCU	100	AGGUGAAGCGAAGUGCACA
54	UGUGCACUUCGCUUCACCU	100	AGGUGAAGCGAAGUGCACA
55	UUGCCCGUUUGUCCUCUAA	101	UUAGAGGACAAACGGGCAACA
56	UUGCCCGUUUGUCCUCUAA	102	UUAGAGGACAAACGGGCAA

TABLE 2

2'-OMe and 2'-F Modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3')
103	mAmCfCmGmUmGfUfGfCmA mCfUmUmCmGmCfUmUmC	159	mGfAmAmGmCmGmAmAmGm UmGmCmAfCmAmCmGmGmUm CmC
104	mAmCfCmGmUmGfUfGfCmA mCfUmUmCmGmCfUmUmC	160	mGfAmAmGmCmGmAmAmGm UmGmCmAfCmAmCmGmGmU
105	mAmCfUmUmCmGfCfUfUmC mAfCmCmUmCmUfGmCmA	161	mUfGmCmAmGmAmGmGmUm GmAmAmGfCmGmAmAmGmU mGmC
106	mAmGfUmGmUmUfUfGfCmU mGfAmCmGmCmAfAmCmC	162	mGfGmUmUmGmCmGmUmCmA mGmCmAfAmAmCmAmCmUmU mG
107	mCmAfGmGmCmGfGfGfGmU mUfUmUmUmCmUfUmGmU	163	mAfCmAmAmGmAmAmAmAm AmCmCmCfCmGmCmCmUmGm UmA
108	mCmAfGmGmCmGfGfGfGmU mUfUmUmUmCmUfUmGmU	164	mAfCmAmAmGmAmAmAmAm AmAmCmCmCfCmGmCmCmUm G
109	mCmAfGmUmUmUfAfCfUmA mGfUmGmCmCmAfUmUmU	165	mAfAmAmUmGmGmCmAmCmU mAmGmUfAmAmAmCmUmGm AmG
110	mCmAfGmUmUmUfAfCfUmA mGfUmGmCmCmAfUmUmU	166	mAfAmAmUmGmGmCmAmCmU mAmGmUfAmAmAmCmUmG
111	mCmAfUmCmCmUfGfCfUmG mCfUmAmUmGmCfCmUmC	167	mGfAmGmGmCmAmUmAmGmC mAmGmCfAmGmGmAmUmGm AmA
112	mCmAmUmCmCmUfGmCfUfG fCmUmAmUmGmCmCmUmCm AmU	168	mAfUmGmAmGfGmCmAmUmA mGmCmAfGmCfAmGmGmAmU mGmAmA
113	mCmAfUmCmCmUfGfCfUmG mCfUmAmUmGmCfCmUmC	169	mGfAmGmGmCmAmUmAmGmC mAmGmCfAmGmGmAmUmG
114	mCmCfGmUmGmUfGfCfAmC mUfUmCmGmCmUfUmCmA	170	mUfGmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGm UmC
115	mCmCfGmUmGmUfGfCfAmC mUfUmCmGmCmUfUmCmA	171	mUfGmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmG

TABLE 2-continued

2'-OMe and 2'-F Modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3')
116	mCmCmUmGmCmUfGmCfUfA fUmGmCmCmUmCmAmUmCm UmU	172	mAfAmGmAmUfGmAmGmGmC mAmUmAfGmCfAmGmCmAmG mGmAmU
117	mCmUfCmAmGmUfUfUfAmC mUfAmGmUmGmCfCmAmU	173	mAfUmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGmC mC
118	mCmUmCmAmGmUfUmUmAm CmUmAmGmUmGmCmCmAm U	173	mAfUmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGmC mC
119	mCmUfCmAmGmUfUfUmAmC mUmAmGmUmGmCfCmAmU	173	mAfUmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGmC mC
120	mCmUfCmAmGmUfUfUfAmC mUfAmGmUmGmCfCmAmU	174	mAfUmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmG
121	mCmUfCmAmGmUfUfUmAmC mUmAmGmUmGmCfCmAmU	174	mAfUmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmG
122	mCmUfGmCmUmAfUfGfCmC mUfCmAmUmCmUfUmCmU	175	mAfGmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmGm CmA
123	mCmUfGmCmUmAfUfGmCmC mUmCmAmUmCmUfUmCmU	175	mAfGmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmGm CmA
124	mCmUfGmCmUmAfUfGfCmC	176	mAfGmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmG
125	mCmUfGmCmUmAfUfGmCmC mUmCmAmUmCmUfUmCmU	176	mAfGmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmG
126	mCmUfGmCmUmGfCfUfAmU mGfCmCmUmCmAfUmCmU	177	mAfGmAmUmGmAmGmGmCm AmUmAmGfCmAmGmCmAmGm GmA
127	mCmUfGmCmUmGfCfUfAmU mGfCmCmUmCmAfUmCmU	178	mAfGmAmUmGmAmGmGmCm AmUmAmGfCmAmGmCmAmG
128	mCmUfGmCmUmGfCfUmAmU mGmCmCmUmCmAfUmCmU	178	mAfGmAmUmGmAmGmGmCm AmUmAmGfCmAmGmCmAmG
129	mCmUmUmCmGmCfUmUfCfA fCmCmUmCmUmGmCmAmCm GmU	179	mAfCmGmUmGfCmAmGmAmG mGmUmGfAmAfGmCmGmAmA mGmUmG
130	mGmCmAmCmUmUfCmGfCfU fUmCmAmCmCmUmCmUmGm CmA	180	mUfGmCmAmGfAmGmGmUmG mAmAmGfCmGfAmAmGmUmG mCmAmC
131	mGmCfCmGmAmUfCfCfAmU mAfCmUmGmCmGfGmAmA	181	mUfUmCmCmGmCmAmGmUmA mUmGmGfAmUmCmGmGmCmA mG
132	mGmCfCmGmGmGfUfUfUmU mUfCmUmUmGmUfUmGmA	182	mUfUmCmCmGmCmAmGmUmA mUmGmGfAmUmCmGmGmC
133	mGmCfGmGmGmGfUfUfUmU mUfCmUmUmGmUfUmGmA	183	mUfCmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCmC mU
134	mGmCfGmGmGmGfUfUmUmU mUmCmUmUmGmUfUmGmA	183	mUfCmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCmC mU

TABLE 2-continued

2'-OMe and 2'-F Modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3')
135	mGmCfGmGmGmGfUfUfUmU mUfCmUmUmUmGmUfUmGmA	184	mUfCmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmC
136	mGmCfGmGmGmGfUfUmUmU mUmCmUmUmGmUfUmGmA	184	mUfCmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmC
137	mGmCmUmGmCmUfAmUfGfC fCmUmCmAmUmCmUmUmCm UmU	185	mAfAmGmAmAfGmAmUmGmA mGmGmCfAmUfAmGmCmAmG mCmAmG
138	mGmGmAmUmGmUfGmUfCfU fGmCmGmGmCmGmUmUmUm UmA	186	mUfAmAmAmAfCmGmCmCmG mCmAmGfAmCfAmCmAmUmC mCmAmG
139	mGmGfCmCmAmAfAfAfUmU mCfGmCmAmGmUfCmCmC	187	mGfGmGmAmCmUmGmCmGmA mAmUmUfUmUmGmGmCmCmA mA
140	mGmGfCmGmCmAfCfCfUmCm UfCmUmUmUmAfCmGmC	188	mGfCmGmUmAmAmAmGmAm GmAmGmGfUmGmCmGmCmCm CmC
141	mGmUfAmUmGmUfUfGfCmC mCfGmUmUmUmGfUmCmC	189	mGfGmAmCmAmAmAmCmGmG mGmCmAfAmCmAmUmAmCmC mU
142	mGmUfGmGmUmGfGfAfCmU mUfCmUmCmUmCfAmAmU	190	mAfUmUmGmAmGmAmGmAm AmGmUmCfCmAmCmCmAmCm GmA
143	mGmUfGmUmGmCfAfCfUmU mCfGmCmUmUmCfAmCmC	191	mGfGmUmGmAmAmGmCmGm AmAmGmUfGmCmAmCmAmCm GmG
144	mGmUfUmGmCmCfCfGfUmU mUfGmUmCmCmUfCmUmA	192	mUfAmGmAmGmGmAmCmAm AmAmCmGfGmGmCmAmAmCm AmU
145	mGmUfUmGmCmCfCfGfUmU mUfGmUmCmCmUfCmUmA	193	mUfAmGmAmGmGmAmCmAm AmAmCmGfGmGmCmAmAmC
146	mUmCfCmAmUmAfCfUfGmC mGfGmAmAmCmUfCmCmU	194	mAfGmGmAmGmUmUmCmCmG mCmAmGfUmAmUmGmGmAm UmC

TABLE 2-continued

2'-OMe and 2'-F Modified Nucleotide Sequences

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3')
147	mUmCfCmAmUmAfCfUfGmC mGfGmAmAmCmUfCmCmU	195	mAfGmGmAmGmUmUmCmCmG mCmAmGfUmAmUmGmGmA
148	mUmCmGmUmGmGfUmGfGfA fCmUmUmCmUmCmUmCmAm AmU	196	mAfUmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCmG mAmGmU
149	mUmGfCmAmCmUfUfCfGmC mUfUmCmAmCmCfUmCmU	197	mAfGmAmGmGmUmGmAmAm GmCmGmAfAmGmUmGmCmAm CmA
150	mUmGfCmCmGmAfUfCfCmA mUfAmCmUmGmCfGmGmA	198	mUfCmCmGmCmAmGmUmAmU mGmGmAfUmCmGmGmCmAmG mA
151	mUmGfCmCmGmAfUfCfCmA mUfAmCmUmGmCfGmGmA	199	mUfCmCmGmCmAmGmUmAmU mGmGmAfUmCmGmGmCmA
152	mUmGfCmUmAmUfGfCfCmU mCfAmUmCmUmUfCmUmU	200	mAfAmGmAmAmGmAmUmGm AmGmGmCfAmUmAmGmCmAm GmC
153	mUmGfUmGmCmAfCfUfUmC mGfCmUmUmCmAfCmCmU	201	mAfGmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmAm CmG
154	mUmGfUmGmCmAfCfUmUmC mGmCmUmUmCmAfCmCmU	201	mAfGmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmAm CmG
155	mUmGfUmGmCmAfCfUfUmC mGfCmUmUmCmAfCmCmU	202	mAfGmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmA
156	mUmGfUmGmCmAfCfUmUmC mGmCmUmUmCmAfCmCmU	202	mAfGmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmA
157	mUmUfGmCmCmCfGfUmUmU mGmUmCmCmUmCfUmAmA	203	mUfUmAmGmAmGmGmAmCm AmAmAmCfGmGmGmCmAmAm CmA
158	mUmUfGmCmCmCfGfUfUmU mGfUmCmCmUmCfUmAmA	204	mUfUmAmGmAmGmGmAmCm AmAmAmCfGmGmGmCmAmA

mX = 2'-O-methyl nucleotide;
fX = 2'-fluoro nucleotide

TABLE 3

2'-O-methyl and 2'-fluoro Modified Nucleotide Sequences with Phosphorothioate Linkages

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
205	mApsmCpsfCmGmUmGfUfGfC mAmCfUmUmCmGmCfUmUmC	261	mGpsfApsmAmGmCmGmAmAmGm UmGmCmAfCmAmCmGmGmUpsmC psmC
206	mApsmCpsfCmGmUmGfUfGfC mAmCfUmUmCmGmCfUmUmC	262	mGpsfApsmAmGmCmGmAmAmGm UmGmCmAfCmAmCmGmGmU
207	mApsmCpsfUmUmCmGfCfUfU mCmAfCmCmUmCmUfGmCmA	263	mUpsfGpsmCmAmGmAmGmGmUm GmAmAmGfCmGmAmAmGmUpsm GpsmC

TABLE 3-continued

2'-O-methyl and 2'-fluoro Modified Nucleotide Sequences with Phosphorothioate Linkages

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
208	mApsmGpsfUmGmUmUfUfGfC mUmGfAmCmGmCmAfAmCmC	264	mGpsfGpsmUmUmGmCmGmUmCm AmGmCmAfAmAmCmAmCmUpsmU psmG
209	mCpsmApsfGmGmCmGfGfGfG mUmUfUmUmUmCmUfUmGm U	265	mApsfCpsmAmAmGmAmAmAmAm AmCmCmCfCmGmCmCmUmGpsmU psmA
210	mCpsmApsfGmGmCmGfGfGfG mUmUfUmUmUmCmUfUmGm U	266	mApsfCpsmAmAmGmAmAmAmAm AmAmCmCmCfCmGmCmCmUmG
211	mCpsmApsfGmUmUmUfAfCfU mAmGfUmGmCmCmAfUmUm U	267	mApsfApsmAmUmGmGmCmAmCm UmAmGmUfAmAmAmCmUmGpsm ApsmG
212	mCpsmApsfGmUmUmUfAfCfU mAmGfUmGmCmCmAfUmUm U	268	mApsfApsmAmUmGmGmCmAmCm UmAmGmUfAmAmAmCmUmG
213	mCpsmApsfUmCmCmUfGfCfU mGmCfUmAmUmGmCfCmUmC	269	mGpsfApsmGmGmCmAmUmAmGm CmAmGmCfAmGmGmAmUmGpsm ApsmA
214	mCpsmApsmUmCmCmUfGmCf UfGfCmUmAmUmGmCmCmUm CmAmU	270	mApsfUpsmGmAmGfGmCmAmUmA mGmCmAfGmCfAmGmGmAmUmGp smApsmA
215	mCpsmApsfUmCmCmUfGfCfU mGmCfUmAmUmGmCfCmUmC	271	mGpsfApsmGmGmCmAmUmAmGm CmAmGmCfAmGmGmAmUmG
216	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	272	mUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsmU psmC
217	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	273	mUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmG
218	mCpsmCpsmUmGmCmUfGmCf UfAfUmGmCmCmUmCmAmUm CmUmU	274	mApsfApsmGmAmUfGmAmGmGmC mAmUmAfGmCfAmGmCmAmGmGp smApsmU
219	mCpsmUpsfCmAmGmUfUfUfA mCmUfAmGmUmGmCfCmAmU	275	mApsfUpsmGmGmCmAmCmUmAm GmUmAmAfAmCmUmGmAmGpsm CpsmC
220	mCpsmUpsmCmAmGmUfUmU mAmCmUmAmGmUmGmCmC mAmU	275	mApsfUpsmGmGmCmAmCmUmAm GmUmAmAfAmCmUmGmAmGpsm CpsmC
221	mCpsmUpsfCmAmGmUfUfUmA mCmUmAmGmUmGmCfCmAm U	275	mApsfUpsmGmGmCmAmCmUmAm GmUmAmAfAmCmUmGmAmGpsm CpsmC
222	mCpsmUpsfCmAmGmUfUfUfA mCmUfAmGmUmGmCfCmAmU	276	mApsfUpsmGmGmCmAmCmUmAm GmUmAmAfAmCmUmGmAmG
223	mCpsmUpsfCmAmGmUfUfUmA mCmUmAmGmUmGmCfCmAm U	276	mApsfUpsmGmGmCmAmCmUmAm GmUmAmAfAmCmUmGmAmG
224	mCpsmUpsfGmCmUmAfUfGfC mCmUfCmAmUmCmUfUmCmU	277	mApsfGpsmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmGpsmC psmA
225	mCpsmUpsfGmCmUmAfUfGmC mCmUmCmAmUmCmUfUmCm U	277	mApsfGpsmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmGpsmC psmA

TABLE 3-continued

2'-O-methyl and 2'-fluoro Modified Nucleotide Sequences with Phosphorothioate Linkages

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
226	mCpsmUpsfGmCmUmAfUfGfC mCmUfCmAmUmCmUfUmCmU	278	mApsfGpsmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmG
227	mCpsmUpsfGmCmUmAfUfGmC mCmUmCmAmUmCmUfUmCm U	278	mApsfGpsmAmAmGmAmUmGmAm GmGmCmAfUmAmGmCmAmG
228	mCpsmUpsfGmCmUmGfCfUfA mUmGfCmCmUmCmAfUmCmU	279	mApsfGpsmAmUmGmAmGmGmCm AmUmAmGfCmAmGmCmAmGpsm GpsmA
229	mCpsmUpsfGmCmUmGfCfUfA mUmGfCmCmUmCmAfUmCmU	280	mApsfGpsmAmUmGmAmGmGmCm AmUmAmGfCmAmGmCmAmG
230	mCpsmUpsfGmCmUmGfCfUmA mUmGmCmCmUmCmAfUmCm U	280	mApsfGpsmAmUmGmAmGmGmCm AmUmAmGfCmAmGmCmAmG
231	mCpsmUpsmUmCmGmCfUmUf CfAfCmCmUmCmUmGmCmAm CmGmU	281	mApsfCpsmGmUmGfCmAmGmAmG mGmUmGfAmAfGmCmGmAmAmG psmUpsmG
232	mGpsmCpsmAmCmUmUfCmGf CfUfUmCmAmCmCmUmCmUm GmCmA	282	mUpsfGpsmCmAmGfAmGmGmUmG mAmAmGfCmGfAmAmGmUmGmCp smApsmC
233	mGpsmCpsfCmGmAmUfCfCfA mUmAfCmUmGmCmGfGmAm A	283	mUpsfUpsmCmCmGmCmAmGmUm AmUmGmGfAmUmCmGmGmCpsm ApsmG
234	mGpsmCpsfCmGmGmGfUfUfU mUmUfCmUmUmGmUfUmGm A	284	mUpsfUpsmCmCmGmCmAmGmUm AmUmGmGfAmUmCmGmGmC
235	mGpsmCpsfGmGmGmGfUfUfU mUmUfCmUmUmGmUfUmGm A	285	mUpsfCpsmAmAmCmAmAmGmAm AmAmAmAfCmCmCmCmGmCpsmC psmU
236	mGpsmCpsfGmGmGmGfUfUmU mUmUmCmUmUmGmUfUmGm A	285	mUpsfCpsmAmAmCmAmAmGmAm AmAmAmAfCmCmCmCmGmCpsmC psmU
237	mGpsmCpsfGmGmGmGfUfUfU mUmUfCmUmUmGmUfUmGm A	286	mUpsfCpsmAmAmCmAmAmGmAm AmAmAmAfCmCmCmCmGmC
238	mGpsmCpsfGmGmGmGfUfUmU mUmUmCmUmUmGmUfUmGm A	286	mUpsfCmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmC
239	mGpsmCpsmUmGmCmUfAmUf GfCfCmUmCmAmUmCmUmUm CmUmU	287	mApsfApsmGmAmAfGmAmUmGmA mGmGmCfAmUfAmGmCmAmGmCp smApsmG
240	mGpsmGpsmAmUmGmUfGmUf CfUfGmCmGmGmCmGmUmUm UmUmA	288	mUpsfApsmAmAmAfCmGmCmCmG mCmAmGfAmCfAmCmAmUmCmCp smApsmG
241	mGpsmGpsfCmCmAmAfAfAfU mUmCfGmCmAmGmUfCmCmC	289	mGpsfGpsmGmAmCmUmGmCmGm AmAmUmUfUmUmGmGmCmCpsm ApsmA
242	mGpsmGpsfCmGmCmAfCfCfU mCmUfCmUmUmUmAfCmGmC	290	mGpsfCpsmGmUmAmAmAmGmAm GmAmGmGfUmGmCmGmCmCpsmC psmC
243	mGpsmUpsfAmUmGmUfUfGfC mCmCfGmUmUmUmGfUmCmC	291	mGpsfGpsmAmCmAmAmAmCmGm GmGmCmAfAmCmAmUmAmCpsmC psmU

TABLE 3-continued

2'-O-methyl and 2'-fluoro Modified Nucleotide Sequences with Phosphorothioate Linkages

SEQ ID NO.	First Nucleotide Sequence (5'-3')	SEQ ID NO.	Second Nucleotide Sequence (5'-3'
244	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	292	mApsfUpsmUmGmAmGmAmGmAm AmGmUmCfCmAmCmCmAmCpsmG psmA
245	mGpsmUpsfGmUmGmCfAfCfU mUmCfGmCmUmUmCfAmCmC	293	mGpsfGpsmUmGmAmAmGmCmGm AmAmGmUfGmCmAmCmAmCpsmG psmG
246	mGpsmUpsfUmGmCmCfCfGfU mUmUfGmUmCmCmUfCmUmA	294	mUpsfApsmGmAmGmGmAmCmAm AmAmCmGfGmGmCmAmAmCpsmA psmU
247	mGpsmUpsfUmGmCmCfCfGfU mUmUfGmUmCmCmUfCmUmA	295	mUpsfApsmGmAmGmGmAmCmAm AmAmCmGfGmGmCmAmAmC
248	mUpsmCpsfCmAmUmAfCfUfG mCmGfGmAmAmCmUfCmCmU	296	mApsfGpsmGmAmGmUmUmCmCm GmCmAmGfUmAmUmGmGmApsm UpsmC
249	mUpsmCpsfCmAmUmAfCfUfG mCmGfGmAmAmCmUfCmCmU	297	mApsfGpsmGmAmGmUmUmCmCm GmCmAmGfUmAmUmGmGmA
250	mUpsmCpsmGmUmGmGfUmGf GfAfCmUmUmCmUmCmUmCm AmAmU	298	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCmGmAp smGpsmU
251	mUpsmGpsfCmAmCmUfUfCfG mCmUfUmCmAmCmCfUmCmU	299	mApsfGpsmAmGmGmUmGmAmAm GmCmGmAfAmGmUmGmCmApsmC psmA
252	mUpsmGpsfCmCmGmAfUfCfC mAmUfAmCmUmGmCfGmGm A	300	mUpsfCpsmCmGmCmAmGmUmAm UmGmGmAfUmCmGmGmCmApsm GpsmA
253	mUpsmGpsfCmCmGmAfUfCfC mAmUfAmCmUmGmCfGmGm A	301	mUpsfCpsmCmGmCmAmGmUmAm UmGmGmAfUmCmGmGmCmA
254	mUpsmGpsfCmUmAmUfGfCfC mUmCfAmUmCmUmUfCmUmU	302	mApsfApsmGmAmAmGmAmUmGm AmGmGmCfAmUmAmGmCmApsm GpsmC
255	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	303	mApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmApsmC psmG
256	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	303	mApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmApsmC psmG
257	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	304	mApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmA
258	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	304	mApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmA
259	mUpsmUpsfGmCmCmCfGfUmU mUmGmUmCmCmUmCfUmAm A	305	mUpsfUpsmAmGmAmGmGmAmCm AmAmAmCfGmGmGmCmAmApsmC psmA
260	mUpsmUpsfGmCmCmCfGfUfU mUmGfUmCmCmUmCfUmAmA	306	mUpsfUpsmAmGmAmGmGmAmCm AmAmAmCfGmGmGmCmAmA

mX = 2'-O-methyl nucleotide;
fX = 2'-fluoro nucleotide;
ps = phosphorothioate linkage

TABLE 4

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
307	mApsmCpsfCmGmUmGfUfGfC mAmCfUmUmCmGmCfUmUmC	363	mGpsfApsmAmGmCmGmAmAmGmU mGmCmAfCmAmCmGmGmUpsmCps mC
308	mApsmCpsfCmGmUmGfUfGfC mAmCfUmUmCmGmCfUmUmC TT	364	mGpsfApsmAmGmCmGmAmAmGmU mGmCmAfCmAmCmGmGmUpsTpsT
309	mApsmCpsfUmUmCmGfCfUfU mCmAfCmCmUmCmUfGmCmA	365	mUpsfGpsmCmAmGmAmGmGmUmG mAmAmGfCmGmAmAmGmUpsmGps mC
310	mApsmGpsfUmGmUmUfUfGfC mUmGfAmCmGmCmAfAmCmC	366	mGpsfGpsmUmUmGmCmGmUmCmA mGmCmAfAmAmCmAmCmUpsmUps mG
311	mCpsmApsfGmGmCmGfGfGfG mUmUfUmUmUmCmUfUmGm U	367	mApsfCpsmAmAmGmAmAmAmAmA mCmCmCfCmGmCmCmUmGpsmUps mA
312	mCpsmApsfGmGmCmGfGfGfG mUmUfUmUmUmCmUfUmGm UTT	368	mApsfCpsmAmAmGmAmAmAmAmA mAmCmCmCfCmGmCmCmUmGpsTp sT
313	mCpsmApsfGmUmUmUfAfCfU mAmGfUmGmCmCmAfUmUm U	369	mApsfApsmAmUmGmGmCmAmCmU mAmGmUfAmAmAmCmUmGpsmAps mG
314	mCpsmApsfGmUmUmUfAfCfU mAmGfUmGmCmCmAfUmUm UTT	370	mApsfApsmAmUmGmGmCmAmCmU mAmGmUfAmAmAmCmUmGpsTpsT
315	mCpsmApsfUmCmCmUfGfCfU mGmCfUmAmUmGmCfCmUmC	371	mGpsfApsmGmGmCmAmUmAmGmC mAmGmCfAmGmGmAmUmGpsmAps mA
316	mCpsmApsmUmCmCmUfGmCf UfGfCmUmAmUmGmCmCmUm CmAmU	372	mApsfUpsmGmAmGfGmCmAmUmA mGmCmAfGmCfAmGmGmAmUmGps mApsmA
317	mCpsmApsfUmCmCmUfGfCfU mGmCfUmAmUmGmCfCmUmC TT	373	mGpsfApsmGmGmCmAmUmAmGmC mAmGmCfAmGmGmAmUmGpsTpsT
318	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	374	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
319	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA TT	375	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsTpsT
320	mCpsmCpsmUmGmCmUfGmCf UfAfUmGmCmCmUmCmAmUm CmUmU	376	mApsfApsmGmAmUfGmAmGmGmC mAmUmAfGmCfAmGmCmAmGmGps mApsmU
321	mCpsmUpsfCmAmGmUfUfUfA mCmUfAmGmUmGmCfCmAmU	377	mApsfUpsmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGpsmCps mC
322	mCpsmUpsmCmAmGmUfUmU mAmCmUmAmGmUmGmCmC mAmU	377	mApsfUpsmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGpsmCps mC
323	mCpsmUpsfCmAmGmUfUfUmA mCmUmAmGmUmGmCfCmAm U	377	mApsfUpsmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGpsmCps mC
324	mCpsmUpsfCmAmGmUfUfUfA mCmUfAmGmUmGmCfCmAmU TT	378	mApsfUpsmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGpsTpsT
325	mCpsmUpsfCmAmGmUfUfUmA mCmUmAmGmUmGmCfCmAm UTT	378	mApsfUpsmGmGmCmAmCmUmAmG mUmAmAfAmCmUmGmAmGpsTpsT
326	mCpsmUpsfGmCmUmAfUfGfC mCmUfCmAmUmCmUfUmCmU	379	mApsfGpsmAmAmGmAmUmGmAmG mGmCmAfUmAmGmCmAmGpsmCps mA
327	mCpsmUpsfGmCmUmAfUfGmC mCmUmCmAmUmCmUfUmCm U	379	mApsfGpsmAmAmGmAmUmGmAmG mGmCmAfUmAmGmCmAmGpsmCps mA
328	mCpsmUpsfGmCmUmAfUfGfC mCmUfCmAmUmCmUfUmCmU TT	380	mApsfGpsmAmAmGmAmUmGmAmG mGmCmAfUmAmGmCmAmGpsTpsT
329	mCpsmUpsfGmCmUmAfUfGmC mCmUmCmAmUmCmUfUmCm UTT	380	mApsfGpsmAmAmGmAmUmGmAmG mGmCmAfUmAmGmCmAmGpsTpsT
330	mCpsmUpsfGmCmUmGfCfUfA mUmGfCmCmUmCmAfUmCmU	381	mApsfGpsmAmUmGmAmGmGmCmA mUmAmGfCmAmGmCmAmGpsmGps mA

TABLE 4-continued

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
331	mCpsmUpsfGmCmUmGfCfUfA mUmGfCmCmUmCmAfUmCmU TT	382	mApsfGpsmAmUmGmAmGmGmCmA mUmAmGfCmAmGmCmAmGpsTpsT
332	mCpsmUpsfGmCmUmGfCfUmA mUmGmCmCmUmCmAfUmCm UTT	383	mApsfGpsmAmUmGmAmGmGmCmA mUmAmGfCmAmGmCmAmGpsTpsT
333	mCpsmUpsmUmCmGmCfUmUf CfAfCmCmUmCmUmGmCmAm CmGmU	384	mApsfCpsmGmUmGfCmAmGmAmG mGmUmGfAmAfGmCmGmAmAmGp smUpsmG
334	mGpsmCpsmAmCmUmUfCmGf CfUfUmCmAmCmCmUmCmUm GmCmA	385	mUpsfGpsmCmAmGfAmGmGmUmG mAmAmGfCmGfAmAmGmUmGmCps mApsmC
335	mGpsmCpsfCmGmAmUfCfCfA mUmAfCmUmGmCmGfGmAm A	386	mUpsfUpsmCmCmGmCmAmGmUmA mUmGmGfAmUmCmGmGmCpsmAps mG
336	mGpsmCpsfCmGmGmGfUfUfU mUmUfCmUmUmGmUfUmGm ATT	387	mUpsfUpsmCmCmGmCmAmGmUmA mUmGmGfAmUmCmGmGmCpsTpsT
337	mGpsmCpsfGmGmGmGfUfUfU mUmUfC mUmUmGmUfUmGm A	388	mUpsfCpsmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCpsmCps mU
338	mGpsmCpsfGmGmGmGfUfUmU mUmUmCmUmUmGmUfUmGm A	388	mUpsfCpsmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCpsmCps mU
339	mGpsmCpsfGmGmGmGfUfUfU mUmUfCmUmUmGmUfUmGm ATT	389	mUpsfCpsmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCpsTpsT
340	mGpsmCpsfGmGmGmGfUfUmU mUmUmCmUmUmGmUfUmGm ATT	389	mUpsfCmAmAmCmAmAmGmAmAm AmAmAfCmCmCmCmGmCpsTpsT
341	mGpsmCpsmUmGmCmUfAmUf GfCfCmUmCmAmUmCmUmUm CmUmU	390	mApsfApsmGmAmAfGmAmUmGmA mGmGmCfAmUfAmGmCmAmGmCps mApsmG
342	mGpsmGpsmAmUmGmUfGmUf CfUfGmCmGmGmCmGmUmUm UmUmA	391	mUpsfApsmAmAmAfCmGmCmCmG mCmAmGfAmCfAmCmAmUmCmCps mApsmG
343	mGpsmGpsfCmCmAmAfAfAfU mUmCfGmCmAmGmUfCmCmC	392	mGpsfGpsmGmAmCmUmGmCmGmA mAmUmUfUmUmGmGmCmCpsmAps mA
344	mGpsmGpsfCmGmCmAfCfCfU mCmUfCmUmUmUmAfCmGmC	393	mGpsfCpsmGmUmAmAmAmGmAmG mAmGmGfUmGmCmGmCmCpsmCps mC
345	mGpsmUpsfAmUmGmUfUfGfC mCmCfGmUmUmUmGfUmCmC	394	mGpsfGpsmAmCmAmAmAmCmGmG mGmCmAfAmCmAmUmAmCpsmCps mU
346	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	395	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
347	mGpsmUpsfGmUmGmCfAfCfU mUmCfGmCmUmUmCfAmCmC	396	mGpsfGpsmUmGmAmAmGmCmGmA mAmGmUfGmCmAmCmAmCpsmGps mG
348	mGpsmUpsfUmGmCmCfCfGfU mUmUfGmUmCmCmUfCmUmA	397	mUpsfApsmGmAmGmGmAmCmAmA mAmCmGfGmGmCmAmAmCpsmAps mU
349	mGpsmUpsfUmGmCmCfCfGfU mUmUfGmUmCmCmUfCmUmA TT	398	mUpsfApsmGmAmGmGmAmCmAmA mAmCmGfGmGmCmAmAmCpsTpsT
350	mUpsmCpsfCmAmUmAfCfUfG mCmGfGmAmAmCmUfCmCmU	399	mApsfGpsmGmAmGmUmUmCmCmG mCmAmGfUmAmUmGmGmApsmUps mC
351	mUpsmCpsfCmAmUmAfCfUfG mCmGfGmAmAmCmUfCmCmU TT	400	mApsfGpsmGmAmGmUmUmCmCmG mCmAmGfUmAmUmGmGmApsTpsT
352	mUpsmCpsmGmUmGmGfUmGf GfAfCmUmUmCmUmCmUmCm AmAmU	401	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCmGmAps mGpsmU
353	mUpsmGpsfCmAmCmUfUfCfG mCmUfUmCmAmCmCfUmCmU	402	mApsfGpsmAmGmGmUmGmAmAmG mCmGmAfAmGmUmGmCmApsmCps mA
354	mUpsmGpsfCmCmGmAfUfCfC mAmUfAmCmUmGmCfGmGm A	403	mUpsfCpsmCmGmCmAmGmUmAmU mGmGmAfUmCmGmGmCmApsmGps mA

TABLE 4-continued

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
355	mUpsmGpsfCmCmGmAfUfCfC mAmUfAmCmUmGmCfGmGm ATT	404	mUpsfCpsmCmGmCmAmGmUmAmU mGmGmAfUmCmGmGmCmApsTpsT
356	mUpsmGpsfCmUmAmUfGfCfC mUmCfAmUmCmUmUfCmUmU	405	mApsfApsmGmAmAmGmAmUmGmA mGmGmCfAmUmAmGmCmApsmGps mC
357	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	406	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsmCps mG
358	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	406	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsmCps mG
359	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU TT	407	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsTpsT
360	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm UTT	407	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsTpsT
361	mUpsmUpsfGmCmCmCfGfUmU mUmGmUmCmCmUmCfUmAm A	408	mUpsfUpsmAmGmAmGmGmAmCmA mAmAmCfGmGmGmCmAmApsmCps mA
362	mUpsmUpsfGmCmCmCfGfUfU mUmGfUmCmCmUmCfUmAmA TT	409	mUpsfUpsmAmGmAmGmGmAmCmA mAmAmCfGmGmGmCmAmApsTpsT
415	5dcd3Cps5dcd3CpsfG5dcd3UmG 5dcd3UfG5dfCfA5dcd3C5dcd3U 5dfU5dcd3CmG5dcd3C5dcd3U5d fU5dcd3CmA	445	5dcd3UpsfGpsmAmAmG5dcd3CmGm AmAmG5dcd3UmG5dcd3CfA5dcd3C mA5dcd3CmGmGps5dcd3Ups5dcd3U
415	5dcd3Cps5dcd3CpsfG5dcd3UmG 5dcd3UfG5dfCfA5dcd3C5dcd3U 5dfU5dcd3CmG5dcd3C5dcd3U5d fU5dcd3CmA	446	5dcd3UpsfGpsmAmAmGmCmGmAm AmGmUmGmCfAmCmAmCmGmGps 5dcd3Ups5dcd3U
415	5dcd3Cps5dcd3CpsfG5dcd3UmG 5dcd3UfG5dfCfA5dcd3C5dcd3U 5dfU5dcd3CmG5dcd3C5dcd3U5d fU5dcd3CmA	447	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mU
416	fCpsmCpsfGmUfGmUfGfCfAmC fUmUfCmGfCmUfUmCfA	448	mUpsfGpsmAfAmGfCmGfAmAfGmU mGmCfAmCfAmCfGmGpsmUpsmC
416	fCpsmCpsfGmUfGmUfGfCfAmC fUmUfCmGfCmUfUmCfA	449	vmUpsfGpsmAfAmGfCmGfAmAfGm UmGmCfAmCfAmCfGmGpsmUpsmC
416	fCpsmCpsfGmUfGmUfGmCfAm CfUmUfCmGfCmUfUmCfA	450	mUpsfGpsmAfAmGfCmGfAmAfGmUf GmCfAmCfAmCfGmGpsmUpsmC
416	fCpsmCpsfGmUfGmUfGmCfAm CfUmUfCmGfCmUfUmCfA	451	vmUp sfGp smAfAm GfCm GfAmAfGm UfGmCfAmCfAmCfGmGpsmUpsmC
417	fCpsmUpsfGmCfUmAfUmGfCm CfUmCfAmUfCmUfUmCfU	452	mApsfGpsmAfAmGfAmUfGmAfGmGf CmAfUmAfGmCfAmGpsmUpsmU
417	fCpsmUpsfGmCfUmAfUmGfCm CfUmCfAmUfCmUfUmCfU	452	mApsfGpsmAfAmGfAmUfGmAfGmGf CmAfUmAfGmCfAmGpsmUpsmU
417	fCpsmUpsfGmCfUmAfUmGfCm CfUmCfAmUfCmUfUmCfU	452	mApsfGpsmAfAmGfAmUfGmAfGmGf CmAfUmAfGmCfAmGpsmUpsmU
417	fCpsmUpsfGmCfUmAfUmGfCm CfUmCfAmUfCmUfUmCfU	452	mApsfGpsmAfAmGfAmUfGmAfGmGf CmAfUmAfGmCfAmGpsmUpsmU
418	fGpsmUpsfGmGfUmGfGfAfCm UfUmCfUmCfUmCfAmAfU	453	mApsfUpsmUfGmAfGmAfGmAfAmG mUmCfCmAfCmCfAmCpsmGpsmA
418	fGpsmUpsfGmGfUmGfGfAfCm UfUmCfUmCfUmCfAmAfU	454	vmApsfUpsmUfGmAfGmAfGmAfAm GmUmCfCmAfCmCfAmCpsmGpsmA
419	fGpsmUpsfGmGfUmGfGmAfCm UfUmCfUmCfUmCfAmAfU	455	mApsfUpsmUfGmAfGmAfGmAfAmGf UmCfCmAfCmCfAmCpsmGpsmA
419	fGpsmUpsfGmGfUmGfGmAfCm UfUmCfUmCfUmCfAmAfU	456	vmApsfUpsmUfGmAfGmAfGmAfAm GfUmCfCmAfCmCfAmCpsmGpsmA
420	mCpsmCpsfGmUfGmUfGfCfAm CmUmUmCmGmCmUmUmCm A	457	mUpsfGpsmAmAmGfCmGmAmAmG mUmGmCfAmCfAmCmGmGpsmUps mC
421	mCpsmCpsfGmUmGmUfGfCfA mAmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
422	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	459	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmU3s mU
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	460	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmG5smU5s mU

TABLE 4-continued

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	461	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmU5s mU
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	462	vmUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsmU psmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	463	vmUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsTps T
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	447	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mU
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	457	mUpsfGpsmAmAmGfCmGmAmAmG mUmGmCfAmCfAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	464	mUpsfGpsmAmAmGfCmGmAmAfGm UmGmCfAmCmAmCfGmGpsmUpsmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	465	vmBpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsmU psmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	466	mesnmUpsfGpsmAmAmGmCmGmAm AmGmUmGmCfAmCmAmCmGmGps mUpsmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	467	cmUpsfGpsmAmAmGmCmGmAmAm GmUmGmCfAmCmAmCmGmGpsmU psmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	468	mesnomUpsfGpsmAmAmGmCmGmA mAmGmUmGmCfAmCmAmCmGmGp smUpsmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	469	mUpsfGpsmAmAmGfCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	470	mUp sfGpsmAmAmGmCmGmAmAmG fUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	471	mUpsfGpsmAmAmGmCmGmAmAmG mUfGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	472	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCfAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	473	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAfCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	474	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCfGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	475	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGfGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	476	mUpsfGpsmAfAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	477	mUpsfGpsmAmAfGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	478	mUpsfGpsmAmAmGmCfGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC

TABLE 4-continued

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	479	mUpsfGpsmAmAmGmCmGfAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	480	mUpsfGpsmAmAmGmCmGmAfAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	481	mUpsfGpsmAmAmGmCmGmAmAfG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	482	d2vmUpsfGpsmAmAmGmCmGmAmA mGmUmGmCfAmCmAmCmGmGpsm UpsmC
423	mCpsmCpsfGmUmGmUfGfCfA mCmUmUmCmGmCmUfUmCm A	483	mUpsfGpsmAfAmGfCmGfAmAmGm UmGmCfAmCmAmCmGmGpsmUpsm C
423	mCpsmCpsfGmUmGmUfGfCfC mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
423	mCpsmCpsfGmUmGmUfGfCmA mCmUmUmCmGmCmUfUmCm A	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
424	mCpsmCpsmGmUfGmUfGfCfA mCmUmUmCmGmCmUmUmC mA	457	mUpsfGpsmAmAmGfCmGmAmAmG mUmGmCfAmCfAmCmGmGpsmUps mC
424	mCpsmCpsmGmUfGmUfGfCfA mCmUmUmCmGmCmUmUmC mA	484	mUpsfGpsmAmAmGfCmGfAfAmGm UmGmCfAmCfAmCmGmGpsmUpsmC
424	mCpsmCpsmGmUfGmUfGfCfA mCmUmUmCmGmCmUmUmC mA	485	mUpsfGpsmAmAfGmCmGfAmAmGm UmGmCfAmCmAfCmGmGpsmUpsmC
425	mCpsmUpsmGmCfUmAfUfGfC mCmUmCmAmUmCmUmUmC mU	486	mApsfGpsmAmAmGfAmUmGmAfGm GmCmAfUmAmGmCfAmGpsmCpsm A
425	mCpsmUpsmGmCfUmAfUfGfC mCmUmCmAmUmCmUmUmC mU	487	mApsfGpsmAmAmGfAmUmGmAmG mGmCmAfUmAfGmCmAmGpsmCps mA
425	mCpsmUpsmGmCfUmAfUfGfC mCmUmCmAmUmCmUmUmC mU	488	mApsfGpsmAmAfGmAmUfGmAmGm GmCmAfUmAmGfCmAmGpsmCpsm A
426	mCpsmUpsmGmCfUmAfUmGfC mCmUfCmAmUmCmUfUmCmU	489	mApsfGpsmAmAmGmAmUmGmAmG mGmCmAfUmAmGmCmAmGpsmCps mA
427	mGpsmCpsfGmGmGmGfUfUfU mUmUfCmUmUmGmUfUmGm A	490	vmUpsfCpsmAmAmCmAmAmGmAm AmAmAmAfCmCmCmCmGmCpsmCp smU
428	mGpsmCpsfGmGmGmGfUmUm UmUmUmCmUmUmGmUfUmG mA	491	mUpsfCpsmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCpsmCps mU
429	mGpsmCpsmGmGfGmGfUfUfU mUmUmCmUmUmGmUmUmG mA	492	mUpsfCpsmAmAmCfAmAmGmAfAm AmAmAfCmCmCmCfGmCpsmCpsmU
429	mGpsmCpsmGmGfGmGfUfUfU mUmUmCmUmUmGmUmUmG mA	493	mUpsfCpsmAmAmCfAmAmGmAmA mAmAmAfCmCfCmCmGmCpsmCpsm U
429	mGpsmCpsmGmGfGmGfUfUfU mUmUmCmUmUmGmUmUmG mA	494	mUpsfCpsmAmAfCmAmAfGmAmAm AmAmAfCmCmCfCmGmCpsmCpsmU
430	mGpsmCpsmUmGfCmUmAmUf GfCfCmUmCfAmUmCmUmUfC mUmU	495	mApsfApsmGmAmAmGmAmUmGmA mGmGmCfAmUmAmGmCmAmGmCp smApsmG
430	mGpsmCpsmUmGfCmUmAmUf GfCfCmUmCfAmUmCmUmUfC mUmU	496	mApsfApsmGmAmAfGmAmUmGmA mGmGmCfAmUfAmGmCmAmGmCps mApsmG
431	mGpsmCpsmUmGmCmUfAmUf GfCfCmUmCmAmUfCmUmUfC mUmU	497	mApsfApsmGmAmAfGmAfUfGmAm GmGmCfAmUfAmGmCmAmGmCpsm ApsmG
432	mGpsmCpsmUmGmCmUfAmUf GfCfCmUmCmAmUmCmUmUm CmUmU	498	vmApsfApsmGmAmAfGmAmUmGmA mGmGmCfAmUfAmGmCmAmGmCps mApsmG
432	mGpsmCpsmUmGmCmUfAmUf GfCfCmUmCmAmUmCmUmUm CmUmU	500	d2vmApsfApsmGmAmAfGmAmUmG mAmGmGmCfAmUfAmGmCmAmGm CpsmApsmG

TABLE 4-continued

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
433	mGpsmUpsfGmGfUmGfGfAfCm UmUmCmUmCmUmCmAmAm U	501	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCpsmGpsm A
434	mGpsmUpsfGmGmUmGfGfAfA mUmUfCmUmCmUmCfAmAmU	502	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mGmUfCmUmCmUmCfAmAmU	502	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	503	vmApsfUpsmUmGmAmGmAmGmAm AmGmUmCfCmAmCmCmAmCpsmGp smA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	501	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCpsmGpsm A
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	504	mApsfUpsmUmGmAfGmAmGmAfAm GmUmCfCmAmCmCfAmCpsmGpsmA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	505	vmNp sfUp smUm GmAm GmAm GmAm AmGmUmCfCmAmCmCmAmCpsmGp smA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	506	vmUpsfUpsmUmGmAmGmAmGmAm AmGmUmCfCmAmCmCmAmCpsmGp smA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	507	cmUpsfUpsmUmGmAmGmAmGmAm AmGmUmCfCmAmCmCmAmCpsmGp smA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	508	mesnmUpsfUpsmUmGmAmGmAmGm AmAmGmUmCfCmAmCmCmAmCps mGpsmA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	509	mesnomUpsfUpsmUmGmAmGmAmG mAmAmGmUmCfCmAmCmCmAmCp smGpsmA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	510	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	511	mApsfUpsmUfGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	512	mApsfUpsmUmGfAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	513	mApsfUpsmUmGmAmGfAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	514	mApsfUpsmUmGmAmGmAmGfAmA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	515	mApsfUpsmUmGmAmGmAmGmAfA mGmUmCfCmAmCmCmAmCpsmGps mA
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	516	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAfCmCmAmCpsmGpsm A
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	517	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCfAmCpsmGpsm A
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	518	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAfCpsmGpsm A
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	519	d2vmApsfUpsmUmGmAmGmAmGmA mAmGmUmCfCmAmCmCmAmCpsm GpsmA
436	mGpsmUpsfGmGmUmGfGfAfC mUmUmCmUmCmUmCfUmAm U	520	mApsfUpsmUfGmAfGmAfGmAmAm GmUmCfCmAmCmCmAmCpsmGpsm A
437	mGpsmUpsfGmGmUmGfGfAmC mUmUmCmUmCmUmCfAmAm U	502	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
438	mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmA mU	501	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCpsmGpsm A

TABLE 4-continued

siNA Sequences

SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
438	mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmA mU	521	mApsfUpsmUmGmAfGmAfGfAmAm GmUmCfCmAfCmCmAmCpsmGpsmA
438	mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmA mU	522	mApsfUpsmUmGfAmGmAfGmAmAm GmUmCfCmAmCfCmAmCpsmGpsmA
439	mUpsmCpsmGmUmGmGfUmGf GfAfCmUmUmCmUmCmUmCm AmAmU	523	vmApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCmGmAps mGpsmU
440	mUpsmGpsfCmCmGmAfUfCfC mAmUfAmCmUmGmCfGmGm A	524	vmUpsfCpsmCmGmCmAmGmUmAm UmGmGmAfUmCmGmGmCmApsmG psmA
441	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	525	vmApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmApsmC psmG
441	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	526	mApsfGpsmGmUmGfAmAmGmCfGm AmAmGfUmGmCmAfCmApsmCpsm G
441	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	527	mApsfGpsmGmUmGfAmAmGmCmG mAmAmGfUmGfCmAmCmApsmCps mG
442	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	525	vmApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmApsmC psmG
442	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	528	vmApsfGpsmGmUmGmAmAmGmCm GmAmAmGfUmGmCmAmCmApsTps T
442	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	529	d2vmApsfGpsmGmUmGmAmAmGmC mGmAmAmGfUmGmCmAmCmApsm CpsmG
443	unCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
444	unGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	502	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	458	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsmUps mC
533	mCpsmUpsfGmCmUmAfUfGfC mCmUfCmAmUmCmUfUmCmU	489	mApsfGpsmAmAmGmAmUmGmAmG mGmCmAfUmAmGmCmAmGpsmCps mA
534	mGpsmCpsfGmGmGmGfUfUmU mUmUmCmUmUmGmUfUmGm A	491	mUpsfCpsmAmAmCmAmAmGmAmA mAmAmAfCmCmCmCmGmCpsmCps mU
432	mGpsmCpsmUmGmCmUfAmUf GfCfCmUmCmAmUmCmUmUm CmUmU	496	mApsfApsmGmAmAfGmAmUmGmA mGmGmCfAmUfAmGmCmAmGmCps mApsmG
435	mGpsmUpsfGmGmUmGfGfAfC mUmUfCmUmCmUmCfAmAmU	502	mApsfUpsmUmGmAmGmAmGmAmA mGmUmCfCmAmCmCmAmCpsmGps mA
442	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	530	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsmCps mG
439	mUpsmCpsmGmUmGmGfUmGf GfAfCmUmUmCmUmCmUmCm AmAmU	531	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCmGmAps mGpsmU
423	mCpsmCpsfGmUmGmUfGfCfA mCmUfUmCmGmCmUfUmCmA	532	mUpsfGpsmAmAmGmCmGmAmAmG mUmGmCfAmCmAmCmGmGpsTpsT
441	mUpsmGpsfUmGmCmAfCfUfU mCmGfCmUmUmCmAfCmCmU	530	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsmCps mG
442	mUpsmGpsfUmGmCmAfCfUmU mCmGmCmUmUmCmAfCmCm U	533	mApsfGpsmGmUmGmAmAmGmCmG mAmAmGfUmGmCmAmCmApsTpsT
424	mCpsmCpsmGmUfGmUfGfCfA mCmUmUmCmGmCmUmUmC mA	536	d2vd3UpsfGpsmAmAfGmCmGfAmAm GmUmGmCfAmCmAfCmGmGpsmUp smC
438	mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmA mU	537	mApsf4PpsmUmGmAfGmAmGmAmA mGmUmCfCmAfCmCmAmCpsmGpsm A

TABLE 4-continued

siNA Sequences			
SEQ ID NO.	Sense Sequence (5'-3')	SEQ ID NO.	Antisense Sequence (5'-3')
438	mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmA mU	538	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCf2PmAfCmCmAmCpsmGps mA
438	mGpsmUpsmGmGfUmGfGfAfC mUmUmCmUmCmUmCmAmA mU	539	mApsfUpsmUmGmAfGmAmGmAmA mGmUmCfCmAfXmCmAmCpsmGps mA

mX = 2'-O-methyl nucleotide;

fX = 2'-fluoro nucleotide;

5dcd3X = nucleotide of Formula 17;

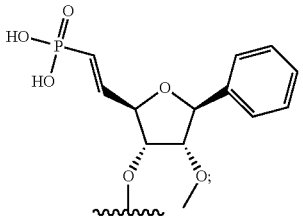
5dfX = nucleotide of Formula 16;

vX = 5' vinyl phosphonate nucleotide;

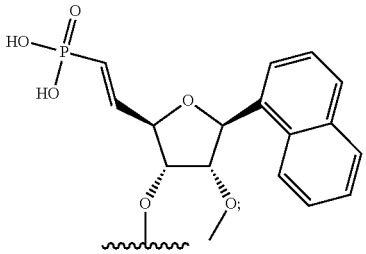
d2vX = deuterated 5' vinyl phosphonate nucleotide;

vmX = 5' vinyl phosphonate, 2'-O-methyl nucleotide;

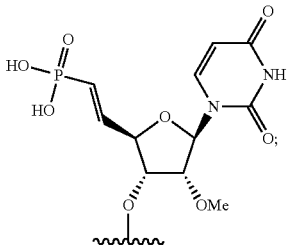
vmB =



vmN =



VmU =



cmU =

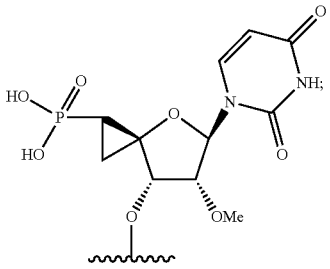
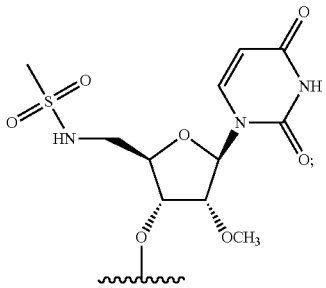


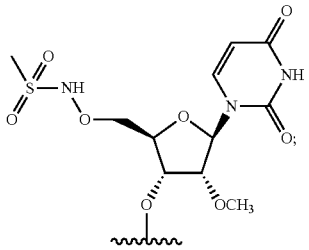
TABLE 4-continued

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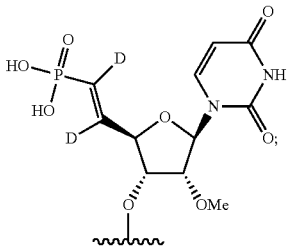
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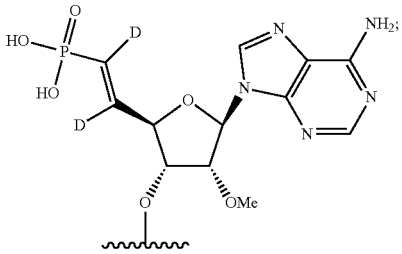
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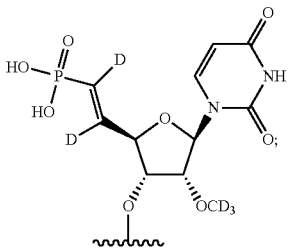
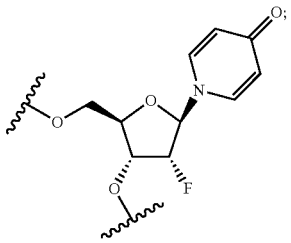


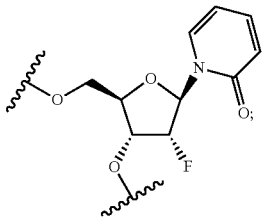
TABLE 4-continued

siNA Sequences			
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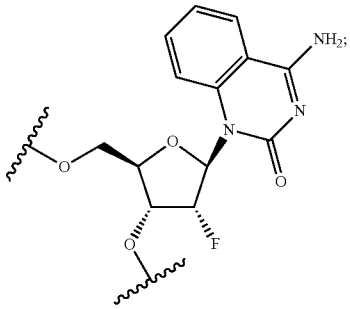
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f2P =



fX =



ps = phosphorothioate linkage

TABLE 5

SEQ ID NO:	Description	Sequence+
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TABLE 5-continued

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TABLE 5-continued

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TABLE 5-continued

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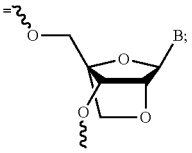
TABLE 5-continued

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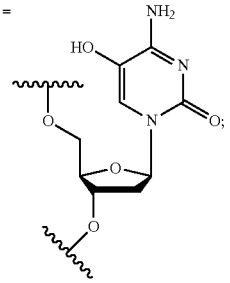
TABLE 5-continued

SEQ ID NO:	Description	Sequence+
534	ASO 1	GalNAc4-ps-GalNAc4-ps-GalNAc4-po-mA-po-lnGpslnApslnTpslnApslnApsApsAps(5OH)CpsGps(5m)Cps(5m)CpsGps(5m)CpslnApslnGpslnApscp(5m)C
535	ASO 2	mA-po-lnGpslnApslnTpslnApslnApsApsAps(5OH)CpsGps(5m)Cps(5m)CpsGps(5m)CpslnApslnGpslnApscp(5m)C

+ln = Locked nucleic acid (LNA) =



lnA = Locked nucleic acid (LNA) A;
ln(5m)C = ln(5m)C = Locked nucleic acid (LNA)-5 methyl C;
lnG = Locked nucleic acid (LNA) G;
lnT = Locked nucleic acid (LNA) T;
(5m)C = 5 methyl C;
cp = scp = cyclopropyl;
cpC = scpC = cyclopropyl C;
scp(5m)C = cyclopropyl-5 methyl C;
(5OH)C =



po = phosphodiester linkage;
ps = phosphorothioate linkage

TABLE 6

	siNA Activity			
ds-siNA ID	Sense Strand SEQ ID NO.	Antisense Strand SEQ ID NO.	HepG2.2.15 in vitro EC50*	HepG2.2.15 in vitro CC50 (nM)
ds-siNA-001	307	363	A	>40
ds-siNA-002	308	364	A	>40
ds-siNA-003	309	365	B	>40
ds-siNA-004	310	366	B	>40
ds-siNA-005	311	367	B	>40
ds-siNA-006	312	368	C	>40
ds-siNA-007	313	369	A	>40
ds-siNA-008	314	370	A	>40
ds-siNA-009	315	371	B	>40
ds-siNA-010	316	372	A	>40
ds-siNA-011	317	373	B	>40
ds-siNA-012	318	374	A	>40
ds-siNA-013	319	375	A	>40
ds-siNA-014	320	376	B	>40
ds-siNA-015	321	377	A	>40
ds-siNA-016	322	377	C	>40
ds-siNA-017	323	377	A	>40
ds-siNA-018	324	378	A	>40
ds-siNA-019	325	378	A	>40
ds-siNA-020	326	379	A	>40
ds-siNA-021	327	379	B	>40
ds-siNA-022	328	380	A	>40
ds-siNA-023	329	380	B	>40
ds-siNA-024	330	381	A	>40

TABLE 6-continued

	siNA Activity			
ds-siNA ID	Sense Strand SEQ ID NO.	Antisense Strand SEQ ID NO.	HepG2.2.15 in vitro EC50*	HepG2.2.15 in vitro CC50 (nM)
ds-siNA-025	331	382	A	>40
ds-siNA-026	332	383	C	>40
ds-siNA-027	333	384	A	>40
ds-siNA-028	334	385	B	>40
ds-siNA-029	335	386	A	>40
ds-siNA-030	336	387	C	>40
ds-siNA-031	337	388	A	>40
ds-siNA-032	338	388	C	>40
ds-siNA-033	339	389	B	>40
ds-siNA-034	340	389	C	>40
ds-siNA-035	341	390	A	>40
ds-siNA-036	342	391	A	>40
ds-siNA-037	343	392	B	>40
ds-siNA-038	344	393	A	>40
ds-siNA-039	345	394	A	>40
ds-siNA-040	346	395	A	>40
ds-siNA-041	347	396	C	>40
ds-siNA-042	348	397	A	>40
ds-siNA-043	349	398	B	>40
ds-siNA-044	350	399	A	>40
ds-siNA-045	351	400	A	>40
ds-siNA-046	352	401	A	>40
ds-siNA-047	353	402	A	>40
ds-siNA-048	354	403	A	>40

TABLE 6-continued

siNA Activity				
ds-siNA ID	Sense Strand SEQ ID NO.	Antisense Strand SEQ ID NO.	HepG2.2.15 in vitro EC50*	HepG2.2.15 in vitro CC50 (nM)
ds-siNA-049	355	404	B	>40
ds-siNA-050	356	405	A	>40
ds-siNA-051	357	406	A	>40
ds-siNA-052	358	406	A	>40
ds-siNA-053	359	407	A	>40
ds-siNA-054	360	407	A	>40

TABLE 6-continued

siNA Activity				
ds-siNA ID	Sense Strand SEQ ID NO.	Antisense Strand SEQ ID NO.	HepG2.2.15 in vitro EC50*	HepG2.2.15 in vitro CC50 (nM)
ds-siNA-055	361	408	A	>40
ds-siNA-056	362	409	A	>40
ds-siNA-0164	423	482		

*A = EC50 < 0.5 nM; B = 0.5 nM < EC50 < 1; C = EC50 > 1 nm

TABLE 10

siNA Activity						
ds-siNA ID	Sense Strand SEQ ID NO	3' Ligand Monomer+	Antisense Strand SEQ ID NO	HepG2.2.15 EC50*	HepG2.2.15 CC50 (nM)	Max HBsAg Knock Down (Log_{10}) **
ds-siNA-057	415	p-(PS)2-GalNac4	445	ND	ND	X
ds-siNA-058	415	p-(PS)2-GalNac4	446	ND	ND	X
ds-siNA-059	415	p-(PS)2-GalNac4	447	ND	ND	Y
ds-siNA-060	416	p-(PS)2-GalNac4	448	ND	ND	Y
ds-siNA-061	416	p-(PS)2-GalNac4	449	ND	ND	Y
ds-siNA-062	416	p-(PS)2-GalNac4	450	ND	ND	Y
ds-siNA-063	416	p-(PS)2-GalNac4	451	ND	ND	X
ds-siNA-064	417	5'-GalNAc4-(PS)2-p-TEG-p	452	ND	ND	Y
ds-siNA-065	417	5'-GalNAc4-(PS)2-p-HEG-p	452	ND	ND	Y
ds-siNA-066	417	5'-GalNAc4-(PS)2-p-(HEG-P)2	452	ND	ND	Y
ds-siNA-067	417	5'-GalNAc4-(PS)2-p-(HEG-P)2	452	ND	ND	Z
ds-siNA-068	418	p-(PS)2-GalNac4	453	ND	ND	Y
ds-siNA-069	418	p-(PS)2-GalNac4	454	ND	ND	Y
ds-siNA-070	419	p-(PS)2-GalNac4	455	ND	ND	Y
ds-siNA-071	419	p-(PS)2-GalNac4	456	ND	ND	Y
ds-siNA-072	420	p-(PS)2-GalNac4	457	ND	ND	X
ds-siNA-073	421	p-(PS)2-GalNac4	458	ND	ND	X
ds-siNA-074	422	p-(PS)2-GalNac4	459	ND	ND	Y
ds-siNA-075	423	p-(PS)2-GalNac4	460	ND	ND	Y
ds-siNA-076	423	p-(PS)2-GalNac4	461	ND	ND	Y
ds-siNA-077	423	5'-GalNAc4-(PS)2-p-TEG-p	458	ND	ND	Y
ds-siNA-078	423	5'-GalNAc4-(PS)2-p-HEG-p	458	ND	ND	X
ds-siNA-079	423	5'-GalNAc4-(PS)2-p-(HEG-P)2	458	ND	ND	Y
ds-siNA-080	423	p-(PS)2-GalNac4	462	ND	ND	X
ds-siNA-081	423	p-(PS)2-GalNac4	463	ND	ND	X
ds-siNA-082	423	p-(PS)2-GalNac4	447	ND	ND	X
ds-siNA-083	423	5'-GalNAc4-(PS)2-p-(HEG-P)2	458	ND	ND	Z
ds-siNA-084	423	p-(PS)2-GalNac4	457	ND	ND	X
ds-siNA-085	423	p-(PS)2-GalNac4	464	ND	ND	X
ds-siNA-086	423	p-(PS)2-GalNac4	465	ND	ND	X
ds-siNA-087	423	p-(PS)2-GalNac4	466	ND	ND	Y
ds-siNA-088	423	p-(PS)2-GalNac4	467	ND	ND	Z
ds-siNA-089	423	p-(PS)2-GalNac4	468	ND	ND	Z
ds-siNA-090	423	p-(PS)2-GalNac4	469	B	>1000	X
ds-siNA-091	423	p-(PS)2-GalNac4	470	C	>1000	ND
ds-siNA-092	423	p-(PS)2-GalNac4	471	B	>1000	ND
ds-siNA-093	423	p-(PS)2-GalNac4	472	B	>1000	ND
ds-siNA-094	423	p-(PS)2-GalNac4	473	B	>1000	ND
ds-siNA-095	423	p-(PS)2-GalNac4	474	C	>1000	ND
ds-siNA-096	423	p-(PS)2-GalNac4	475	B	>1000	ND
ds-siNA-097	423	p-(PS)2-GalNac4	476	B	>1000	ND
ds-siNA-098	423	p-(PS)2-GalNac4	477	A	>1000	ND
ds-siNA-099	423	p-(PS)2-GalNac4	478	B	>1000	ND
ds-siNA-0100	423	p-(PS)2-GalNac4	479	B	>1000	ND
ds-siNA-0101	423	p-(PS)2-GalNac4	480	B	>1000	ND
ds-siNA-0102	423	p-(PS)2-GalNac4	481	A	>1000	ND

TABLE 10-continued

siNA Activity						
ds-siNA ID	Sense Strand SEQ ID NO	3' Ligand Monomer+	Antisense Strand SEQ ID NO	HepG2.2.15 EC50*	HepG2.2.15 CC50 (nM)	Max HBsAg Knock Down (Log_{10}) **
ds-siNA-0103	423	p-(PS)2-GalNac4	482	ND	ND	ND
ds-siNA-0104	423	p-(PS)2-GalNac4	483	ND	ND	ND
ds-siNA-0105	423	p-(PS)2-GalNac4	458	ND	ND	Z
ds-siNA-0106	423	p-(PS)2-GalNac4	458	ND	ND	Y
ds-siNA-0107	424	p-(PS)2-GalNac4	457	ND	ND	X
ds-siNA-0108	424	p-(PS)2-GalNac4	484	ND	ND	X
ds-siNA-0109	424	p-(PS)2-GalNac4	485	ND	ND	X
ds-siNA-0110	425	p-(PS)2-GalNac4	486	ND	ND	ND
ds-siNA-0111	425	p-(PS)2-GalNac4	487	ND	ND	ND
ds-siNA-0112	425	p-(PS)2-GalNac4	488	ND	ND	ND
ds-siNA-0113	426	p-(PS)2-GalNac4	489	ND	ND	ND
ds-siNA-0114	427	p-(PS)2-GalNac4	490	ND	ND	X
ds-siNA-0115	428	p-(PS)2-GalNac4	491	ND	ND	Y
ds-siNA-0116	429	p-(PS)2-GalNac4	492	ND	ND	ND
ds-siNA-0117	429	p-(PS)2-GalNac4	493	ND	ND	ND
ds-siNA-0118	429	p-(PS)2-GalNac4	494	ND	ND	ND
ds-siNA-0119	430	p-(PS)2-GalNac4	495	ND	ND	X
ds-siNA-0120	430	p-(PS)2-GalNac4	496	ND	ND	ND
ds-siNA-0121	431	p-(PS)2-GalNac4	497	ND	ND	Y
ds-siNA-0122	432	p-(PS)2-GalNac4	498	ND	ND	ND
ds-siNA-0123	432	p-(PS)2-GalNac4	500	ND	ND	ND
ds-siNA-0124	433	p-(PS)2-GalNac4	501	ND	ND	ND
ds-siNA-0125	434	p-(PS)2-GalNac4	502	ND	ND	Y
ds-siNA-0126	435	p-(PS)2-GalNac4	502	ND	ND	Y
ds-siNA-0127	435	p-(PS)2-GalNac4	503	ND	ND	X
ds-siNA-0128	435	p-(PS)2-GalNac4	501	ND	ND	X
ds-siNA-0129	435	p-(PS)2-GalNac4	504	ND	ND	Y
ds-siNA-0130	435	p-(PS)2-GalNac4	505	ND	ND	Z
ds-siNA-0131	435	p-(PS)2-GalNac4	506	ND	ND	Y
ds-siNA-0132	435	p-(PS)2-GalNac4	507	ND	ND	Z
ds-siNA-0133	435	p-(PS)2-GalNac4	508	ND	ND	Z
ds-siNA-0134	435	p-(PS)2-GalNac4	509	ND	ND	Z
ds-siNA-0135	435	p-(PS)2-GalNac4	510	ND	ND	Y
ds-siNA-0136	435	p-(PS)2-GalNac4	511	B	>1000	ND
ds-siNA-0137	435	p-(PS)2-GalNac4	512	B	>1000	ND
ds-siNA-0138	435	p-(PS)2-GalNac4	513	A	>1000	ND
ds-siNA-0139	435	p-(PS)2-GalNac4	514	B	>1000	ND
ds-siNA-0140	435	p-(PS)2-GalNac4	515	C	>1000	ND
ds-siNA-0141	435	p-(PS)2-GalNac4	516	A	>1000	ND
ds-siNA-0142	435	p-(PS)2-GalNac4	517	C	>1000	ND
ds-siNA-0143	435	p-(PS)2-GalNac4	518	C	>1000	ND
ds-siNA-0144	435	p-(PS)2-GalNac4	519	ND	ND	ND
ds-siNA-0145	436	p-(PS)2-GalNac4	520	ND	ND	ND
ds-siNA-0146	437	p-(PS)2-GalNac4	502	ND	ND	Y
ds-siNA-0147	438	p-(PS)2-GalNac4	501	ND	ND	X
ds-siNA-0148	438	p-(PS)2-GalNac4	521	ND	ND	X
ds-siNA-0149	438	p-(PS)2-GalNac4	522	ND	ND	X
ds-siNA-0150	439	p-(PS)2-GalNac4	523	ND	ND	X
ds-siNA-0151	440	p-(PS)2-GalNac4	524	ND	ND	Y
ds-siNA-0152	441	p-(PS)2-GalNac4	525	ND	ND	Y
ds-siNA-0153	441	p-(PS)2-GalNac4	526	ND	ND	X
ds-siNA-0154	441	p-(PS)2-GalNac4	527	ND	ND	ND
ds-siNA-0155	442	p-(PS)2-GalNac4	525	ND	ND	X
ds-siNA-0156	442	p-(PS)2-GalNac4	528	ND	ND	Y
ds-siNA-0157	442	p-(PS)2-GalNac4	529	ND	ND	ND
ds-siNA-0158	443	p-(PS)2-GalNac4	458	ND	ND	Y
ds-siNA-0159	444	p-(PS)2-GalNac4	502	ND	ND	Y
ds-siNA-0160	423	p-(PS)2-GalNac4	458	ND	ND	ND
ds-siNA-0161	533	p-(PS)2-GalNac4	489	ND	ND	ND
ds-siNA-0162	534	p-(PS)2-GalNac4	491	ND	ND	ND
ds-siNA-0163	432	p-(PS)2-GalNac4	496	ND	ND	ND
ds-siNA-0165	435	p-(PS)2-GalNac4	502	ND	ND	ND
ds-siNA-0166	442	p-(PS)2-GalNac4	530	ND	ND	ND
ds-siNA-0167	427	p-(PS)2-GalNAc4	491	ND	ND	ND
ds-siNA-0168	439	p-(PS)2-GalNac4	531	ND	ND	ND
ds-siNA-0169	423	p-(PS)2-GalNac4	532	ND	ND	ND
ds-siNA-0170	441	p-(PS)2-GalNAc4	530	ND	ND	ND
ds-siNA-0171	442	p-(PS)2-GalNAc4	533	ND	ND	ND
ds-siNA-0172	424	p-(PS)2-GalNAc4	536	A	>1	ND
ds-siNA-0173	438	None	537			
ds-siNA-0174	438	None	538			

TABLE 10-continued

siNA Activity

ds-siNA ID	Sense Strand SEQ ID NO	3' Ligand Monomer[+]	Antisense Strand SEQ ID NO	HepG2.2.15 EC50*	HepG2.2.15 CC50 (nM)	Max HBsAg Knock Down (Log_{10}) **
ds-siNA-0175	438	None	501			
ds-siNA-0176	438	p-(PS)2-GalNAc4	537			
ds-siNA-0177	438	p-(PS)2-GalNAc4	538			
ds-siNA-0178	438	p-(PS)2-GalNAc4	539			

[+]Ligand monomers are attached to the 3' end of the sense strand, unless the ligand monomer is annotated with 5', in which the ligand monomer is attached to the 5' end of the sense strand. Linkers are represented as p-(PS)2, (PS)2-p-TEG-p, (PS)2-p-HEG-p, or (PS)2-p-(HEG-p)2.

*For EC50, A = EC50 ≤ 5 nM; B = 5 nM < EC50 < 10; C = EC50 ≥ 10.

** For Max HBsAg knock down, X ≥ 1 log_{10} reduction in HBsAg, Y is 0.5-1 log_{10} reduction in HBsAg, and Z is < 0.5 log_{10} reduction in HBsAg.

SEQUENCE LISTING

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<220> FEATURE:
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accgugugca cuucgcuuc 19

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acuucgcuuc accucugca 19

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caggcggggu uuuucuugu 19

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caggcggggu uuuucuugu 19

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caguuuacua gugccauuu 19

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caguuuacua gugccauuu 19

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cauccugcug cuaugccuca u 21

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cauccugcug cuaugccuc 19

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ccgugugcac uucgcuuca 19

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ccugcugcua ugccucaucu u 21

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cucaguuuac uagugccau 19

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cucaguuuac uagugccau 19

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cugcuaugcc ucaucuucu 19

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cugcuaugcc ucaucuucu 19

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cugcuaugcc ucaucuucu 19

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cugcuaugcc ucaucuucu 19

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cugcugcuau gccucaucu 19

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cugcugcuau gccucaucu 19

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cugcugcuau gccucaucu 19

<210> SEQ ID NO 27
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cuucgcuuca ccucugcacg u 21

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gccggguuuu ucuuguuga 19

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gcgggguuuu ucuuguuga 19

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gcgggguuuu ucuuguuga 19

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gcgggguuuu ucuuguuga 19

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gcugcuaugc cucaucuucu u 21

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ggaugugucu gcggcguuuu a 21

<210> SEQ ID NO 37
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ggccaaaauu cgcaguccc 19

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ggcgcaccuc ucuuuacgc 19

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guauguugcc cguuugucc 19

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gugguggacu ucucucaau 19

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gugugcacuu cgcuucacc 19

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ucguggugga cuucucucaa u 21

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ugcacuucgc uucaccucu 19

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ugccgaucca uacugcgga 19

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ugcuaugccu caucuucuu 19

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ugugcacuuc gcuucaccu 19

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 63

aaauggcacu aguaaacuga g 21

<210> SEQ ID NO 64
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 64

aaauggcacu aguaaacug 19

<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 65

gaggcauagc agcaggauga a 21

<210> SEQ ID NO 66
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 66

augaggcaua gcagcaggau gaa 23

<210> SEQ ID NO 67
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 67

gaggcauagc agcaggaug 19

<210> SEQ ID NO 68
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 68

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 69
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 69

ugaagcgaag ugcacacgg 19

<210> SEQ ID NO 70
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 70

aagaugaggc auagcagcag gau 23

<210> SEQ ID NO 71
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 71

auggcacuag uaaacugagc c 21

<210> SEQ ID NO 72
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 72

auggcacuag uaaacugag 19

<210> SEQ ID NO 73
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 73

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 74
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 74

agaagaugag gcauagcag 19

<210> SEQ ID NO 75
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<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 75

agaugaggca uagcagcagg a 21

<210> SEQ ID NO 76
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 76

agaugaggca uagcagcag 19

<210> SEQ ID NO 77
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 77

acgugcagag gugaagcgaa gug 23

<210> SEQ ID NO 78
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 78

ugcagaggug aagcgaagug cac 23

<210> SEQ ID NO 79
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 79

uuccgcagua uggaucggca g 21

<210> SEQ ID NO 80
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 80

uuccgcagua uggaucggc 19

<210> SEQ ID NO 81

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<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 81

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 82
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 82

ucaacaagaa aaaccccgc 19

<210> SEQ ID NO 83
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 83

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 84
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 84

uaaaacgccg cagacacauc cag 23

<210> SEQ ID NO 85
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 85

gggacugcga auuuuggcca a 21

<210> SEQ ID NO 86
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 86

gcguaaagag aggugcgccc c 21

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<210> SEQ ID NO 87
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 87

ggacaaacgg gcaacauacc u 21

<210> SEQ ID NO 88
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 88

auugagagaa guccaccacg a 21

<210> SEQ ID NO 89
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 89

ggugaagcga agugcacacg g 21

<210> SEQ ID NO 90
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 90

uagaggacaa acgggcaaca u 21

<210> SEQ ID NO 91
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 91

uagaggacaa acgggcaac 19

<210> SEQ ID NO 92
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 92

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aggaguuccg caguauggau c 21

<210> SEQ ID NO 93
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 93

aggaguuccg caguaugga 19

<210> SEQ ID NO 94
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 94

auugagagaa guccaccacg agu 23

<210> SEQ ID NO 95
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 95

agaggugaag cgaagugcac a 21

<210> SEQ ID NO 96
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 96

uccgcaguau ggaucggcag a 21

<210> SEQ ID NO 97
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 97

uccgcaguau ggaucggca 19

<210> SEQ ID NO 98
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 98

aagaagauga ggcauagcag c 21

<210> SEQ ID NO 99
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 99

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 100
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 100

aggugaagcg aagugcaca 19

<210> SEQ ID NO 101
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 101

uuagaggaca aacgggcaac a 21

<210> SEQ ID NO 102
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 102

uuagaggaca aacgggcaa 19

<210> SEQ ID NO 103
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 103

accgugugca cuucgcuuc 19

<210> SEQ ID NO 104
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 104

accgugugca cuucgcuuc 19

<210> SEQ ID NO 105
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 105

acuucgcuuc accucugca 19

<210> SEQ ID NO 106
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 106

aguguuugcu gacgcaacc 19

<210> SEQ ID NO 107
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 107

caggcggggu uuuucuugu 19

<210> SEQ ID NO 108
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 108

caggcggggu uuuucuugu 19

<210> SEQ ID NO 109
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 109

caguuuacua gugccauuu 19

<210> SEQ ID NO 110
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 110

caguuuacua gugccauuu 19

<210> SEQ ID NO 111
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 111

cauccugcug cuaugccuc 19

<210> SEQ ID NO 112
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 112

cauccugcug cuaugccuca u 21

<210> SEQ ID NO 113
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 113

cauccugcug cuaugccuc 19

<210> SEQ ID NO 114
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 114

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 115
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 115

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 116
<211> LENGTH: 21

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 116

ccugcugcua ugccucaucu u 21

<210> SEQ ID NO 117
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 117

cucaguuuac uagugccau 19

<210> SEQ ID NO 118
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 118

cucaguuuac uagugccau 19

<210> SEQ ID NO 119
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 119

cucaguuuac uagugccau 19

<210> SEQ ID NO 120
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 120

cucaguuuac uagugccau 19

<210> SEQ ID NO 121
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 121

cucaguuuac uagugccau 19

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<210> SEQ ID NO 122
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 122

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 123
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 123

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 124
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 124

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 125
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 125

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 126
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 126

cugcugcuau gccucaucu 19

<210> SEQ ID NO 127
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 127

cugcugcuau gccucaucu 19

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<210> SEQ ID NO 128
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 128

cugcugcuau gccucaucu 19

<210> SEQ ID NO 129
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 129

cuucgcuuca ccucugcacg u 21

<210> SEQ ID NO 130
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 130

gcacuucgcu ucaccucugc a 21

<210> SEQ ID NO 131
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 131

gccgauccau acugcggaa 19

<210> SEQ ID NO 132
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 132

gccggguuuu ucuuguuga 19

<210> SEQ ID NO 133
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 133

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gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 134
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 134

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 135
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 135

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 136
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 136

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 137
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 137

gcugcuaugc cucaucuucu u 21

<210> SEQ ID NO 138
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 138

ggaugugucu gcggcguuuu a 21

<210> SEQ ID NO 139
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 139

ggccaaaauu cgcaguccc 19

<210> SEQ ID NO 140
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 140

ggcgcaccuc ucuuuacgc 19

<210> SEQ ID NO 141
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 141

guauguugcc cguuugucc 19

<210> SEQ ID NO 142
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 142

gugguggacu ucucucaau 19

<210> SEQ ID NO 143
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 143

gugugcacuu cgcuucacc 19

<210> SEQ ID NO 144
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 144

guugcccguu uguccucua 19

<210> SEQ ID NO 145
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 145

guugcccguu uguccucua 19

<210> SEQ ID NO 146
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 146

uccauacugc ggaacuccu 19

<210> SEQ ID NO 147
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 147

uccauacugc ggaacuccu 19

<210> SEQ ID NO 148
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 148

ucguggugga cuucucucaa u 21

<210> SEQ ID NO 149
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 149

ugcacuucgc uucaccucu 19

<210> SEQ ID NO 150
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 150

ugccgaucca uacugcgga 19

<210> SEQ ID NO 151
<211> LENGTH: 19
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 151

ugccgaucca uacugcgga 19

<210> SEQ ID NO 152
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 152

ugcuaugccu caucuucuu 19

<210> SEQ ID NO 153
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 153

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 154
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 154

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 155
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 155

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 156
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 156

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 157

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<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 157

uugcccguuu guccucuaa 19

<210> SEQ ID NO 158
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 158

uugcccguuu guccucuaa 19

<210> SEQ ID NO 159
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 159

gaagcgaagu gcacacgguc c 21

<210> SEQ ID NO 160
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 160

gaagcgaagu gcacacggu 19

<210> SEQ ID NO 161
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 161

ugcagaggug aagcgaagug c 21

<210> SEQ ID NO 162
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 162

gguugcguca gcaaacacuu g 21

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<210> SEQ ID NO 163
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 163

acaagaaaaa ccccgccugu a 21

<210> SEQ ID NO 164
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 164

acaagaaaaa accccgccug 20

<210> SEQ ID NO 165
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 165

aaauggcacu aguaaacuga g 21

<210> SEQ ID NO 166
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 166

aaauggcacu aguaaacug 19

<210> SEQ ID NO 167
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 167

gaggcauagc agcaggauga a 21

<210> SEQ ID NO 168
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 168

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augaggcaua gcagcaggau gaa 23

<210> SEQ ID NO 169
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 169

gaggcauagc agcaggaug 19

<210> SEQ ID NO 170
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 170

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 171
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 171

ugaagcgaag ugcacacgg 19

<210> SEQ ID NO 172
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 172

aagaugaggc auagcagcag gau 23

<210> SEQ ID NO 173
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 173

auggcacuag uaaacugagc c 21

<210> SEQ ID NO 174
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 174

auggcacuag uaaacugag 19

<210> SEQ ID NO 175
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 175

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 176
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 176

agaagaugag gcauagcag 19

<210> SEQ ID NO 177
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 177

agaugaggca uagcagcagg a 21

<210> SEQ ID NO 178
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 178

agaugaggca uagcagcag 19

<210> SEQ ID NO 179
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 179

acgugcagag gugaagcgaa gug 23

<210> SEQ ID NO 180
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 180

ugcagaggug aagcgaagug cac 23

<210> SEQ ID NO 181
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 181

uuccgcagua uggaucggca g 21

<210> SEQ ID NO 182
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 182

uuccgcagua uggaucggc 19

<210> SEQ ID NO 183
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 183

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 184
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 184

ucaacaagaa aaaccccgc 19

<210> SEQ ID NO 185
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 185

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 186
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 186

uaaaacgccg cagacacauc cag 23

<210> SEQ ID NO 187
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 187

gggacugcga auuuuggcca a 21

<210> SEQ ID NO 188
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 188

gcguaaagag aggugcgccc c 21

<210> SEQ ID NO 189
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 189

ggacaaacgg gcaacauacc u 21

<210> SEQ ID NO 190
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 190

auugagagaa guccaccacg a 21

<210> SEQ ID NO 191
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 191

ggugaagcga agugcacacg g 21

<210> SEQ ID NO 192
<211> LENGTH: 21

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 192

uagaggacaa acgggcaaca u 21

<210> SEQ ID NO 193
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 193

uagaggacaa acgggcaac 19

<210> SEQ ID NO 194
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 194

aggaguuccg caguauggau c 21

<210> SEQ ID NO 195
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 195

aggaguuccg caguaugga 19

<210> SEQ ID NO 196
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 196

auugagagaa guccaccacg agu 23

<210> SEQ ID NO 197
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 197

agaggugaag cgaagugcac a 21

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<210> SEQ ID NO 198
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 198

uccgcaguau ggaucggcag a 21

<210> SEQ ID NO 199
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 199

uccgcaguau ggaucggca 19

<210> SEQ ID NO 200
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 200

aagaagauga ggcauagcag c 21

<210> SEQ ID NO 201
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 201

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 202
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 202

aggugaagcg aagugcaca 19

<210> SEQ ID NO 203
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 203

uuagaggaca aacgggcaac a 21

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<210> SEQ ID NO 204
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 204

uuagaggaca aacgggcaa 19

<210> SEQ ID NO 205
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 205

accgugugca cuucgcuuc 19

<210> SEQ ID NO 206
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 206

accgugugca cuucgcuuc 19

<210> SEQ ID NO 207
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 207

acuucgcuuc accucugca 19

<210> SEQ ID NO 208
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 208

aguguuugcu gacgcaacc 19

<210> SEQ ID NO 209
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 209

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caggcggggu uuuucuugu 19

<210> SEQ ID NO 210
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 210

caggcggggu uuuucuugu 19

<210> SEQ ID NO 211
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 211

caguuuacua gugccauuu 19

<210> SEQ ID NO 212
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 212

caguuuacua gugccauuu 19

<210> SEQ ID NO 213
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 213

cauccugcug cuaugccuc 19

<210> SEQ ID NO 214
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 214

cauccugcug cuaugccuca u 21

<210> SEQ ID NO 215
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 215

cauccugcug cuaugccuc 19

<210> SEQ ID NO 216
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 216

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 217
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 217

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 218
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 218

ccugcugcua ugccucaucu u 21

<210> SEQ ID NO 219
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 219

cucaguuuac uagugccau 19

<210> SEQ ID NO 220
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 220

cucaguuuac uagugccau 19

<210> SEQ ID NO 221
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 221

cucaguuuac uagugccau 19

<210> SEQ ID NO 222
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 222

cucaguuuac uagugccau 19

<210> SEQ ID NO 223
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 223

cucaguuuac uagugccau 19

<210> SEQ ID NO 224
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 224

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 225
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 225

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 226
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 226

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 227
<211> LENGTH: 19
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 227

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 228
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 228

cugcugcuau gccucaucu 19

<210> SEQ ID NO 229
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 229

cugcugcuau gccucaucu 19

<210> SEQ ID NO 230
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 230

cugcugcuau gccucaucu 19

<210> SEQ ID NO 231
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 231

cuucgcuuca ccucugcacg u 21

<210> SEQ ID NO 232
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 232

gcacuucgcu ucaccucugc a 21

<210> SEQ ID NO 233

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<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 233

gccgauccau acugcggaa 19

<210> SEQ ID NO 234
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 234

gccggguuuu ucuuguuga 19

<210> SEQ ID NO 235
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 235

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 236
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 236

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 237
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 237

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 238
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 238

gcgggguuuu ucuuguuga 19

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<210> SEQ ID NO 239
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 239

gcugcuaugc cucaucuucu u 21

<210> SEQ ID NO 240
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 240

ggaugugucu gcggcguuuu a 21

<210> SEQ ID NO 241
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 241

ggccaaaauu cgcaguccc 19

<210> SEQ ID NO 242
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 242

ggcgcaccuc ucuuuacgc 19

<210> SEQ ID NO 243
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 243

guauguugcc cguuugucc 19

<210> SEQ ID NO 244
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 244

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gugguggacu ucucucaau 19

<210> SEQ ID NO 245
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 245

gugugcacuu cgcuucacc 19

<210> SEQ ID NO 246
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 246

guugcccguu uguccucua 19

<210> SEQ ID NO 247
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 247

guugcccguu uguccucua 19

<210> SEQ ID NO 248
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 248

uccauacugc ggaacuccu 19

<210> SEQ ID NO 249
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 249

uccauacugc ggaacuccu 19

<210> SEQ ID NO 250
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 250

ucguggugga cuucucucaa u 21

<210> SEQ ID NO 251
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 251

ugcacuucgc uucaccucu 19

<210> SEQ ID NO 252
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 252

ugccgaucca uacugcgga 19

<210> SEQ ID NO 253
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 253

ugccgaucca uacugcgga 19

<210> SEQ ID NO 254
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 254

ugcuaugccu caucuucuu 19

<210> SEQ ID NO 255
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 255

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 256
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 256

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 257
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 257

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 258
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 258

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 259
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 259

uugcccguuu guccucuaa 19

<210> SEQ ID NO 260
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 260

uugcccguuu guccucuaa 19

<210> SEQ ID NO 261
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 261

gaagcgaagu gcacacgguc c 21

<210> SEQ ID NO 262
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 262

gaagcgaagu gcacacggu 19

<210> SEQ ID NO 263
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 263

ugcagaggug aagcgaagug c 21

<210> SEQ ID NO 264
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 264

gguugcguca gcaaacacuu g 21

<210> SEQ ID NO 265
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 265

acaagaaaaa ccccgccugu a 21

<210> SEQ ID NO 266
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 266

acaagaaaaa accccgccug 20

<210> SEQ ID NO 267
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 267

aaauggcacu aguaaacuga g 21

<210> SEQ ID NO 268
<211> LENGTH: 19

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 268

aaauggcacu aguaaacug 19

<210> SEQ ID NO 269
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 269

gaggcauagc agcaggauga a 21

<210> SEQ ID NO 270
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 270

augaggcaua gcagcaggau gaa 23

<210> SEQ ID NO 271
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 271

gaggcauagc agcaggaug 19

<210> SEQ ID NO 272
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 272

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 273
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 273

ugaagcgaag ugcacacgg 19

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<210> SEQ ID NO 274
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 274

aagaugaggc auagcagcag gau 23

<210> SEQ ID NO 275
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 275

auggcacuag uaaacugagc c 21

<210> SEQ ID NO 276
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 276

auggcacuag uaaacugag 19

<210> SEQ ID NO 277
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 277

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 278
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 278

agaagaugag gcauagcag 19

<210> SEQ ID NO 279
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 279

agaugaggca uagcagcagg a 21

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<210> SEQ ID NO 280
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 280

agaugaggca uagcagcag 19

<210> SEQ ID NO 281
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 281

acgugcagag gugaagcgaa gug 23

<210> SEQ ID NO 282
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 282

ugcagaggug aagcgaagug cac 23

<210> SEQ ID NO 283
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 283

uuccgcagua uggaucggca g 21

<210> SEQ ID NO 284
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 284

uuccgcagua uggaucggc 19

<210> SEQ ID NO 285
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 285

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ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 286
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 286

ucaacaagaa aaaccccgc 19

<210> SEQ ID NO 287
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 287

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 288
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 288

uaaaacgccg cagacacauc cag 23

<210> SEQ ID NO 289
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 289

gggacugcga auuuuggcca a 21

<210> SEQ ID NO 290
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 290

gcguaaagag aggugcgccc c 21

<210> SEQ ID NO 291
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 291

ggacaaacgg gcaacauacc u 21

<210> SEQ ID NO 292
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 292

auugagagaa guccaccacg a 21

<210> SEQ ID NO 293
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 293

ggugaagcga agugcacacg g 21

<210> SEQ ID NO 294
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 294

uagaggacaa acgggcaaca u 21

<210> SEQ ID NO 295
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 295

uagaggacaa acgggcaac 19

<210> SEQ ID NO 296
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 296

aggaguuccg caguauggau c 21

<210> SEQ ID NO 297
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 297

aggaguuccg caguaugga 19

<210> SEQ ID NO 298
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 298

auugagagaa guccaccacg agu 23

<210> SEQ ID NO 299
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 299

agaggugaag cgaagugcac a 21

<210> SEQ ID NO 300
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 300

uccgcaguau ggaucggcag a 21

<210> SEQ ID NO 301
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 301

uccgcaguau ggaucggca 19

<210> SEQ ID NO 302
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 302

aagaagauga ggcauagcag c 21

<210> SEQ ID NO 303
<211> LENGTH: 21
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 303

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 304
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 304

aggugaagcg aagugcaca 19

<210> SEQ ID NO 305
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 305

uuagaggaca aacgggcaac a 21

<210> SEQ ID NO 306
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 306

uuagaggaca aacgggcaa 19

<210> SEQ ID NO 307
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 307

accgugugca cuucgcuuc 19

<210> SEQ ID NO 308
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 308

accgugugca cuucgcuuct t 21

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<210> SEQ ID NO 309
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 309

acuucgcuuc accucugca 19

<210> SEQ ID NO 310
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 310

aguguuugcu gacgcaacc 19

<210> SEQ ID NO 311
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 311

caggcggggu uuuucuugu 19

<210> SEQ ID NO 312
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 312

caggcggggu uuuucuugut t 21

<210> SEQ ID NO 313
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 313

caguuuacua gugccauuu 19

<210> SEQ ID NO 314
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 314

caguuuacua gugccauuut t 21

<210> SEQ ID NO 315
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 315

cauccugcug cuaugccuc 19

<210> SEQ ID NO 316
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 316

cauccugcug cuaugccuca u 21

<210> SEQ ID NO 317
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 317

cauccugcug cuaugccuct t 21

<210> SEQ ID NO 318
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 318

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 319
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide

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<400> SEQUENCE: 319

ccgugugcac uucgcuucat t 21

<210> SEQ ID NO 320
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 320

ccugcugcua ugccucaucu u 21

<210> SEQ ID NO 321
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 321

cucaguuuac uagugccau 19

<210> SEQ ID NO 322
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 322

cucaguuuac uagugccau 19

<210> SEQ ID NO 323
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 323

cucaguuuac uagugccau 19

<210> SEQ ID NO 324
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 324

cucaguuuac uagugccaut t 21

<210> SEQ ID NO 325
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 325

cucaguuuac uagugccaut t 21

<210> SEQ ID NO 326
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 326

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 327
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 327

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 328
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 328

cugcuaugcc ucaucuucut t 21

<210> SEQ ID NO 329
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 329

cugcuaugcc ucaucuucut t 21

<210> SEQ ID NO 330
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 330

cugcugcuau gccucaucu 19

<210> SEQ ID NO 331
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 331

cugcugcuau gccucaucut t 21

<210> SEQ ID NO 332
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 332

cugcugcuau gccucaucut t 21

<210> SEQ ID NO 333
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 333

cuucgcuuca ccucugcacg u 21

<210> SEQ ID NO 334
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 334

gcacuucgcu ucaccucugc a 21

<210> SEQ ID NO 335
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 335

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gccgauccau acugcggaa 19

<210> SEQ ID NO 336
<211> LENGTH: 21
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 336

gccgggguuuu ucuuguugat t 21

<210> SEQ ID NO 337
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 337

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 338
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 338

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 339
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 339

gcgggguuuu ucuuguugat t 21

<210> SEQ ID NO 340
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 340

gcgggguuuu ucuuguugat t 21

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<210> SEQ ID NO 341
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 341

gcugcuaugc cucaucuucu u 21

<210> SEQ ID NO 342
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 342

ggaugugucu gcggcguuuu a 21

<210> SEQ ID NO 343
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 343

ggccaaaauu cgcaguccc 19

<210> SEQ ID NO 344
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<212> TYPE: RNA
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<400> SEQUENCE: 344

ggcgcaccuc ucuuuacgc 19

<210> SEQ ID NO 345
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<212> TYPE: RNA
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<400> SEQUENCE: 345

guauguugcc cguuugucc 19

<210> SEQ ID NO 346
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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gugguggacu ucucucaau 19

<210> SEQ ID NO 347
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 347

gugugcacuu cgcuucacc 19

<210> SEQ ID NO 348
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 348

guugcccguu uguccucua 19

<210> SEQ ID NO 349
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 349

guugcccguu uguccucuat t 21

<210> SEQ ID NO 350
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 350

uccauacugc ggaacuccu 19

<210> SEQ ID NO 351
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 351

uccauacugc ggaacuccut t 21

<210> SEQ ID NO 352
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 352

ucguggugga cuucucucaa u 21

<210> SEQ ID NO 353
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 353

ugcacuucgc uucaccucu 19

<210> SEQ ID NO 354
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 354

ugccgaucca uacugcgga 19

<210> SEQ ID NO 355
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 355

ugccgaucca uacugcggat t 21

<210> SEQ ID NO 356
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 356

ugcuaugccu caucuucuu 19

<210> SEQ ID NO 357
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 357

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ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 358
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 358

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 359
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 359

ugugcacuuc gcuucaccut t 21

<210> SEQ ID NO 360
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 360

ugugcacuuc gcuucaccut t 21

<210> SEQ ID NO 361
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 361

uugcccguuu guccucuaa 19

<210> SEQ ID NO 362
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 362

uugcccguuu guccucuaat t 21

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<210> SEQ ID NO 363
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 363

gaagcgaagu gcacacgguc c 21

<210> SEQ ID NO 364
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 364

gaagcgaagu gcacacggut t 21

<210> SEQ ID NO 365
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 365

ugcagaggug aagcgaagug c 21

<210> SEQ ID NO 366
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 366

gguugcguca gcaaacacuu g 21

<210> SEQ ID NO 367
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 367

acaagaaaaa ccccgccugu a 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 368

acaagaaaaa accccgccug tt 22

<210> SEQ ID NO 369
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 369

aaauggcacu aguaaacuga g 21

<210> SEQ ID NO 370
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 370

aaauggcacu aguaaacugt t 21

<210> SEQ ID NO 371
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 371

gaggcauagc agcaggauga a 21

<210> SEQ ID NO 372
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 372

augaggcaua gcagcaggau gaa 23

<210> SEQ ID NO 373
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA
Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 373

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gaggcauagc agcaggaugt t 21

<210> SEQ ID NO 374
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 374

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 375
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 375

ugaagcgaag ugcacacggt t 21

<210> SEQ ID NO 376
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 376

aagaugaggc auagcagcag gau 23

<210> SEQ ID NO 377
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 377

auggcacuag uaaacugagc c 21

<210> SEQ ID NO 378
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 378

auggcacuag uaaacugagt t 21

<210> SEQ ID NO 379

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 379

agaagaugag gcauagcagc a 21

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<400> SEQUENCE: 380

agaagaugag gcauagcagt t 21

<210> SEQ ID NO 381
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 381

agaugaggca uagcagcagg a 21

<210> SEQ ID NO 382
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 382

agaugaggca uagcagcagt t 21

<210> SEQ ID NO 383
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<400> SEQUENCE: 383

agaugaggca uagcagcagt t 21

<210> SEQ ID NO 384
<211> LENGTH: 23
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 384

acgugcagag gugaagcgaa gug 23

<210> SEQ ID NO 385
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 385

ugcagaggug aagcgaagug cac 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 386

uuccgcagua uggaucggca g 21

<210> SEQ ID NO 387
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 387

uuccgcagua uggaucggct t 21

<210> SEQ ID NO 388
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 388

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 389
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 389

ucaacaagaa aaaccccgct t 21

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aagaagauga ggcauagcag cag 23

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 391

uaaaacgccg cagacacauc cag 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 392

gggacugcga auuuuggcca a 21

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 393

gcguaaagag aggugcgccc c 21

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 394

ggacaaacgg gcaacauacc u 21

<210> SEQ ID NO 395
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 395

auugagagaa guccaccacg a 21

<210> SEQ ID NO 396
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<220> FEATURE:
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ggugaagcga agugcacacg g 21

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<400> SEQUENCE: 397

uagaggacaa acgggcaaca u 21

<210> SEQ ID NO 398
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<220> FEATURE:
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uagaggacaa acgggcaact t 21

<210> SEQ ID NO 399
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 399

aggaguuccg caguauggau c 21

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<220> FEATURE:
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<400> SEQUENCE: 400

aggaguuccg caguauggat t 21

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 401

auugagagaa guccaccacg agu 23

<210> SEQ ID NO 402
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 402

agaggugaag cgaagugcac a 21

<210> SEQ ID NO 403
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 403

uccgcaguau ggaucggcag a 21

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 404

uccgcaguau ggaucggcat t 21

<210> SEQ ID NO 405
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 405

aagaagauga ggcauagcag c 21

<210> SEQ ID NO 406
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 406

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 407
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 407

aggugaagcg aagugcacat t 21

<210> SEQ ID NO 408
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 408

uuagaggaca aacgggcaac a 21

<210> SEQ ID NO 409
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
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<400> SEQUENCE: 409

uuagaggaca aacgggcaat t 21

<210> SEQ ID NO 410
<211> LENGTH: 3182
<212> TYPE: DNA
<213> ORGANISM: Hepatitis B virus

<400> SEQUENCE: 410

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gctggtggct ccagttcagg agcagtaaac cctgttccga ctactgcctc tcccttatcg 120

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atcacaaagc aaaaggacac ttcaactgtc cagagggtta ttcaggaggc tggtggtggc 1260

atgatgagtg tggagaaaac aacctaaatg gtaaatataa caaaccaaga gcaaaatcta 1320

agccagagag gagaagagga ttatcttgga agtctcaaaa tggaaggtta tactctataa 1380

aatcaaccaa aatgttgatc catccaacag attcagaaag ctttgaatga actgaggcaa 1440

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ggtattaaat ccttaagaga aagcttgaga aatagatttt ttttatctta aagtcactgt 1560

ctatttaaga ttaaacatac aatcacataa ccttaaagaa taccgtttac atttctcaat 1620

caaaattctt ataatactat ttgttttaaa ttttgtgatg tgggaatcaa ttttagatgg 1680

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gtaaatgttt gatatgattt atttatgaaa cctaatgaag cagaattaaa tactgtatta 2040

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aataatctat aattttcagg accacagact aagctgtcga aattaacgct gatttttтta 2820

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<211> LENGTH: 2336
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 414

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caacttccga atgcctgtgt tgagggagta cctgatgtct ggaggtatct gccctgtcag 780

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gaaccgcaag ggctttgtga aactggccct gcgtcatgga gctgacctgg ttcccatcta 960

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aaacccaacc ctctcctgtg tgttctgtta tctcttgatg agatcattgc accatgtcag 2280

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<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 415

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 416
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<400> SEQUENCE: 416

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 417
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<400> SEQUENCE: 417

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 418
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<212> TYPE: RNA
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<400> SEQUENCE: 418

gugguggacu ucucucaau 19

<210> SEQ ID NO 419
<211> LENGTH: 19
<212> TYPE: RNA
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<400> SEQUENCE: 419

gugguggacu ucucucaau 19

<210> SEQ ID NO 420
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<212> TYPE: RNA
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<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 420

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 421
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 421

ccgugugcaa uucgcuuca 19

<210> SEQ ID NO 422
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<400> SEQUENCE: 422

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 423
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 423

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 424
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 424

ccgugugcac uucgcuuca 19

<210> SEQ ID NO 425
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 425

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 426
<211> LENGTH: 19
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 426

cugcuaugcc ucaucuucu 19

<210> SEQ ID NO 427
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 427

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 428
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 428

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 429
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<212> TYPE: RNA
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<400> SEQUENCE: 429

gcgggguuuu ucuuguuga 19

<210> SEQ ID NO 430
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 430

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<210> SEQ ID NO 431
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 431

gcugcuaugc cucaucuucu u 21

<210> SEQ ID NO 432

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<211> LENGTH: 21
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 432

gcugcuaugc cucaucuucu u 21

<210> SEQ ID NO 433
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 433

gugguggacu ucucucaau 19

<210> SEQ ID NO 434
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 434

gugguggaau ucucucaau 19

<210> SEQ ID NO 435
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 435

gugguggacu ucucucaau 19

<210> SEQ ID NO 436
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 436

gugguggacu ucucucuau 19

<210> SEQ ID NO 437
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 437

gugguggacu ucucucaau 19

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<210> SEQ ID NO 438
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 438

gugguggacu ucucucaau 19

<210> SEQ ID NO 439
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 439

ucguggugga cuucucucaa u 21

<210> SEQ ID NO 440
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<212> TYPE: RNA
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<400> SEQUENCE: 440

ugccgaucca uacugcgga 19

<210> SEQ ID NO 441
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<400> SEQUENCE: 441

ugugcacuuc gcuucaccu 19

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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 442

ugugcacuuc gcuucaccu 19

<210> SEQ ID NO 443
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<212> TYPE: RNA
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<400> SEQUENCE: 443

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ccgugugcac uucgcuuca 19

<210> SEQ ID NO 444
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<212> TYPE: RNA
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<400> SEQUENCE: 444

gugguggacu ucucucaau 19

<210> SEQ ID NO 445
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 445

ugaagcgaag ugcacacggu u 21

<210> SEQ ID NO 446
<211> LENGTH: 21
<212> TYPE: RNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 446

ugaagcgaag ugcacacggu u 21

<210> SEQ ID NO 447
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 447

ugaagcgaag ugcacacggu u 21

<210> SEQ ID NO 448
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 448

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 449
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 449

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 450
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 450

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 451
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 451

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 452
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 452

agaagaugag gcauagcagu u 21

<210> SEQ ID NO 453
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 453

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<210> SEQ ID NO 454
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 454

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<210> SEQ ID NO 455
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 455

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<210> SEQ ID NO 456
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 456

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<210> SEQ ID NO 457
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 457

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<210> SEQ ID NO 458
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 458

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 459
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 459

ugaagcgaag ugcacacggu u 21

<210> SEQ ID NO 460
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 460

ugaagcgaag ugcacacggu u 21

<210> SEQ ID NO 461
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 461

ugaagcgaag ugcacacggu u 21

<210> SEQ ID NO 462
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 462

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 463
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

<400> SEQUENCE: 463

ugaagcgaag ugcacacggt t 21

<210> SEQ ID NO 464
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 464

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 465
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 465

bgaagcgaag ugcacacggu c 21

<210> SEQ ID NO 466
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 466

ugaagcgaag ugcacacggu c 21

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<210> SEQ ID NO 467
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 467

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 468
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 468

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 469
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 469

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 470
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 470

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 471
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 471

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 472
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 472

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ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 473
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 473

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 474
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 474

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 475
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 475

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 476
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 476

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 477
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 477

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 478
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 478

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 479
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 479

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 480
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 480

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 481
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 481

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 482
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 482

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 483
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 483

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 484
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 484

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 485
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 485

ugaagcgaag ugcacacggu c 21

<210> SEQ ID NO 486
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 486

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 487
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 487

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 488
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 488

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 489
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 489

agaagaugag gcauagcagc a 21

<210> SEQ ID NO 490
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 490

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 491
<211> LENGTH: 21
<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 491

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 492
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 492

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 493
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 493

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 494
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 494

ucaacaagaa aaaccccgcc u 21

<210> SEQ ID NO 495
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 495

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 496
<211> LENGTH: 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 496

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 497
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 497

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 498
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 498

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 499

<400> SEQUENCE: 499

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<210> SEQ ID NO 500
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 500

aagaagauga ggcauagcag cag 23

<210> SEQ ID NO 501
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 501

auugagagaa guccaccacg a 21

<210> SEQ ID NO 502
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 502

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<210> SEQ ID NO 503
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 503

auugagagaa guccaccacg a 21

<210> SEQ ID NO 504
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 504

auugagagaa guccaccacg a 21

<210> SEQ ID NO 505
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: a, c, u, g, unknown or other

<400> SEQUENCE: 505

nuugagagaa guccaccacg a 21

<210> SEQ ID NO 506
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 506

uuugagagaa guccaccacg a 21

<210> SEQ ID NO 507
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 507

uuugagagaa guccaccacg a 21

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<210> SEQ ID NO 508
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 508

uuugagagaa guccaccacg a 21

<210> SEQ ID NO 509
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 509

uuugagagaa guccaccacg a 21

<210> SEQ ID NO 510
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 510

auugagagaa guccaccacg a 21

<210> SEQ ID NO 511
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 511

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<210> SEQ ID NO 512
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 512

auugagagaa guccaccacg a 21

<210> SEQ ID NO 513
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<220> FEATURE:
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auugagagaa guccaccacg a 21

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<400> SEQUENCE: 514

auugagagaa guccaccacg a 21

<210> SEQ ID NO 515
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 515

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<210> SEQ ID NO 516
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<400> SEQUENCE: 516

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<210> SEQ ID NO 517
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<400> SEQUENCE: 517

auugagagaa guccaccacg a 21

<210> SEQ ID NO 518
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<220> FEATURE:
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<400> SEQUENCE: 518

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<210> SEQ ID NO 519
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auugagagaa guccaccacg a 21

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<400> SEQUENCE: 520

auugagagaa guccaccacg a 21

<210> SEQ ID NO 521
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<400> SEQUENCE: 521

auugagagaa guccaccacg a 21

<210> SEQ ID NO 522
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 522

auugagagaa guccaccacg a 21

<210> SEQ ID NO 523
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 523

auugagagaa guccaccacg agu 23

<210> SEQ ID NO 524
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 524

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<400> SEQUENCE: 525

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 526
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<400> SEQUENCE: 526

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 527
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 527

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 528
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
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<400> SEQUENCE: 528

aggugaagcg aagugcacat t 21

<210> SEQ ID NO 529
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 529

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 530
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 530

aggugaagcg aagugcacac g 21

<210> SEQ ID NO 531
<211> LENGTH: 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 531

auugagagaa guccaccacg agu 23

<210> SEQ ID NO 532
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<400> SEQUENCE: 532

ugaagcgaag ugcacacggt t 21

<210> SEQ ID NO 533
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<212> TYPE: DNA
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agataaaacg ccgcagac 18

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ugaagcgaag ugcacacggu c 21

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<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: a, c, u, g, unknown or other

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<210> SEQ ID NO 595
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 595

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<210> SEQ ID NO 596

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<211> LENGTH: 3215
<212> TYPE: DNA
<213> ORGANISM: Hepatitis B virus

<400> SEQUENCE: 596

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aggacccctg ctcgtgttac aggcggggtt tttcttgttg acaagaatcc tcacaatacc 240

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1. A short interfering nucleic acid (siNA) molecule comprising:

(a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence:

(i) is 15 to 30 nucleotides in length; and

(ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, 17, and/or 19 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide or wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and

(b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence:

(iii) is 15 to 30 nucleotides in length; and

(iv) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide or wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; or

(b) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence:

(i) is 15 to 30 nucleotides in length; and

(ii) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and at least one modified nucleotide is a 2'-fluoro nucleotide; and

an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence:

(iii) is 15 to 30 nucleotides in length; and

(iv) comprises 15 or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide, wherein at least one modified nucleotide is a 2'-O-methyl nucleotide and the nucleotide at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

2. (canceled)

3. The siNA of claim **1**, wherein the first nucleotide sequence comprises 16, 17, 18, 19, 20, 21, 22, 23, or more modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

4. The siNA of claim **1**, wherein 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the first nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

5. The siNA of claim **1**, wherein:

(i) at least 2, 3, 4, 5, or 6 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides;

(ii) no more than 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-fluoro nucleotides;

(iii) at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides; and/or

(iv) no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the first nucleotide sequence are 2'-O-methyl nucleotides.

6. The siRNA of claim **1**, wherein the second nucleotide sequence comprises 16, 17, 18, 19, 20, 21, 22, 23, or more

modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

7. The siNA of claim **1**, wherein 70%, 75%, 80%, 85%, 90%, 95% or 100% of the nucleotides in the second nucleotide sequence are modified nucleotides independently selected from a 2'-O-methyl nucleotide and a 2'-fluoro nucleotide.

8. The siNA of claim **1**, wherein:

(i) at least 2, 3, 4, 5, or 6 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides;

(ii) less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-fluoro nucleotides;

(iii) at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides; and/or

(iv) less than or equal to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 modified nucleotides of the second nucleotide sequence are 2'-O-methyl nucleotides.

9. The siNA of claim **1** further comprising 1 or more phosphorothioate internucleoside linkage in the sense strand and/or antisense strand.

10. The siNA of claim **1** further comprising a phosphorylation blocker, a galactosamine, or 5'-stabilized end cap.

11. The siNA of claim **1**, wherein at least 1, 2, 3, 4, 5, 6, or 7 nucleotides at position 3, 5, 7, 8, 9, 10, 11, 12, and/or 17 from the 5' end of the first nucleotide sequence is a 2'-fluoro nucleotide.

12. The siNA of claim **1**, wherein at least 1, 2, 3, 4, 5, 6, 7, 8, or 9 nucleotides at position 2, 5, 6, 8, 10, 14, 16, 17, and/or 18 from the 5' end of the second nucleotide sequence is a 2'-fluoro nucleotide.

13. The siNA of claim **1**, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides.

14. The siNA of claim **13**, wherein the alternating 1:3 modification pattern occurs 2-5 times.

15. The siNA according to claim **13**, wherein:

(i) at least two of the alternating 1:3 modification pattern occur consecutively;

(ii) at least two of the alternating 1:3 modification pattern occurs nonconsecutively; and/or

(iii) at least 1, 2, 3, 4, or 5 alternating 1:3 modification pattern begins at nucleotide position 2, 6, 10, 14, and/or 18 from the 5' end of the antisense strand.

16. The siNA of claim **1**, wherein:

(i) the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, and

(ii) 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides.

17. The siNA of claim **16**, wherein the alternating 1:2 modification pattern occurs 2-5 times.

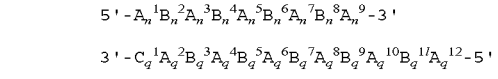
18. The siNA according to claim **16**, wherein:

(i) at least two of the alternating 1:2 modification pattern occurs consecutively;

(ii) at least two of the alternating 1:2 modification pattern occurs nonconsecutively; and/or

(iii) at least 1, 2, 3, 4, or 5 alternating 1:2 modification pattern begins at nucleotide position 2, 5, 8, 14, and/or 17 from the 5' end of the antisense strand.

19. A short interfering nucleic acid (siNA) molecule represented by Formula (VIII):



wherein:

the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5'-stabilized end cap or a phosphorylation blocker;

B is a 2'-fluoro nucleotide;

C represents overhanging nucleotides and is a 2'-O-methyl nucleotide;

n^1=1-4 nucleotides in length;

each n^2, n^6, n^8, q^3, q^5, q^7, q^9, q^{11}, and q^{12} is independently 0-1 nucleotides in length;

each n^3 and n^4 is independently 1-3 nucleotides in length;

n^5 is 1-10 nucleotides in length;

n^7 is 0-4 nucleotides in length;

each n^9, q^1, and q^2 is independently 0-2 nucleotides in length;

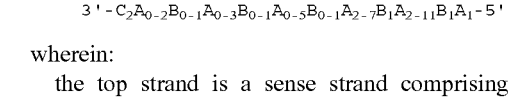
q^4 is 0-3 nucleotides in length;

q^6 is 0-5 nucleotides in length;

q^8 is 2-7 nucleotides in length; and

q^{10} is 2-11 nucleotides in length.

20. A short interfering nucleic acid (siNA) molecule represented by Formula (IX):



wherein:

the top strand is a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises 15 to 30 nucleotides;

the bottom strand is an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises 15 to 30 nucleotides;

each A is independently a 2'-O-methyl nucleotide or a nucleotide comprising a 5'-stabilized end cap or a phosphorylation blocker;

B is a 2'-fluoro nucleotide;

C represents overhanging nucleotides and is a 2'-O-methyl nucleotide.

21. A short interfering nucleic acid (siNA) molecule comprising:

(a) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12, and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, and 13-16 from the 5' end of the first nucleotide sequence, and

an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end of the second nucleotide sequence

(b) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7, 8, and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, and 9-16 from the 5' end of the first nucleotide sequence, and

an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the first nucleotide sequence; and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end of the first nucleotide sequence;

(c) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 3, 7-9, 12 and 17 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 2, 4-6, 10, 11, and 13-16 from the 5' end of the first nucleotide sequence, and

an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides;

(d) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence, and an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:3 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 3 nucleotides are 2'-O-methyl nucleotides;

(e) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence, and an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein the nucleotides in the second nucleotide sequence are arranged in an alternating 1:2 modification pattern, and wherein 1 nucleotide is a 2'-fluoro nucleotide and 2 nucleotides are 2'-O-methyl nucleotides;

(f) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5 and 7-9 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6, and 10-17 from the 5' end of the first nucleotide sequence, and an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2, 6, 14, and 16 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-5, 7-13, 15, and 17 from the 5' end the second nucleotide sequence; or

(g) a sense strand comprising a first nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 5, 9-11, and 14 from the 5' end of the first nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1-4, 6-8, and 12-17 from the 5' end of the first nucleotide sequence, and

an antisense strand comprising a second nucleotide sequence consisting of 17 to 23 nucleotides, wherein 2'-fluoro nucleotides are at positions 2 and 14 from the 5' end of the second nucleotide sequence, and wherein 2'-O-methyl nucleotides are at positions 1, 3-13, and 15-17 from the 5' end the second nucleotide sequence.

22-58. (canceled)

59. The siNA of claim **1**, wherein the sense strand further comprises TT sequence adjacent to the first nucleotide sequence.

60. The siNA of claim **1**, wherein the sense strand further comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate internucleoside linkages.

61. The siNA of claim **60**, wherein:

(i) at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the first nucleotide sequence;

(ii) at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the first nucleotide sequence.

62. The siNA of claim **1**, wherein the antisense strand further comprises TT sequence adjacent to the second nucleotide sequence.

63. The siNA of claim **1**, wherein the antisense strand further comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more phosphorothioate internucleoside linkages.

64. The siNA of claim **63**, wherein:

(i) at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 5' end of the second nucleotide sequence;

(ii) at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 5' end of the second nucleotide sequence;

(iii) at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 1 and 2 from the 3' end of the second nucleotide sequence; and/or

(iv) at least one phosphorothioate internucleoside linkage is between the nucleotides at positions 2 and 3 from the 3' end of the second nucleotide sequence.

65. The siNA of claim **1**, wherein:

(i) the first nucleotide from the 5' end of the first nucleotide sequence comprises a 5' stabilizing end cap;

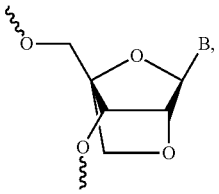
(ii) the first nucleotide from the 5' end of the second nucleotide sequence comprises a 5' stabilizing end cap;

(iii) the first nucleotide from the 5' end of the first nucleotide sequence comprises a phosphorylation blocker; and/or

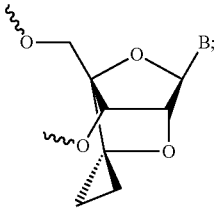
(iv) the first nucleotide from the 5' end of the second nucleotide sequence comprises a phosphorylation blocker.

66. The siNA of claim **1**, wherein the first nucleotide sequence or second nucleotide sequence comprises at least one modified nucleotide selected from

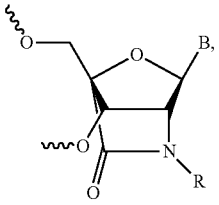
(LNA)



(ScpBNA or "cp")

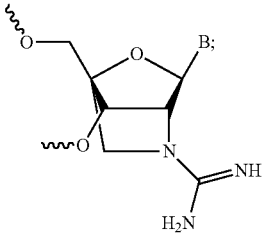


(AmNA)



where R is H or alkyl (or AmNA(N-Me)) when R is alkyl);

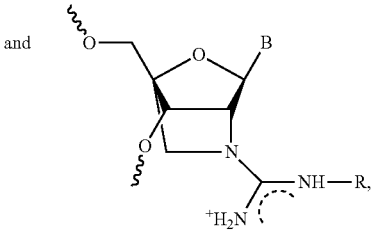
(GuNA)



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GuNA(N-R), R = Me, Et, iPr, tBu

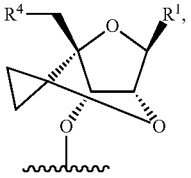
and



wherein B is a nucleobase.

67. A short-interfering nucleic acid (siNA) molecule comprising:

a. a phosphorylation blocker of Formula (IV):



wherein

R^1 is a nucleobase,

R^4 is —O—R^{30} or —$NR^{31}R^{32}$,

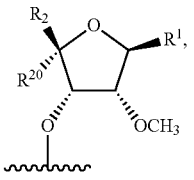
R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and

R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring; and

b. a short interfering nucleic acid (siNA).

68. A short-interfering nucleic acid (siNA) molecule comprising:

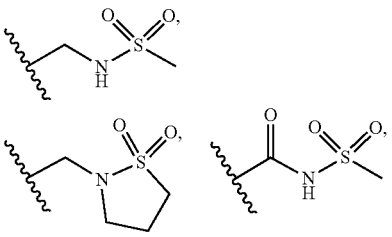
c. a 5'-stabilized end cap of Formula (Ia):



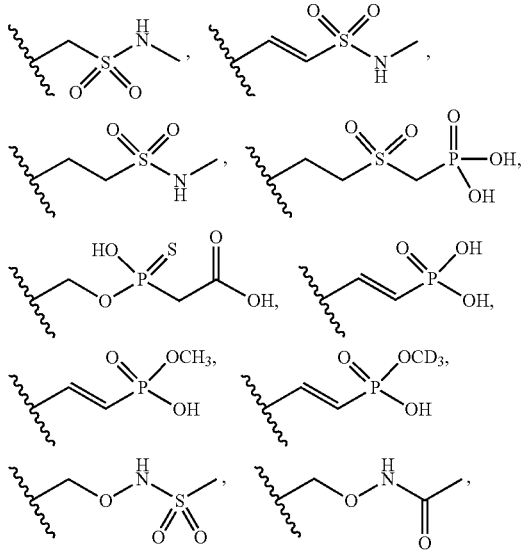
wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is



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—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl; R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

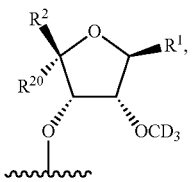
R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4; and

d. a short interfering nucleic acid (siNA).

69. A short-interfering nucleic acid (siNA) molecule comprising:

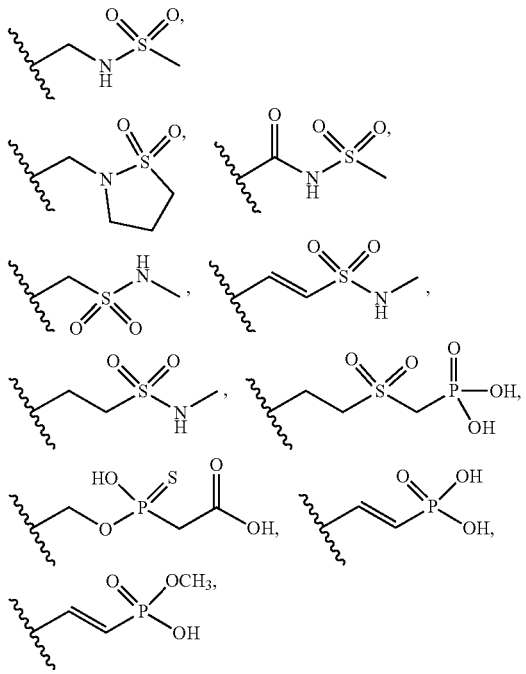
e. a 5'-stabilized end cap of Formula (Ib):



wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6 alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, R^{21} and R^{22} are independently hydrogen or C_1-C_6 alkyl; R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

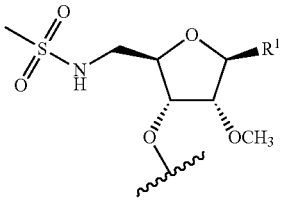
m is 1, 2, 3, or 4; and

f. a short interfering nucleic acid (siNA).

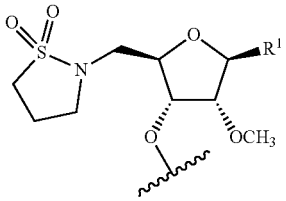
70. A short-interfering nucleic acid (siNA) molecule comprising:

g. a 5'-stabilized end cap selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

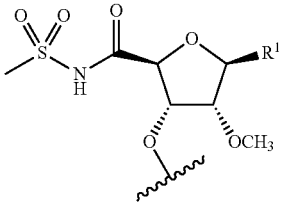
Formula (1)



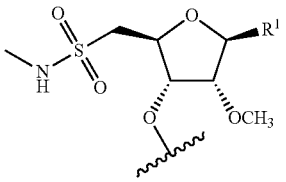
Formula (2)



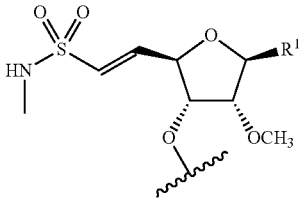
Formula (3)



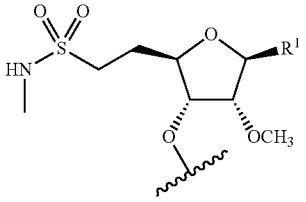
Formula (4)



Formula (5)

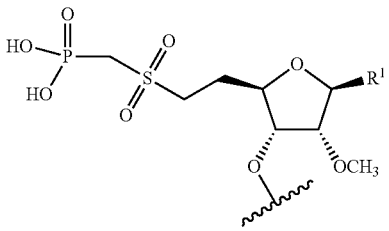


Formula (6)

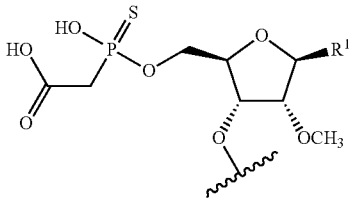


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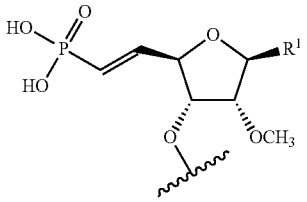
Formula (7)



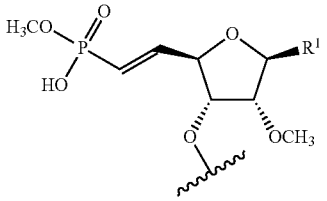
Formula (8)



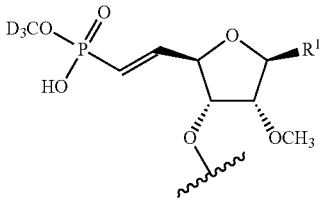
Formula (9)



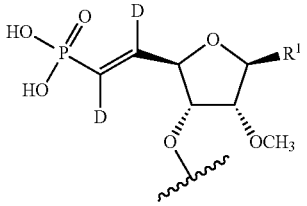
Formula (9X)



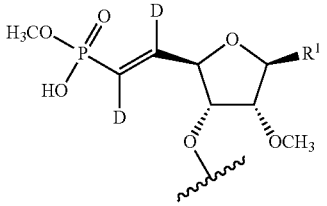
Formula (9Y)



Formula (10)

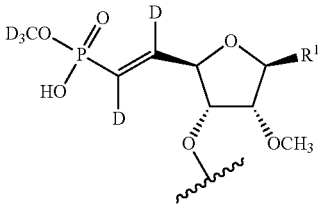


Formula (10X)

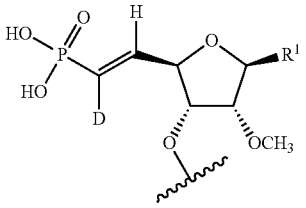


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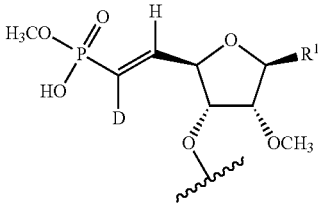
Formula (10Y)



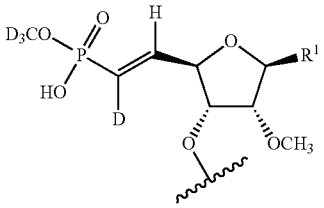
Formula (11)



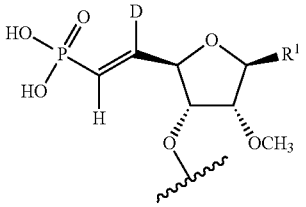
Formula (11X)



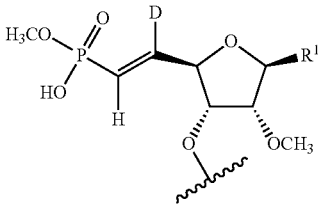
Formula (11Y)



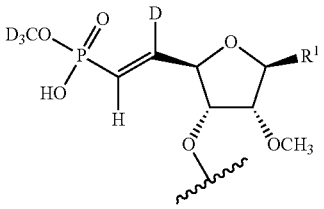
Formula (12)



Formula (12X)

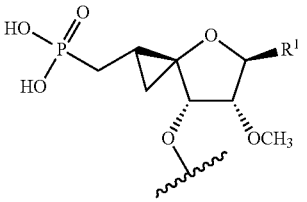


Formula (12Y)

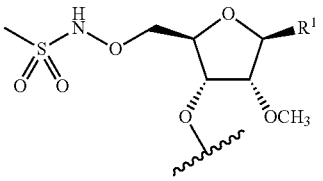


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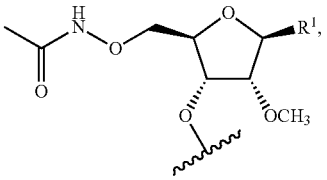
Formula (13)



Formula (14)



Formula (15)



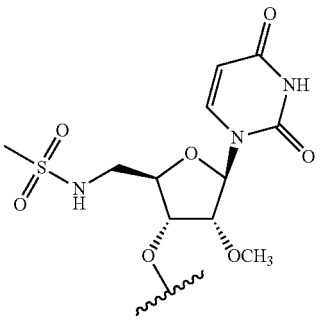
wherein R^1 is a nucleobase, aryl, heteroaryl, or H; and

h. a short interfering nucleic acid (siNA).

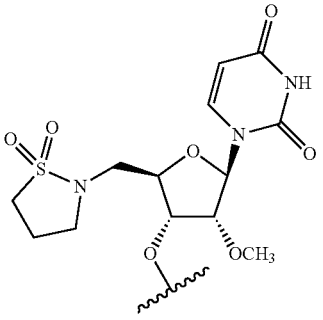
71. A short-interfering nucleic acid (siNA) molecule comprising:

i. a 5'-stabilized end cap selected from the group consisting of Formulas (1A)-(15A), Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

Formula (1A)

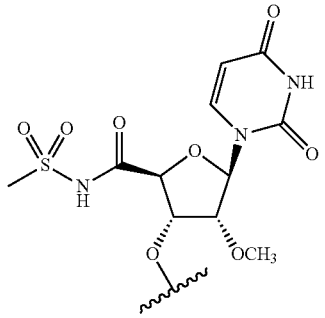


Formula (2A)

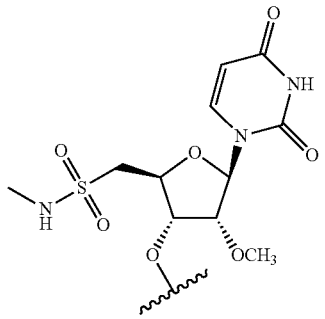


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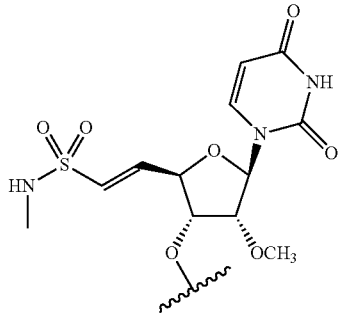
Formula (3A)



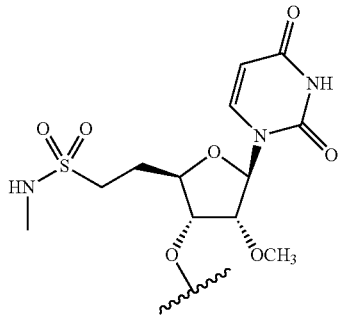
Formula (4A)



Formula (5A)

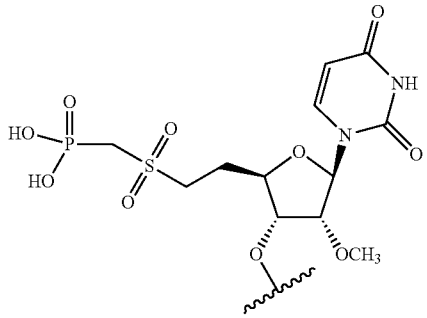


Formula (6A)

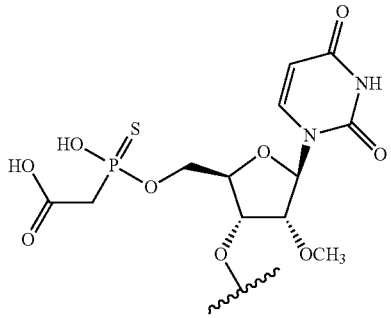


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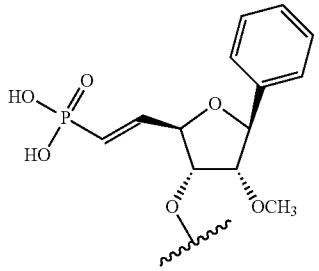
Formula (7A)



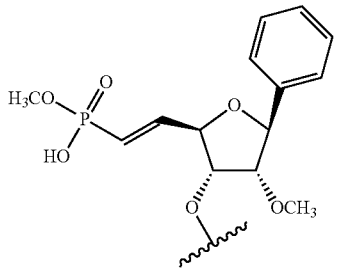
Formula (8A)



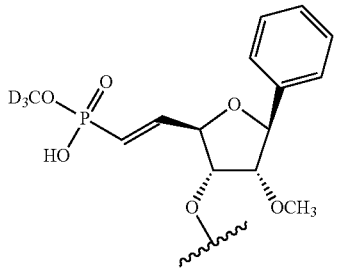
Formula (9A)



Formula (9AX)

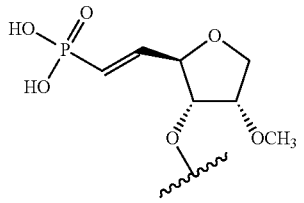


Formula (9AY)

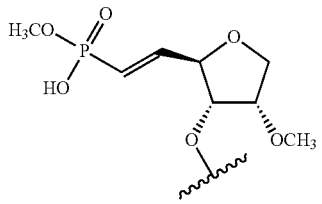


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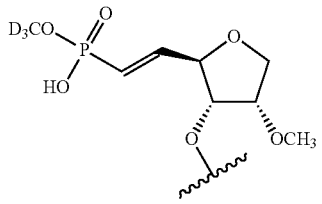
Formula (9BX)



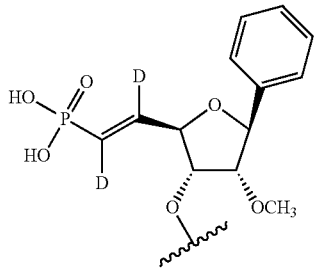
Formula (9BX)



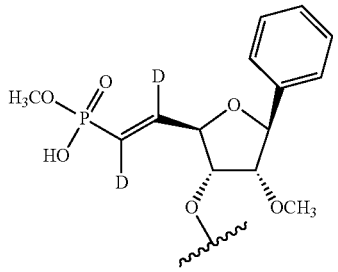
Formula (9BY)



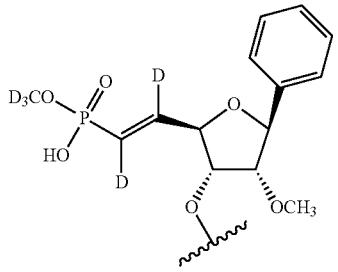
Formula (10A)



Formula (10AX)

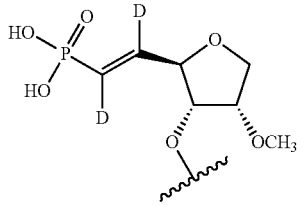


Formula (10AY)

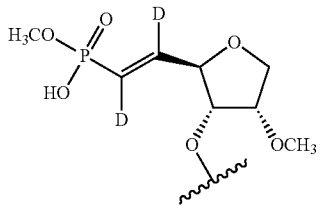


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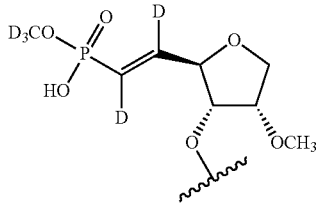
Formula (10B)



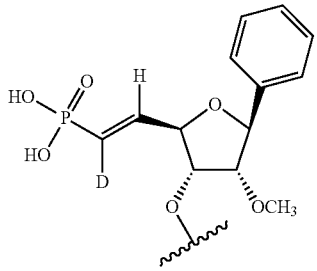
Formula (10BX)



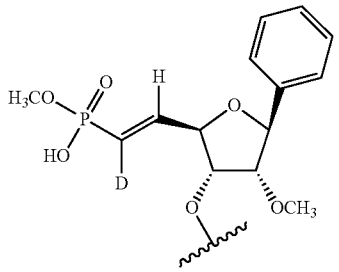
Formula (10BY)



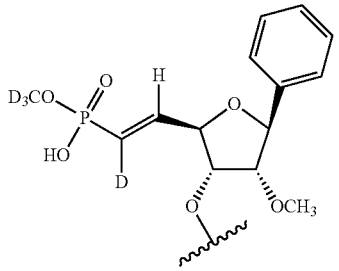
Formula (11A)



Formula (11AX)

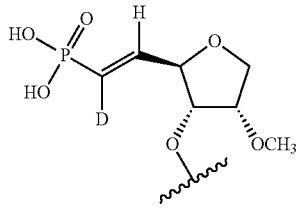


Formula (11AY)

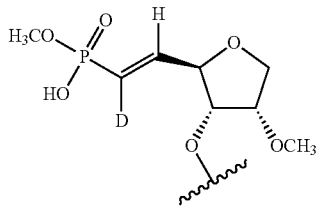


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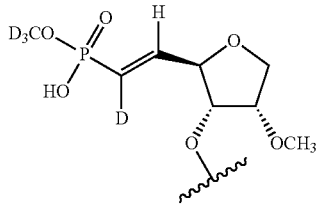
Formula (11B)



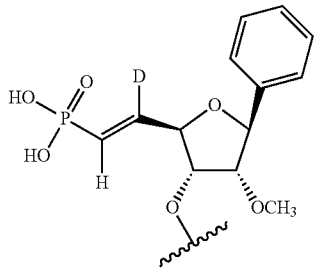
Formula (11BX)



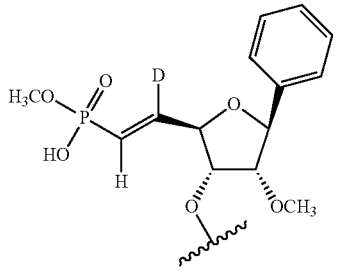
Formula (11BY)



Formula (12A)

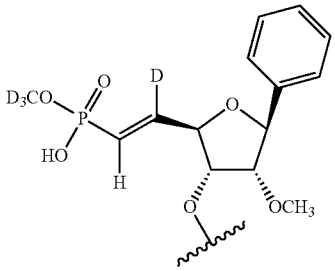


Formula (12AX)

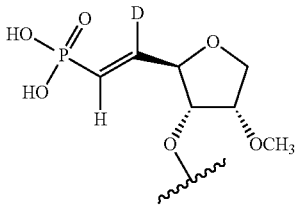


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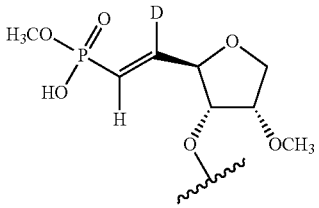
Formula (12AY)



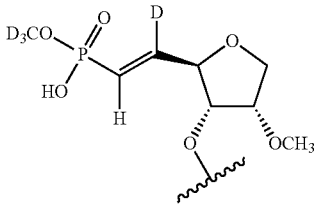
Formula (12B)



Formula (12BX)

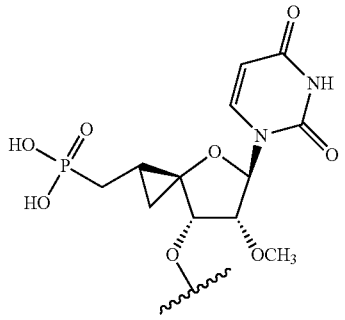


Formula (12BY)

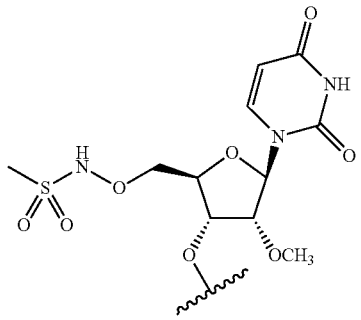


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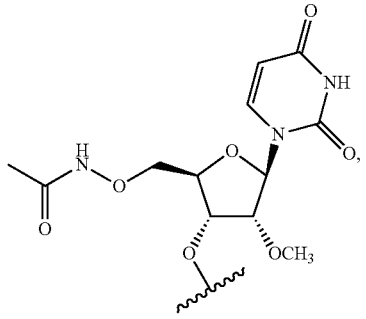
Formula (13A)



Formula (14A)



Formula (15A)



j. a short interfering nucleic acid (siNA).

72-73. (canceled)

74. A short interfering nucleic acid (siNA) molecule comprising:

(a) a sense strand comprising a first nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to an RNA corresponding to a target gene, wherein the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260; and

(b) an antisense strand comprising a second nucleotide sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to the RNA corresponding to the target gene, wherein the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306.

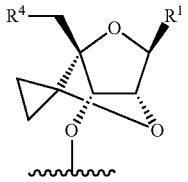
75. A interfering nucleic acid (siNA) molecule comprising:

(a) a sense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444; and

(b) an antisense strand comprising a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

76. (canceled)

77. The siNA according to claim **10**, wherein the phosphorylation blocker has the structure of Formula (IV):



wherein

R^1 is a nucleobase,

R^4 is —O—R^{30} or —$NR^{31}R^{32}$, R^{30} is C_1-C_8 substituted or unsubstituted alkyl; and

R^{31} and R^{32} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring.

78. The siNA of claim **67**, wherein R^4 is —OCH_3 or —$N(CH_2CH_2)_2O$.

79. The siNA according to claim **10**, wherein: (i) the phosphorylation blocker is attached to the 5' end of the sense strand; (ii) the phosphorylation blocker is attached to the 3' end of the sense strand; (iii) the phosphorylation blocker is attached to the 5' end of the antisense strand; or (iv) the phosphorylation blocker is attached to the 3' end of the antisense strand.

80. The siNA of claim **78**, wherein:

(i) the phosphorylation blocker is attached to the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker;

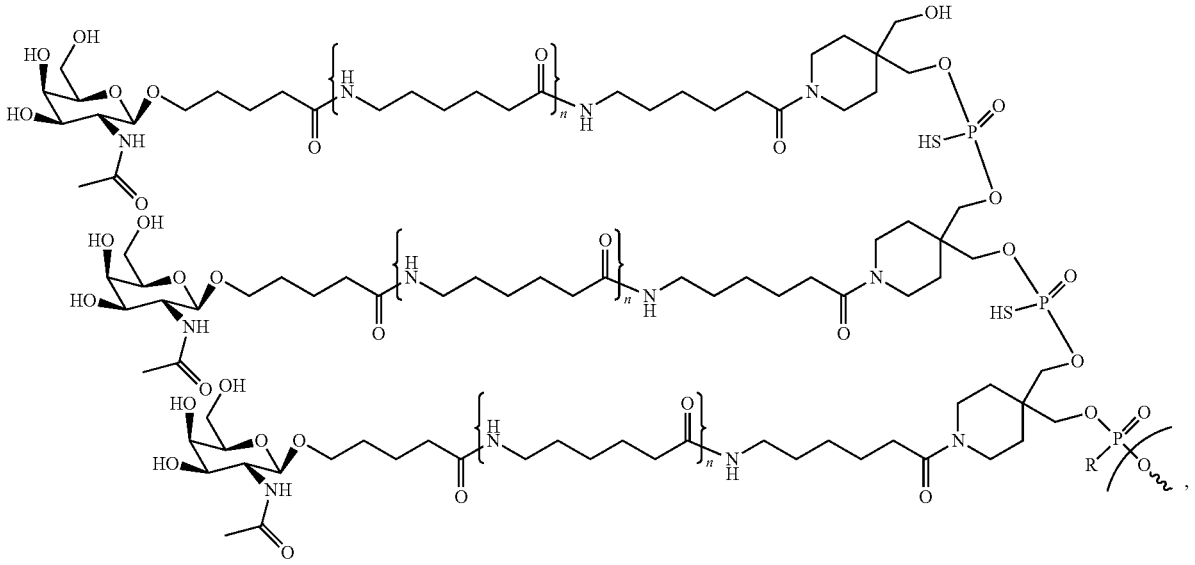
(ii) the phosphorylation blocker is attached to the 3' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker;

(iii) the phosphorylation blocker is attached to the 5' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker; or

(iv) the phosphorylation blocker is attached to the 3' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, and phosphorodithioate linker.

81. The siNA of claim **1**, wherein the siNA further comprises a galactosamine.

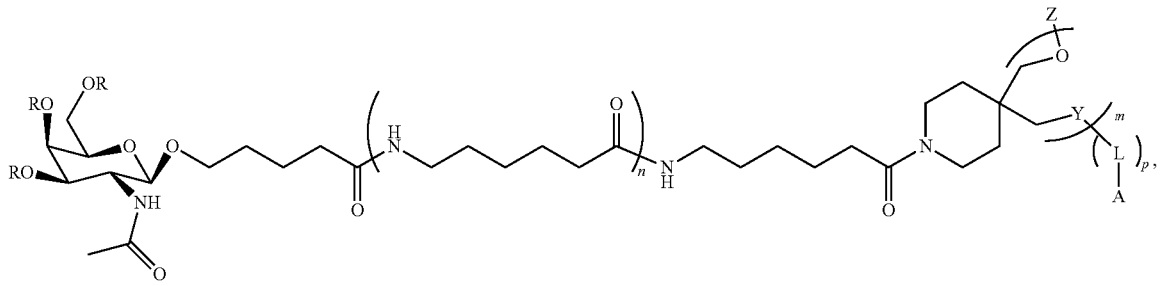
82. The siNA of claim **81**, wherein the galactosamine is N-acetylgalactosamine (GalNAc) of Formula (VII):



R = OH or SH

wherein each n is independently 1 or 2.

83. The siNA of claim **81**, wherein the galactosamine is N-acetylgalactosamine (GalNAc) of Formula (VI):



wherein

m is 1, 2, 3, 4, or 5;

each n is independently 1 or 2;

p is 0 or 1;

each R is independently H;

each Y is independently selected from —O—P(═O)(SH)—, —O—P(═O)(O)—, —O—P(═O)(OH)—, and —O—P(S)S—;

Z is H or a second protecting group;

either L is a linker or L and Y in combination are a linker; and

A is H, OH, a third protecting group, an activated group, or an oligonucleotide.

84. The siNA of claim **83**, wherein: (i) A is an oligonucleotide;

or (ii) A is 1-2 oligonucleotides.

85. The siNA of any one of claim **84**, wherein the oligonucleotide is dTdT.

86. The siNA according to claim **84**, wherein the galactosamine is attached to (i) the 3' end of the sense strand; (ii) the 5' end of the sense strand; (iii) the 3' end of the antisense strand; or (iv) the 5' end of the antisense strand.

87. The siNA of claim **86**, wherein the galactosamine is attached to:

(i) the 3' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker;

(ii) the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker;

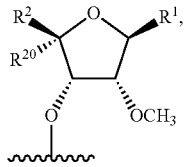
(iii) the 3' end of the atnisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker; or

(iv) the 5' end of the atnisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

88. The siNA according to claim **1**, wherein the siNA further comprises a 5'-stabilized end cap.

89. The siNA according to claim **88**, wherein the 5'-stabilized end cap is a 5' vinyl phosphonate or deuterated 5' vinyl phosphonate.

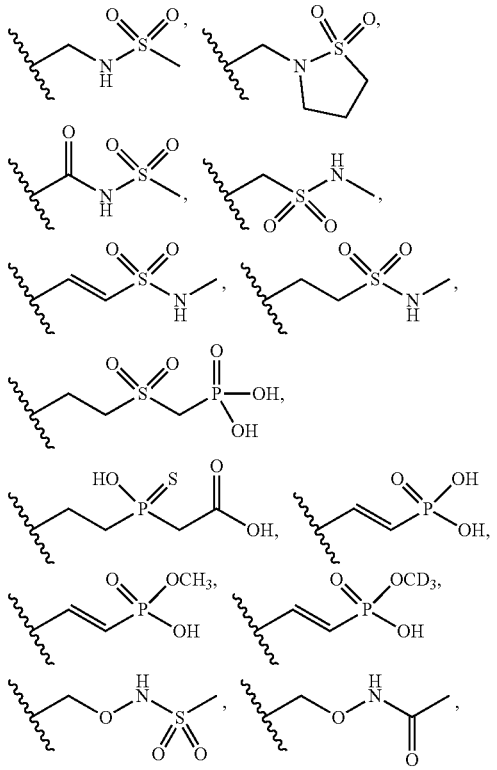
90. The siNA according to claim **88**, wherein the 5'-stabilized end cap has the structure of Formula (Ia):



wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —P(O)(OH)($OCH_3$), —P(O)(OH)($OCD_3$), —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$;

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

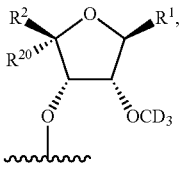
R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

m is 1, 2, 3, or 4.

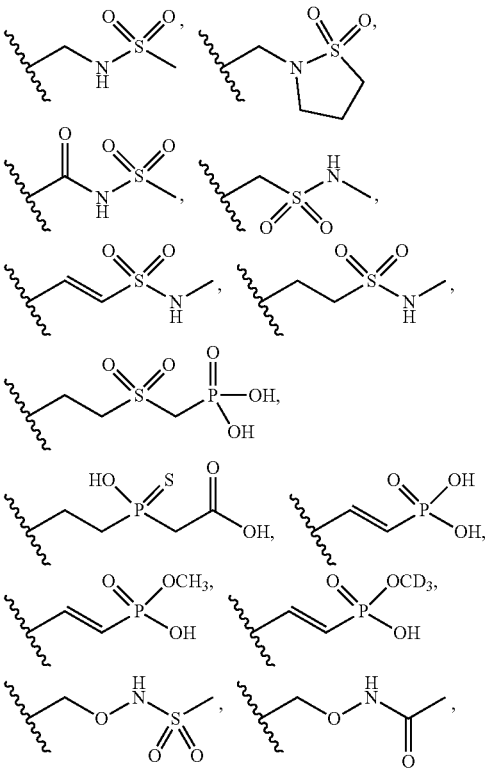
91. The siNA according to claim **88**, wherein the 5'-stabilized end cap has the structure of Formula (Ib):



wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$;

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

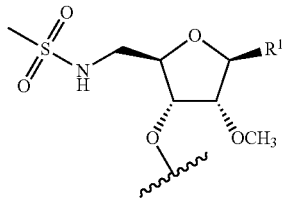
m is 1, 2, 3, or 4.

92. The siNA of claim **90**, wherein R^1 is an aryl.

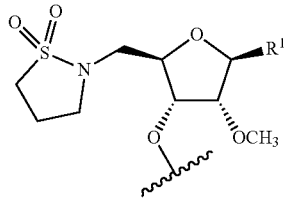
93. The siNA of claim **92**, wherein the aryl is a phenyl.

94. The siNA according to claim **88**, wherein the 5'-stabilized end cap is selected from the group consisting of Formula (1) to Formula (15), Formula (9X) to Formula (12X), and Formula (9Y) to Formula (12Y):

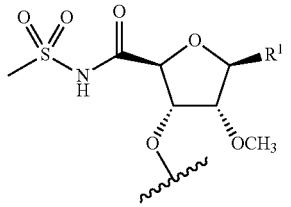
Formula (1)



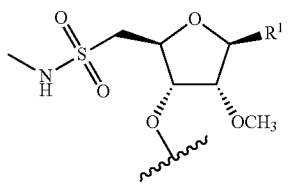
Formula (2)



Formula (3)

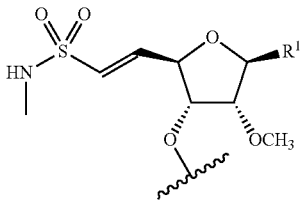


Formula (4)

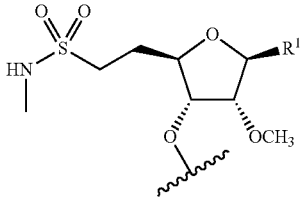


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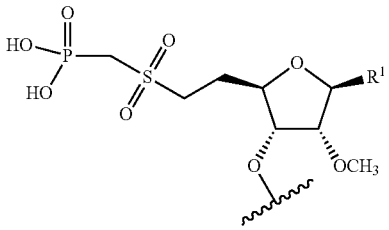
Formula (5)



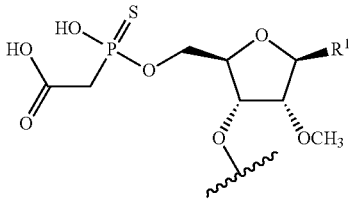
Formula (6)



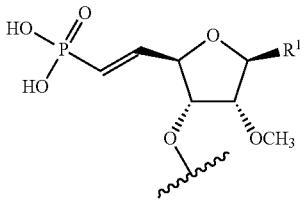
Formula (7)



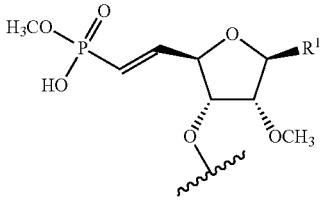
Formula (8)



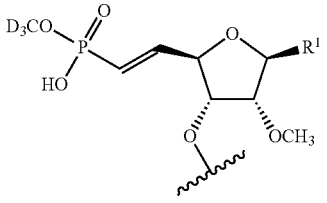
Formula (9)



Formula (9X)

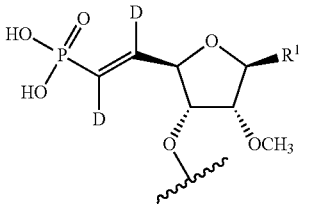


Formula (9Y)

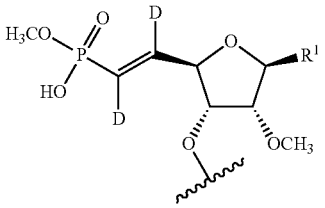


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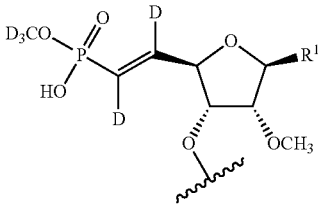
Formula (10)



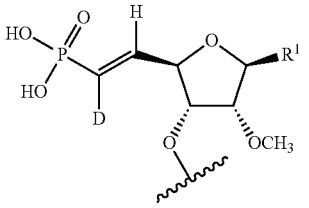
Formula (10X)



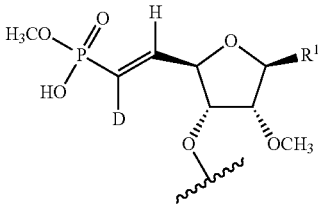
Formula (10Y)



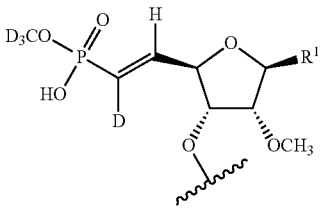
Formula (11)



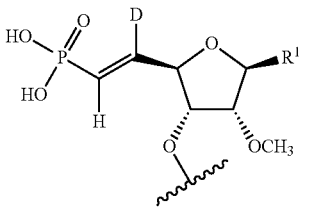
Formula (11X)



Formula (11Y)

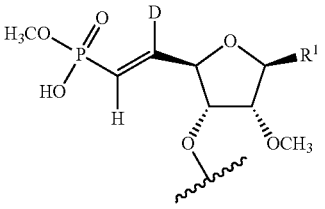


Formula (12)

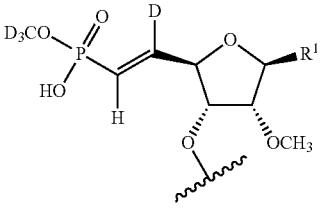


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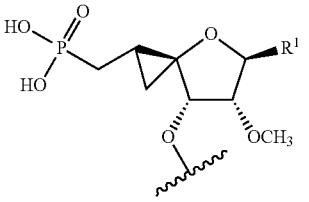
Formula (12X)



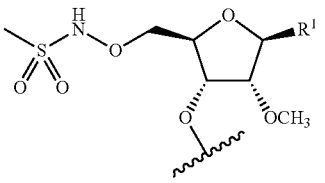
Formula (12Y)



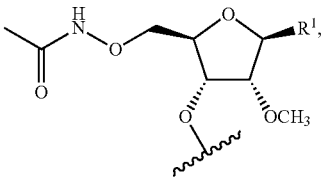
Formula (13)



Formula (14)



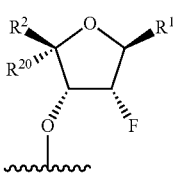
Formula (15)



wherein R^1 is a nucleobase, aryl, heteroaryl, or H.

95. The siNA according to claim **88**, wherein the 5'-stabilized end cap is selected from the group consisting of Formulas (IA)-(15A), Formulas (9B)-(12B), Formulas (9AX)-(12AX), Formulas (9AY)-(12AY), Formulas (9BX)-(12BX), and Formulas (9BY)-(12BY):

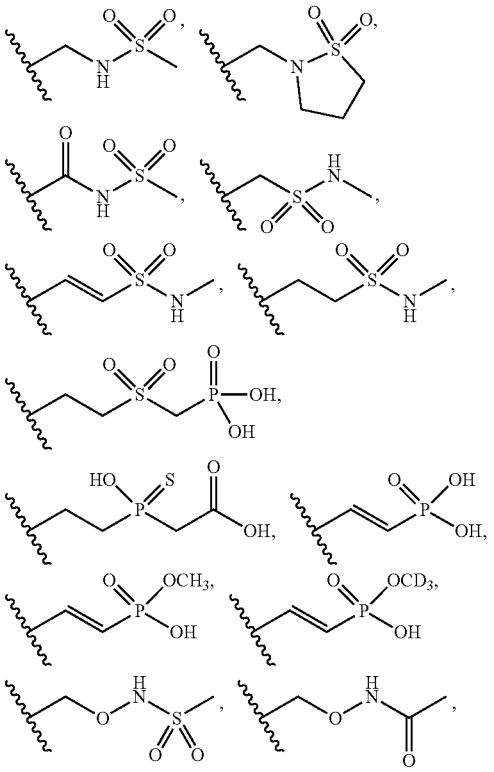
96. The siNA according to claim **88**, wherein the 5'-stabilized end cap has the structure of Formula (Ic):



wherein

R^1 is a nucleobase, aryl, heteroaryl, or H,

R^2 is



—CH═CD-Z,-CD═CH—Z,-CD═CD-Z, —$(CR^{21}R^{22})_n$—Z, or —(C_2-C_6alkenylene)-Z and R^{20} is hydrogen; or

R^2 and R^{20} together form a 3- to 7-membered carbocyclic ring substituted with —$(CR^{21}R^{22})_n$—Z or —(C_2-C_6 alkenylene)-Z;

n is 1, 2, 3, or 4;

Z is —$ONR^{23}R^{24}$, —$OP(O)OH(CH_2)_mCO_2R^{23}$, —$OP(S)OH(CH_2)_mCO_2R^{23}$, —$P(O)(OH)_2$, —$P(O)(OH)(OCH_3)$, —$P(O)(OH)(OCD_3)$, —$SO_2(CH_2)_mP(O)(OH)_2$, —$SO_2NR^{23}R^{25}$, —$NR^{23}R^{24}$, or —$NR^{23}SO_2R^{24}$;

R^{21} and R^{22} either are independently hydrogen or C_1-C_6 alkyl, or R^{21} and R^{22} together form an oxo group;

R^{23} is hydrogen or C_1-C_6 alkyl;

R^{24} is —SO_2R^{25} or —$C(O)R^{25}$; or

R^{23} and R^{24} together with the nitrogen to which they are attached form a substituted or unsubstituted heterocyclic ring;

R^{25} is C_1-C_6 alkyl; and

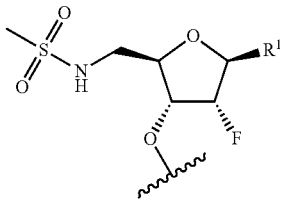
m is 1, 2, 3, or 4.

97. The siNA of claim **96**, wherein R^1 is an aryl.

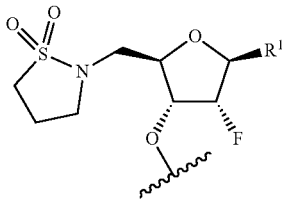
98. The siNA of claim **97**, wherein the aryl is a phenyl.

99. The siNA according to claim **88**, wherein the 5'-stabilized end cap is selected from the group consisting of Formula (21) to Formula (35):

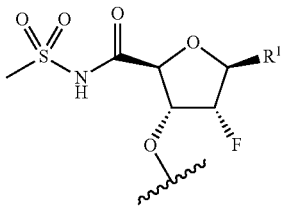
Formula (21)



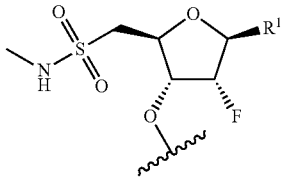
Formula (22)



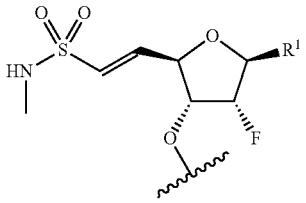
Formula (23)



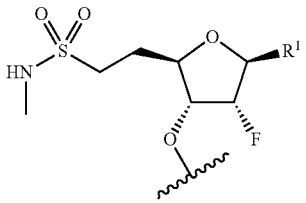
Formula (24)



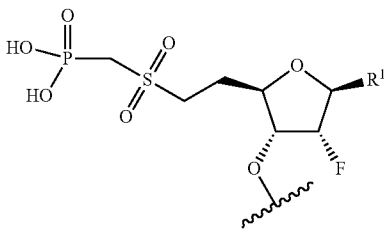
Formula (25)



Formula (26)

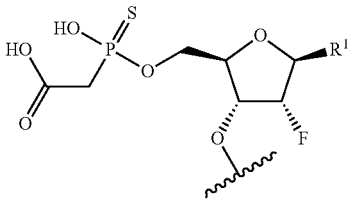


Formula (27)

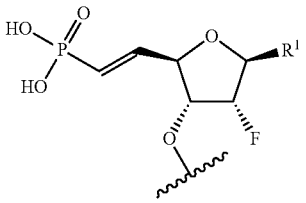


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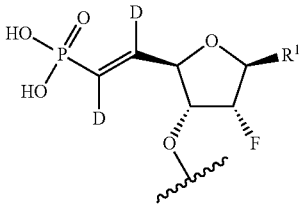
Formula (28)



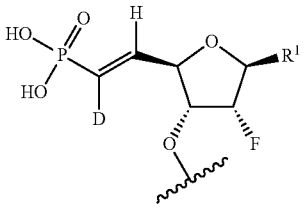
Formula (29)



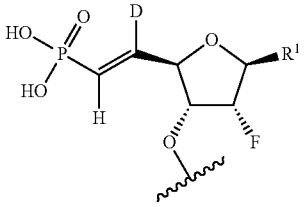
Formula (30)



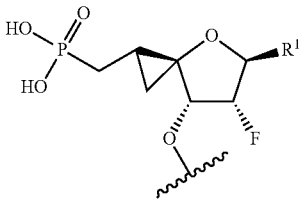
Formula (31)



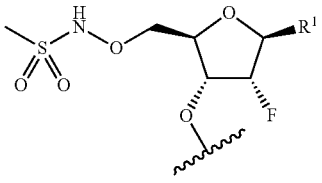
Formula (32)



Formula (33)

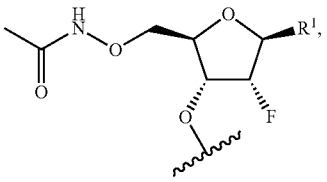


Formula (34)



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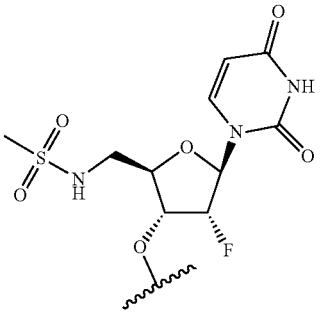
Formula (35)



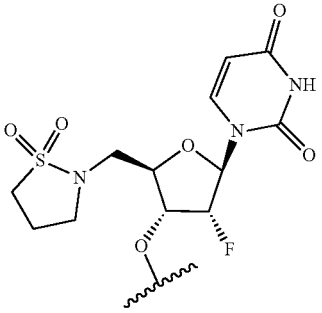
wherein R^1 is a nucleobase, aryl, heteroaryl, or H.

100. The siNA according to claim **88**, wherein the 5'-stabilized end cap is selected from the group consisting of Formulas (21A)-(35A), Formulas (29B)-(32B), Formulas (29AX)-(32AX), Formulas (29AY)-(32AY), Formulas (29BX)-(32BX), and Formulas (29BY)-(32BY):

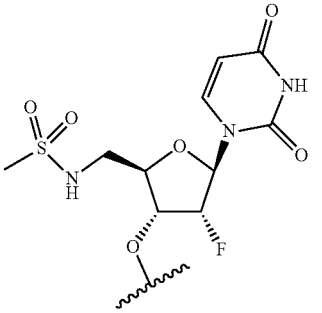
Formula (21A)



Formula (22A)

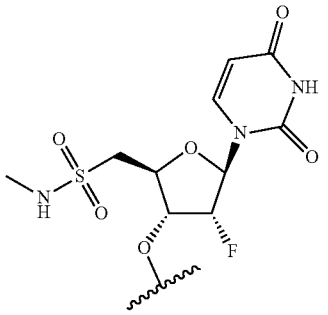


Formula (23A)

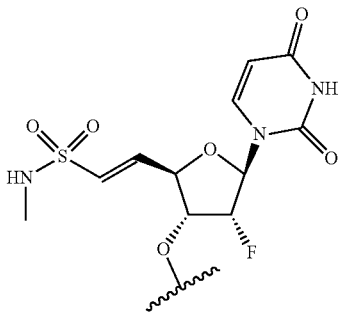


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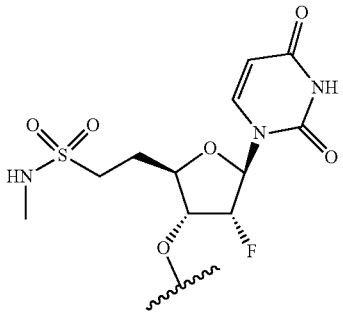
Formula (24A)



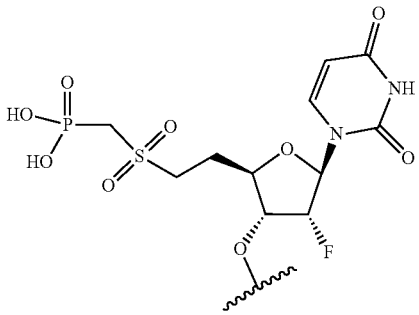
Formula (25A)



Formula (26A)

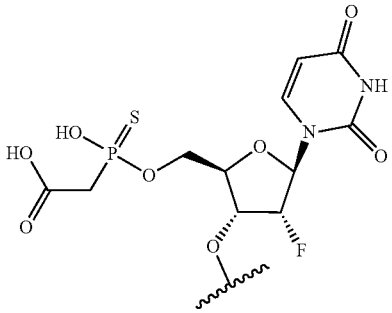


Formula (27A)

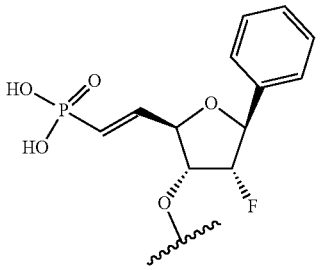


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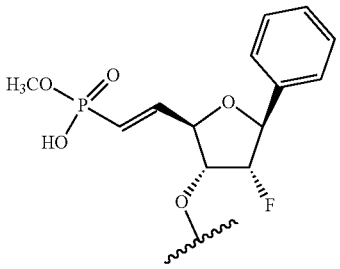
Formula (28A)



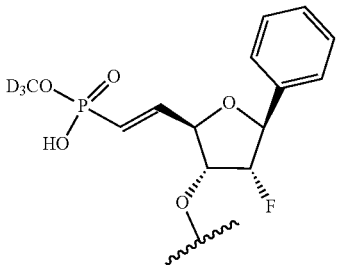
Formula (29A)



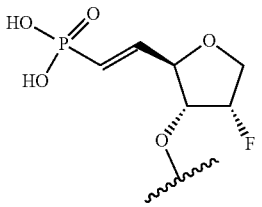
Formula (29AX)



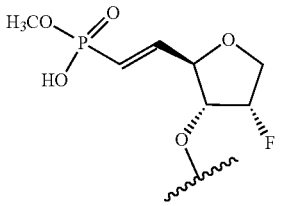
Formula (29AY)



Formula (29B)

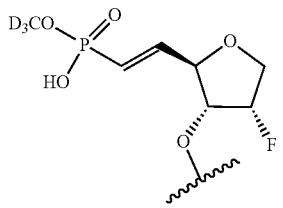


Formula (29BX)

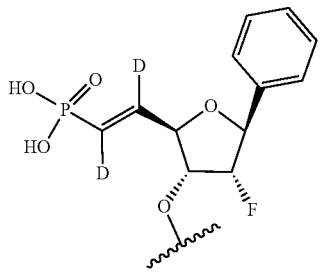


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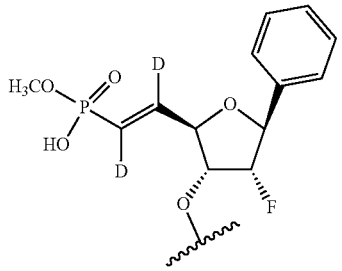
Formula (29BY)



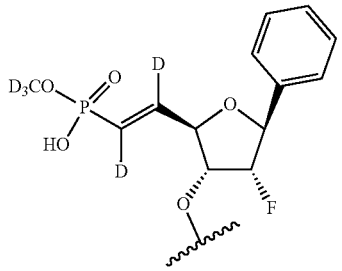
Formula (30A)



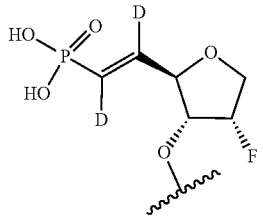
Formula (30AX)



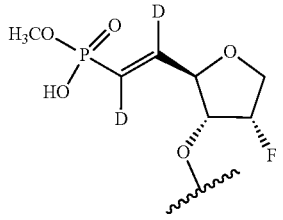
Formula (30AY)



Formula (30B)

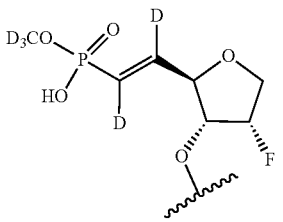


Formula (30BX)

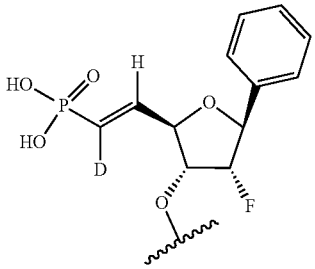


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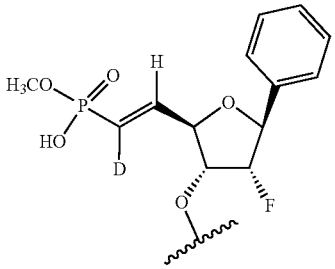
Formula (30BY)



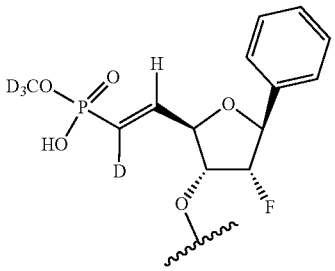
Formula (31A)



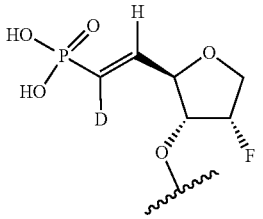
Formula (31AX)



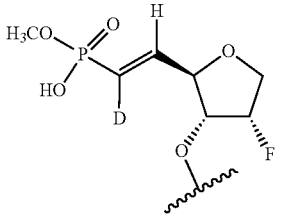
Formula (31AY)



Formula (31B)

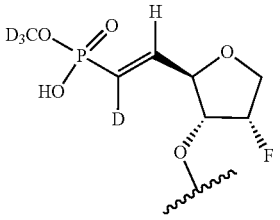


Formula (31BX)

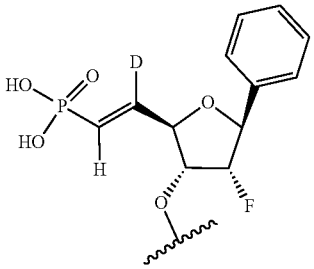


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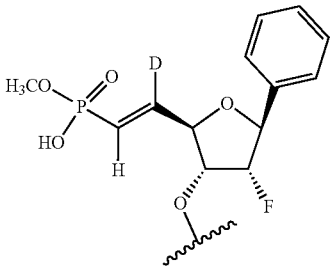
Formula (31BY)



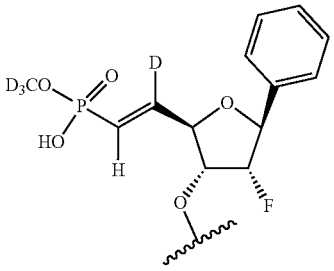
Formula (32A)



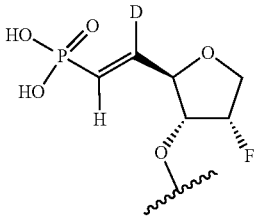
Formula (32AX)



Formula (32AY)

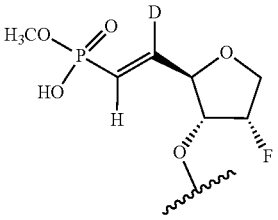


Formula (32B)

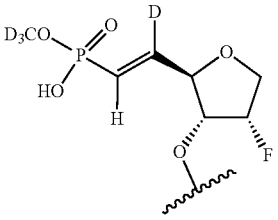


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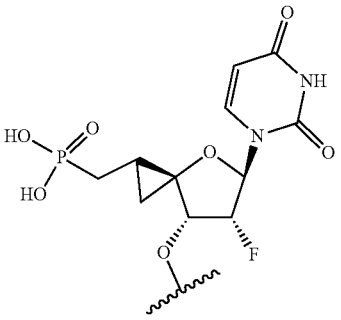
Formula (32BX)



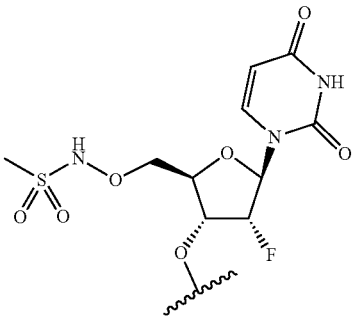
Formula (32BY)



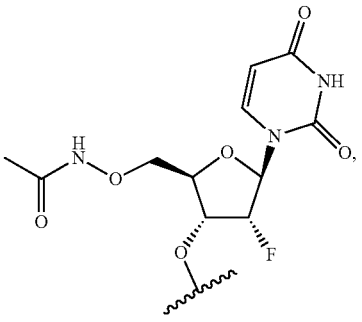
Formula (33A)



Formula (34A)

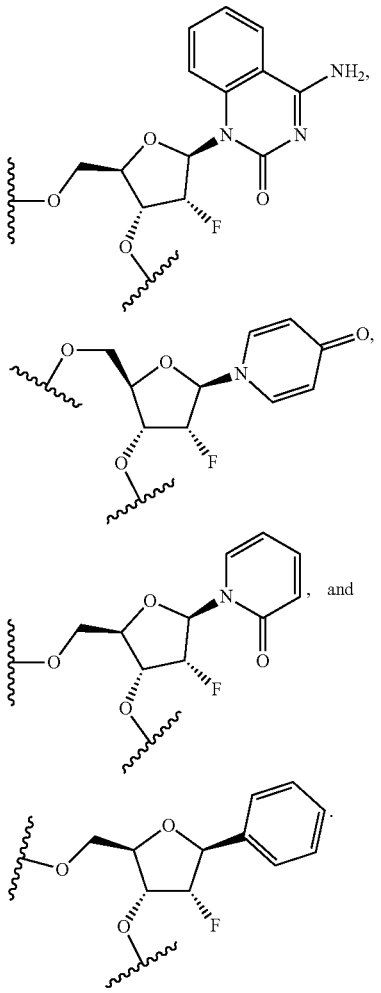


Formula (35A)



wherein R^1 is a nucleobase, aryl, heteroaryl, or H.

101. The siNA according to claim **1**, wherein the antisense strand and/or sense strand comprises at least one thermally destabilizing nucleotide selected from:



, and

102. The siNA according to claim **10**, wherein the 5'-stabilized end cap is attached to (i) the 5' end of the antisense strand; or (ii) the 5' end of the sense strand.

103. The siNA of claim **102**, wherein the 5'-stabilized end cap is attached to:

(i) the 5' end of the antisense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker; or

(ii) the 5' end of the sense strand via one or more linkers independently selected from a phosphodiester linker, phosphorothioate linker, or phosphorodithioate linker.

104. The siNA of claim **1**, wherein;

(i) the target gene is a viral gene;

(ii) the target gene is a gene is from a DNA virus;

(iii) the target gene is a gene from a double-stranded DNA (dsDNA) virus;

(iv) the target gene is a gene from a hepadnavirus;

(v) the target gene is a gene from a hepatitis B virus (HBV);

(vi) the target gene is a gene from a HBV of any one of genotypes A-J; or

(vii) the target gene is selected from the S gene or X gene of a HBV.

105. The siNA according to claim **1**, wherein:

(i) the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410;

(ii) the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410;

(iii) the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410;

(iv) the second nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% complementary to 15 to 30 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410;

(v) the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-720 or 1100-1700 of SEQ ID NO: 410;

(vi) the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-280, 300-445, 460-510, 650-720, 1170-1220, 1250-1300, or 1550-1630 of SEQ ID NO: 410;

(vii) the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides within positions 200-230, 250-280, 300-330, 370-400, 405-445, 460-500, 670-700, 1180-1210, 1260-1295, 1520-1550, or 1570-1610 of SEQ ID NO: 410; and/or

(viii) the first nucleotide sequence is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to 15 to 30 nucleotides starting at position 203, 206, 254, 305, 375, 409, 412, 415, 416, 419, 462, 466, 467, 674, 676, 1182, 1262, 1263, 1268, 1526, 1577, 1578, 1580, 1581, 1583, or 1584 of SEQ ID NO: 410.

106. The siNA of claim **1**, wherein:

(i) the first nucleotide sequence comprises a nucleotide sequence of any one SEQ ID NOs: 1-56, 103-158, and 205-260;

(ii) the second nucleotide sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 57-102, 159-204, and 261-306; (iii) the sense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 307-362 and 415-444; and/or

(iv) the antisense strand comprises a nucleotide sequence of any one of SEQ ID NOs: 363-409, 445-533, and 536-539.

107. The siNA of claim **1**, wherein:

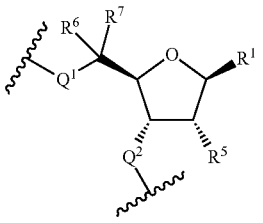
(i) at least one end of the siNA is a blunt end;

(ii) at least one end of the siNA comprises an overhang, wherein the overhang comprises at least one nucleotide; or

(iii) both ends of the siNA comprise an overhang, wherein the overhang comprises at least one nucleotide.

108. The siNA of claim **1**, wherein the siNA is selected from ds-siNA-001 to ds-siNA-0178.

109. The siNA of claim **1**, wherein at least one 2'-fluoro nucleotide or 2'-O-methyl nucleotide is a 2'-fluoro or 2-O-methyl nucleotide mimic of Formula (V):



wherein

R^1 is independently a nucleobase, aryl, heteroaryl, or H,

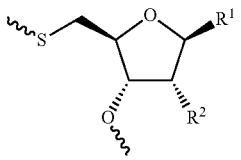
Q^1 and Q^2 are independently S or O,

R^5 is independently-OCD_3, —F, or —OCH_3, and

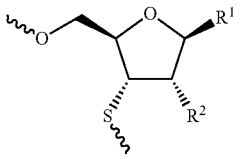
R^6 and R^7 are independently H, D, or CD_3.

110. The siNA of claim **109**, wherein the 2'-fluoro or 2'-O-methyl nucleotide mimic is a nucleotide mimic of Formula (16)-Formula (20):

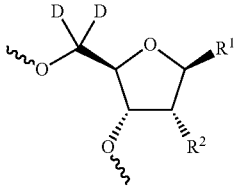
Formula (16)



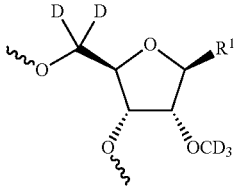
Formula (17)



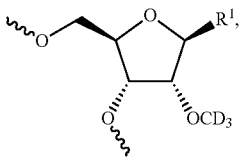
Formula (18)



Formula (19)



Formula (20)



wherein R^1 is a nucleobase and R^2 is independently F or —OCH_3.

111. The siNA of claim **1**, wherein at least one 2'-fluoro nucleotide is a 2'-fluoro nucleotide mimic.

112. The siNA according to claim **111**, wherein:

(i) at least 1, 2, 3, 4, 5, or more 2'-fluoro nucleotides on the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic;

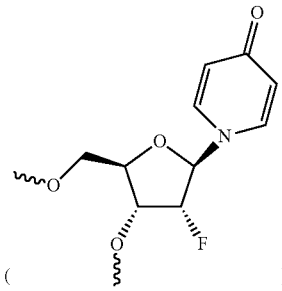
(ii) the nucleotide at position 2, 5, 6, 8, 10, 14, 16, and/or 17 from the 5' end of the antisense strand or the second nucleotide sequence is a 2'-fluoro nucleotide mimic;

(iii) at least 1, 2, 3, 4, 5, or more 2'-fluoro nucleotides on the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic; and/or

(iv) the nucleotide at position 3, 5, 7, 8, 9, 10, 11, 12, 14, and/or 17 from the 5' end of the sense strand or the first nucleotide sequence is a 2'-fluoro nucleotide mimic.

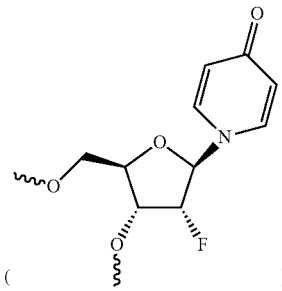
113. The siNA according to claim **111**, wherein:

(i) at least 1, 2, 3, 4, 5, 6, or more 2'-fluoro nucleotide mimics is a f4P nucleotide



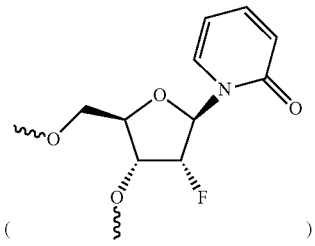
( );

(ii) less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 2'-fluoro nucleotide mimics is a f4P nucleotide



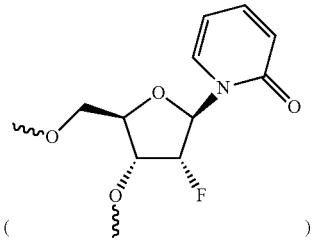
( );

(iii) 1, 2, 3, 4, 5, 6, or more 2'-fluoro nucleotide mimics is a f2P nucleotide



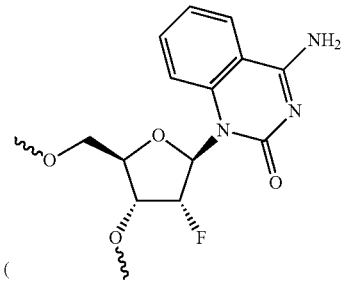
( );

(iv) less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 2'-fluoro nucleotide mimics is a f2P nucleotide



( ) ;

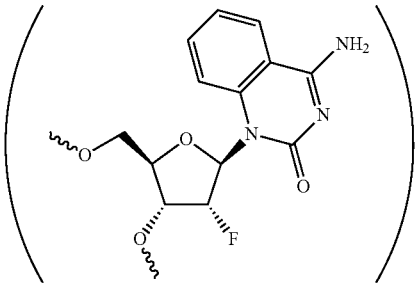
(v) 1, 2, 3, 4, 5, 6, or more 2'-fluoro nucleotide mimics is a fX nucleotide



( ) ;

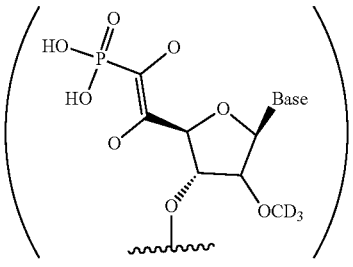
and/or

(vi) less than or equal to 10, 9, 8, 7, 6, 5, 4, 3, or 2 2'-fluoro nucleotide mimics is a fX nucleotide



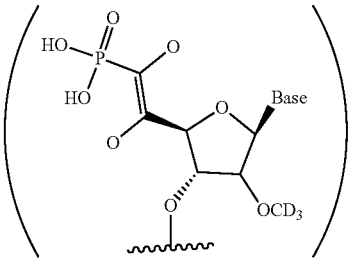
114. The siNA of claim **1**, wherein:

(i) the first nucleotide from the 5' end of the antisense strand or second nucleotide sequence is a d2vd3 nucleotide



and/or

(ii) the first nucleotide from the 3' end of the antisense strand or second nucleotide sequence is a d2vd3 nucleotide



115. A composition comprising:

(I) at least one siNA according to claim **1**; and (b) a pharmaceutically acceptable excipient.

116. The composition of claim **115**, comprising:

(i) at least 1, 2, 3, 4, 5, or more siNAs that target an S gene of HBV; and/or

(ii) at least 1, 2, 3, 4, 5, or more siNAs that target an X gene of HBV.

117. The composition according to claim **115**, further comprising:

(i) an additional HBV treatment agent;

(ii) an additional HBV treatment agent selected from a nucleotide analog, nucleoside analog, a capsid assembly modulator (CAM), a recombinant interferon, an entry inhibitor, a small molecule immunomodulator and oligonucleotide therapy;

(iii) an additional siNA;

(iv) an additional siNA selected from any of ds-siNA-001 to ds-siNA-0178;

(v) an oligonucleotide therapy selected from an antisense oligonucleotide (ASO), NAPs, or STOPs;

(vi) an ASO selected from ASO 1 or ASO 2; and/or

(vii) an additional HBV treatment agent selected from HBV STOPS™ ALG-010133, HBV CAM ALG-000184, ASO 1, recombinant interferon alpha 2b, IFN-a, PEG-IFN-a-2a, lamivudine, telbivudine, adefovir dipivoxil, clevudine, entecavir, tenofovir alafenamide, tenofovir disoproxil, NVR3-778, BAY41-4109, JNJ-632, JNJ-3989 (ARO-HBV), RG6004, GSK3228836, REP-2139, REP-2165, AB-729, VIR-2218, RG6346 (DCR-HBVS), JNJ-6379, GLS4, ABI-HO731, JNJ-440, NZ-4, RG7907, EDP-514, AB-423, AB-506, ABI-H03733 and ABI-H_{2158}.

118-129. (canceled)

130. A method of treating hepatitis B virus (HBV), comprising administering to a subject with HBV at least one siNA according to claim **1**.

* * * * *